25 OCT 2006

CELLULAR ACCUMULATION OF PHOSPHONATE ANALOGS OF HIV PROTEASE INHIBITOR COMPOUNDS

This non-provisional application claims the benefit of Provisional Applications 60/375,622, filed April 26, 2002; Provisional Application No. 60/375,779 filed April 26, 2002; Provisional Application No. 60/375,834, filed April 26, 2002, and Provisional Application No. 60/375,665 filed April 26, 2002, all of which are incorporated herein by reference. Additionally, copending applications Attorney Docket Nos. 259.PC and 260.PC filed concurrently with this application are also incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The invention relates generally to compounds with antiviral activity and more specifically with anti-HIV protease properties.

BACKGROUND OF THE INVENTION

AIDS is a major public health problem worldwide. Although drugs targeting HIV viruses are in wide use and have shown effectiveness, toxicity and development of resistant strains have limited their usefulness. Assay methods capable of determining the presence, absence or amounts of HIV viruses are of practical utility in the search for inhibitors as well as for diagnosing the presence of HIV.

Human immunodeficiency virus (HIV) infection and related disease is a major public health problem worldwide. The retrovirus human immunodeficiency virus type 1 (HIV-1), a member of the primate lentivirus family (DeClercq E (1994) *Annals of the New York Academy of Sciences*, 724:438-456; Barre-Sinoussi F (1996) *Lancet*, 348:31-35), is generally accepted to be the causative agent of acquired immunodeficiency syndrome (AIDS) Tarrago etal *FASEB Journal* 1994, 8:497-503). AIDS is the result of repeated replication of HIV-1 and a decrease in immune capacity, most prominently a fall in the number of CD4+ lymphocytes. The mature virus has a single stranded RNA genome that encodes 15 proteins (Frankel etal (1998) *Annual Review of Biochemistry*, 67:1-25; Katz etal (1994) *Annual Review of Biochemistry*, 63:133-173), including three key enzymes: (i) protease (Prt) (von der Helm K (1996) *Biological Chemistry*, 377:765-774); (ii) reverse transcriptase (RT) (Hottiger etal (1996) *Biological Chemistry Hoppe-Seyler*, 377:97-120), an enzyme unique to retroviruses; and (iii) integrase (Asante etal (1999) *Advances in Virus Research* 52:351-369; Wlodawer A (1999) *Advances in Virus Research* 52:335-350; Esposito etal (1999) *Advances in Virus Research* 52:319-333). Protease is responsible for processing the viral precursor polyproteins, integrase is responsible for the integration of the double stranded DNA form of the viral genome into host DNA and RT is the key enzyme in the replication of the viral genome. In viral replication, RT acts as both an RNA- and a DNA-dependent DNA polymerase, to convert the single stranded RNA genome into double stranded DNA. Since virally encoded Reverse Transcriptase (RT) mediates specific reactions during the natural reproduction of the virus, inhibition of HIV RT is an important therapeutic target for treatment of HIV infection and related disease.

Sequence analysis of the complete genomes from several infective and non-infective HIV-isolates has shed considerable light on the make-up of the virus and the types of molecules that are essential for its replication and maturation to an infective species. The HIV protease is essential for the processing of the viral gag and gag-pol polypeptides into mature virion proteins. L. Ratner, et al., Nature, 313:277-284 (1985); L. H. Pearl and W. R. Taylor, Nature, 329:351 (1987). HIV exhibits the same gag/pol/env organization seen in other retroviruses. L. Ratner, et al., above; S. Wain-Hobson, et al., Cell, 40:9-17 (1985); R. Sanchez-Pescador, et al., Science, 227:484-492 (1985); and M. A. Muesing, et al., Nature, 313:450-458 (1985).

A therapeutic target in AIDS involves inhibition of the viral protease (or proteinase)

that is essential for processing HIV-fusion polypeptide precursors. In HIV and several other retroviruses, the proteolytic maturation of the gag and gag/pol fusion polypeptides (a process indispensable for generation of infective viral particles) has been shown to be mediated by a protease that is, itself, encoded by the pol region of the viral genome. Y. Yoshinaka, et al., Proc. Natl. Acad. Sci. USA, 82:1618-1622 (1985); Y. Yoshinaka, et al., J. Virol., 55:870-873 (1985); Y. Yoshinaka, et al., J. Virol., 57:826-832 (1986); and K. von der Helm, Proc. Natl. Acad. Sci., USA, 74:911-915 (1977). Inhibition of the protease has been shown to inhibit the processing of the HIV p55 in mammalian cell and HIV replication in T lymphocytes. T. J. McQuade, et al., Science, 247:454 (1990).

Drugs approved in the United States for AIDS therapy include nucleoside inhibitors of RT (Smith et al (1994) *Clinical Investigator*, 17:226-243), protease inhibitors and non-nucleoside RT inhibitors (NNRTI), (Johnson et al (2000) *Advances in Internal Medicine*, 45 (1-40; Porche DJ (1999) *Nursing Clinics of North America*, 34:95-112).

The protease (or proteinase), consisting of only 99 amino acids, is among the smallest enzymes known, and its demonstrated homology to aspartyl proteases such as pepsin and renin (L. H. Pearl and W. R. Taylor, Nature, 329:351-354 (1987); and I. Katoh, et al., Nature, 329:654-656 (1987)), led to inferences regarding the three-dimensional structure and mechanism of the enzyme (L. H. Pearl and W. R. Taylor, above) that have since been borne out experimentally. Active HIV protease has been expressed in bacteria (see, e.g., P. L. Darke, et al., J. Biol. Chem., 264:2307-2312 (1989)) and chemically synthesized (J. Schneider and S. B. Kent, Cell, 54:363-368 (1988); and R. F. Nutt, et al., Proc. Natl. Acad. Sci., USA, 85:7129-7133 (1988)). Site directed mutagenesis (P. L. Darke, et al., above); and N. E. Kohl, et al., Proc. Natl. Acad. Sci., USA, 85:4686-4690 (1988)) and pepstatin inhibition (P. L. Darke, et al., J. Biol. Chem., 264:2307-2312 (1989); S. Seelmeier, et al., Proc. Natl. Acad. Sci., USA, 85:6612-6616 (1988); C.-Z. Giam and I. Borsos, J. Biol. Chem., 263:14617-14720 (1988); and J. Hansen, et al., EMBO J., 7:1785-1791 (1988)) have provided evidence for HIV protease's mechanistic function as an aspartyl protease. A study has demonstrated that the protease cleaves at the sites expected in peptides modeled after the regions actually cleaved by the enzyme in the gag and pol precursor proteins during viral maturation. P. L. Darke, et al., Biochem. Biophys. Res. Communs., 156:297-303 (1988). X-ray crystallographic analysis of the HIV-protease (M. A. Navia, et al., Nature, 337:615-620 (1989)) and a related retroviral enzyme from Rous sarcoma virus (M. Miller, et al., Nature,

337:576-579 (1989)) reveal an active site in the protease dimer that is identical to that seen in other aspartyl proteases, thus supporting the supposition (L. H. Pearl and W. R. Taylor, above) that the HIV enzyme is active as a dimer. See also Joseph A. Martin, "Recent Advances in the Design of HIV Proteinase Inhibitors," Antiviral Research, 17 (1992) 265-278.

Inhibitors of HIV protease are useful to limit the establishment and progression of infection by therapeutic administration as well as in diagnostic assays for HIV. Protease inhibitor drugs approved by the FDA include:

- saquinavir (Invirase®, Fortovase®, Hoffman-La Roche, EP-00432695 and EP-00432694)
- ritonavir (Norvir®, Abbott Laboratories)
- indinavir (Crixivan®, Merck & Co.)
- nelfinavir (Viracept®, Pfizer)
- amprenavir (Agenerase®, GlaxoSmithKline, Vertex Pharmaceuticals)
- lopinavir/ritonavir (Kaletra®, Abbott Laboratories)

Experimental protease inhibitor drugs include:

- fosamprenavir (GlaxoSmithKline, Vertex Pharmaceuticals)
- tipranavir (Boehringer Ingelheim)
- atazanavir (Bristol-Myers Squibb).

There is a need for anti-HIV therapeutic agents, i.e. drugs having improved antiviral and pharmacokinetic properties with enhanced activity against development of HIV resistance, improved oral bioavailability, greater potency and extended effective half-life *in vivo*. New HIV protease inhibitors (PI) should be active against mutant HIV strains, have distinct resistance profiles, fewer side effects, less complicated dosing schedules, and orally active. In particular, there is a need for a less onerous dosage regimen, such as one pill, once per day. Although drugs targeting HIV protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant strains have limited their usefulness (Palella, et al *N. Engl. J. Med.* (1998) 338:853-860; Richman, D. D. *Nature* (2001) 410:995-1001).

Combination therapy of PI and RT inhibitors has proven to be highly effective in suppressing viral replication to unquantifiable levels for a sustained period of time. Also,

combination therapy with RT and protease inhibitors have shown synergistic effects in suppressing HIV replication. Unfortunately, many patients currently fail combination therapy due to the development of drug resistance, non-compliance with complicated dosing regimens, pharmacokinetic interactions, toxicity, and lack of potency. Therefore, there is a need for new HIV protease inhibitors that are synergistic in combination with other HIV inhibitors.

Improving the delivery of drugs and other agents to target cells and tissues has been the focus of considerable research for many years. Though many attempts have been made to develop effective methods for importing biologically active molecules into cells, both *in vivo* and *in vitro*, none has proved to be entirely satisfactory. Optimizing the association of the inhibitory drug with its intracellular target, while minimizing intercellular redistribution of the drug, e.g. to neighboring cells, is often difficult or inefficient.

Most agents currently administered to a patient parenterally are not targeted, resulting in systemic delivery of the agent to cells and tissues of the body where it is unnecessary, and often undesirable. This may result in adverse drug side effects, and often limits the dose of a drug (e.g., cytotoxic agents and other anti-cancer or anti-viral drugs) that can be administered. By comparison, although oral administration of drugs is generally recognized as a convenient and economical method of administration, oral administration can result in either (a) uptake of the drug through the cellular and tissue barriers, e.g. blood/brain, epithelial, cell membrane, resulting in undesirable systemic distribution, or (b) temporary residence of the drug within the gastrointestinal tract. Accordingly, a major goal has been to develop methods for specifically targeting agents to cells and tissues. Benefits of such treatment includes avoiding the general physiological effects of inappropriate delivery of such agents to other cells and tissues, such as uninfected cells. Intracellular targeting may be achieved by methods and compositions which allow accumulation or retention of biologically active agents inside cells.

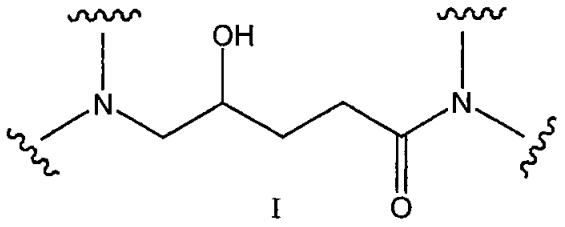
SUMMARY OF THE INVENTION

The present invention provides novel compounds with HIV protease activity, i.e. novel human retroviral protease inhibitors. Therefore, the compounds of the invention may inhibit retroviral proteases and thus inhibit the replication of the virus. They are useful for treating human patients infected with a human retrovirus, such as human immunodeficiency virus (strains of HIV-1 or HIV-2) or human T-cell leukemia viruses (HTLV-I or HTLV-II) which results in acquired immunodeficiency syndrome (AIDS) and/or related diseases. The present invention includes novel phosphonate HIV protease inhibitor (PI) compounds and phosphonate analogs of known approved and experimental protease inhibitors. The compounds of the invention optionally provide cellular accumulation as set forth below.

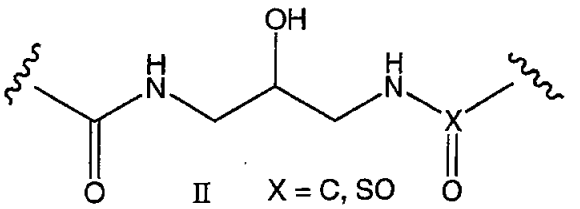
The present invention relates generally to the accumulation or retention of therapeutic compounds inside cells. The invention is more particularly related to attaining high concentrations of phosphonate-containing molecules in HIV infected cells. Intracellular targeting may be achieved by methods and compositions which allow accumulation or retention of biologically active agents inside cells. Such effective targeting may be applicable to a variety of therapeutic formulations and procedures.

Compositions of the invention include new PI compounds having at least one phosphonate group. The invention includes all known approved and experimental protease inhibitors with at least one phosphonate group.

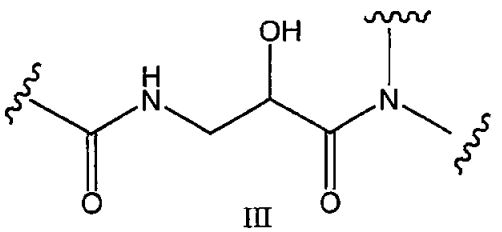
In one aspect, the invention includes compounds having Formulas I, II, III, IV, V, VI, VII and VIIIa-d:



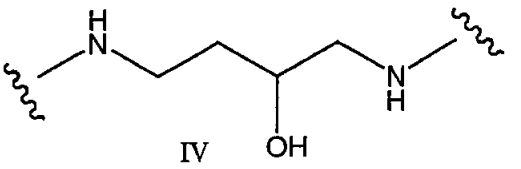
I



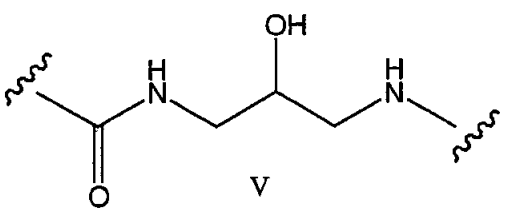
II X = C, SO



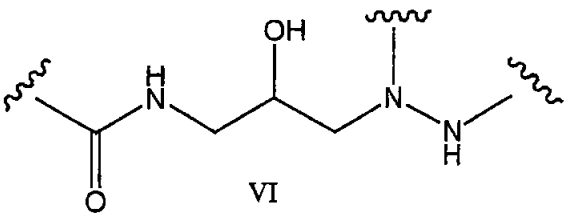
III



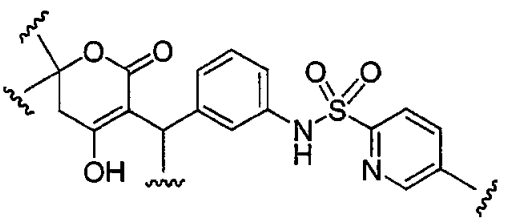
IV



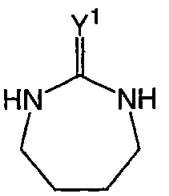
V



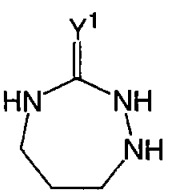
VI



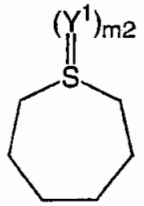
VII



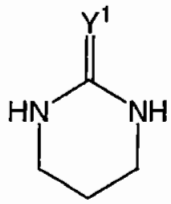
VIIIa



VIIIb



VIIIc and



VIIId;

where a wavy line indicates the other structural moieties of the compounds.

Formulas I- VIII are substituted with one or more covalently attached groups, including at least one phosphonate group. Formulas I-VIII are "scaffolds", i.e. substructures which are common to the specific compounds encompassed therein.

Another aspect of the invention provides a pharmaceutical combination comprising an effective amount of a compound selected from Formulas I-VIII and a second compound having anti-HIV properties.

Another aspect of the invention provides a method for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal which comprises administering to, i.e. treating, said animal with a pharmaceutical combination comprising an effective amount of a compound selected from Formulas I-VIII and a second compound having anti-HIV properties.

The invention provides a pharmaceutical composition comprising an effective amount of a compound selected from Formulas I-VIII, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

This invention pertains to a method of increasing cellular accumulation and retention of drug compounds, thus improving their therapeutic and diagnostic value.

The invention also provides a method of inhibiting HIV, comprising administering to a mammal infected with HIV (HIV positive) an amount of a compound of Formulas I-VIII, effective to inhibit the growth of said HIV infected cells.

The invention also provides a compound selected from Formulas I-VIII for use in medical therapy (preferably for use in treating cancer, e.g. solid tumors), as well as the use of a compound of Formulas I-VIII for the manufacture of a medicament useful for the treatment of cancer, e.g. solid tumors.

The invention also provides processes and novel intermediates disclosed herein which are useful for preparing compounds of the invention. Some of the compounds of Formulas I-

VIII are useful to prepare other compounds of Formulas I-VIII.

In another aspect of the invention, the activity of HIV protease is inhibited by a method comprising the step of treating a sample suspected of containing HIV virus with a compound or composition of the invention.

Another aspect of the invention provides a method for inhibiting the activity of HIV protease comprising the step of contacting a sample suspected of containing HIV virus with a composition of the invention.

In other aspects, novel methods for synthesis analysis, separation, isolation, purification, characterization, and testing of the compounds of this invention are provided.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying description, structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

DEFINITIONS

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

The terms "phosphonate" and "phosphonate group" mean a functional group or moiety within a molecule that comprises at least one phosphorus-carbon bond, and at least one phosphorus-oxygen double bond. The phosphorus atom is further substituted with oxygen, sulfur, and nitrogen substituents. These substituents may be part of a prodrug moiety. As defined herein, "phosphonate" and "phosphonate group" include molecules with phosphonic acid, phosphonic monoester, phosphonic diester, phosphonamidate, phosphondiamidate and phosphonthioate functional groups.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e. active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or

metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically-active compound.

"Pharmaceutically acceptable prodrug" refers to a compound that is metabolized in the host, for example hydrolyzed or oxidized, by either enzymatic action or by general acid or base solvolysis, to form an active ingredient. Typical examples of prodrugs of the compounds of the invention have biologically labile protecting groups on a functional moiety of the compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, esterified, deesterified, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated, photolyzed, hydrolyzed, or other functional group change or conversion involving forming or breaking chemical bonds on the prodrug.

"Prodrug moiety" means a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, "Design and Application of Prodrugs" in Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-CH_2OC(=O)R^9$ and acyloxymethyl carbonates $-CH_2OC(=O)OR^9$ where R^9 is C_1–C_6 alkyl, C_1–C_6 substituted alkyl, C_6–C_{20} aryl or C_6–C_{20} substituted aryl. The acyloxyalkyl ester was first used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. In certain compounds of the invention, a prodrug moiety is part of a phosphonate group. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-CH_2OC(=O)C(CH_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-CH_2OC(=O)OC(CH_3)_3$.

The phosphonate group may be a phosphonate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphonamidate-ester group.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (DeLambert et al (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the *ortho*-or *para*-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, e.g. esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C–O bond to generate the phosphoric acid and the quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al (1992) *J. Chem. Soc. Perkin Trans. I* 2345; Brook et al WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier et al WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al (1996) *J. Med. Chem.* 39: 4958). Cyclic phosphonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion et al, US Patent No. 6312662).

"Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as intermediates in the synthesis of the parental drug substance. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g. making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound

alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro,* in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, e.g. alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

Any reference to any of the compounds of the invention also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1–C_4 alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound of an hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a C_1–C_4 alkyl group).

For therapeutic use, salts of active ingredients of the compounds of the invention will be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable

compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

"Alkyl" is C_1-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, -CH_3), ethyl (Et, -CH_2CH_3), 1-propyl (n-Pr, n-propyl, -$CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, -$CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, -$CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, -$CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, -$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, -$C(CH_3)_3$), 1-pentyl (n-pentyl, -$CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (-$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (-$CH(CH_2CH_3)_2$), 2-methyl-2-butyl (-$C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl (-$CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl (-$CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl (-$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (-$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (-$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (-$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (-$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (-$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (-$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (-$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (-$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (-$C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl (-$CH(CH_3)C(CH_3)_3$.

"Alkenyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp^2 double bond. Examples include, but are not limited to: ethylene or vinyl (-$CH=CH_2$), allyl (-$CH_2CH=CH_2$), cyclopentenyl (-C_5H_7), and 5-hexenyl (-CH_2 $CH_2CH_2CH_2CH=CH_2$)

"Alkynyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, *sp* triple bond. Examples include, but are not limited to: acetylenic (-C≡CH) and propargyl (-CH_2C≡CH),

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to: methylene (-CH_2-) 1,2-ethyl (-CH_2CH_2-), 1,3-propyl (-$CH_2CH_2CH_2$-), 1,4-butyl (-$CH_2CH_2CH_2CH_2$-), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to: 1,2-ethylene (-CH=CH-).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. Typical alkynylene radicals include, but are not limited to: acetylene (-C≡C-), propargyl (-CH_2C≡C-), and 4-pentynyl (-$CH_2CH_2CH_2$C≡CH-).

"Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, biphenyl, and the like.

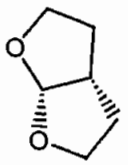
"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group comprises 6 to 20 carbon atoms, e.g. the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 5 to 14 carbon atoms.

"Substituted alkyl", "substituted aryl", and "substituted arylalkyl" mean alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a substituent. Typical substituents include, but are not limited to, -X, -R, -O-, -OR, -SR, -S^-, -NR_2, -NR_3, =NR, -CX_3, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO_2, =N_2, -N_3, NC(=O)R, -C(=O)R, -C(=O)NRR -$S(=O)_2O^-$, -$S(=O)_2$OH, -$S(=O)_2$R, -$OS(=O)_2$OR, -$S(=O)_2$NR, -S(=O)R, -$OP(=O)O_2RR$, -$P(=O)O_2RR$ -$P(=O)(O^-)_2$, -$P(=O)(OH)_2$, -C(=O)R, -C(=O)X, -C(S)R, -C(O)OR, -$C(O)O^-$, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(NR)NRR, where each X is independently a halogen: F, Cl, Br, or I; and each R is independently -H, alkyl, aryl, heterocycle, protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

"Heterocycle" as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566.

Examples of heterocycles include by way of example and not limitation pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, bis-tetrahydrofuranyl, tetrahydropyranyl, bis-tetrahydropyranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl.

One embodiment of the bis-tetrahydrofuranyl group is:



By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at

position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Carbocycle" means a saturated, unsaturated or aromatic ring having 3 to 7 carbon atoms as a monocycle or 7 to 12 carbon atoms as a bicycle. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, e.g. arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

"Linker" or "link" means a chemical moiety comprising a covalent bond or a chain of atoms that covalently attaches a phosphonate group to a drug. Linkers include portions of substituents A^1 and A^3 enumerated in Formula I, or substituents A_1 and A_3 enumerated in Formula II, which include moieties such as: repeating units of alkyloxy (e.g. polyethylenoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethyleneamino, Jeffamine™); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l, D and L, or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

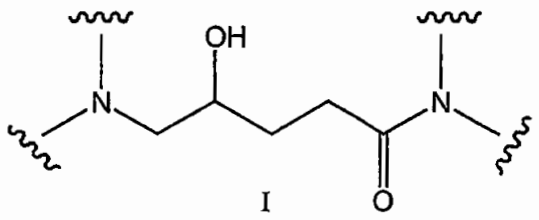
HIV Protease Inhibitor Compounds

The compounds of the invention include those with HIV protease inhibitory activity. In particular, the compounds include HIV protease inhibitors. The compounds of the inventions bear a phosphonate group, which may be a prodrug moiety.

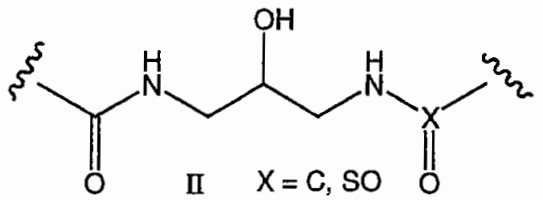
In various embodiments of the invention one identifies compounds that may fall within the generic scope of the documents cited under the definition of the terms ILPPI (Indinavir-like phosphonate protease inhibitors, Formula I); AMLPPI (Amprenavir-like phosphonate protease inhibitors, Formula II); KNILPPI (KNI-like phosphonate protease inhibitors, Formula III); RLPPI (Ritonavir-like phosphonate protease inhibitors, Formula IV); LLPPI (Lopinavir-like phosphonate protease inhibitors, Formula IV); NLPPI (Nelfinavir-like phosphonate protease inhibitors, Formula V); SLPPI (Saquinavir-like phosphonate protease inhibitors, Formula V); ATLPPI (Atanzavir-like phosphonate protease inhibitors, Formula VI); TLPPI (Tipranavir-like phosphonate protease inhibitors, Formula VII); and CCLPPI (Cyclic carbonyl-like phosphonate protease inhibitors, Formula VIIIa-d) all of which comprise a phosphonate group, e.g. a phosphonate diester, phosphonamidate-ester prodrug, or a phosphondiamidate-ester (Jiang et al, US 2002/0173490 A1).

Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R^1" or "R^{6a}", then it will be understood that the groups may be the same or different, i.e., each group is independently selected. Wavy lines indicate the site of covalent bond attachments to the adjoining groups, moieties, or atoms.

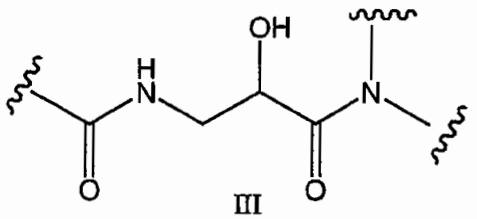
Compounds of the invention are set forth in the schemes, examples, descriptions and claims below and include the invention includes compounds having Formulas I, II, III, IV, V, VI, VII and VIIIa-d:



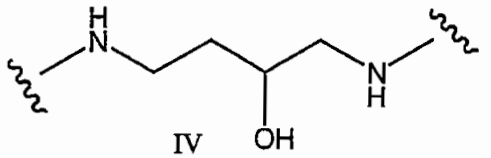
I



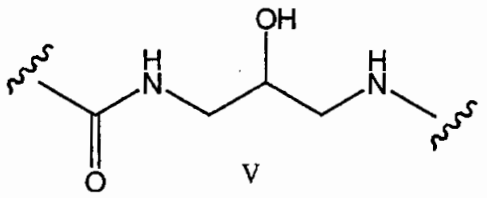
II X = C, SO



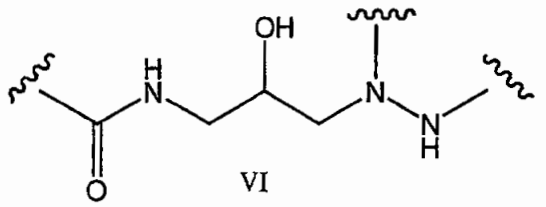
III



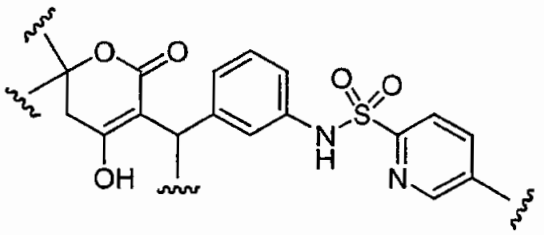
IV



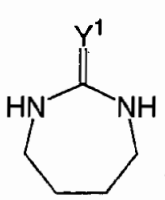
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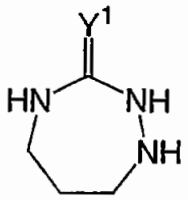


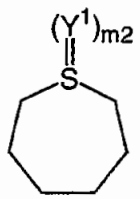
VI

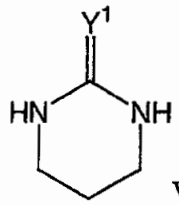


VII


VIIIa


VIIIb


VIIIc and

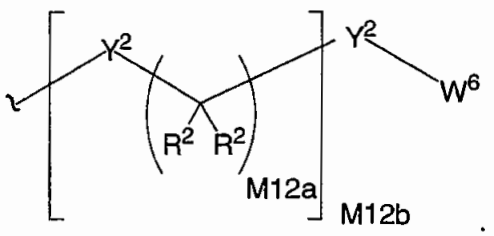

VIIId;

where a wavy line indicates the other structural moieties of the compounds.

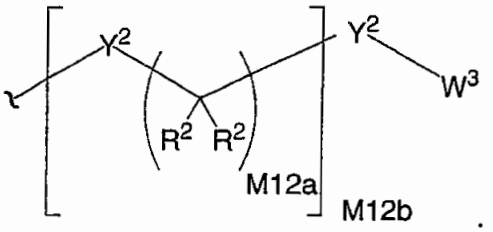
Formula I compounds have a 3-hydroxy-5-amino-pentamide core. Formula II compounds have a 2-hydroxy-1, 3-amino-propylamide or 2-hydroxy-1,3-amino-propylaminosulfone core. Formula III compounds have a 2-hydroxy-3-amino-propylamide core. Formula IV compounds have a 2-hydroxy-4-amino-butylamine core. Formula V compounds have a acylated 1,3-diaminopropane core. Formula VI compounds have a 2-hydroxy-3-diaza-propylamide core. Formula VII compounds have a sulfonamide 5,6-dihydro-4-hydroxy-2-pyrone core. Formula VIIIa-d compounds have a six or seven-membered ring, and a cyclic carbonyl, sulfhydryl, sulfoxide or sulfone core, where Y^1 is oxygen, sulfur, or substituted nitrogen and m2 is 0, 1 or 2.

Formulas I, II, III, IV, V, VI, VII and VIIIa-d are substituted with one or more covalently attached groups, including at least one phosphonate group. Formulas I, II, III, IV, V, VI, VII and VIIIa-d are substituted with one or more covalently attached A^0 groups, including simultaneous substitutions at any or all A^0. A^0 is A^1, A^2 or W^3. Compounds of Formulas I, II, III, IV, V, VI, VII and VIIIa-d include at least one A^1.

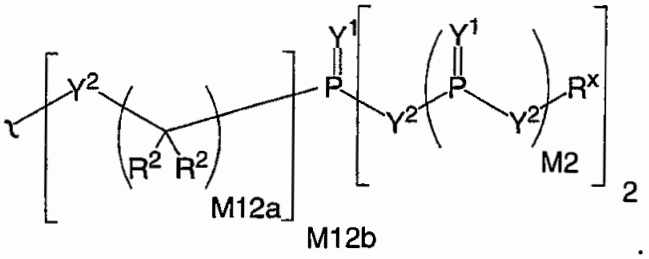
A^1 is:



A^2 is:



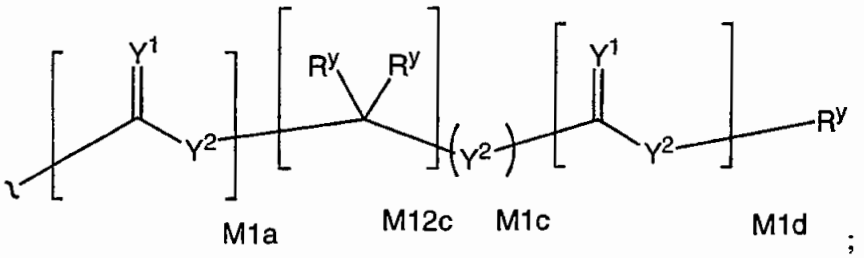
A^3 is:



Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$.

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$.

R^x is independently H, W^3, a protecting group, or the formula:



;

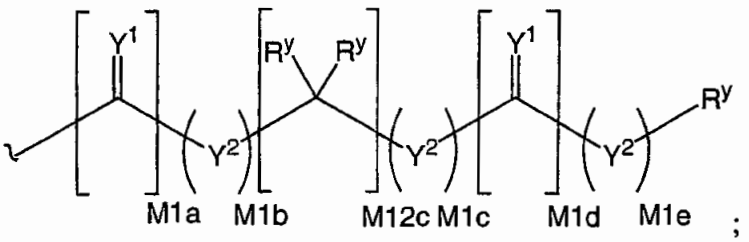
wherein:

M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12; and

R^y is independently H, W^3, R^2 or a protecting group.

Alternatively, R^x is a group of the formula:



;

wherein:

m1a, m1b, m1c, m1d and m1e are independently 0 or 1;

m12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

R^y is H, W^3, R^2 or a protecting group;

provided that:

if m1a, m12c, and m1d are 0, then m1b, m1c and m1e are 0;

if m1a and m12c are 0 and m1d is not 0, then m1b and m1c are 0;

if m1a and m1d are 0 and m12c is not 0, then m1b and at least one of m1c and m1e are 0;

if m1a is 0 and m12c and m1d are not 0, then m1b is 0;

if m12c and m1d are 0 and m1a is not 0, then at least two of m1b, m1c and m1e are 0;

if m12c is 0 and m1a and m1d are not 0, then at least one of m1b and m1c are 0; and

if m1d is 0 and m1a and m12c are not 0, then at least one of m1c and m1e are 0.

R^1 is independently H or alkyl of 1 to 18 carbon atoms.

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups. Alternatively, taken together at a carbon atom, two R^2 groups form a ring, i.e. a spiro carbon. The ring may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The ring may be substituted with 0 to 3 R^3 groups.

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d}.

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$.

R^{3b} is Y^1.

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$.

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$.

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms.

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups.

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups.

W^3 is W^4 or W^5.

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$.

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups.

W^{3a} is W^{4a} or W^{5a}.

W^{4a} is R^{5a}, $-C(Y^1)R^{5a}$, $-C(Y^1)W^{5a}$, $-SO_2R^{5a}$, or $-SO_2W^{5a}$.

W^{5a} is a multivalent substituted carbocycle or heterocycle wherein W^{5a} is independently substituted with 0 to 3 R^2 groups.

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups.

M2 is 0, 1 or 2;

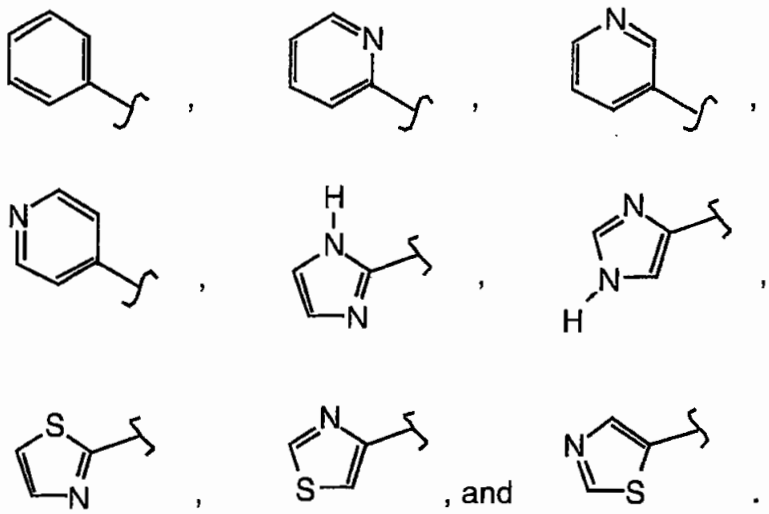
M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12; and

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

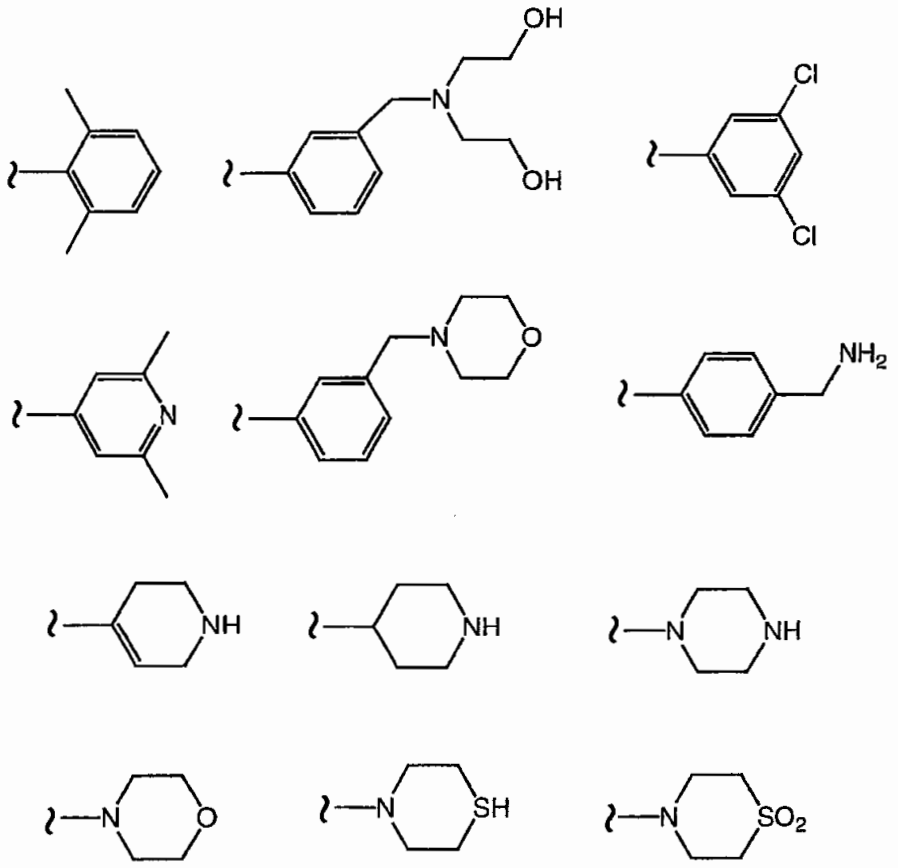
W^5 and W^{5a} carbocycles and W^5 and W^{5a} heterocycles may be independently substituted with 0 to 3 R^2 groups. W^5 may be a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. W^5 may have 3 to 10 ring atoms, e.g., 3 to 7 ring atoms. The W^5 rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

A W^5 or W^{5a} heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). W^5 and W^{5a} heterocyclic monocycles may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). W^5 and W^{5a} heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 hetero atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The W^5 heterocycle may be bonded to Y^2 through a carbon, nitrogen, sulfur or other atom by a stable covalent bond.

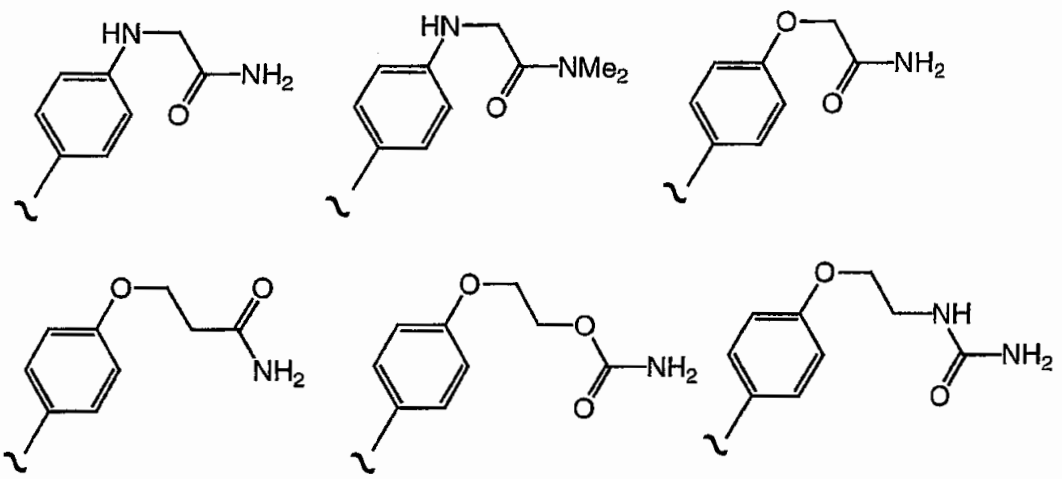
W^5 and W^{5a} heterocycles include for example, pyridyl, dihydropyridyl isomers, piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl. W^5 also includes, but is not limited to, examples such as:



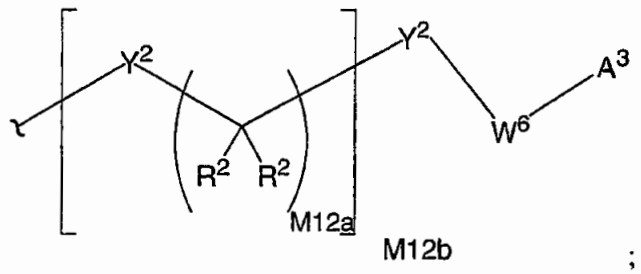
W^5 and W^{5a} carbocycles and heterocycles may be independently substituted with 0 to 3 R^2 groups, as defined above. For example, substituted W^5 carbocycles include:



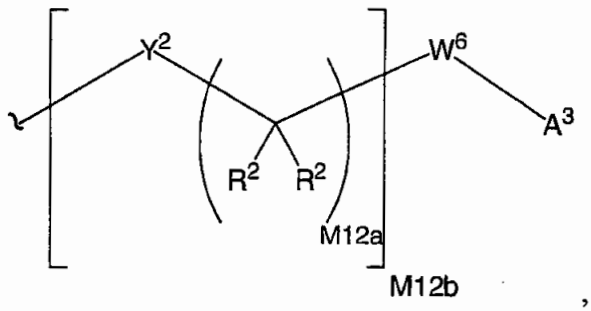
Examples of substituted phenyl carbocycles include:



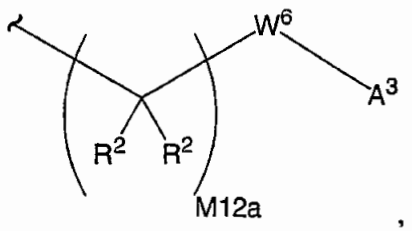
Embodiments of A^1 include:



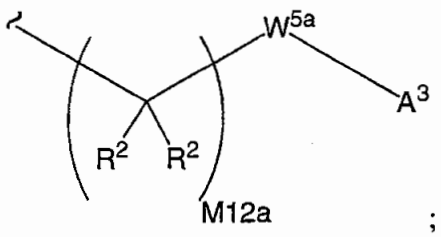
; and where one or more Y^2 are a bond, such as:



,



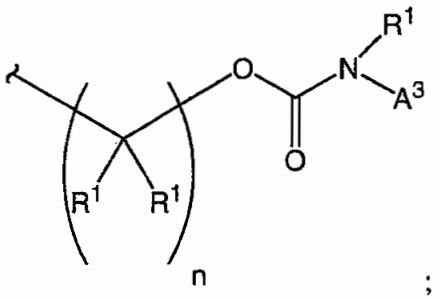
, and



;

where W^{5a} is a carbocycle or a heterocycle and W^{5a} is independently substituted with 0 or 1 R^2 groups.

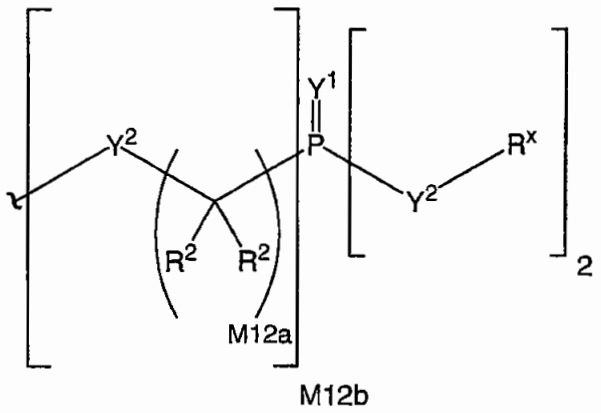
Embodiments of A^1 also include:



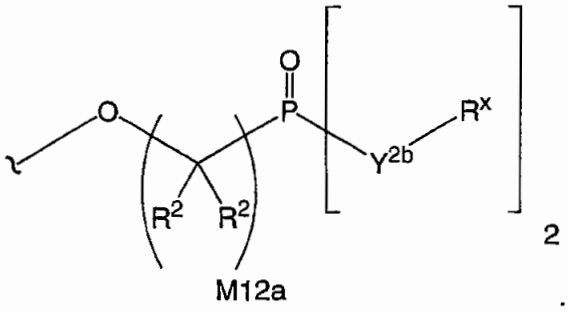
;

where n is an integer from 1 to 18.

Embodiments of A^3 include where M2 is 0, such as:

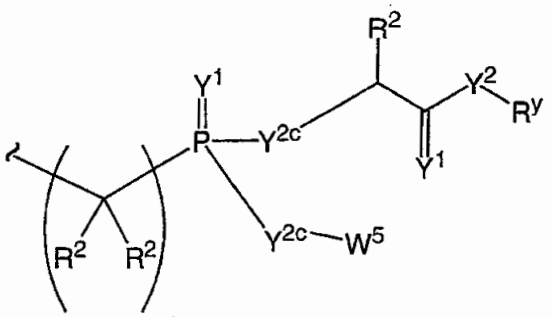


and where M12b is 1, Y^1 is oxygen, and Y^{2b} is oxygen (O) or nitrogen ($N(R^x)$) such as:



.

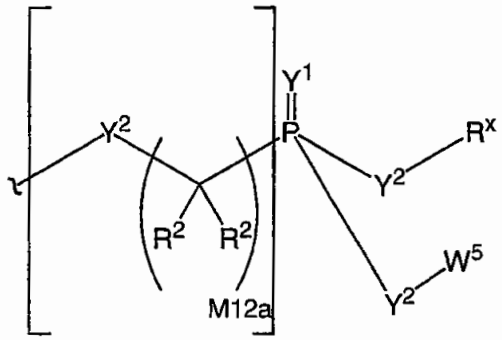
An embodiment of A^3 includes:



M12a ;

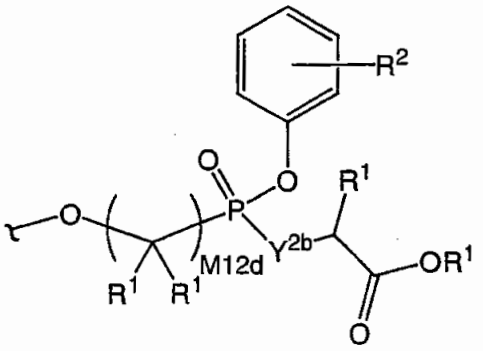
where Y^{2c} is O, N(R^y) or S. For example, R^1 may be H and n may be 1.

Another embodiment of A^3 includes:

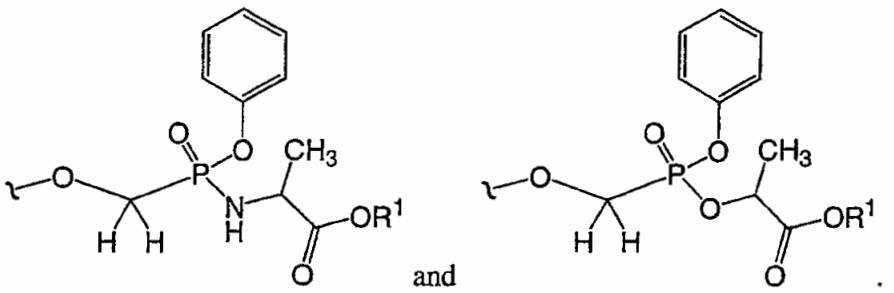


M12b

where W^5 is a carbocycle such as phenyl or substituted phenyl. Such embodiments include:

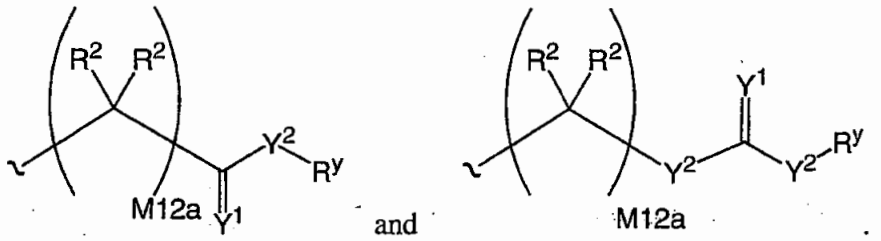


where Y^{2b} is O or N(R^x); M12d is 1, 2, 3, 4, 5, 6, 7 or 8; and the phenyl carbocycle is substituted with 0 to 3 R^2 groups. Such embodiments of A^3 include phenyl phosphonamidate amino acid, e.g. alanate esters and phenyl phosphonate-lactate esters:

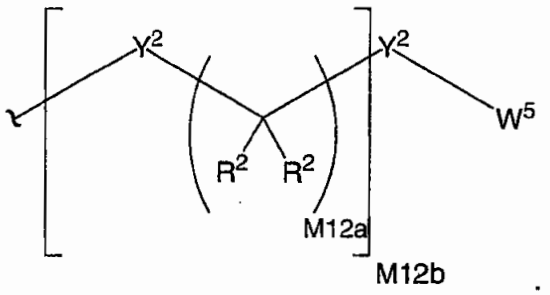


The chiral carbon of the amino acid and lactate moieties may be either the R or S configuration or the racemic mixture.

Embodiments of R^x include esters, carbamates, carbonates, thioesters, amides, thioamides, and urea groups:

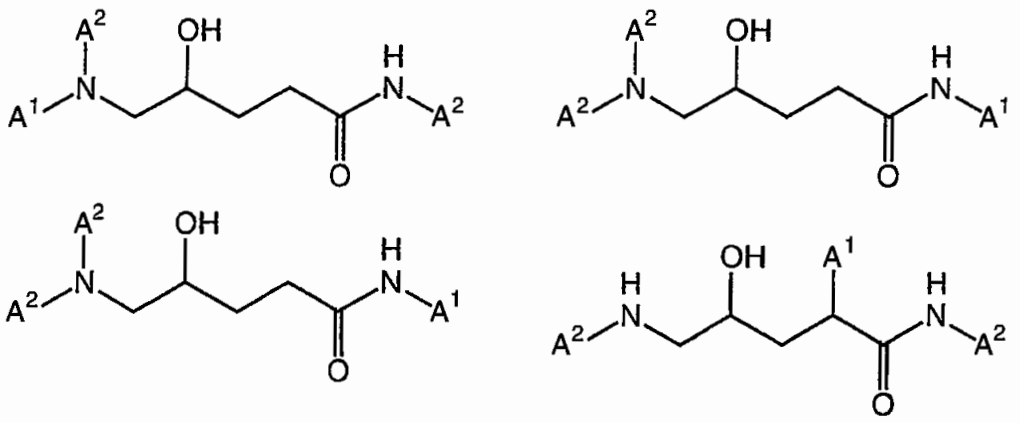


Embodiments of A^2 include where W^3 is W^5, such as:



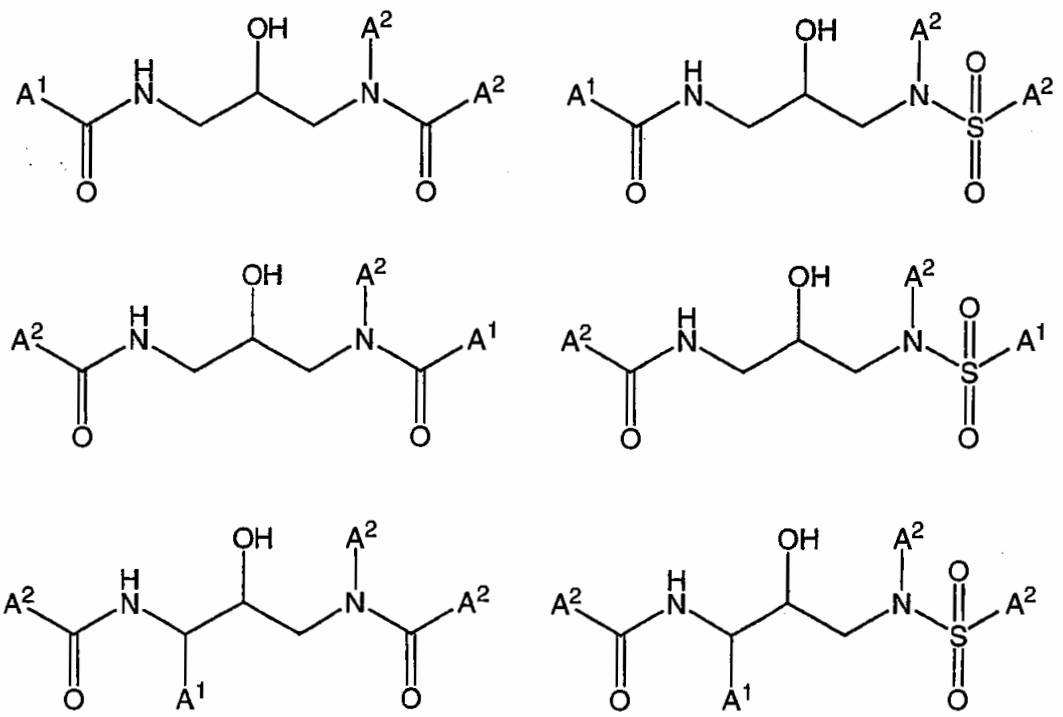
Alternatively, A^2 is phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl or substituted pyridyl.

Exemplary embodiments of Formula I compounds include, but are not limited to, structures:



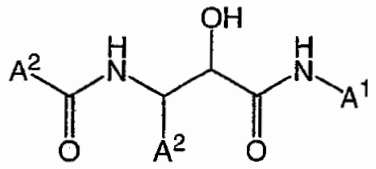
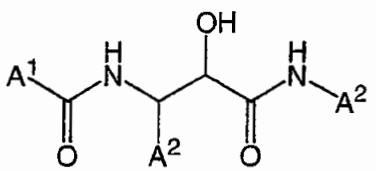
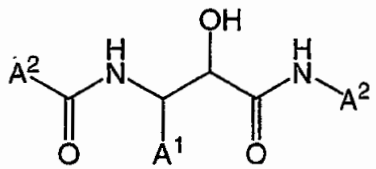
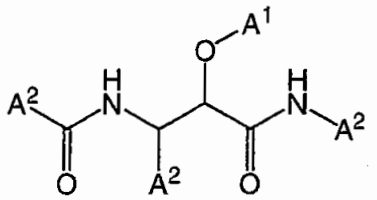
where A^1 denotes a covalent attachment site of a phosphonate group.

Exemplary embodiments of Formula II compounds include, but are not limited to, structures:



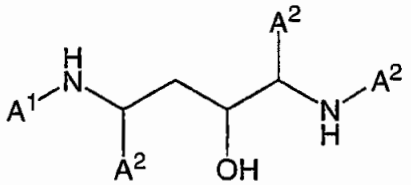
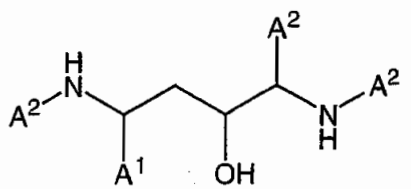
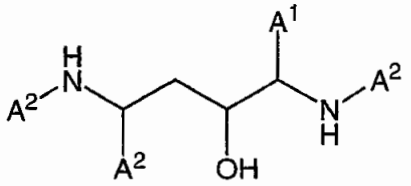
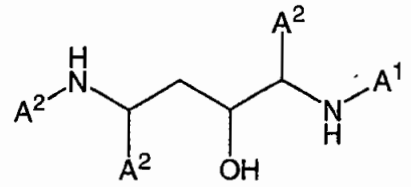
where A^1 denotes a covalent attachment site of a phosphonate group.

Exemplary embodiments of Formula III compounds include, but are not limited to, structures:

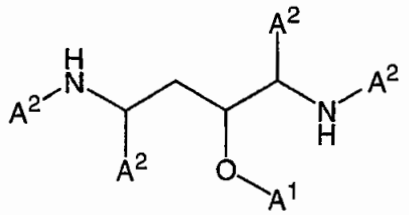





where A^1 denotes a covalent attachment site of a phosphonate group.

Exemplary embodiments of Formula IV compounds include, but are not limited to, structures:

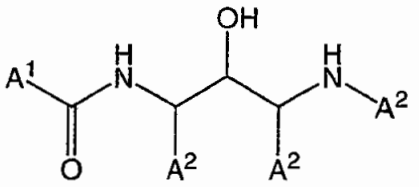





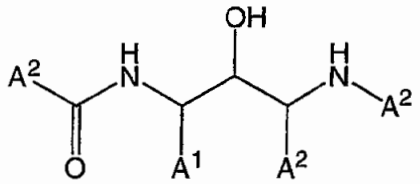
and

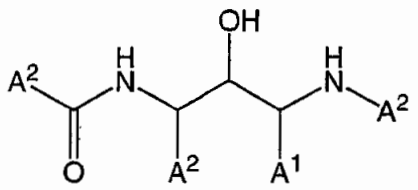


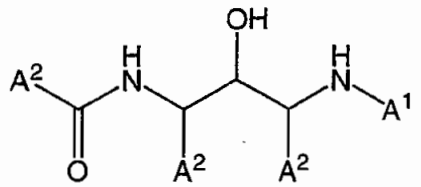
where A^1 denotes a covalent attachment site of a phosphonate group.

Exemplary embodiments of Formula V compounds include, but are not limited to, structures:

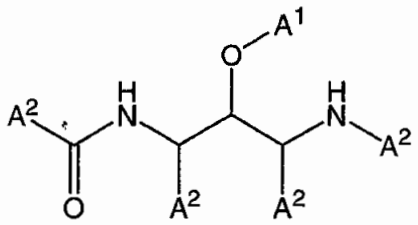






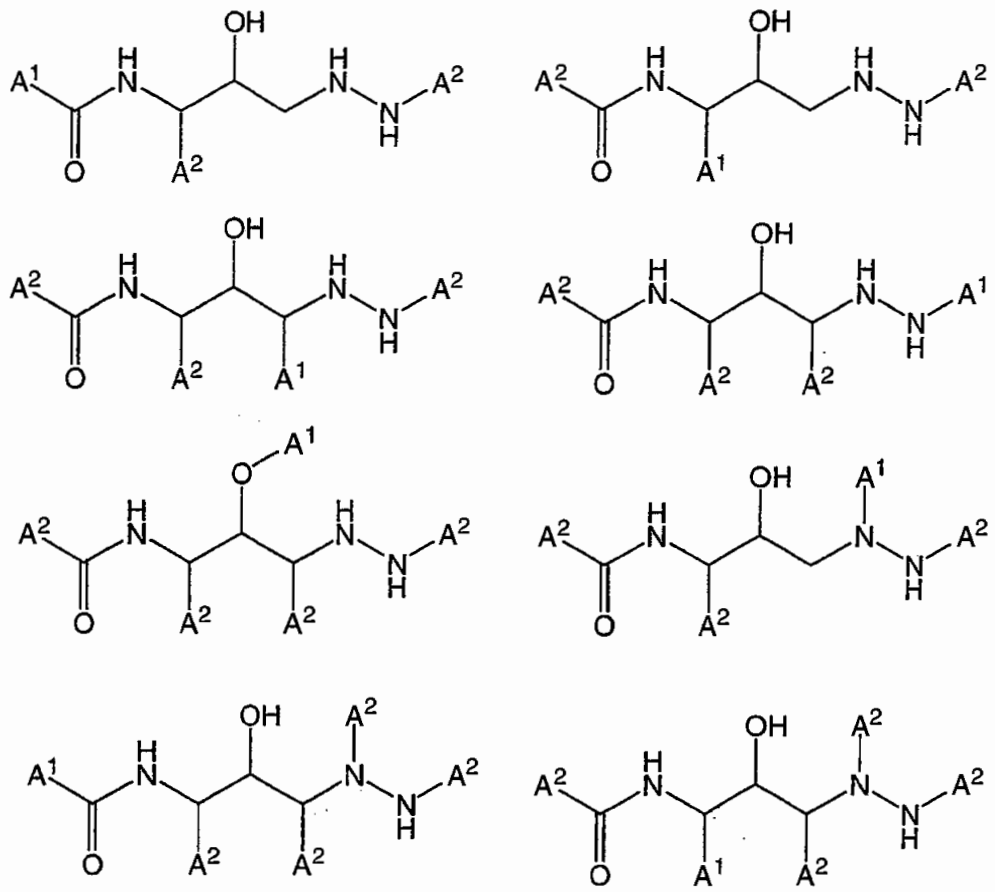


and



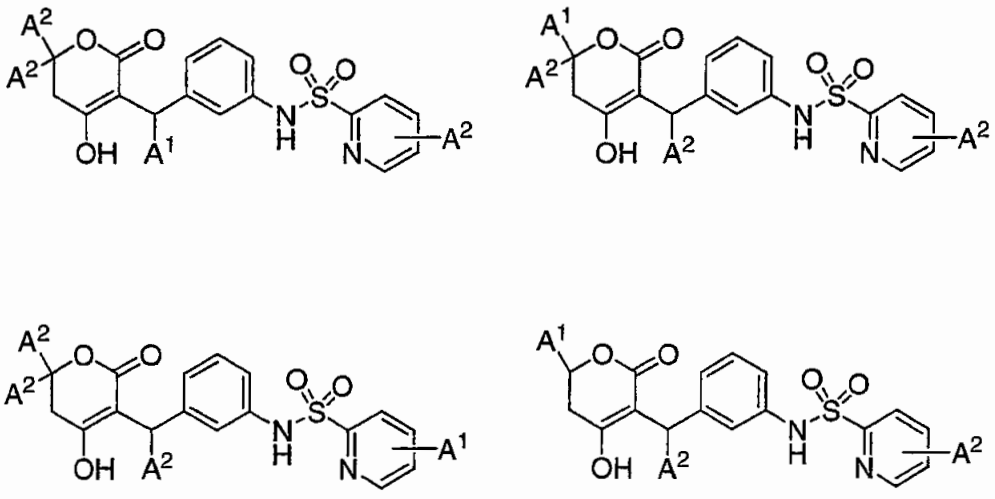
where A^1 denotes a covalent attachment site of a phosphonate group.

Exemplary embodiments of Formula VI compounds include, but are not limited to, structures:



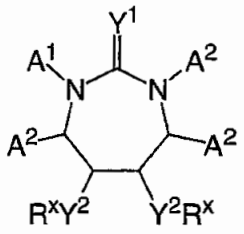
where A^1 denotes a covalent attachment site of a phosphonate group.

Exemplary embodiments of Formula VII compounds include, but are not limited to, structures:

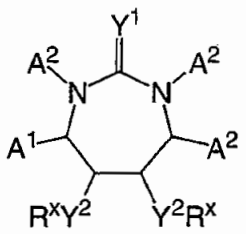


where A^1 denotes a covalent attachment site of a phosphonate group.

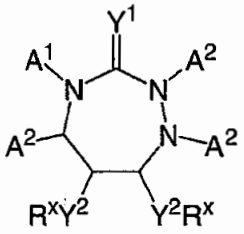
Exemplary embodiments of Formula VIIIa compounds include structures:

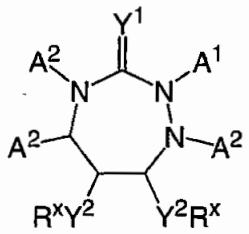


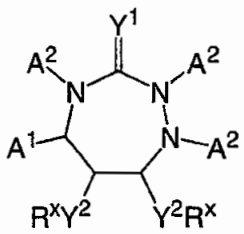
and



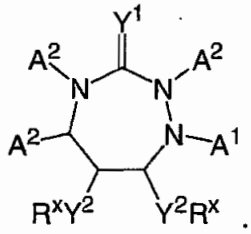
Exemplary embodiments of Formula VIIIb compounds include structures:



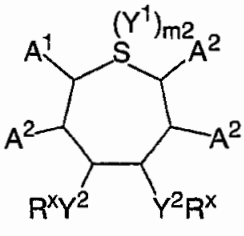




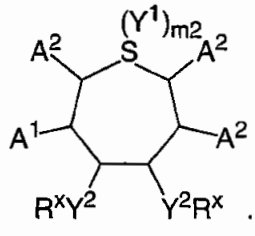
and



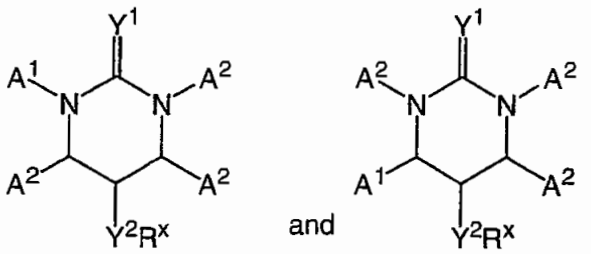
Exemplary embodiments of Formula VIIIc compounds include structures:



and



Exemplary embodiments of Formula VIIId compounds include structures:



where A^1 denotes a covalent attachment site of a phosphonate group.

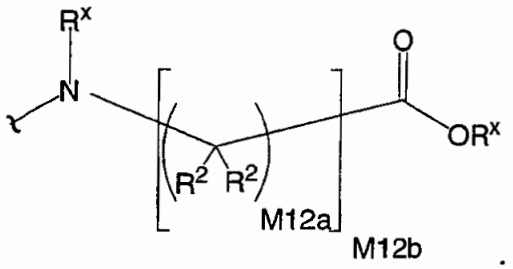
A Cellular Accumulation Embodiment

Another embodiment of the invention is directed toward an HIV protease inhibitor compound capable of accumulating in human PBMCs. Accumulation in human PBMCs is described in the examples herein. Typically, the compounds of this embodiment further comprise a phosponate or phosphonate prodrug. More typically, the phosphonate or phosphonate prodrug has the structure A^3 as described herein. Each of the preferred embodiments of A^3 described herein is a preferred embodiment of A^3 in the present embodiment.

Optionally, the compounds of this embodiment demonstrate improved intracellular half-life of the compounds or intracellular metabolites of the compounds in human PBMCs when compared to analogs of the compounds not having the phosphonate or phosphonate prodrug. Typically, the half-life is improved by at least about 50%, more typically at least in the range 50-100%, still more typically at least about 100%, more typically yet greater than about 100%.

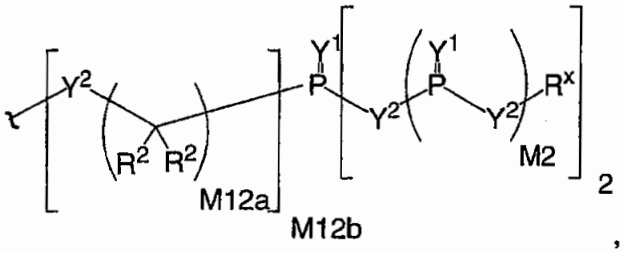
In a preferred embodiment, the intracellular half-life of a metabolite of the compound in human PBMCs is improved when compared to an analog of the compound not having the phosphonate or phosphonate prodrug. In such embodiments, the metabolite is typically generated intracellularly, more typically, it is generated within human PBMCs. Still more typically, the metabolite is a product of the cleavage of a phosphonate prodrug within human PBMCs. More typically yet, the phosphonate prodrug is cleaved to form a metabolite having at least one negative charge at physiological pH. Most typically, the phosphonate prodrug is enzymatically cleaved within human PBMCs to form a phosphonate having at least one active hydrogen atom of the form P-OH.

Not withstanding other disclosure herein which describes the role or presents of phosphonates in the compounds of the invention, in another embodiment of the invention A^3 is A^{3a} which is of the formula:



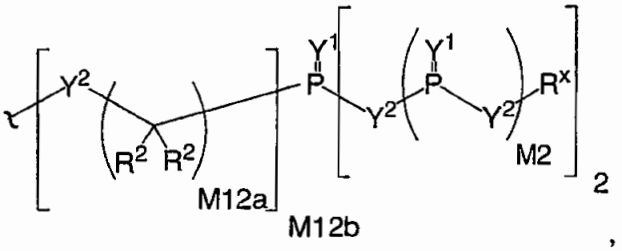
In this embodiment of the invention, any A^3 group may be A^{3a}.

In another aspect of the invention, A^3 is of the formula:



M12a is other than 0 and at least one phosphonate group present in the compound is not bonded directly to W^3. More typically, the phosphonate is not bonded directly to W^5. In such an embodiment, the phosphorous atom of the phosphonate is not bonded directly to a carbon atom of a ring.

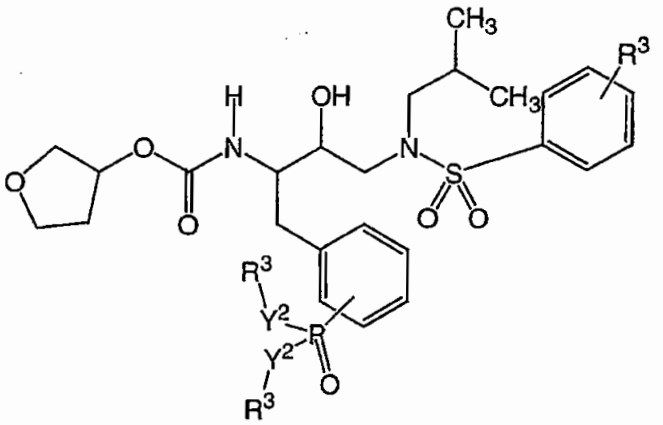
In another aspect of the invention an Amprenavir like phosphonate protease inhibitor, as described above in the description and below in the claims, contains an A^3 group of the formula:



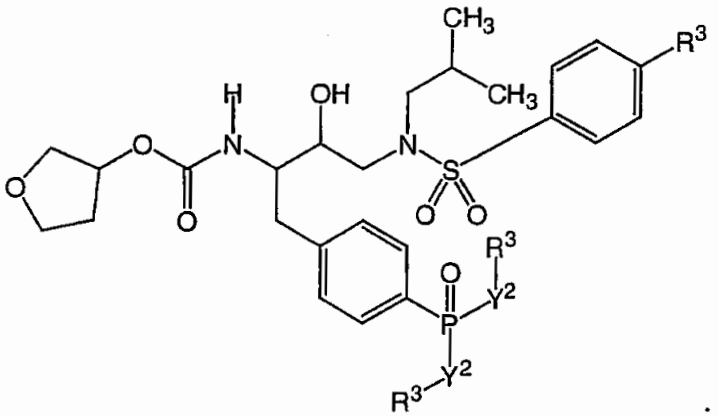
M12a is other than 0 and at least one phosphonate group present in the compound is not bonded directly to W^3. More typically, the phosphonate is not bonded directly to W^5. In

such an embodiment, the phosphorous atom of the phosphonate is not bonded directly to a carbon atom of a ring.

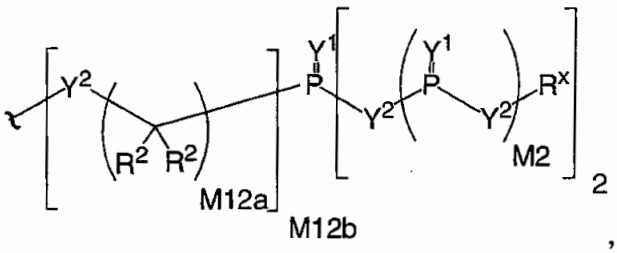
One embodiment of Amprenavir like phosphonate protease inhibitors as described above in the description and below in the claims excludes compounds of the formulas:



or

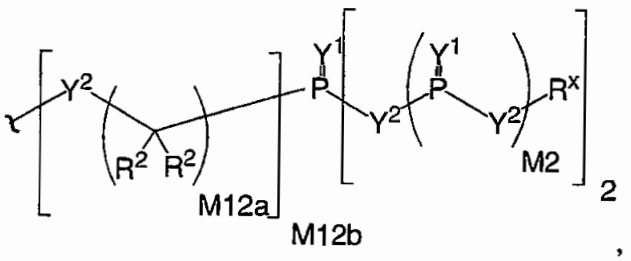


In another aspect of the invention, A^3 is of the formula:



M12a is 0 and at least one phosphonate group present in the compound is bonded directly to W^3. More typically, the phosphonate is bonded directly to W^5. In such an embodiment, the phosphorous atom of the phosphonate is bonded directly to a carbon atom of a ring.

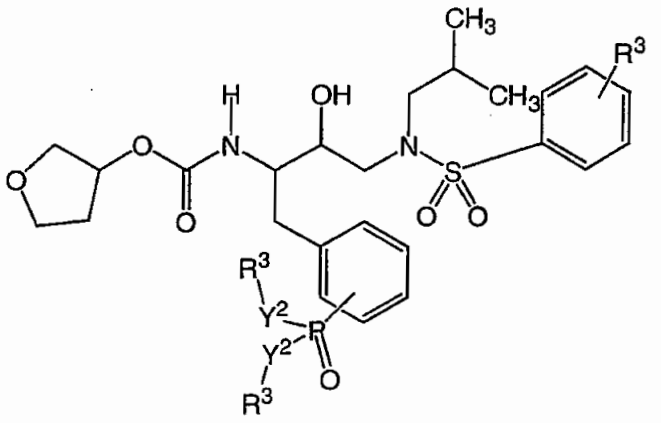
In another aspect of the invention an Amprenavir like phosphonate protease inhibitor, as described above in the description and below in the claims, contains an A^3 group of the formula:



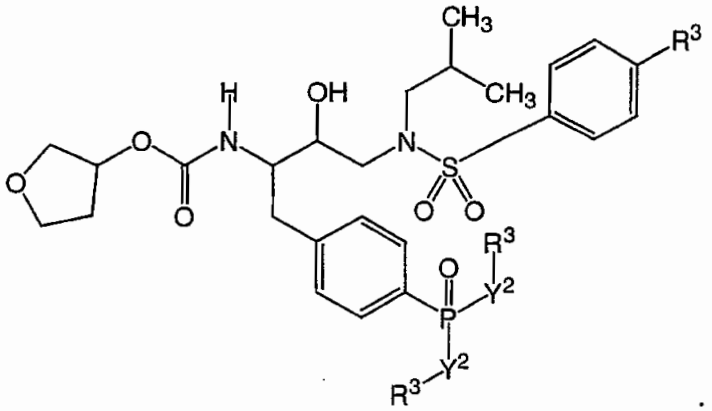
,

M12a is 0 and at least one phosphonate group present in the compound is bonded directly to W^3. More typically, the phosphonate is bonded directly to W^5. In such an embodiment, the phosphorous atom of the phosphonate is bonded directly to a carbon atom of a ring.

One embodiment of Amprenavir like phosphonate protease inhibitors as described above in the description and below in the claims is directed to compounds of the formulas:



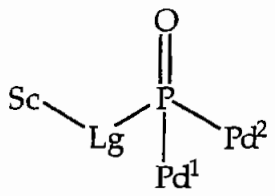
or



.

Exemplary Enumerated Compounds.

By way of example and not limitation, embodiments of the invention are named below in tabular format (Table 100). These embodiments are of the general formula "MBF":



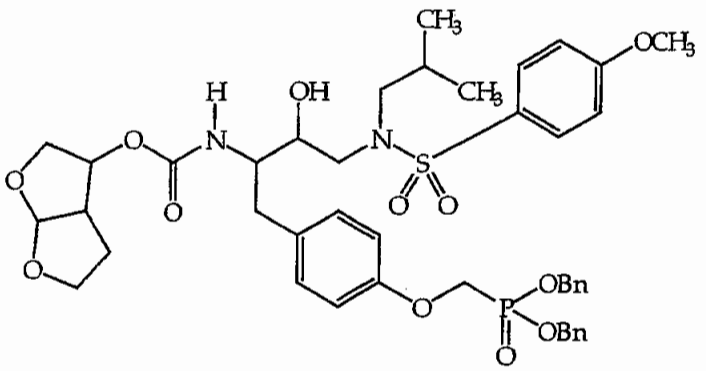
MBF

Each embodiment of MBF is depicted as a substituted nucleus (Sc) in which the nucleus is designated by a number and each substituent is designated in order by letter or number. Tables 1.1 to 1.5 are a schedule of nuclei used in forming the embodiments of Table 100. Each nucleus (Sc) is given a number designation from Tables 1.1 to 1.5, and this designation appears first in each embodiment name. Similarly, Tables 10.1 to 10.19 and 20.1 to 20.36 list the selected linking groups (Lg) and prodrug (Pd^1 and Pd^2) substituents, again by letter or number designation, respectively.

Accordingly, each named embodiment of Table 100 is depicted by a number designating the nucleus from Table 1.1-1.5, followed by a letter designating the linking group (Lg) from Table 10.1-10.19, and two numbers designating the two prodrug groups (Pd^1 and Pd^2) from Table 20.1-20.36. In graphical tabular form, each embodiment of Table 100 appears as a name having the syntax:

$$Sc.Lg.Pd^1.Pd^2$$

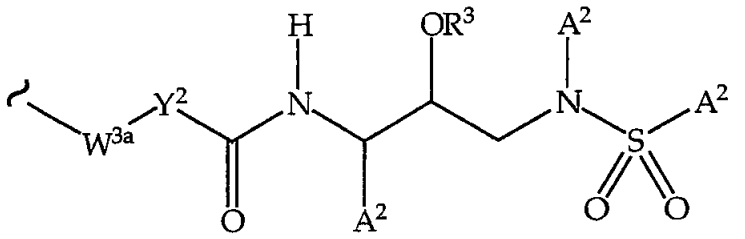
Thus, ignoring stereochemistry, structure 10, Scheme 2, Scheme Section A, is represented by 12.AH.247.247.



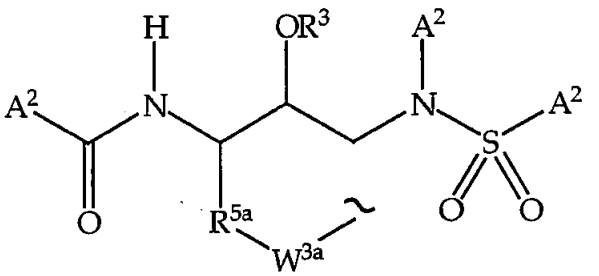
12.AH247.247

Each Sc group is shown having a tilda ("~"). The tilda is the point of covalent attachment of Sc to Lg. Q^1 and Q^2 of the linking groups (Lg), it should be understood, do not represent groups or atoms but are simply connectivity designations. Q^1 is the site of the covalent bond to the nucleus (Sc) and Q^2 is the site of the covalent bond to the phosphorous atom of formula MBF. Each prodrug group (Pd^1 and Pd^2) are covalently bonded to the phosphorous atom of MBF at the tilda symbol ("~"). Some embodiments of Tables 10.1-10.19 and 20.1-20.36 may be designated as a combination of letters and numbers (Table 10.1-10.19) or number and letter (Table 20.1-20.36). For example there are Table 10 entries for BJ1 and BJ2. In any event, entries of Table 10.1-10.19 always begin with a letter and those of Table 20.1-20.36 always begin with a number. When a nucleus (Sc) is shown enclosed within square brackets ("[]") and a covalent bond extends outside the brackets, the point of covalent attachment of Sc to Lg may be at any substitutable site on SC. Selection of the point of attachment is described herein. By way of example and not limitation, the point of attachment is selected from those depicted in the schemes and examples.

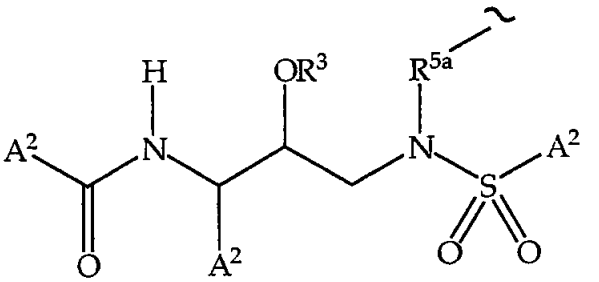
Table 1.1



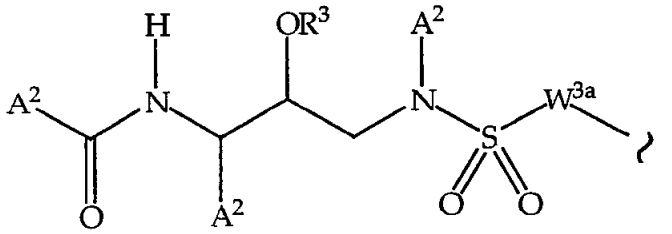
1



2

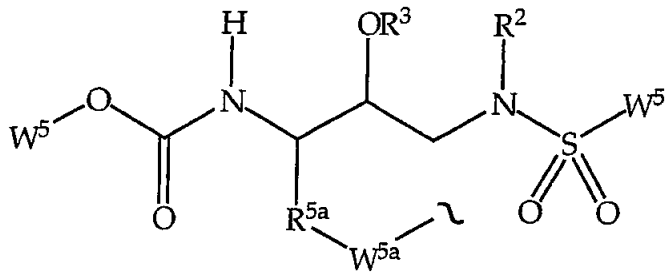


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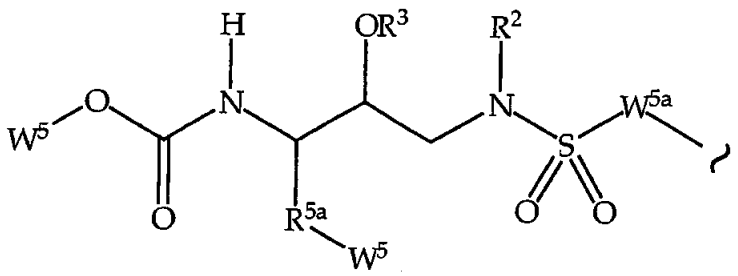


4

Table 1.2

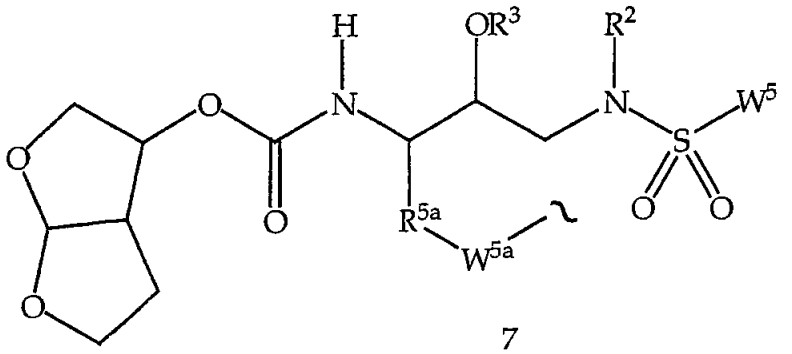


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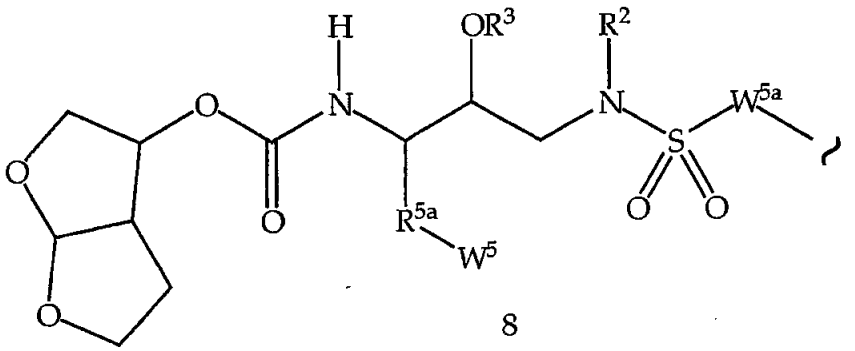


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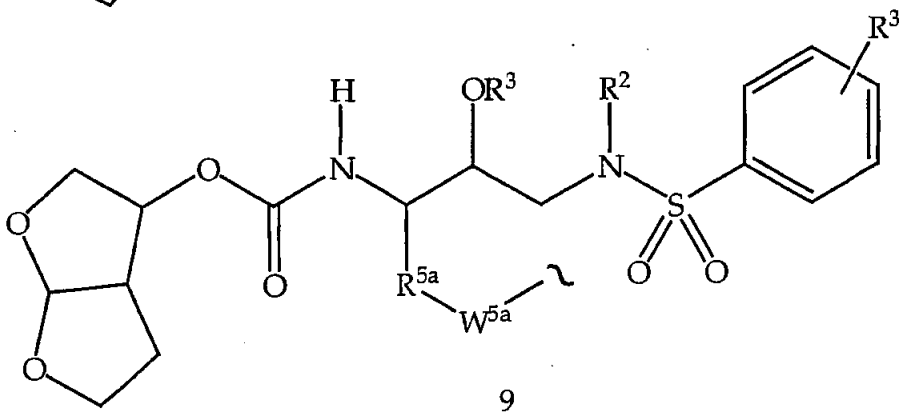
Table 1.3



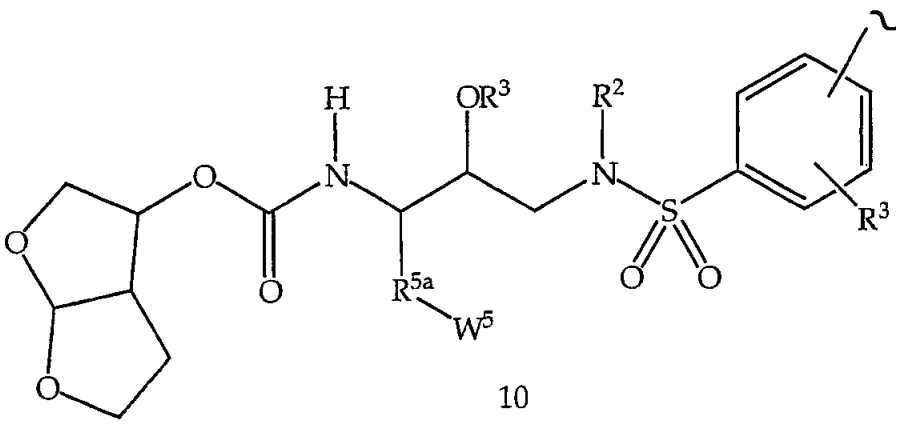
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8

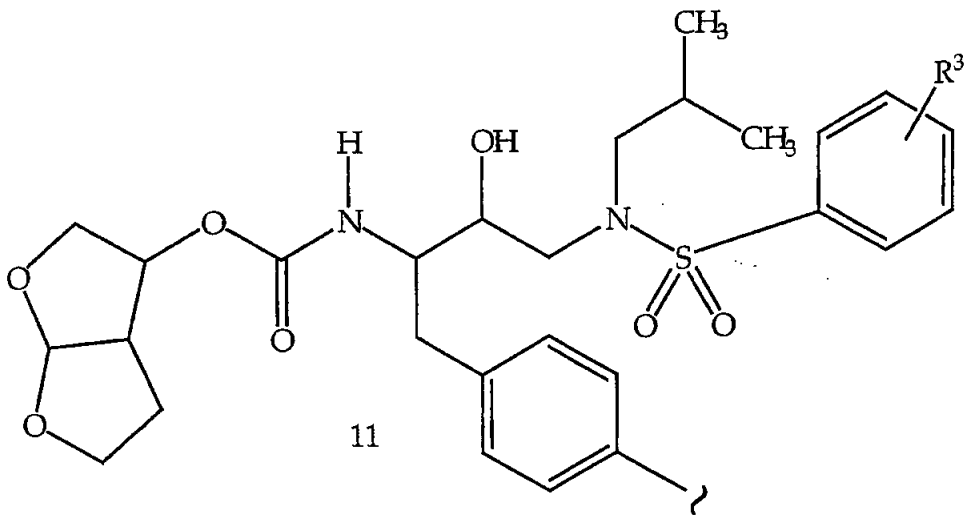


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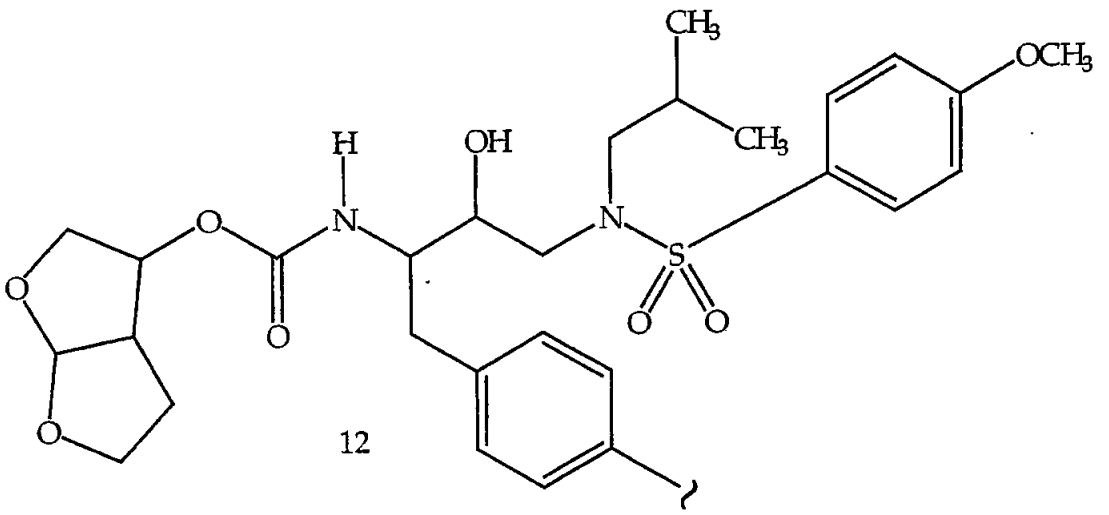


10

Table 1.4

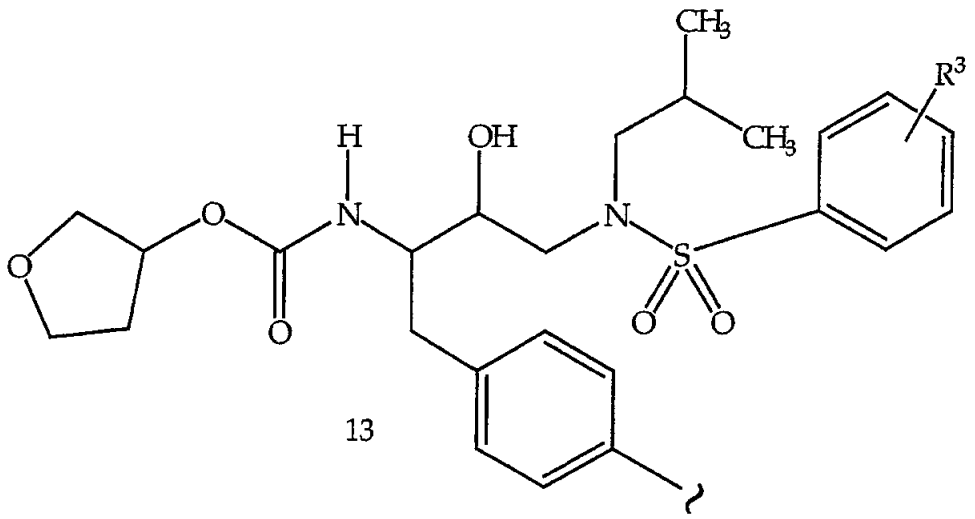


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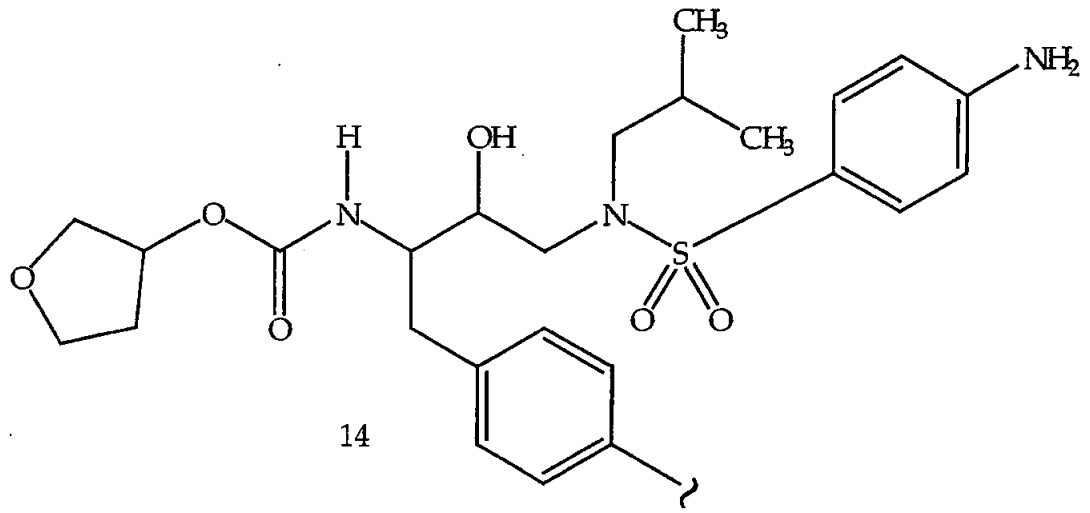


12

Table 1.5

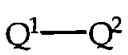


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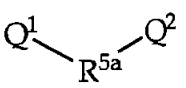


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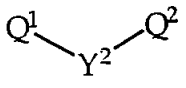
Table 10.1



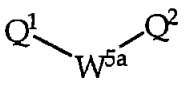
A



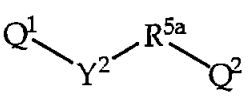
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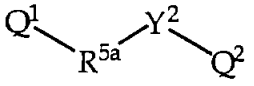
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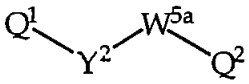
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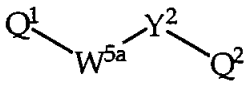
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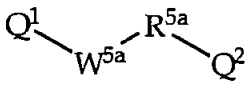
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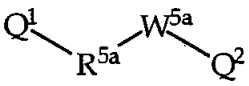
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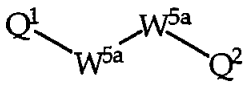
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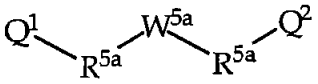
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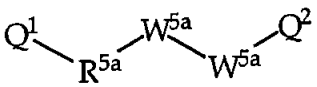
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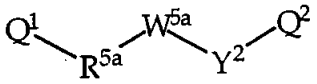
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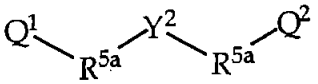
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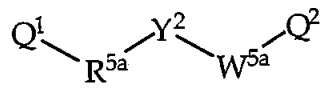


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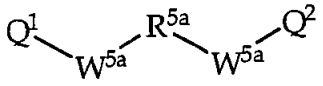


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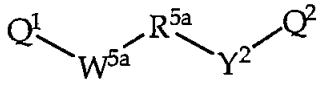
Table 10.2



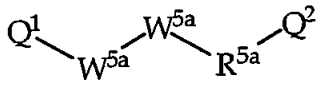
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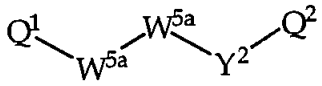
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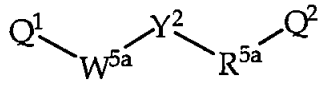
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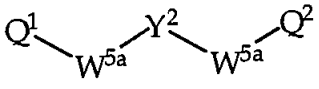
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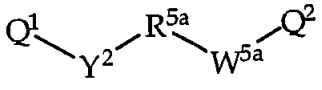
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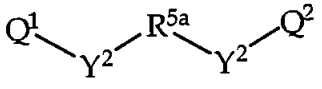
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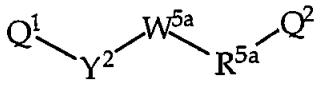
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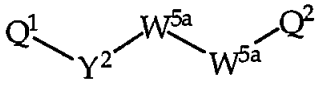
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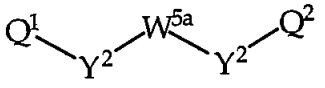
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Y

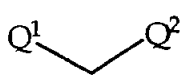


Z

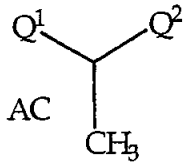


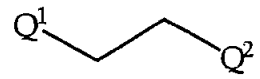
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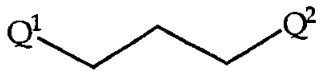


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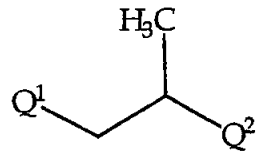




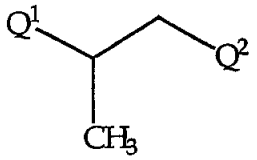
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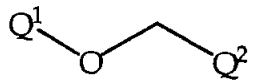
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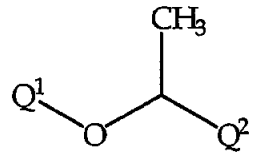
AF



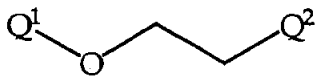
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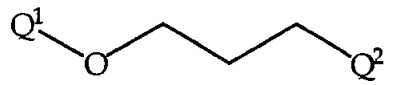
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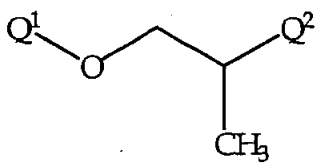
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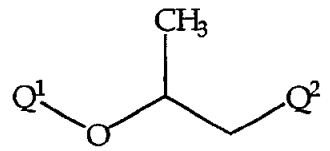
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AK



AL



AM

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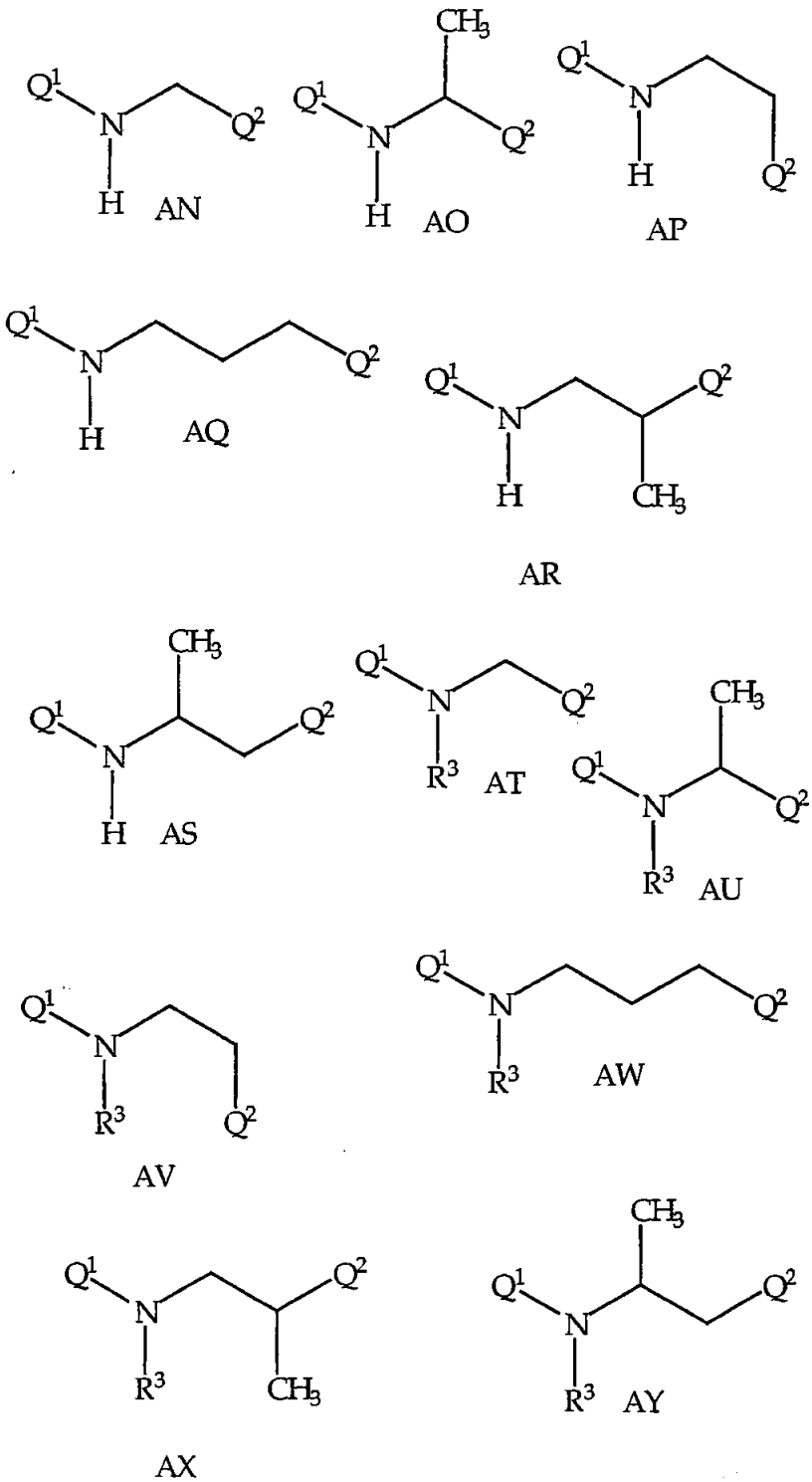
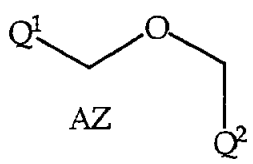
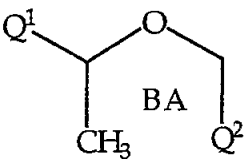
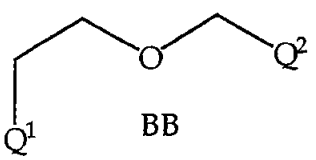
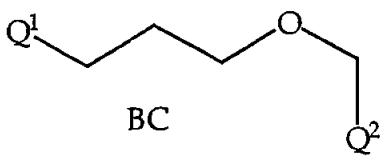


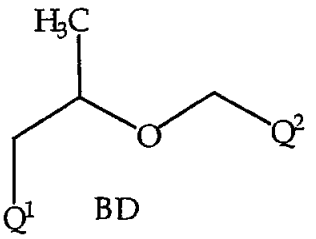
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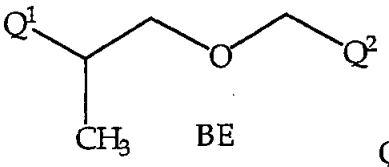

Q1
O
AZ
Q2

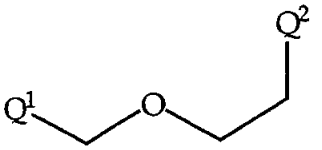

Q1
O
BA
CH3
Q2

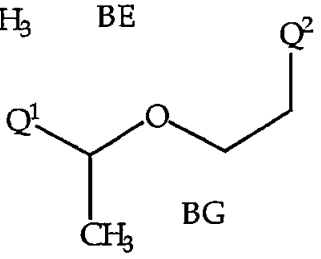

O
Q2
Q1
BB


Q1
O
BC
Q2

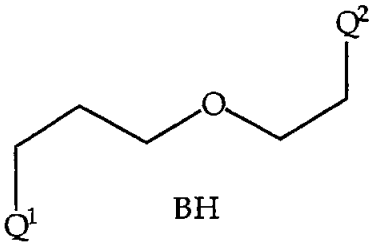

H3C
O
Q2
Q1
BD

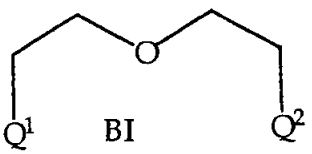

Q1
O
Q2
CH3
BE

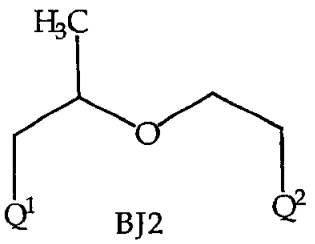

Q2
Q1
O


Q2
Q1
O
CH3
BG

BF


Q2
O
Q1
BH


O
Q1
BI
Q2


H3C
O
Q1
BJ2
Q2

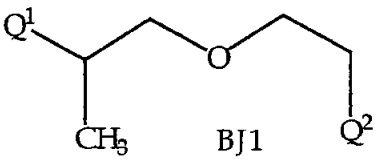
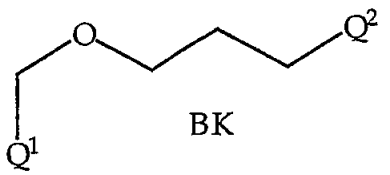
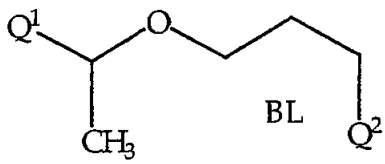

Q1
O
CH3
BJ1
Q2

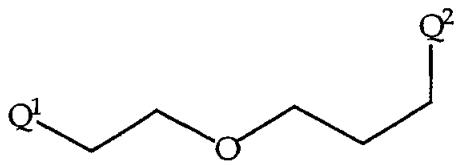
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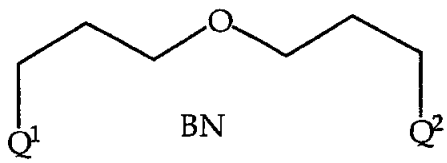
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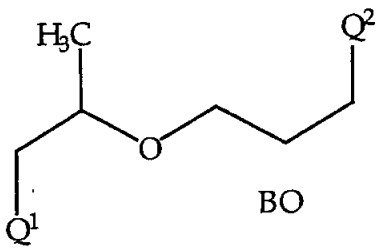
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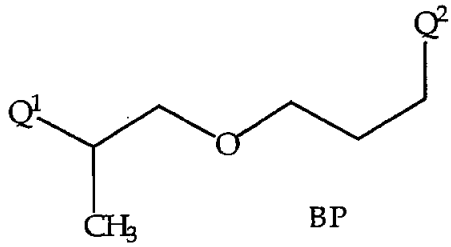
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BN

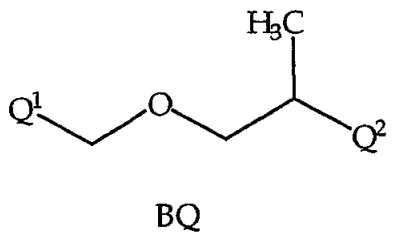


BO

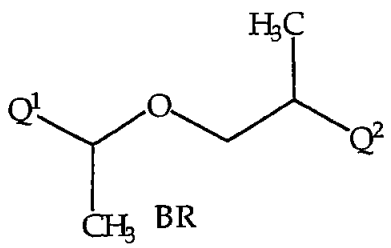


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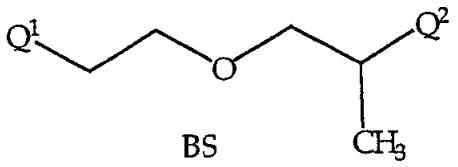
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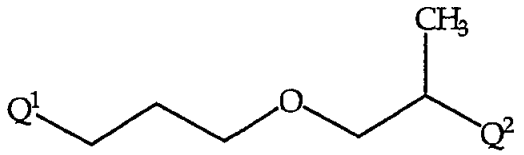
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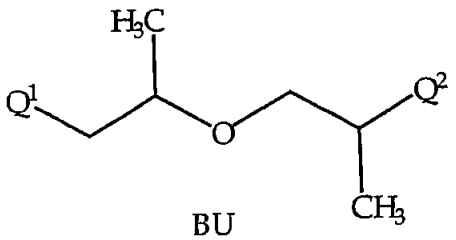
BR



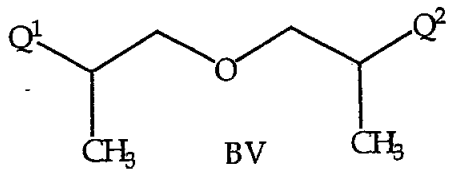
BS



BT

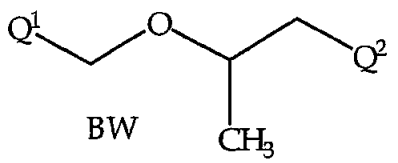


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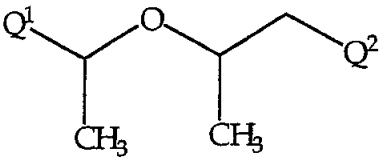


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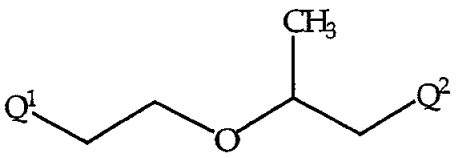
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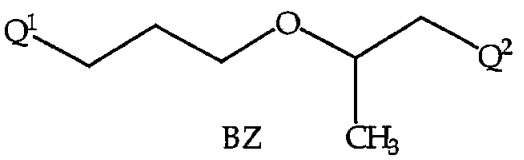
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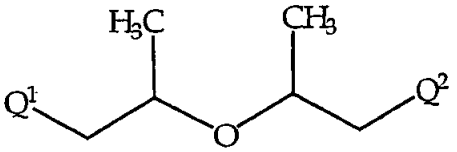


BX

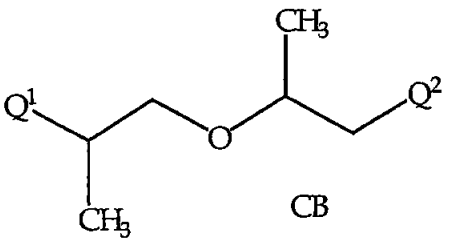


BY



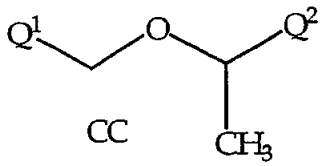


CA

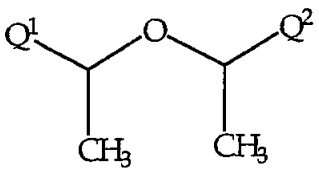


CB

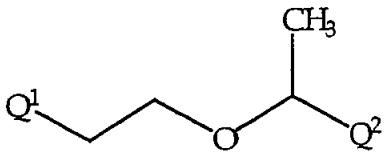
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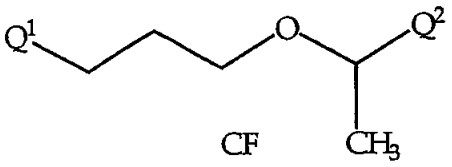
CC



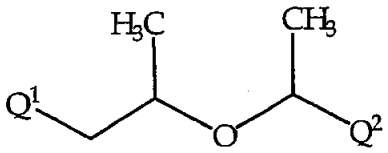
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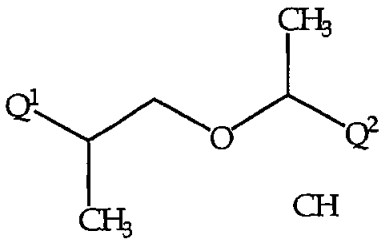
CE



CF

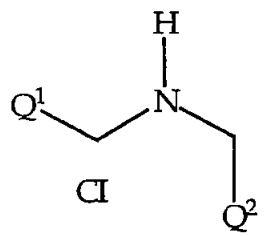


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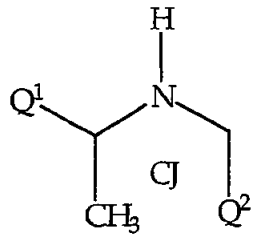


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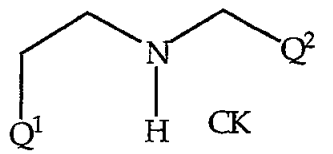
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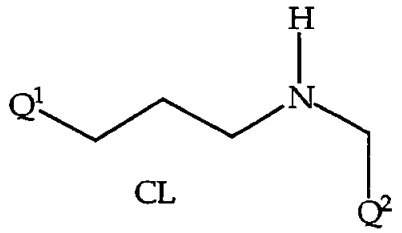
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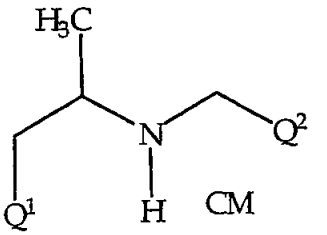
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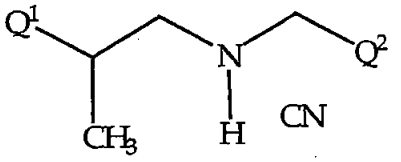
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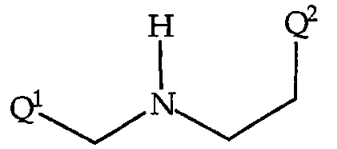
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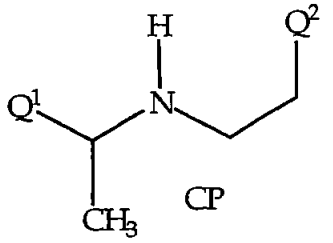
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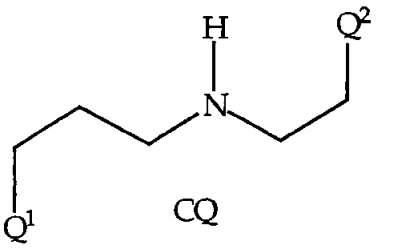
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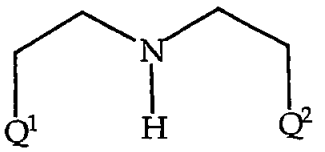
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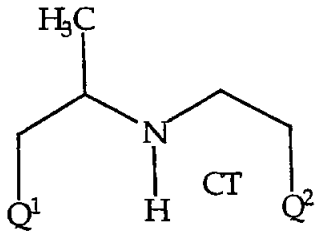
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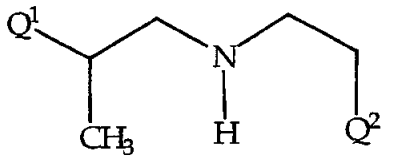
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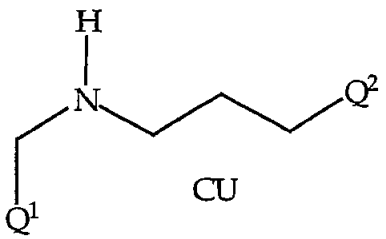


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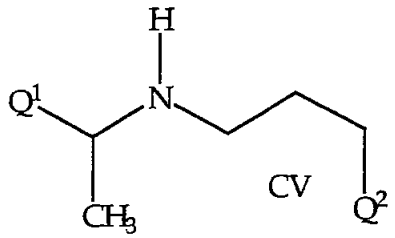


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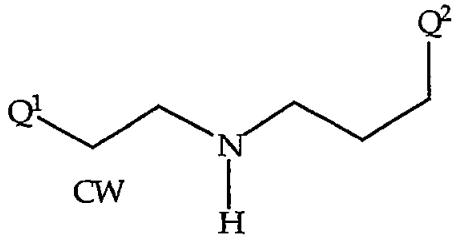
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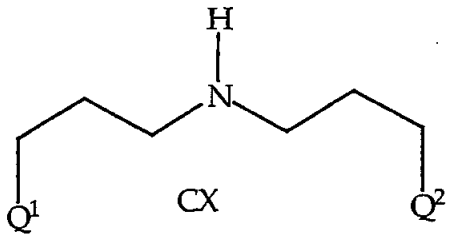
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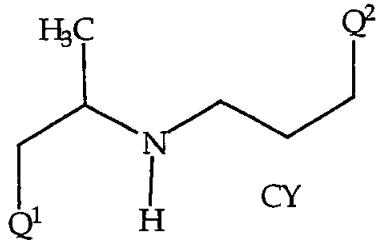
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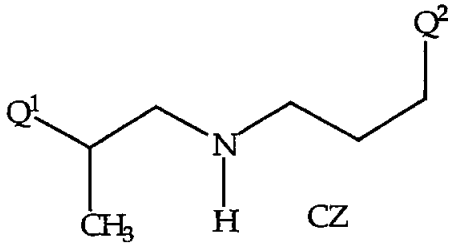
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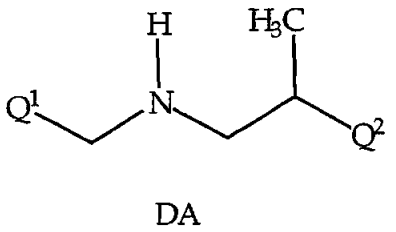


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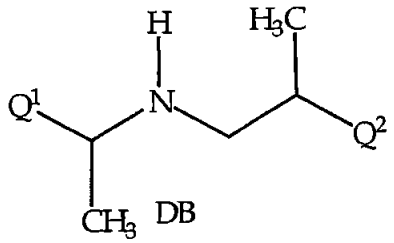


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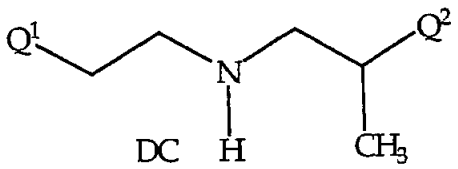
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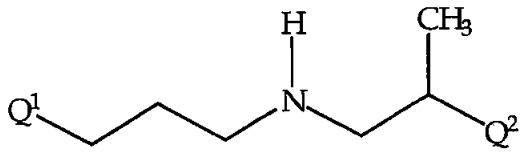
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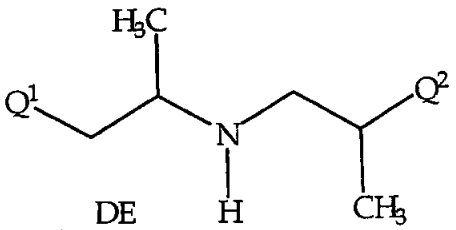
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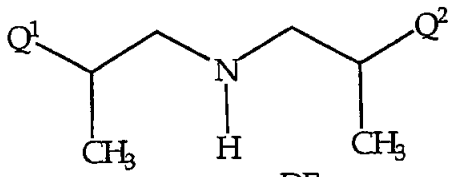
DC



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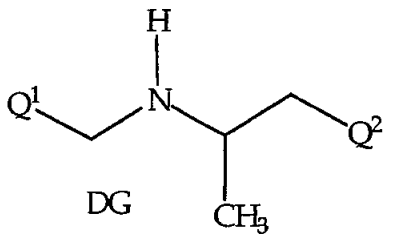


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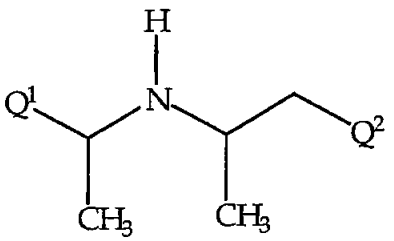


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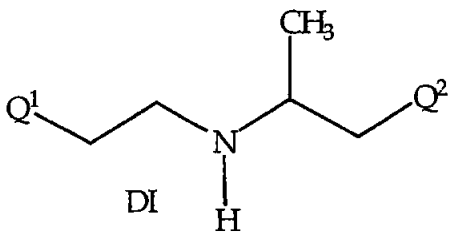
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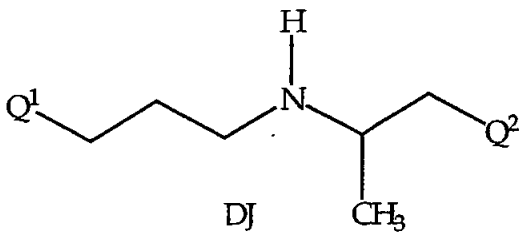
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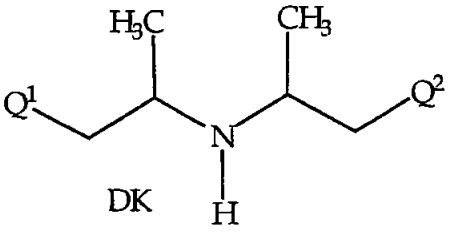
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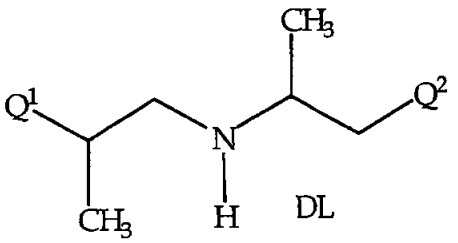
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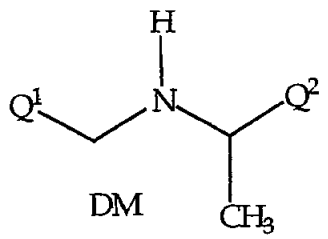


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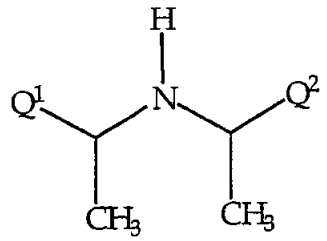


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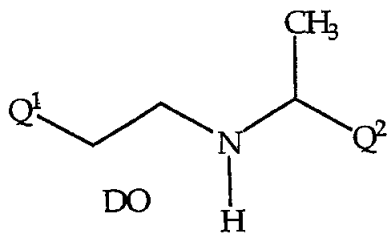
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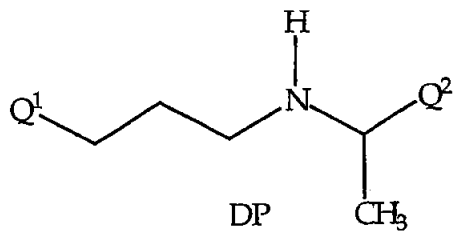
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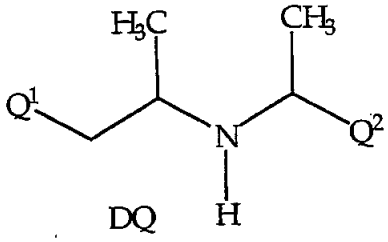
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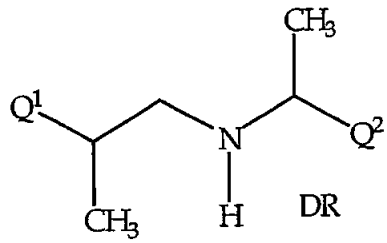
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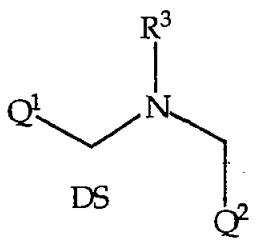


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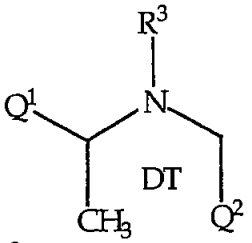


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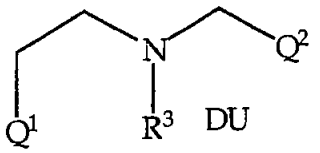
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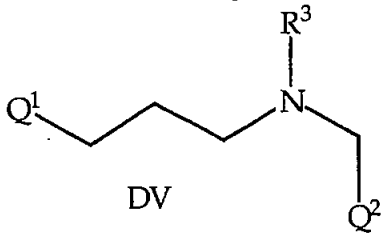
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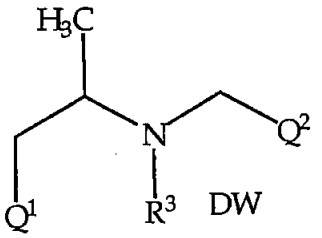
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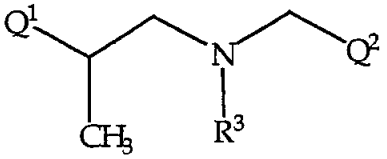
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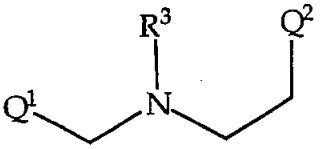
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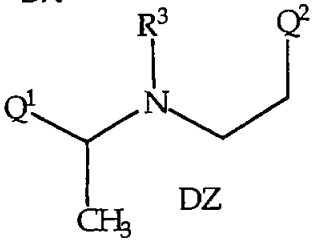
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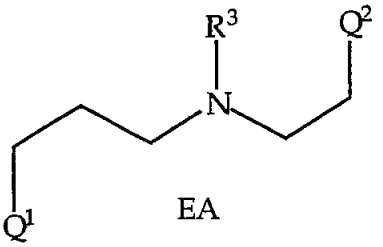
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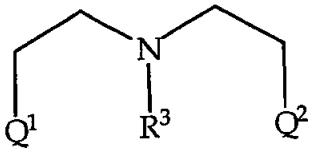
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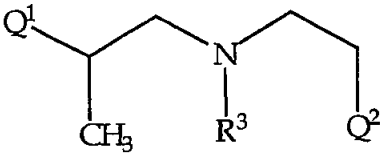
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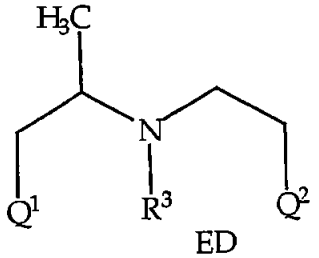
EA



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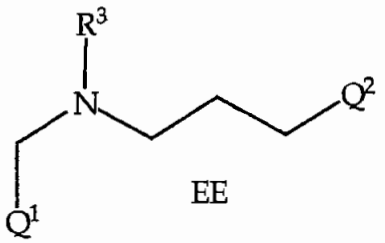


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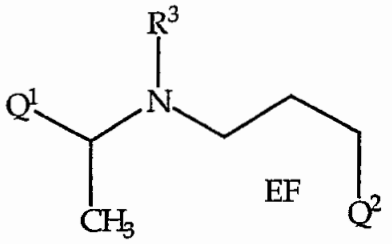


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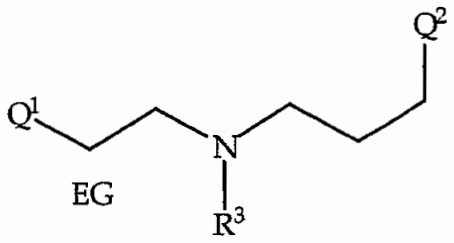
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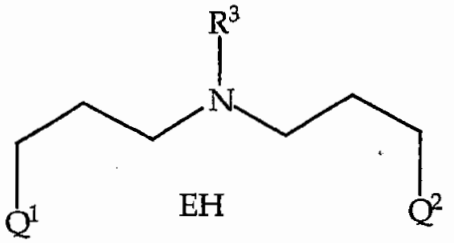
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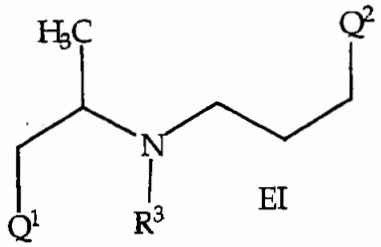
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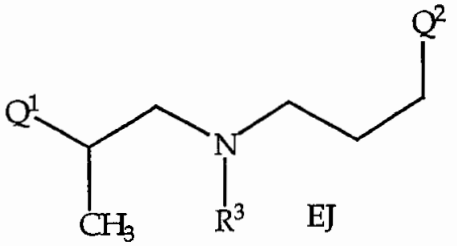
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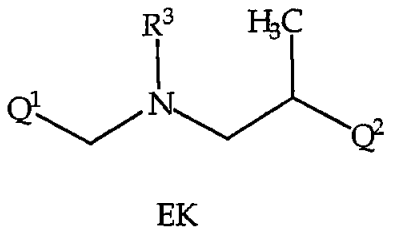


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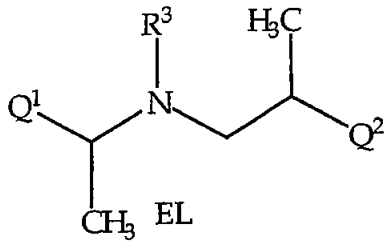


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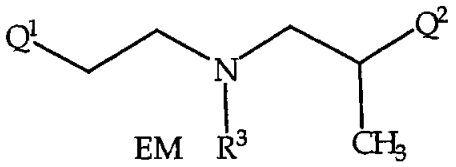
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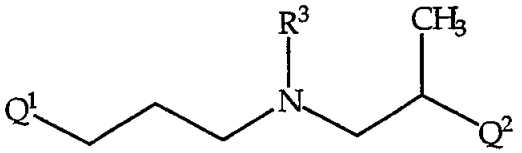
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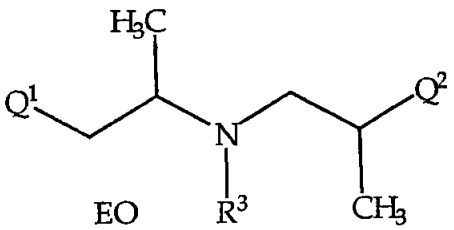
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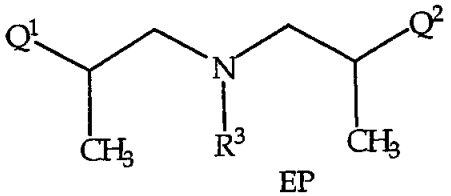
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EN

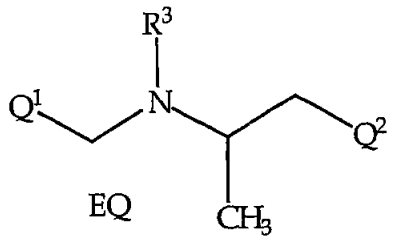


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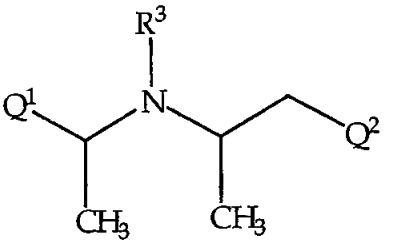


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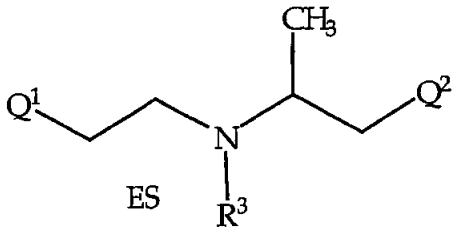
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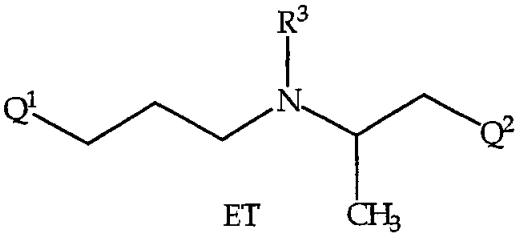
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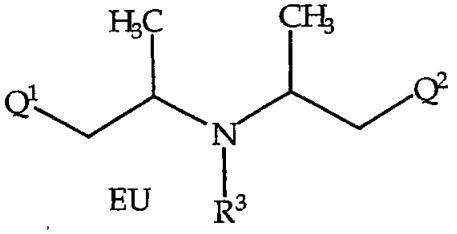
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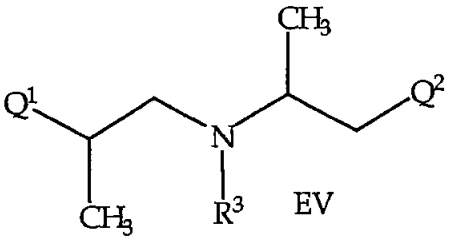
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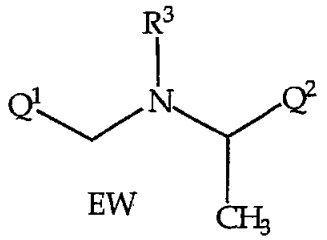


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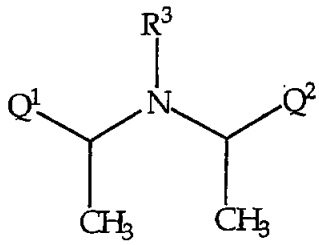


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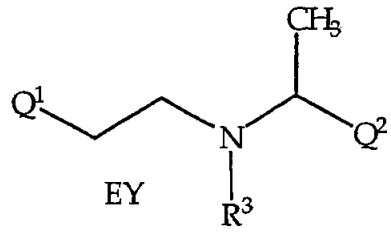
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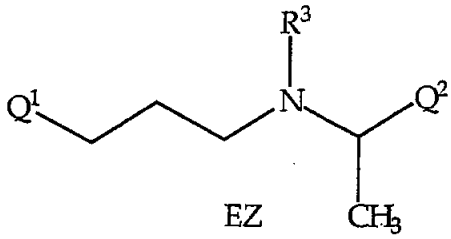
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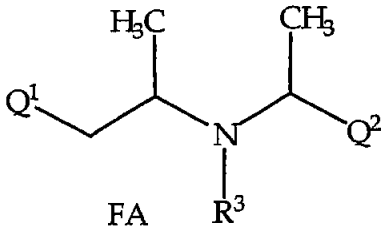
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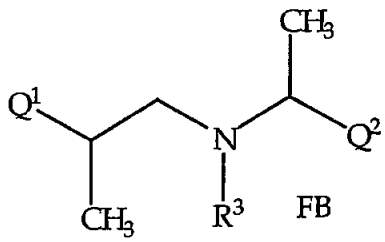
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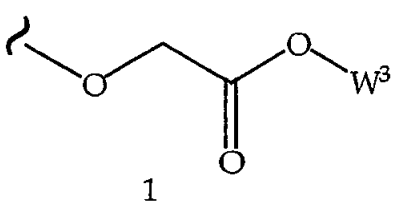


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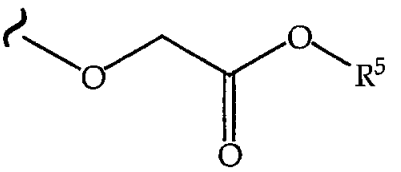


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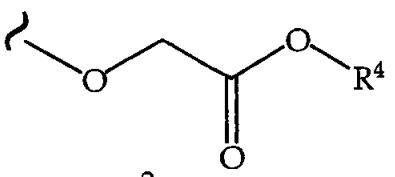
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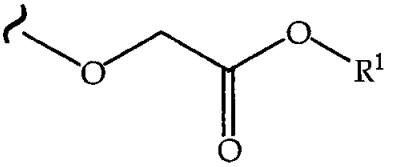
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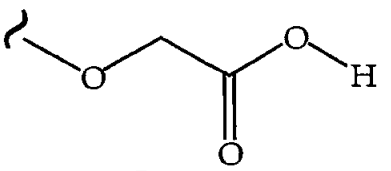
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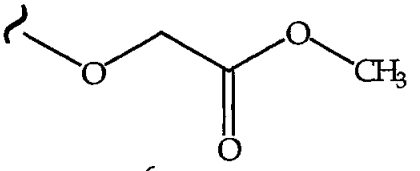
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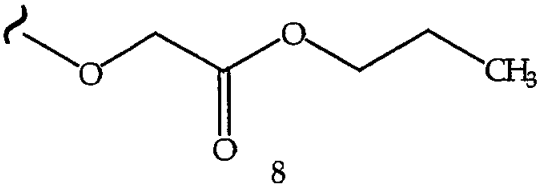
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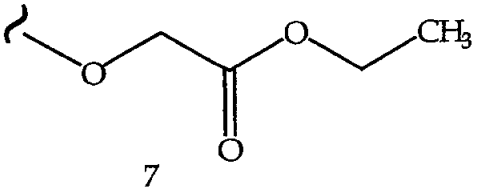
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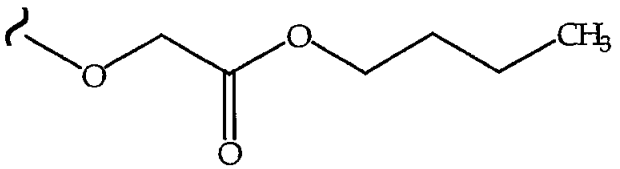


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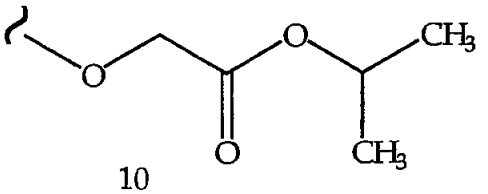


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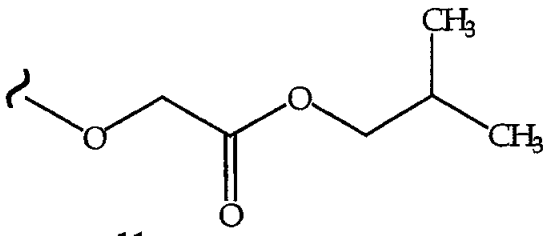
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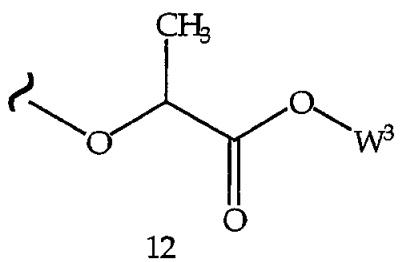


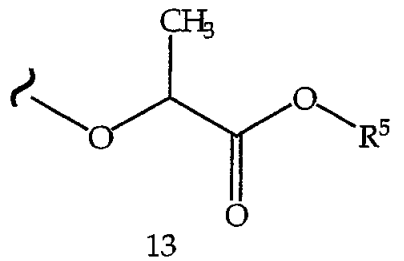
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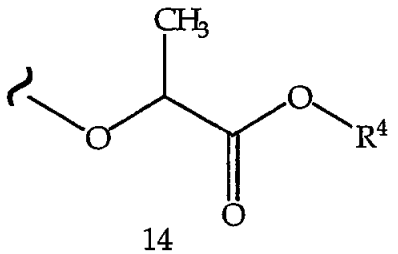


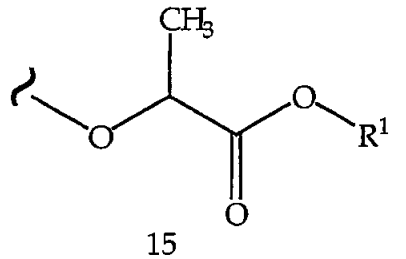
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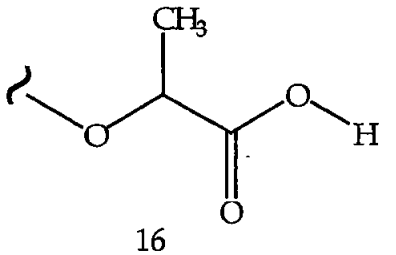
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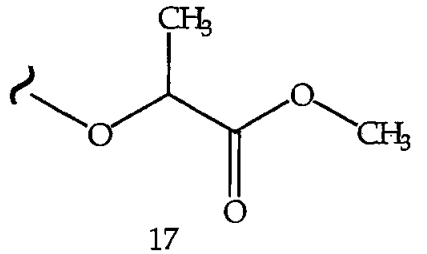

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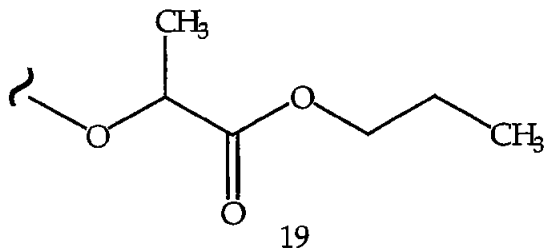

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19

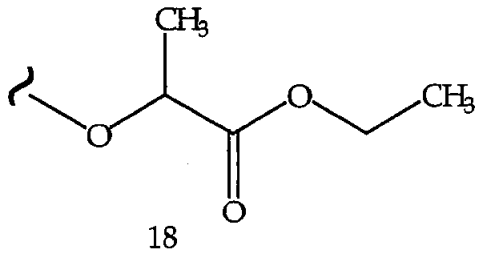
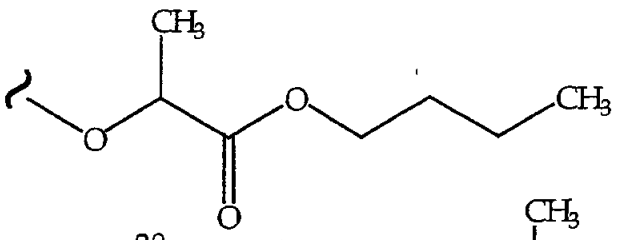
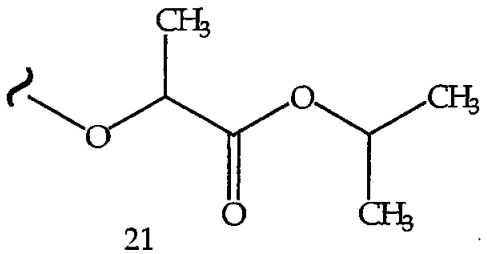

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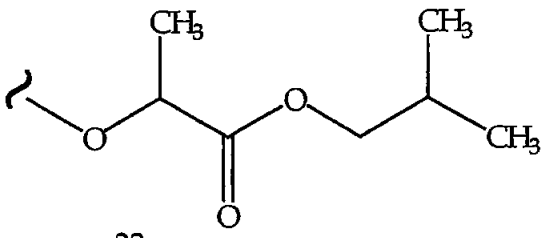
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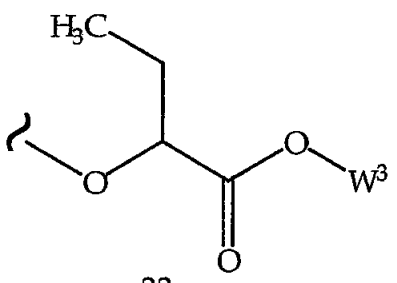


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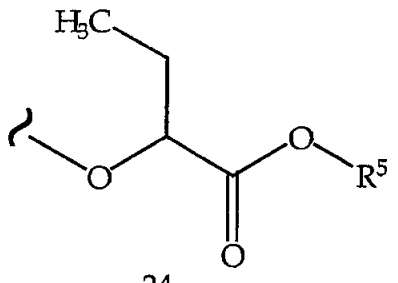


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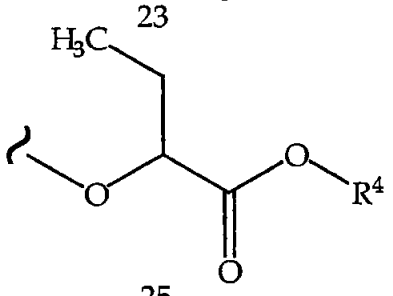
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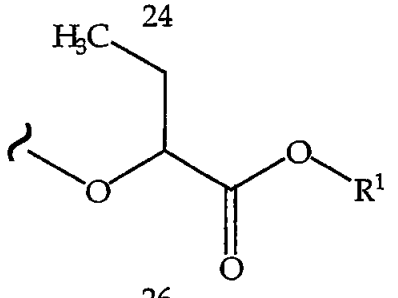
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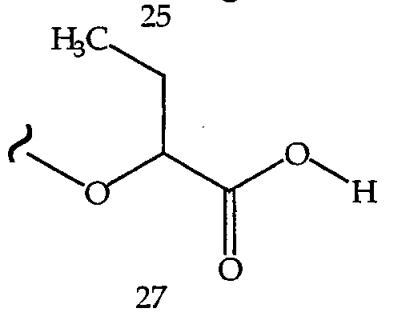
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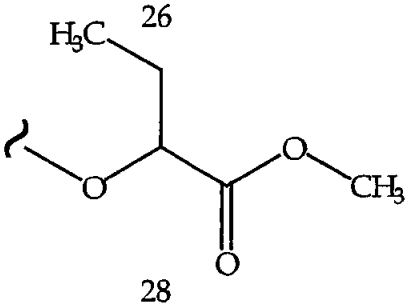
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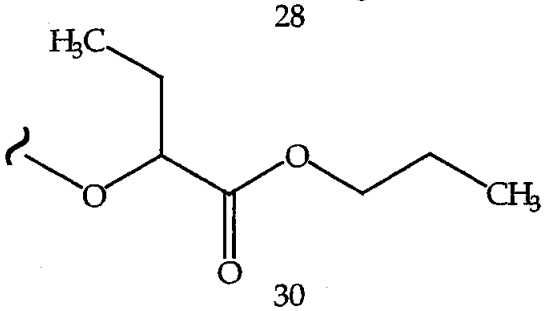
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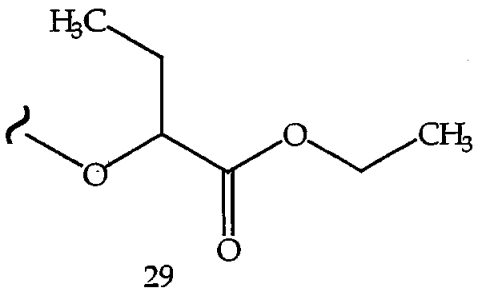
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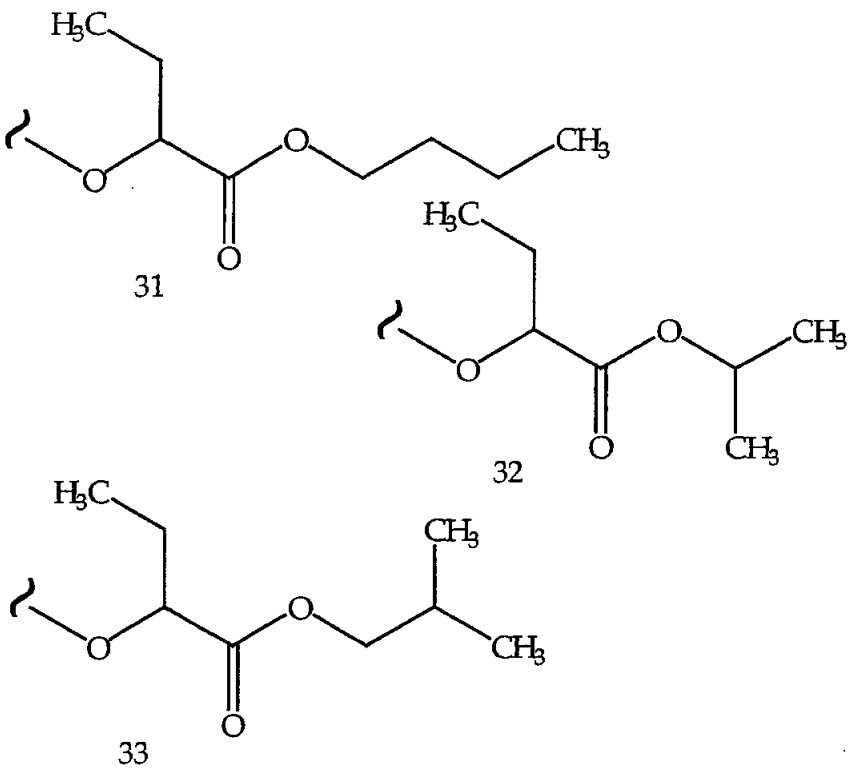


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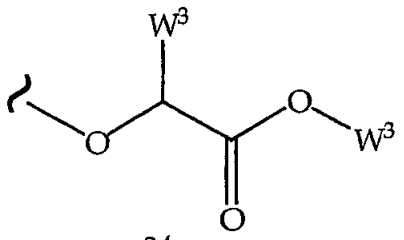


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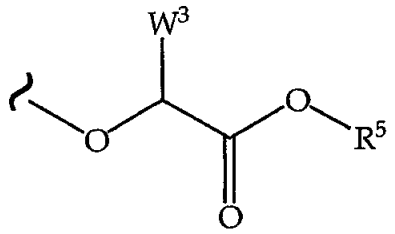
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33

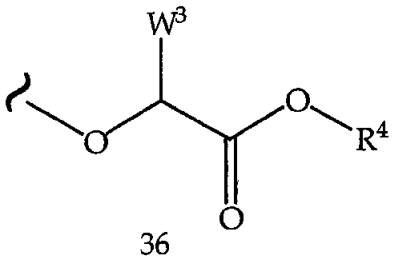
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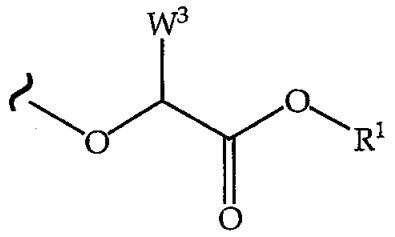
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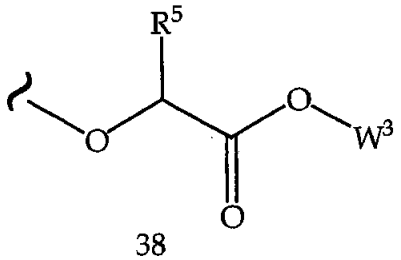
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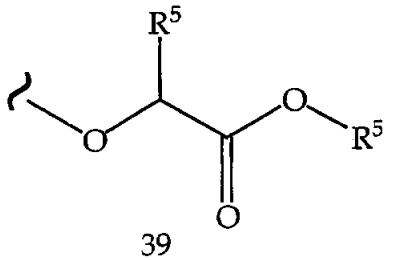
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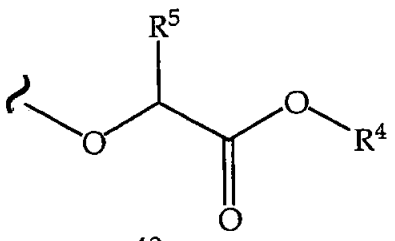
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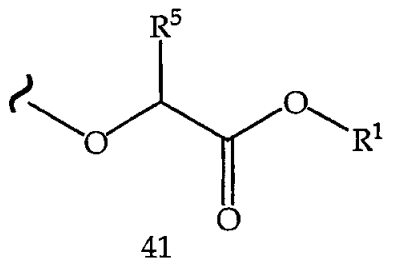
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39

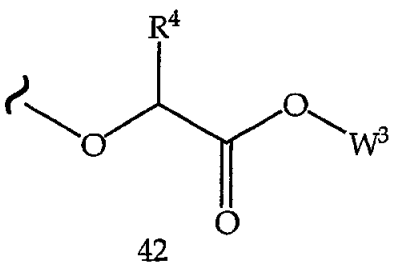


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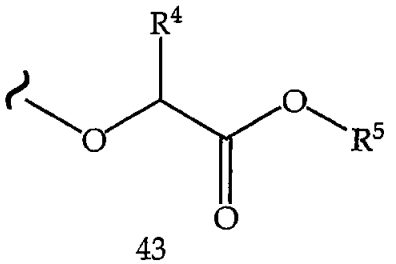


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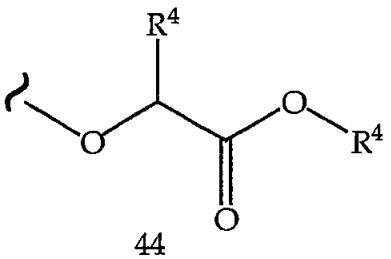
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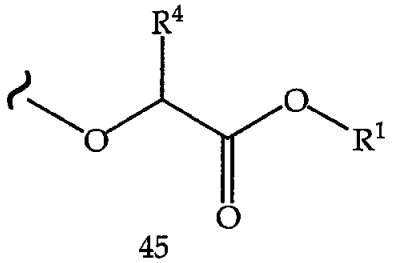
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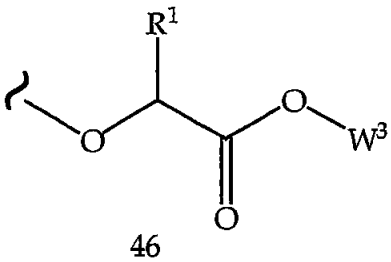
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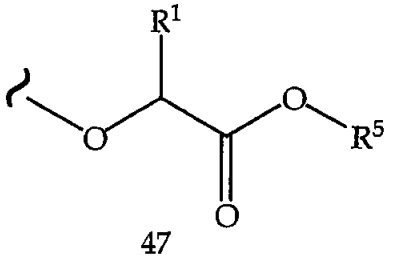
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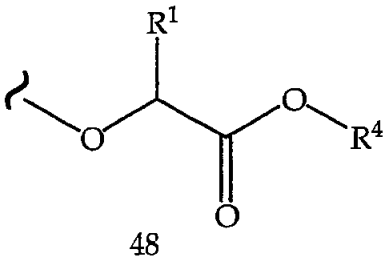
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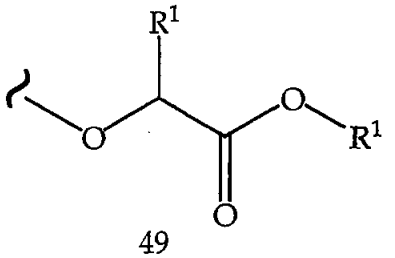
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47

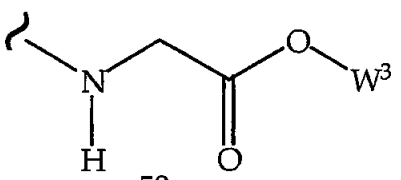


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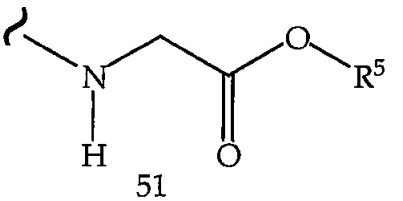


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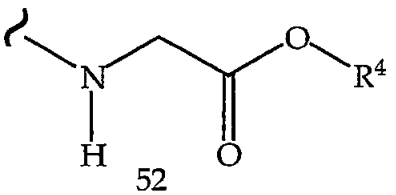
Table 20.9



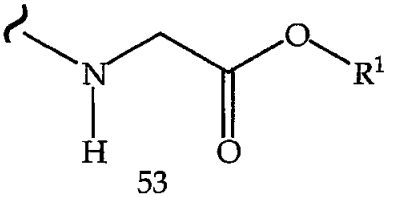
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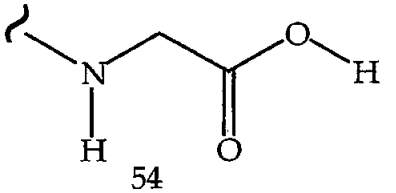
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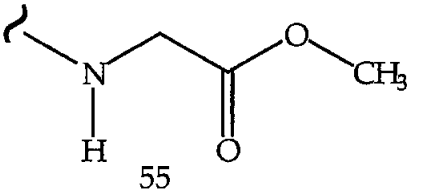
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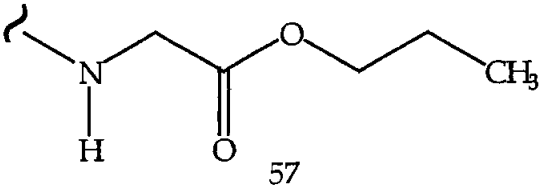
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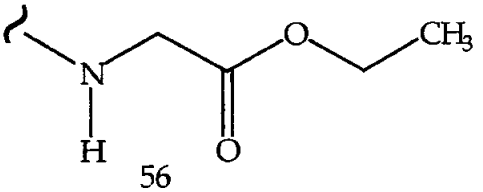
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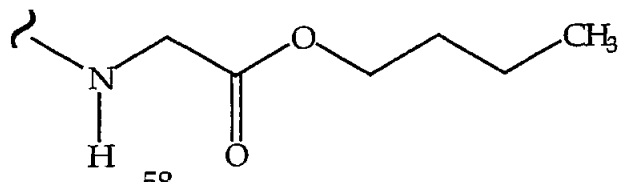


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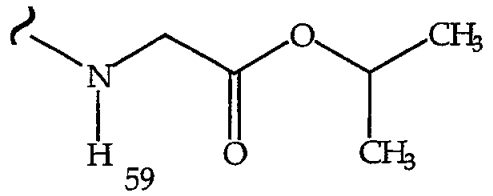


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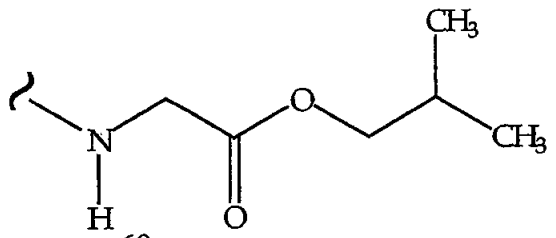
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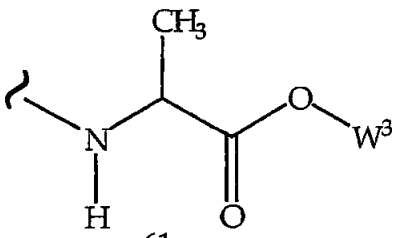


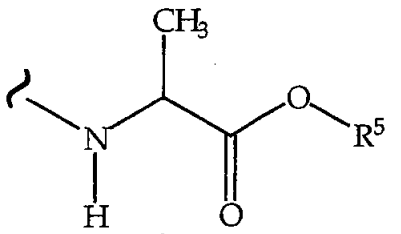
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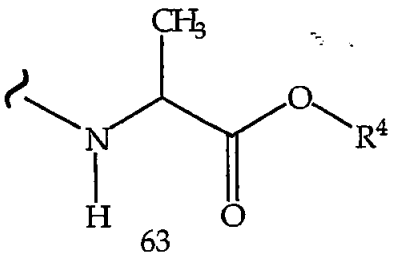


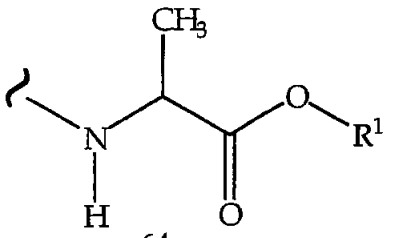
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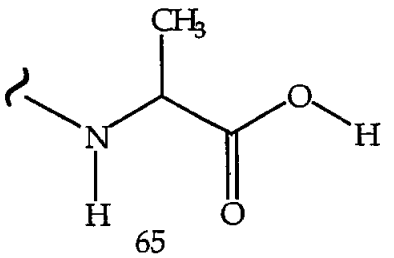
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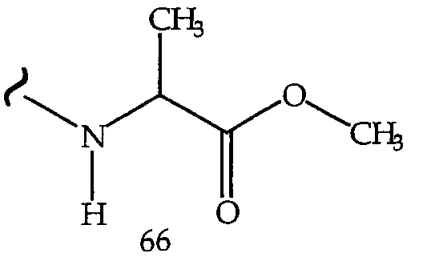

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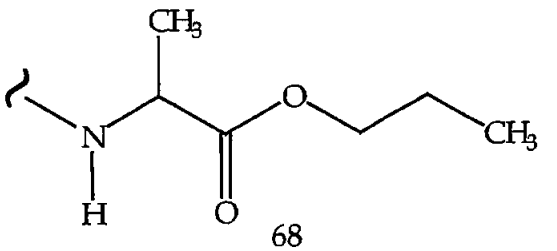

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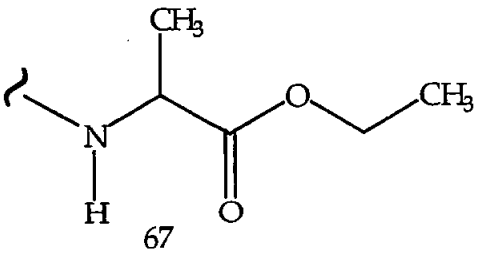
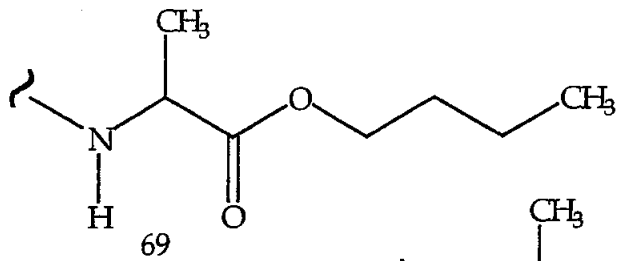
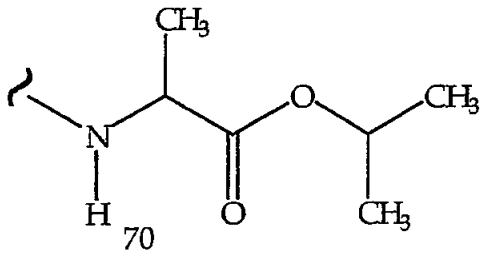

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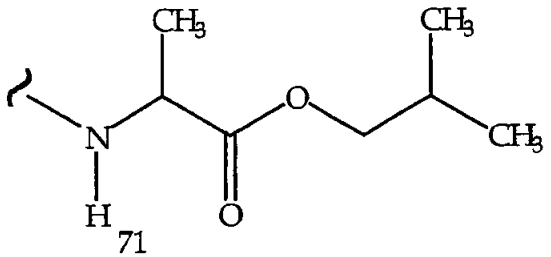
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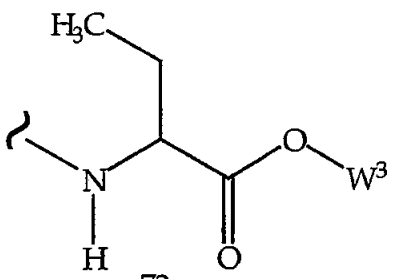


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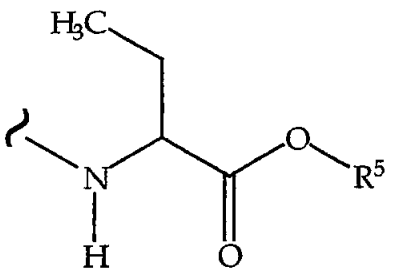


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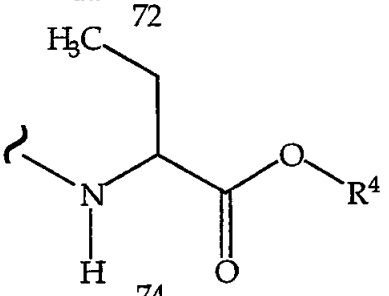
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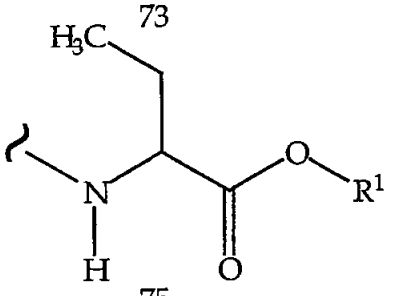
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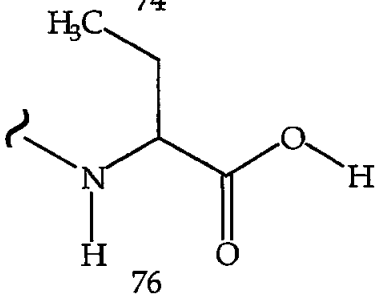
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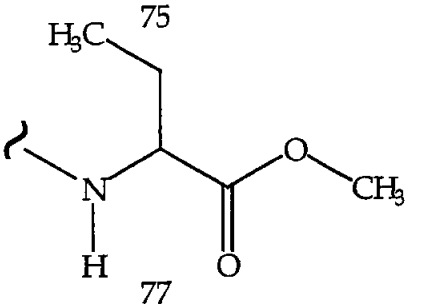
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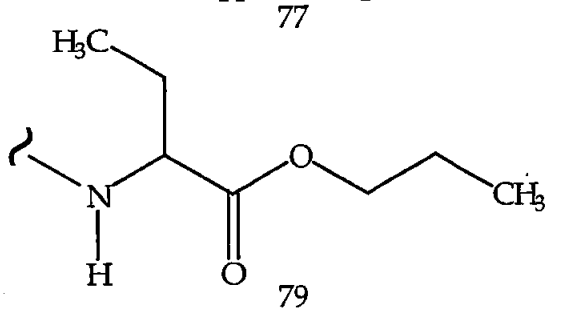
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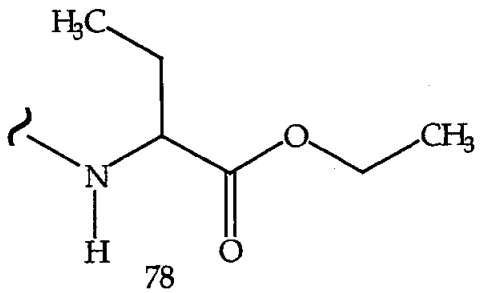
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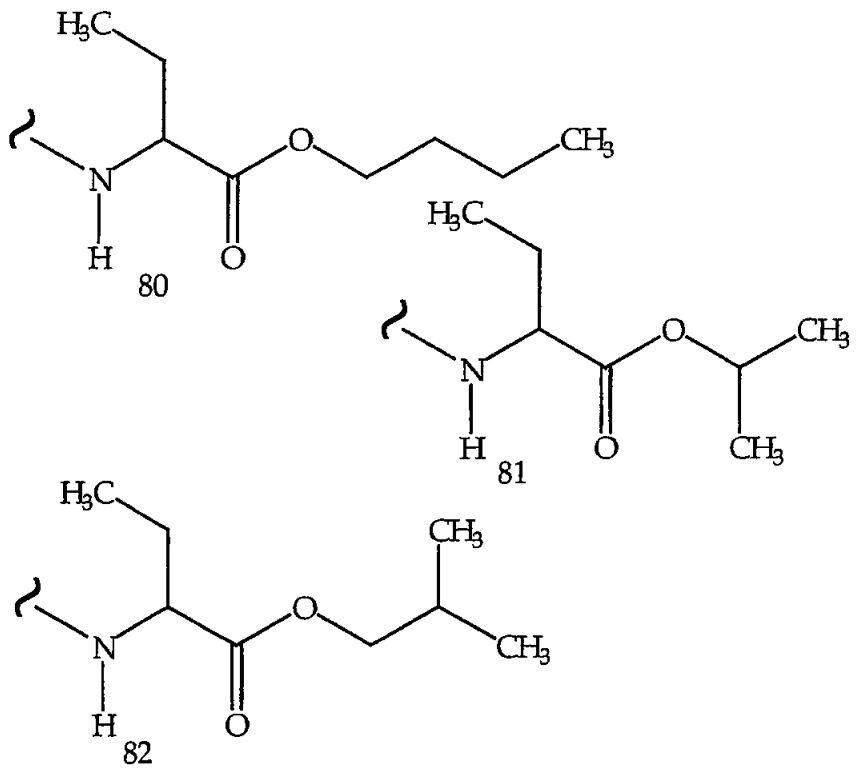
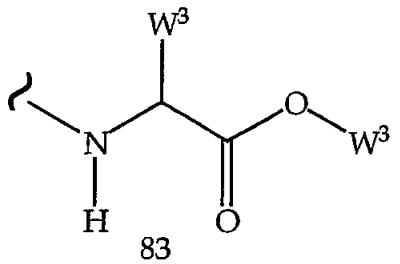
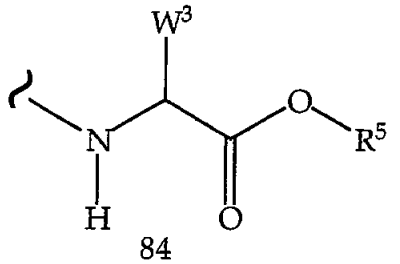
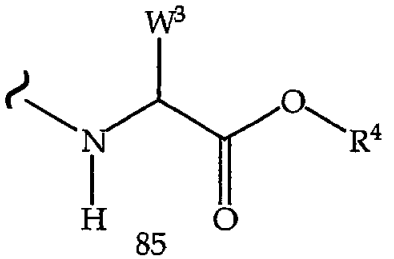
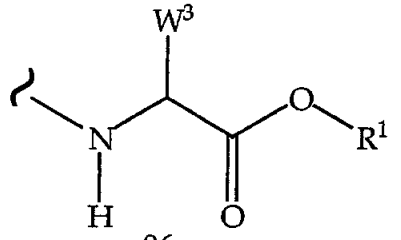


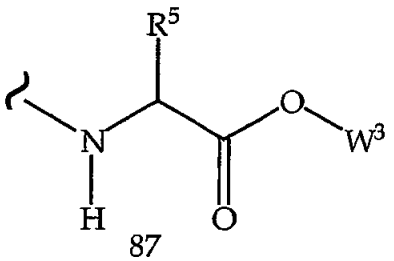
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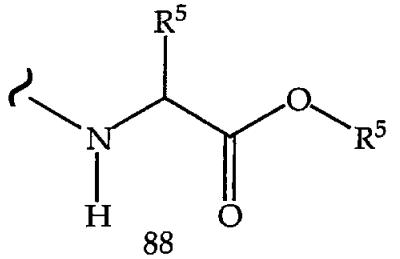

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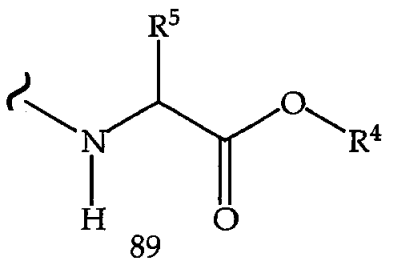

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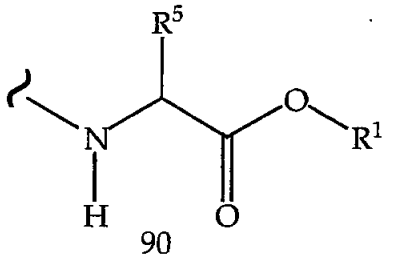
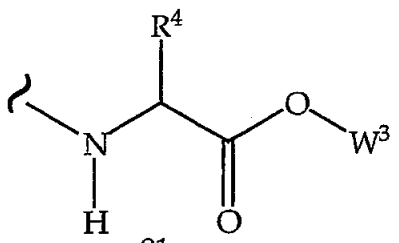
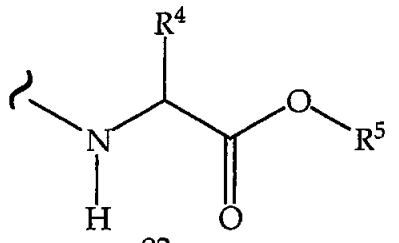
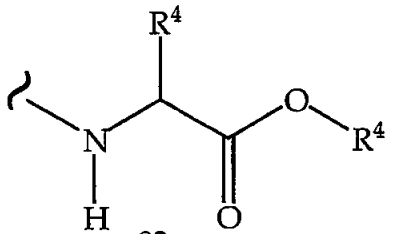
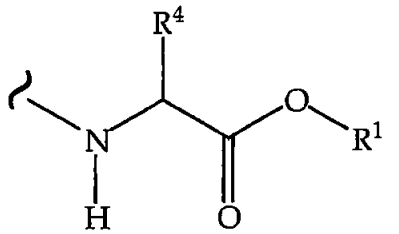

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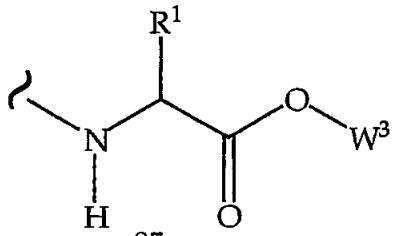
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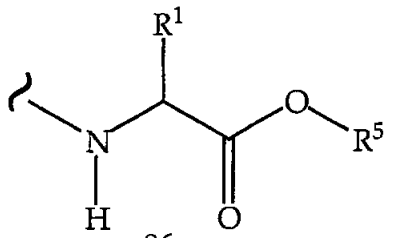

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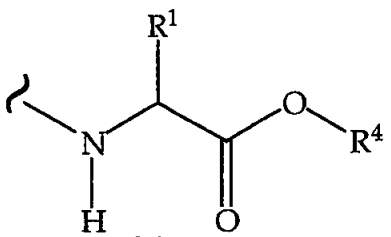

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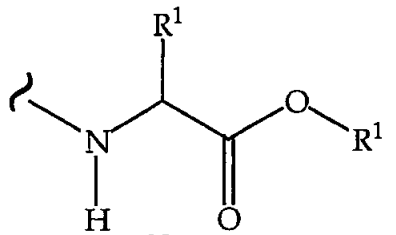
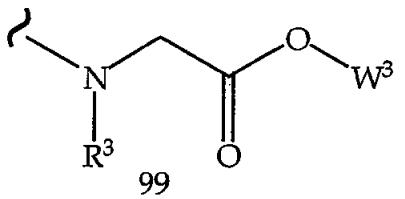
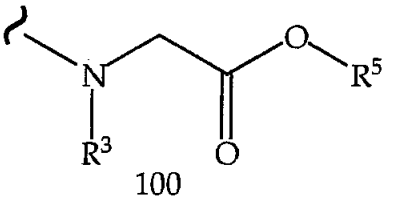
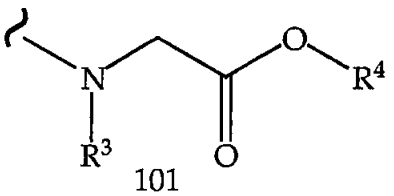
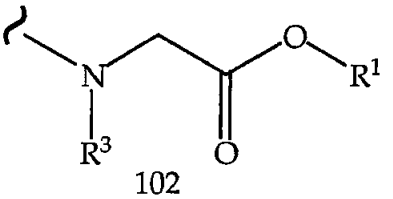

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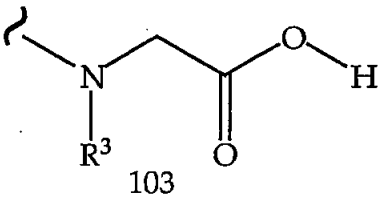
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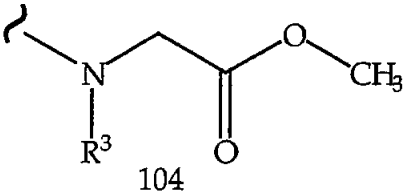

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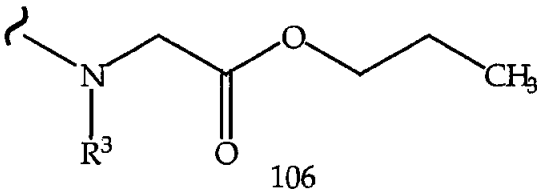

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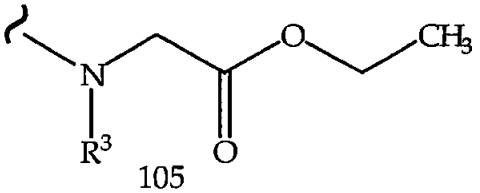
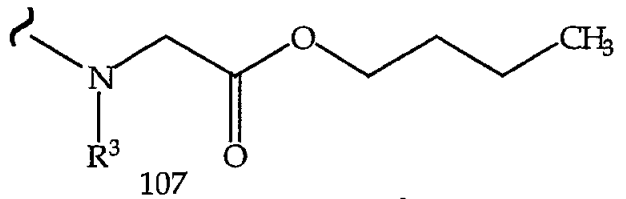
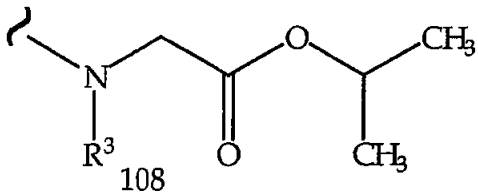

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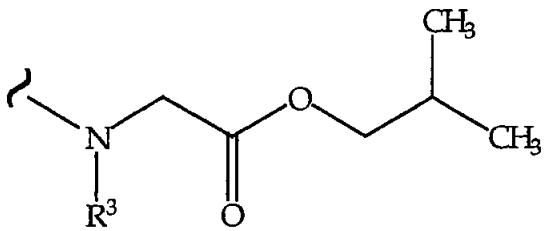
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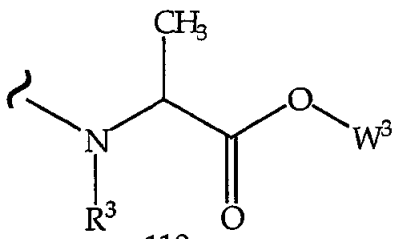


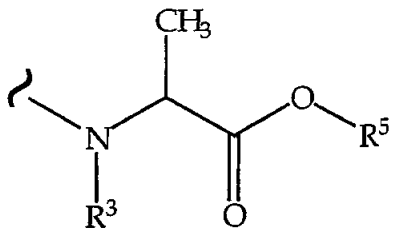
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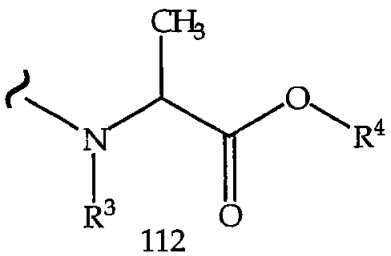


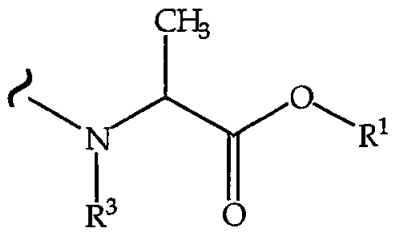
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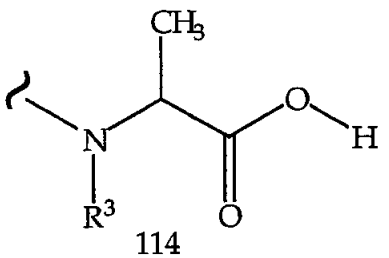
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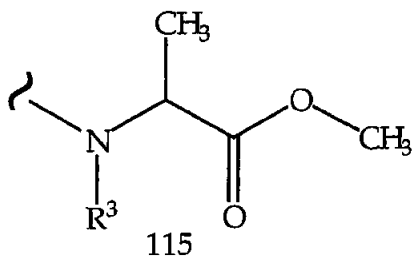

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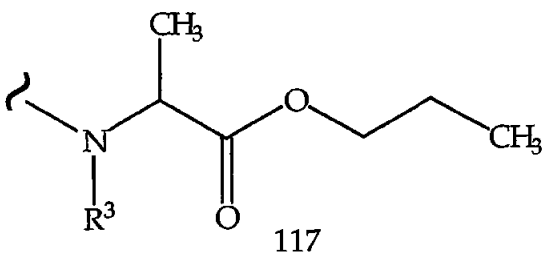

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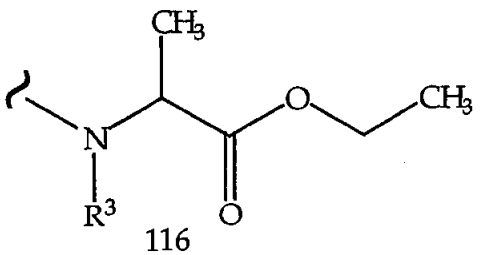

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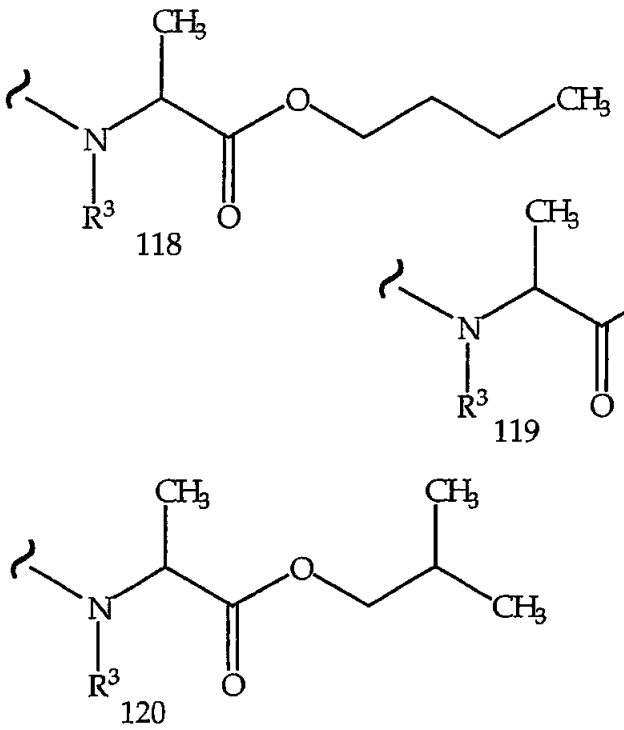
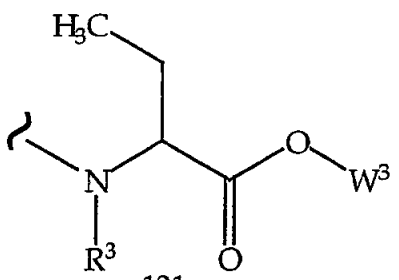
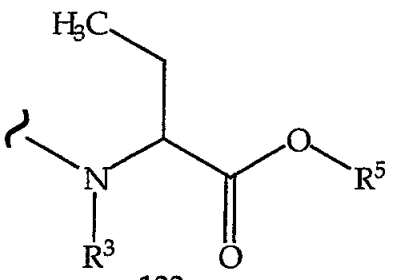
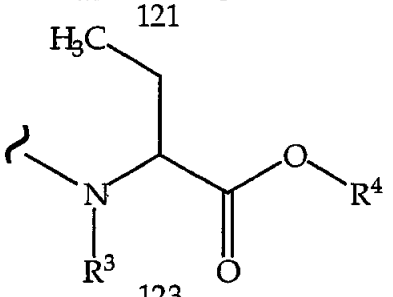
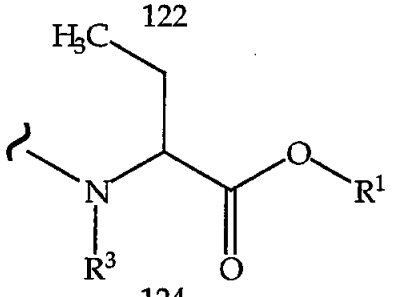


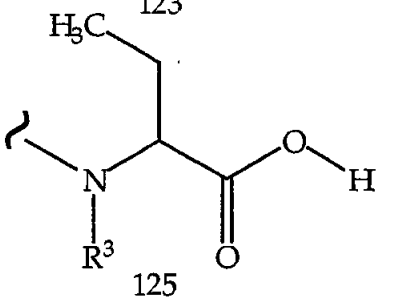
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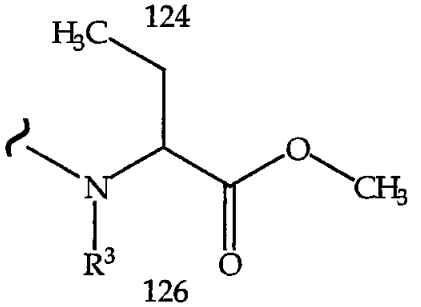

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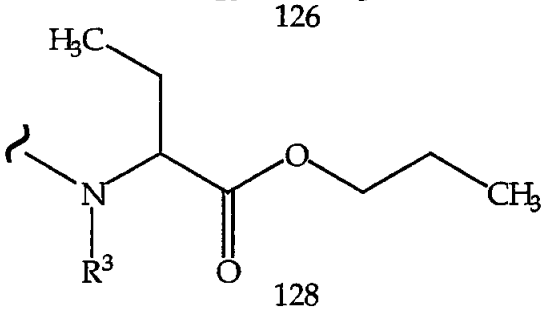

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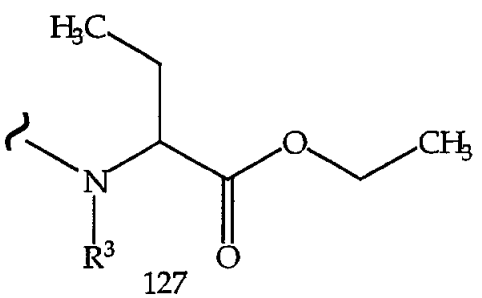

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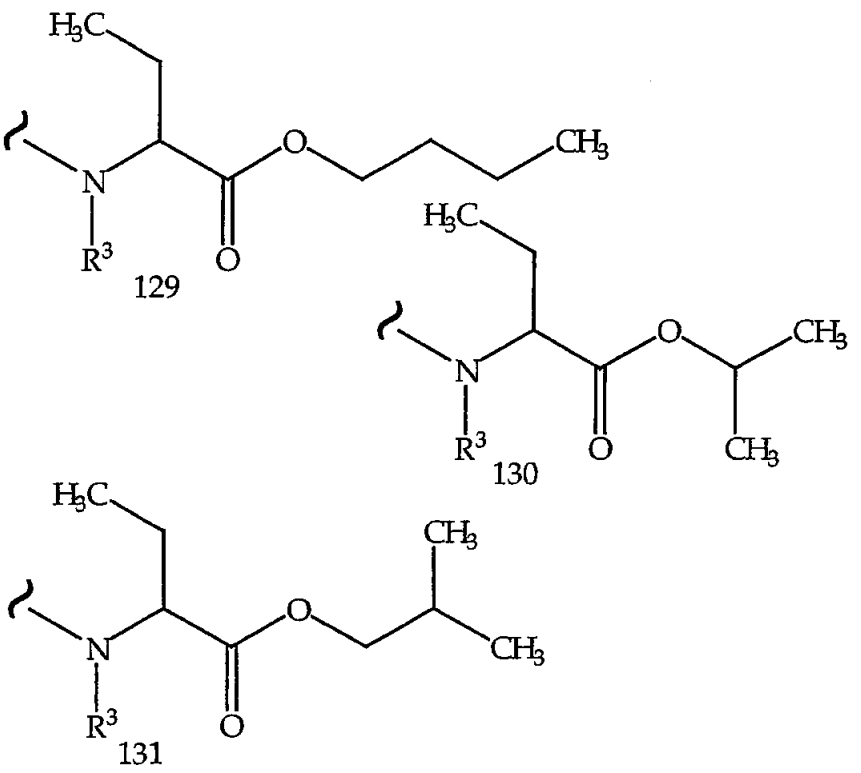
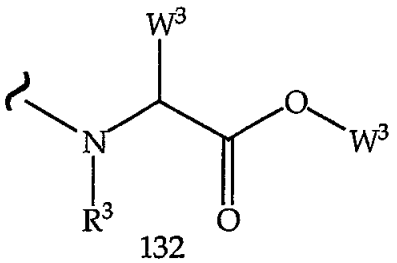
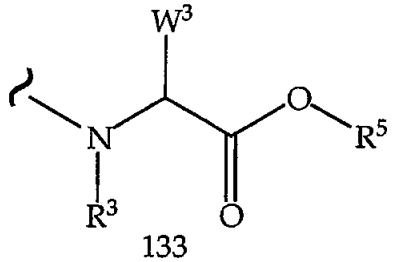
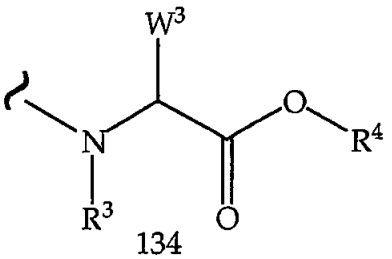
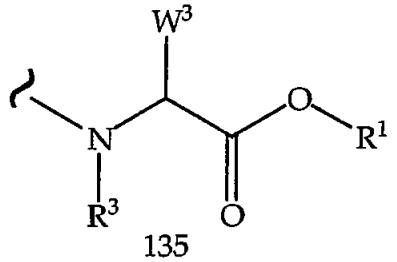


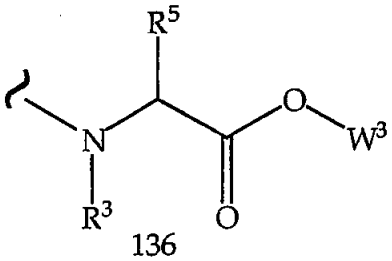
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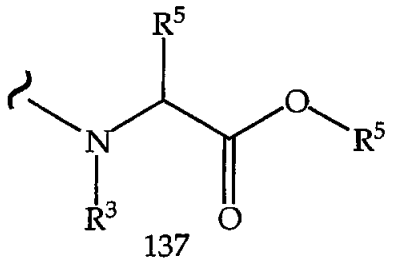

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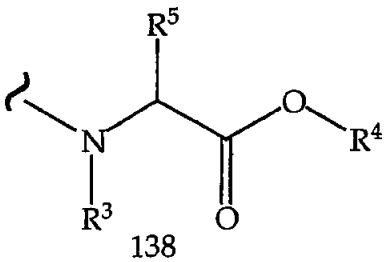

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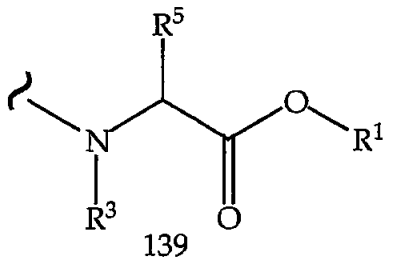
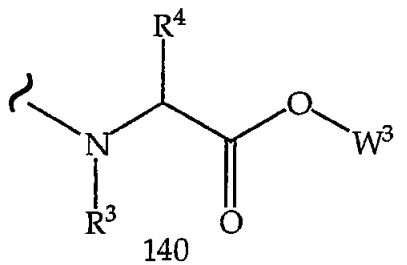
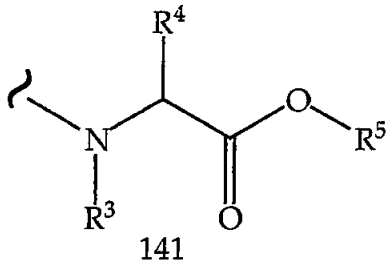
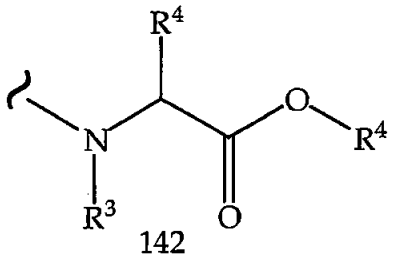
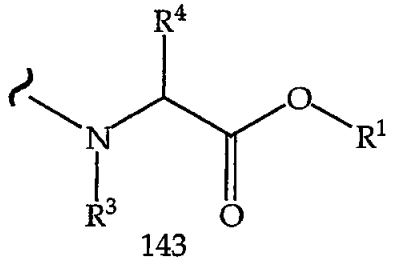

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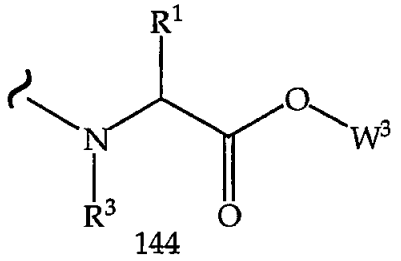
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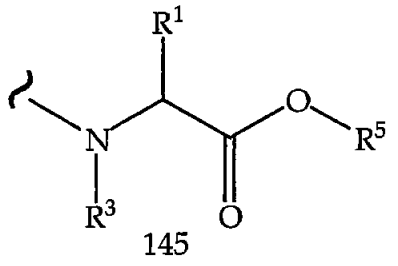

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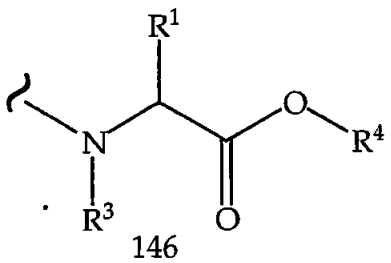

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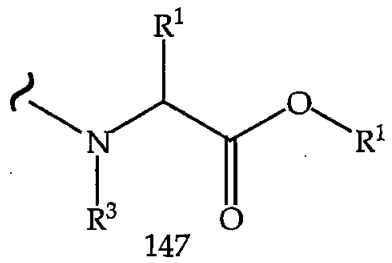
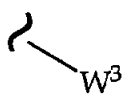
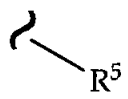

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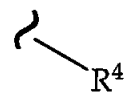
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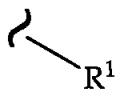
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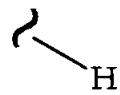
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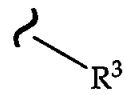
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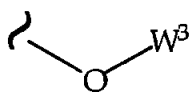
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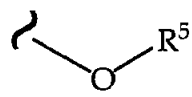
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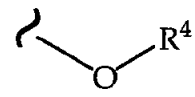
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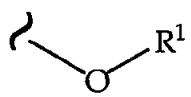
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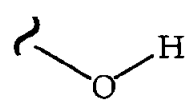
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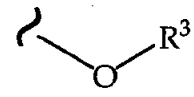
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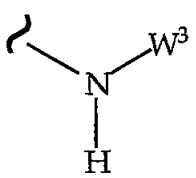


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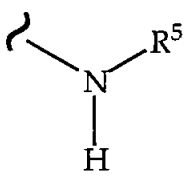


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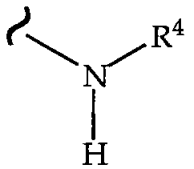
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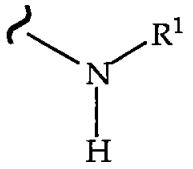
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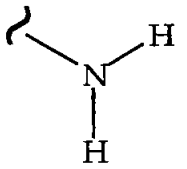
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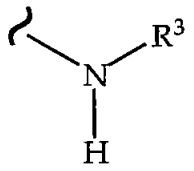
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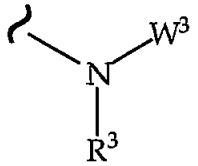
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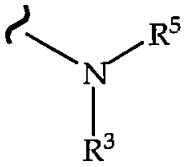
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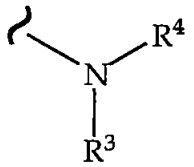
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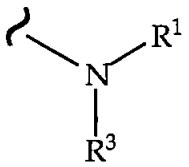
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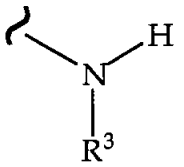
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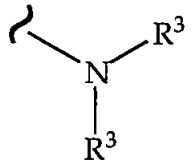
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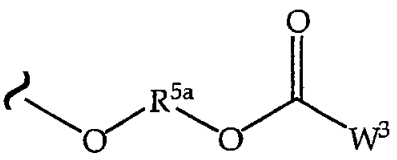


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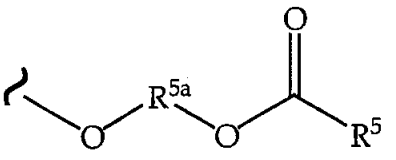


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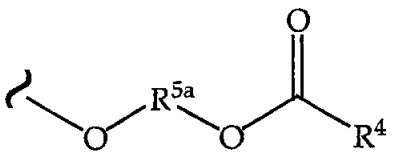
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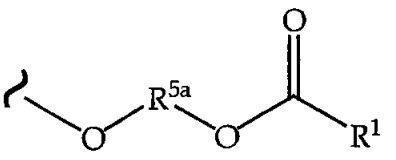
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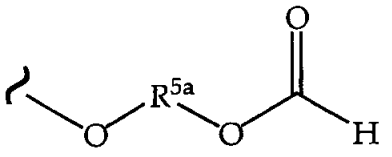
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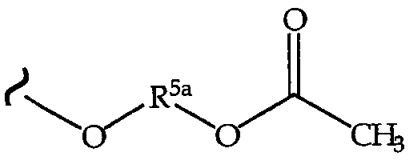
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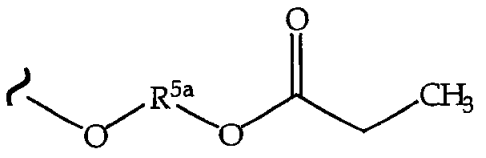
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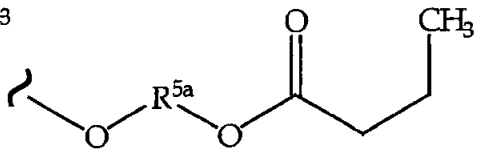
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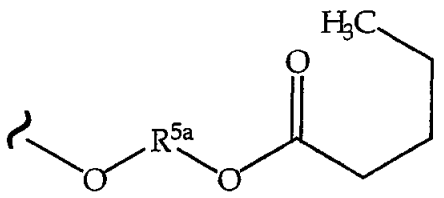


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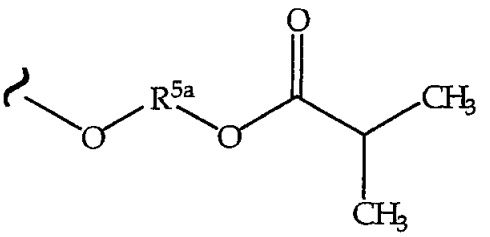


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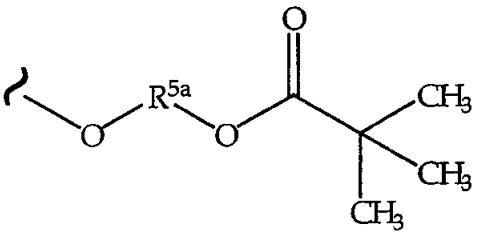
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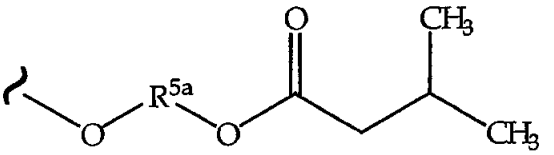
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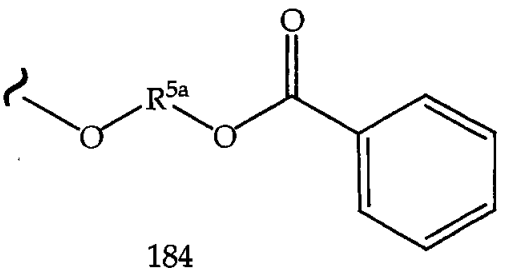
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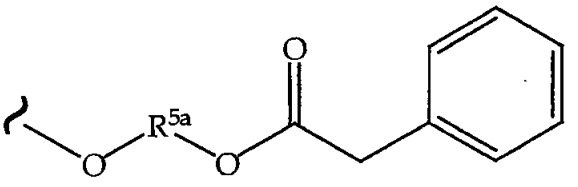
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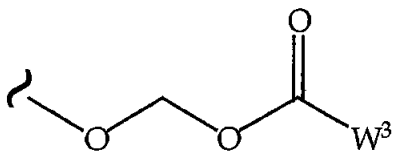


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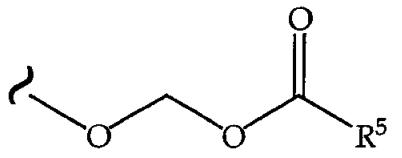


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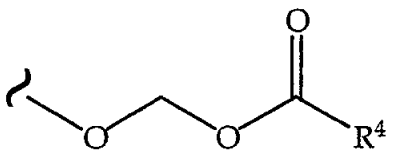
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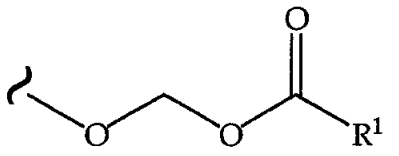
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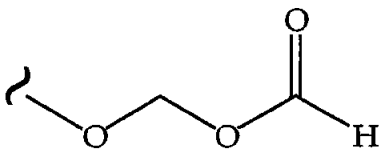
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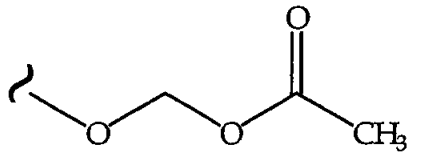
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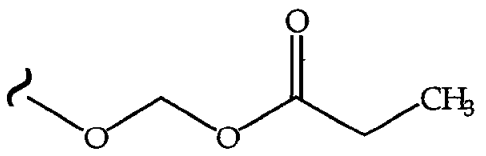
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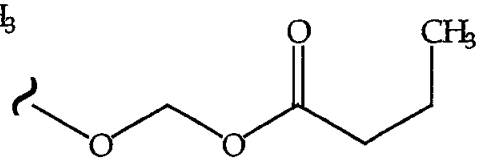
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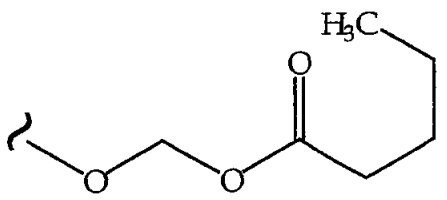


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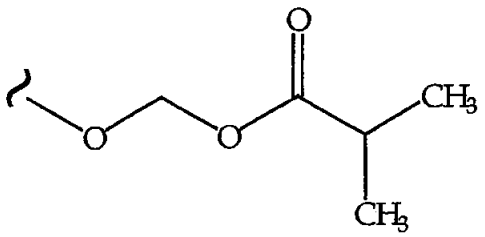


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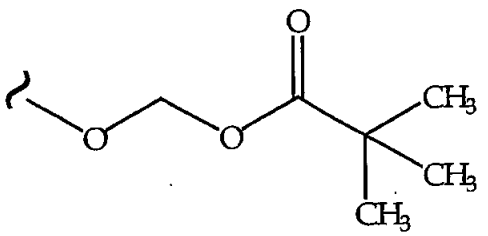
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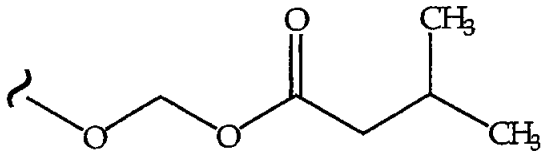
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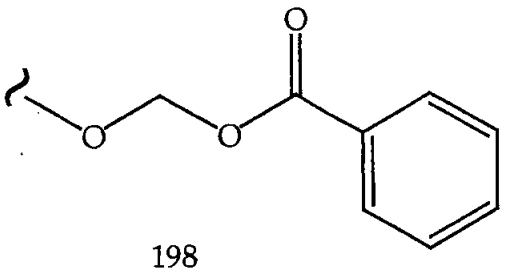
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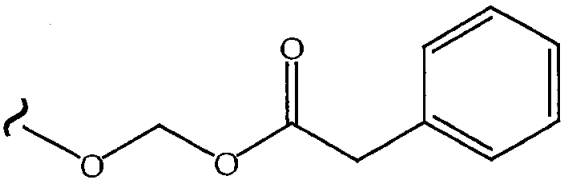
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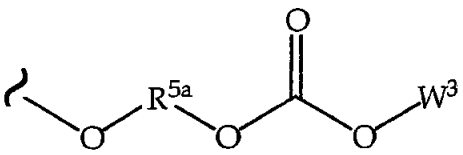


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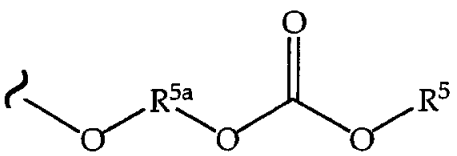


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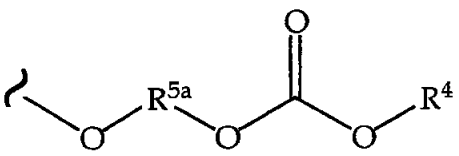
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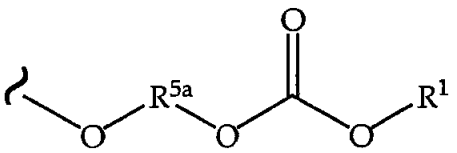
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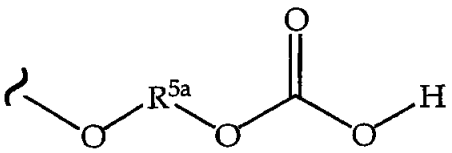
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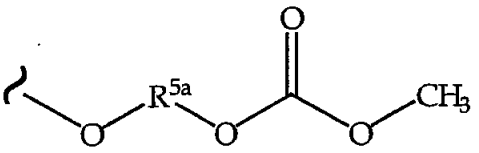
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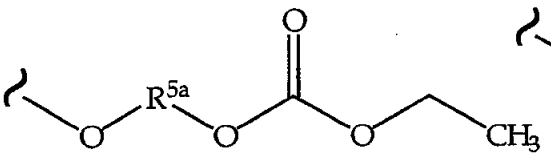
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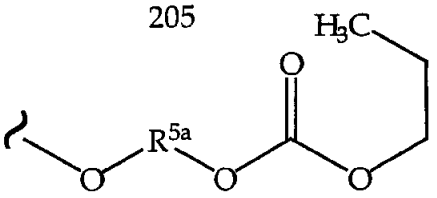
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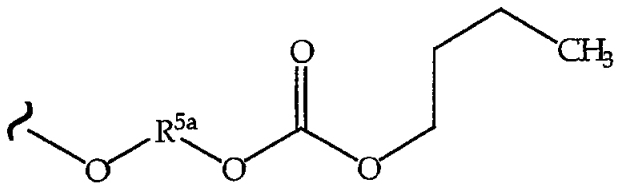


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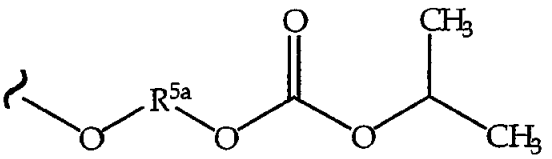


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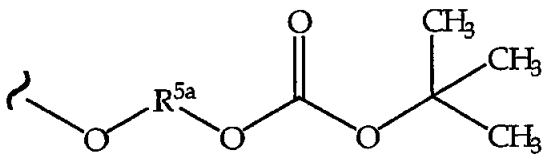
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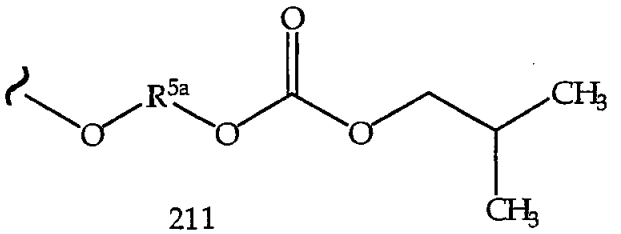
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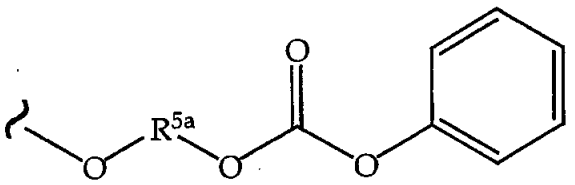
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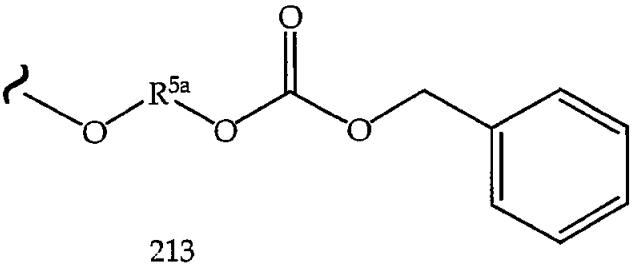
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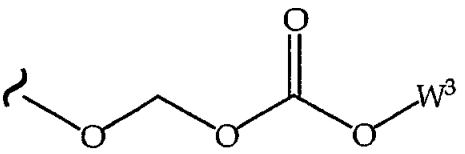


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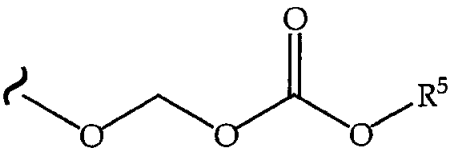


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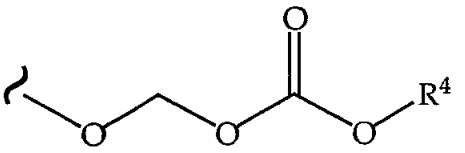
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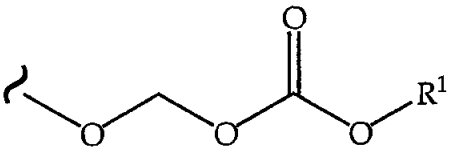
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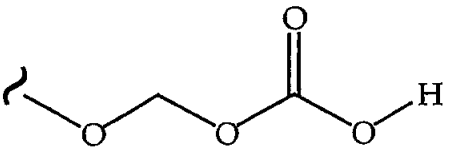
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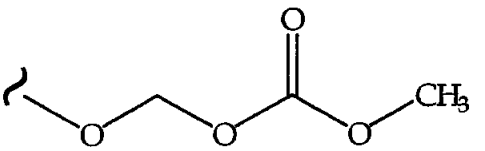
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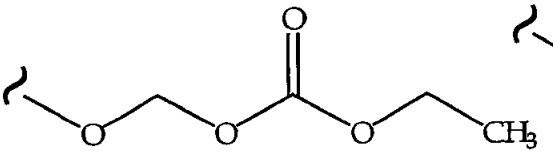
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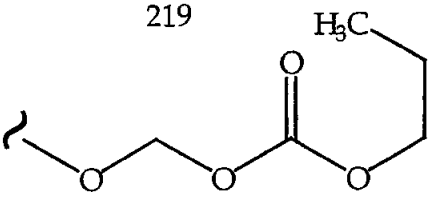
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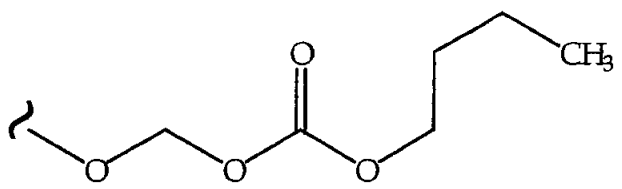


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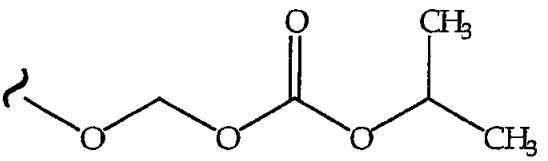


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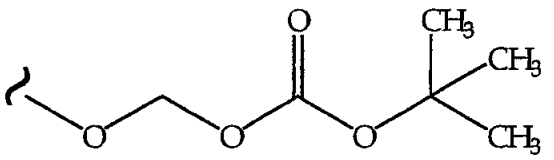
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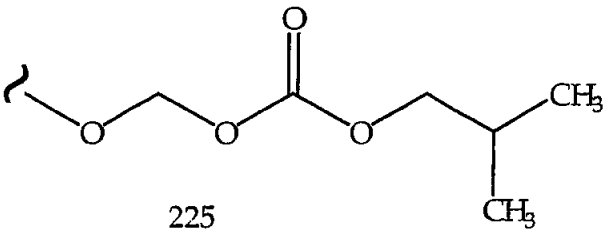
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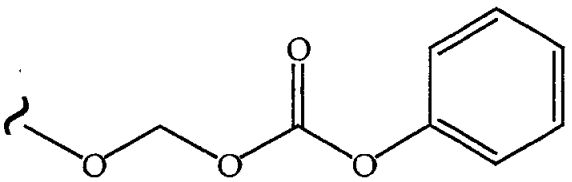
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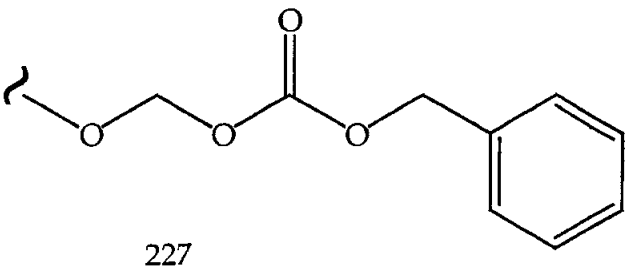
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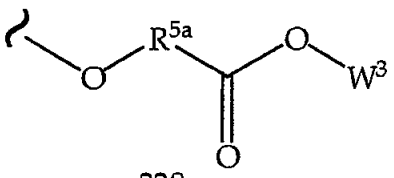


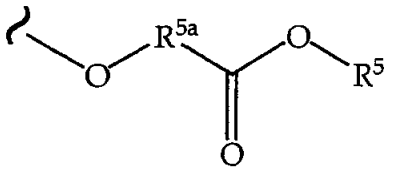
226

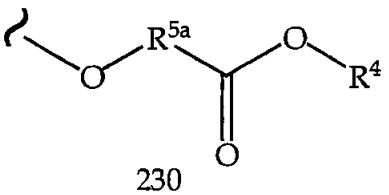


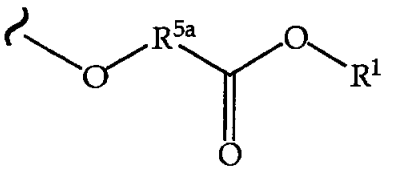
227

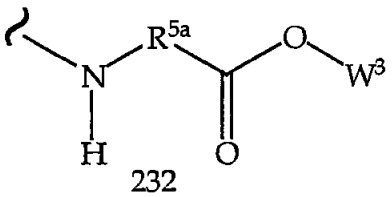
Table 20.35

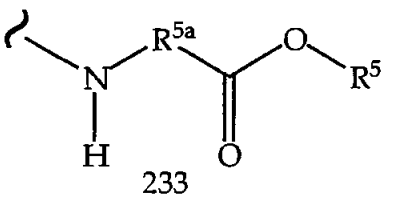

228

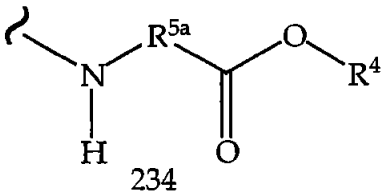

229


230


231


232


233


234

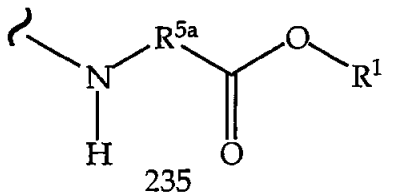
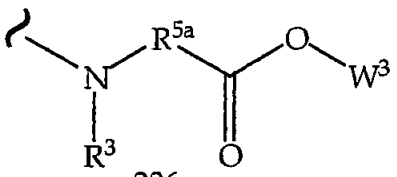
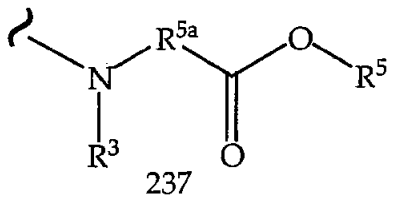

235

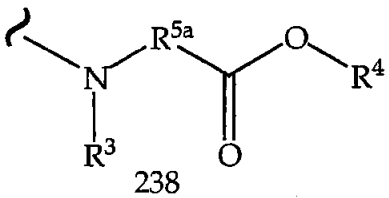
Table 20.36



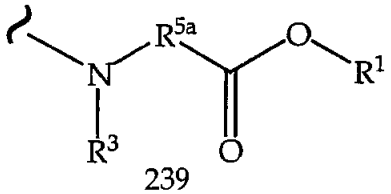
236



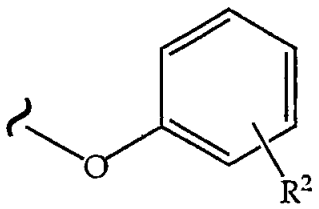
237



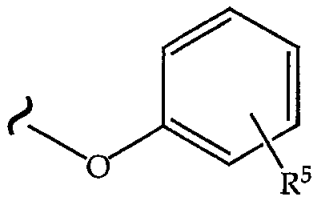
238



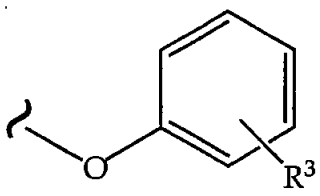
239



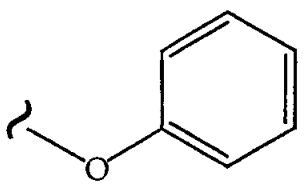
240



241

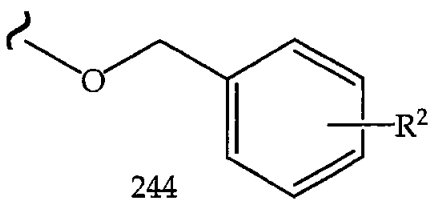


242

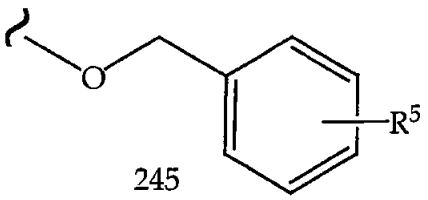


243

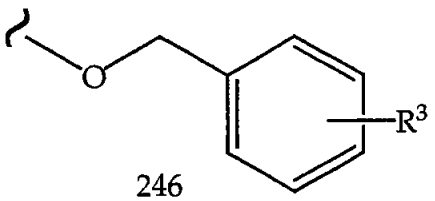
Table 20.37



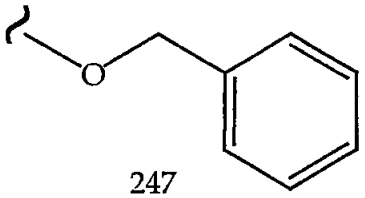
244



245



246



247

Table 100

Prodrugs of 1.B

1.B.228.228; 1.B.228.229; 1.B.228.230; 1.B.228.231; 1.B.228.236; 1.B.228.237; 1.B.228.238; 1.B.228.239; 1.B.228.154; 1.B.228.157; 1.B.228.166; 1.B.228.169; 1.B.228.172; 1.B.228.175; 1.B.228.240; 1.B.228.244; 1.B.229.228; 1.B.229.229; 1.B.229.230; 1.B.229.231; 1.B.229.236; 1.B.229.237; 1.B.229.238; 1.B.229.239; 1.B.229.154; 1.B.229.157; 1.B.229.166; 1.B.229.169; 1.B.229.172; 1.B.229.175; 1.B.229.240; 1.B.229.244; 1.B.230.228; 1.B.230.229; 1.B.230.230; 1.B.230.231; 1.B.230.236; 1.B.230.237; 1.B.230.238; 1.B.230.239; 1.B.230.154; 1.B.230.157; 1.B.230.166; 1.B.230.169; 1.B.230.172; 1.B.230.175; 1.B.230.240; 1.B.230.244; 1.B.231.228; 1.B.231.229; 1.B.231.230; 1.B.231.231; 1.B.231.236; 1.B.231.237; 1.B.231.238; 1.B.231.239; 1.B.231.154; 1.B.231.157; 1.B.231.166; 1.B.231.169; 1.B.231.172; 1.B.231.175; 1.B.231.240; 1.B.231.244; 1.B.236.228; 1.B.236.229; 1.B.236.230; 1.B.236.231; 1.B.236.236; 1.B.236.237; 1.B.236.238; 1.B.236.239; 1.B.236.154; 1.B.236.157; 1.B.236.166; 1.B.236.169; 1.B.236.172; 1.B.236.175; 1.B.236.240; 1.B.236.244; 1.B.237.228; 1.B.237.229; 1.B.237.230; 1.B.237.231; 1.B.237.236; 1.B.237.237; 1.B.237.238; 1.B.237.239; 1.B.237.154; 1.B.237.157; 1.B.237.166; 1.B.237.169; 1.B.237.172; 1.B.237.175; 1.B.237.240; 1.B.237.244; 1.B.238.228; 1.B.238.229; 1.B.238.230; 1.B.238.231; 1.B.238.236; 1.B.238.237; 1.B.238.238; 1.B.238.239; 1.B.238.154; 1.B.238.157; 1.B.238.166; 1.B.238.169; 1.B.238.172; 1.B.238.175; 1.B.238.240; 1.B.238.244; 1.B.239.228; 1.B.239.229; 1.B.239.230; 1.B.239.231; 1.B.239.236; 1.B.239.237; 1.B.239.238; 1.B.239.239; 1.B.239.154; 1.B.239.157; 1.B.239.166; 1.B.239.169; 1.B.239.172; 1.B.239.175; 1.B.239.240; 1.B.239.244; 1.B.154.228; 1.B.154.229; 1.B.154.230; 1.B.154.231; 1.B.154.236; 1.B.154.237; 1.B.154.238; 1.B.154.239; 1.B.154.154; 1.B.154.157; 1.B.154.166; 1.B.154.169; 1.B.154.172; 1.B.154.175; 1.B.154.240; 1.B.154.244; 1.B.157.228; 1.B.157.229; 1.B.157.230; 1.B.157.231; 1.B.157.236; 1.B.157.237; 1.B.157.238; 1.B.157.239; 1.B.157.154; 1.B.157.157; 1.B.157.166; 1.B.157.169; 1.B.157.172; 1.B.157.175; 1.B.157.240; 1.B.157.244; 1.B.166.228; 1.B.166.229; 1.B.166.230; 1.B.166.231; 1.B.166.236; 1.B.166.237; 1.B.166.238; 1.B.166.239; 1.B.166.154; 1.B.166.157; 1.B.166.166; 1.B.166.169; 1.B.166.172; 1.B.166.175; 1.B.166.240; 1.B.166.244; 1.B.169.228; 1.B.169.229; 1.B.169.230; 1.B.169.231; 1.B.169.236; 1.B.169.237; 1.B.169.238; 1.B.169.239; 1.B.169.154; 1.B.169.157; 1.B.169.166; 1.B.169.169; 1.B.169.172; 1.B.169.175; 1.B.169.240; 1.B.169.244; 1.B.172.228; 1.B.172.229; 1.B.172.230; 1.B.172.231; 1.B.172.236; 1.B.172.237; 1.B.172.238; 1.B.172.239; 1.B.172.154; 1.B.172.157; 1.B.172.166; 1.B.172.169; 1.B.172.172; 1.B.172.175; 1.B.172.240; 1.B.172.244; 1.B.175.228; 1.B.175.229; 1.B.175.230; 1.B.175.231; 1.B.175.236; 1.B.175.237; 1.B.175.238; 1.B.175.239; 1.B.175.154; 1.B.175.157; 1.B.175.166; 1.B.175.169; 1.B.175.172; 1.B.175.175; 1.B.175.240; 1.B.175.244; 1.B.240.228; 1.B.240.229; 1.B.240.230; 1.B.240.231; 1.B.240.236; 1.B.240.237; 1.B.240.238; 1.B.240.239; 1.B.240.154; 1.B.240.157; 1.B.240.166; 1.B.240.169; 1.B.240.172; 1.B.240.175; 1.B.240.240; 1.B.240.244; 1.B.244.228; 1.B.244.229; 1.B.244.230; 1.B.244.231; 1.B.244.236; 1.B.244.237; 1.B.244.238; 1.B.244.239; 1.B.244.154; 1.B.244.157; 1.B.244.166; 1.B.244.169; 1.B.244.172; 1.B.244.175; 1.B.244.240; 1.B.244.244;

Prodrugs of 1.D

1.D.228.228; 1.D.228.229; 1.D.228.230; 1.D.228.231; 1.D.228.236; 1.D.228.237; 1.D.228.238; 1.D.228.239; 1.D.228.154; 1.D.228.157; 1.D.228.166; 1.D.228.169; 1.D.228.172; 1.D.228.175; 1.D.228.240; 1.D.228.244; 1.D.229.228; 1.D.229.229; 1.D.229.230; 1.D.229.231; 1.D.229.236; 1.D.229.237; 1.D.229.238; 1.D.229.239;

1.D.229.154; 1.D.229.157; 1.D.229.166; 1.D.229.169; 1.D.229.172; 1.D.229.175; 1.D.229.240; 1.D.229.244; 1.D.230.228; 1.D.230.229; 1.D.230.230; 1.D.230.231; 1.D.230.236; 1.D.230.237; 1.D.230.238; 1.D.230.239; 1.D.230.154; 1.D.230.157; 1.D.230.166; 1.D.230.169; 1.D.230.172; 1.D.230.175; 1.D.230.240; 1.D.230.244; 1.D.231.228; 1.D.231.229; 1.D.231.230; 1.D.231.231; 1.D.231.236; 1.D.231.237; 1.D.231.238; 1.D.231.239; 1.D.231.154; 1.D.231.157; 1.D.231.166; 1.D.231.169; 1.D.231.172; 1.D.231.175; 1.D.231.240; 1.D.231.244; 1.D.236.228; 1.D.236.229; 1.D.236.230; 1.D.236.231; 1.D.236.236; 1.D.236.237; 1.D.236.238; 1.D.236.239; 1.D.236.154; 1.D.236.157; 1.D.236.166; 1.D.236.169; 1.D.236.172; 1.D.236.175; 1.D.236.240; 1.D.236.244; 1.D.237.228; 1.D.237.229; 1.D.237.230; 1.D.237.231; 1.D.237.236; 1.D.237.237; 1.D.237.238; 1.D.237.239; 1.D.237.154; 1.D.237.157; 1.D.237.166; 1.D.237.169; 1.D.237.172; 1.D.237.175; 1.D.237.240; 1.D.237.244; 1.D.238.228; 1.D.238.229; 1.D.238.230; 1.D.238.231; 1.D.238.236; 1.D.238.237; 1.D.238.238; 1.D.238.239; 1.D.238.154; 1.D.238.157; 1.D.238.166; 1.D.238.169; 1.D.238.172; 1.D.238.175; 1.D.238.240; 1.D.238.244; 1.D.239.228; 1.D.239.229; 1.D.239.230; 1.D.239.231; 1.D.239.236; 1.D.239.237; 1.D.239.238; 1.D.239.239; 1.D.239.154; 1.D.239.157; 1.D.239.166; 1.D.239.169; 1.D.239.172; 1.D.239.175; 1.D.239.240; 1.D.239.244; 1.D.154.228; 1.D.154.229; 1.D.154.230; 1.D.154.231; 1.D.154.236; 1.D.154.237; 1.D.154.238; 1.D.154.239; 1.D.154.154; 1.D.154.157; 1.D.154.166; 1.D.154.169; 1.D.154.172; 1.D.154.175; 1.D.154.240; 1.D.154.244; 1.D.157.228; 1.D.157.229; 1.D.157.230; 1.D.157.231; 1.D.157.236; 1.D.157.237; 1.D.157.238; 1.D.157.239; 1.D.157.154; 1.D.157.157; 1.D.157.166; 1.D.157.169; 1.D.157.172; 1.D.157.175; 1.D.157.240; 1.D.157.244; 1.D.166.228; 1.D.166.229; 1.D.166.230; 1.D.166.231; 1.D.166.236; 1.D.166.237; 1.D.166.238; 1.D.166.239; 1.D.166.154; 1.D.166.157; 1.D.166.166; 1.D.166.169; 1.D.166.172; 1.D.166.175; 1.D.166.240; 1.D.166.244; 1.D.169.228; 1.D.169.229; 1.D.169.230; 1.D.169.231; 1.D.169.236; 1.D.169.237; 1.D.169.238; 1.D.169.239; 1.D.169.154; 1.D.169.157; 1.D.169.166; 1.D.169.169; 1.D.169.172; 1.D.169.175; 1.D.169.240; 1.D.169.244; 1.D.172.228; 1.D.172.229; 1.D.172.230; 1.D.172.231; 1.D.172.236; 1.D.172.237; 1.D.172.238; 1.D.172.239; 1.D.172.154; 1.D.172.157; 1.D.172.166; 1.D.172.169; 1.D.172.172; 1.D.172.175; 1.D.172.240; 1.D.172.244; 1.D.175.228; 1.D.175.229; 1.D.175.230; 1.D.175.231; 1.D.175.236; 1.D.175.237; 1.D.175.238; 1.D.175.239; 1.D.175.154; 1.D.175.157; 1.D.175.166; 1.D.175.169; 1.D.175.172; 1.D.175.175; 1.D.175.240; 1.D.175.244; 1.D.240.228; 1.D.240.229; 1.D.240.230; 1.D.240.231; 1.D.240.236; 1.D.240.237; 1.D.240.238; 1.D.240.239; 1.D.240.154; 1.D.240.157; 1.D.240.166; 1.D.240.169; 1.D.240.172; 1.D.240.175; 1.D.240.240; 1.D.240.244; 1.D.244.228; 1.D.244.229; 1.D.244.230; 1.D.244.231; 1.D.244.236; 1.D.244.237; 1.D.244.238; 1.D.244.239; 1.D.244.154; 1.D.244.157; 1.D.244.166; 1.D.244.169; 1.D.244.172; 1.D.244.175; 1.D.244.240; 1.D.244.244;

Prodrugs of 1.E

1.E.228.228; 1.E.228.229; 1.E.228.230; 1.E.228.231; 1.E.228.236; 1.E.228.237; 1.E.228.238; 1.E.228.239; 1.E.228.154; 1.E.228.157; 1.E.228.166; 1.E.228.169; 1.E.228.172; 1.E.228.175; 1.E.228.240; 1.E.228.244; 1.E.229.228; 1.E.229.229; 1.E.229.230; 1.E.229.231; 1.E.229.236; 1.E.229.237; 1.E.229.238; 1.E.229.239; 1.E.229.154; 1.E.229.157; 1.E.229.166; 1.E.229.169; 1.E.229.172; 1.E.229.175; 1.E.229.240; 1.E.229.244; 1.E.230.228; 1.E.230.229;

1.E.230.230; 1.E.230.231; 1.E.230.236; 1.E.230.237; 1.E.230.238; 1.E.230.239; 1.E.230.154; 1.E.230.157; 1.E.230.166; 1.E.230.169; 1.E.230.172; 1.E.230.175; 1.E.230.240; 1.E.230.244; 1.E.231.228; 1.E.231.229; 1.E.231.230; 1.E.231.231; 1.E.231.236; 1.E.231.237; 1.E.231.238; 1.E.231.239; 1.E.231.154; 1.E.231.157; 1.E.231.166; 1.E.231.169; 1.E.231.172; 1.E.231.175; 1.E.231.240; 1.E.231.244; 1.E.236.228; 1.E.236.229; 1.E.236.230; 1.E.236.231; 1.E.236.236; 1.E.236.237; 1.E.236.238; 1.E.236.239; 1.E.236.154; 1.E.236.157; 1.E.236.166; 1.E.236.169; 1.E.236.172; 1.E.236.175; 1.E.236.240; 1.E.236.244; 1.E.237.228; 1.E.237.229; 1.E.237.230; 1.E.237.231; 1.E.237.236; 1.E.237.237; 1.E.237.238; 1.E.237.239; 1.E.237.154; 1.E.237.157; 1.E.237.166; 1.E.237.169; 1.E.237.172; 1.E.237.175; 1.E.237.240; 1.E.237.244; 1.E.238.228; 1.E.238.229; 1.E.238.230; 1.E.238.231; 1.E.238.236; 1.E.238.237; 1.E.238.238; 1.E.238.239; 1.E.238.154; 1.E.238.157; 1.E.238.166; 1.E.238.169; 1.E.238.172; 1.E.238.175; 1.E.238.240; 1.E.238.244; 1.E.239.228; 1.E.239.229; 1.E.239.230; 1.E.239.231; 1.E.239.236; 1.E.239.237; 1.E.239.238; 1.E.239.239; 1.E.239.154; 1.E.239.157; 1.E.239.166; 1.E.239.169; 1.E.239.172; 1.E.239.175; 1.E.239.240; 1.E.239.244; 1.E.154.228; 1.E.154.229; 1.E.154.230; 1.E.154.231; 1.E.154.236; 1.E.154.237; 1.E.154.238; 1.E.154.239; 1.E.154.154; 1.E.154.157; 1.E.154.166; 1.E.154.169; 1.E.154.172; 1.E.154.175; 1.E.154.240; 1.E.154.244; 1.E.157.228; 1.E.157.229; 1.E.157.230; 1.E.157.231; 1.E.157.236; 1.E.157.237; 1.E.157.238; 1.E.157.239; 1.E.157.154; 1.E.157.157; 1.E.157.166; 1.E.157.169; 1.E.157.172; 1.E.157.175; 1.E.157.240; 1.E.157.244; 1.E.166.228; 1.E.166.229; 1.E.166.230; 1.E.166.231; 1.E.166.236; 1.E.166.237; 1.E.166.238; 1.E.166.239; 1.E.166.154; 1.E.166.157; 1.E.166.166; 1.E.166.169; 1.E.166.172; 1.E.166.175; 1.E.166.240; 1.E.166.244; 1.E.169.228; 1.E.169.229; 1.E.169.230; 1.E.169.231; 1.E.169.236; 1.E.169.237; 1.E.169.238; 1.E.169.239; 1.E.169.154; 1.E.169.157; 1.E.169.166; 1.E.169.169; 1.E.169.172; 1.E.169.175; 1.E.169.240; 1.E.169.244; 1.E.172.228; 1.E.172.229; 1.E.172.230; 1.E.172.231; 1.E.172.236; 1.E.172.237; 1.E.172.238; 1.E.172.239; 1.E.172.154; 1.E.172.157; 1.E.172.166; 1.E.172.169; 1.E.172.172; 1.E.172.175; 1.E.172.240; 1.E.172.244; 1.E.175.228; 1.E.175.229; 1.E.175.230; 1.E.175.231; 1.E.175.236; 1.E.175.237; 1.E.175.238; 1.E.175.239; 1.E.175.154; 1.E.175.157; 1.E.175.166; 1.E.175.169; 1.E.175.172; 1.E.175.175; 1.E.175.240; 1.E.175.244; 1.E.240.228; 1.E.240.229; 1.E.240.230; 1.E.240.231; 1.E.240.236; 1.E.240.237; 1.E.240.238; 1.E.240.239; 1.E.240.154; 1.E.240.157; 1.E.240.166; 1.E.240.169; 1.E.240.172; 1.E.240.175; 1.E.240.240; 1.E.240.244; 1.E.244.228; 1.E.244.229; 1.E.244.230; 1.E.244.231; 1.E.244.236; 1.E.244.237; 1.E.244.238; 1.E.244.239; 1.E.244.154; 1.E.244.157; 1.E.244.166; 1.E.244.169; 1.E.244.172; 1.E.244.175; 1.E.244.240; 1.E.244.244;

Prodrugs of 1.G

1.G.228.228; 1.G.228.229; 1.G.228.230; 1.G.228.231; 1.G.228.236; 1.G.228.237; 1.G.228.238; 1.G.228.239; 1.G.228.154; 1.G.228.157; 1.G.228.166; 1.G.228.169; 1.G.228.172; 1.G.228.175; 1.G.228.240; 1.G.228.244; 1.G.229.228; 1.G.229.229; 1.G.229.230; 1.G.229.231; 1.G.229.236; 1.G.229.237; 1.G.229.238; 1.G.229.239; 1.G.229.154; 1.G.229.157; 1.G.229.166; 1.G.229.169; 1.G.229.172; 1.G.229.175; 1.G.229.240; 1.G.229.244; 1.G.230.228; 1.G.230.229; 1.G.230.230; 1.G.230.231; 1.G.230.236; 1.G.230.237; 1.G.230.238; 1.G.230.239; 1.G.230.154; 1.G.230.157; 1.G.230.166; 1.G.230.169; 1.G.230.172; 1.G.230.175; 1.G.230.240; 1.G.230.244; 1.G.231.228; 1.G.231.229; 1.G.231.230; 1.G.231.231; 1.G.231.236; 1.G.231.237; 1.G.231.238; 1.G.231.239; 1.G.231.154; 1.G.231.157; 1.G.231.166; 1.G.231.169; 1.G.231.172; 1.G.231.175; 1.G.231.240; 1.G.231.244; 1.G.236.228; 1.G.236.229; 1.G.236.230; 1.G.236.231; 1.G.236.236; 1.G.236.237; 1.G.236.238; 1.G.236.239;

1.G.236.154; 1.G.236.157; 1.G.236.166; 1.G.236.169; 1.G.236.172; 1.G.236.175; 1.G.236.240; 1.G.236.244; 1.G.237.228; 1.G.237.229; 1.G.237.230; 1.G.237.231; 1.G.237.236; 1.G.237.237; 1.G.237.238; 1.G.237.239; 1.G.237.154; 1.G.237.157; 1.G.237.166; 1.G.237.169; 1.G.237.172; 1.G.237.175; 1.G.237.240; 1.G.237.244; 1.G.238.228; 1.G.238.229; 1.G.238.230; 1.G.238.231; 1.G.238.236; 1.G.238.237; 1.G.238.238; 1.G.238.239; 1.G.238.154; 1.G.238.157; 1.G.238.166; 1.G.238.169; 1.G.238.172; 1.G.238.175; 1.G.238.240; 1.G.238.244; 1.G.239.228; 1.G.239.229; 1.G.239.230; 1.G.239.231; 1.G.239.236; 1.G.239.237; 1.G.239.238; 1.G.239.239; 1.G.239.154; 1.G.239.157; 1.G.239.166; 1.G.239.169; 1.G.239.172; 1.G.239.175; 1.G.239.240; 1.G.239.244; 1.G.154.228; 1.G.154.229; 1.G.154.230; 1.G.154.231; 1.G.154.236; 1.G.154.237; 1.G.154.238; 1.G.154.239; 1.G.154.154; 1.G.154.157; 1.G.154.166; 1.G.154.169; 1.G.154.172; 1.G.154.175; 1.G.154.240; 1.G.154.244; 1.G.157.228; 1.G.157.229; 1.G.157.230; 1.G.157.231; 1.G.157.236; 1.G.157.237; 1.G.157.238; 1.G.157.239; 1.G.157.154; 1.G.157.157; 1.G.157.166; 1.G.157.169; 1.G.157.172; 1.G.157.175; 1.G.157.240; 1.G.157.244; 1.G.166.228; 1.G.166.229; 1.G.166.230; 1.G.166.231; 1.G.166.236; 1.G.166.237; 1.G.166.238; 1.G.166.239; 1.G.166.154; 1.G.166.157; 1.G.166.166; 1.G.166.169; 1.G.166.172; 1.G.166.175; 1.G.166.240; 1.G.166.244; 1.G.169.228; 1.G.169.229; 1.G.169.230; 1.G.169.231; 1.G.169.236; 1.G.169.237; 1.G.169.238; 1.G.169.239; 1.G.169.154; 1.G.169.157; 1.G.169.166; 1.G.169.169; 1.G.169.172; 1.G.169.175; 1.G.169.240; 1.G.169.244; 1.G.172.228; 1.G.172.229; 1.G.172.230; 1.G.172.231; 1.G.172.236; 1.G.172.237; 1.G.172.238; 1.G.172.239; 1.G.172.154; 1.G.172.157; 1.G.172.166; 1.G.172.169; 1.G.172.172; 1.G.172.175; 1.G.172.240; 1.G.172.244; 1.G.175.228; 1.G.175.229; 1.G.175.230; 1.G.175.231; 1.G.175.236; 1.G.175.237; 1.G.175.238; 1.G.175.239; 1.G.175.154; 1.G.175.157; 1.G.175.166; 1.G.175.169; 1.G.175.172; 1.G.175.175; 1.G.175.240; 1.G.175.244; 1.G.240.228; 1.G.240.229; 1.G.240.230; 1.G.240.231; 1.G.240.236; 1.G.240.237; 1.G.240.238; 1.G.240.239; 1.G.240.154; 1.G.240.157; 1.G.240.166; 1.G.240.169; 1.G.240.172; 1.G.240.175; 1.G.240.240; 1.G.240.244; 1.G.244.228; 1.G.244.229; 1.G.244.230; 1.G.244.231; 1.G.244.236; 1.G.244.237; 1.G.244.238; 1.G.244.239; 1.G.244.154; 1.G.244.157; 1.G.244.166; 1.G.244.169; 1.G.244.172; 1.G.244.175; 1.G.244.240; 1.G.244.244;

<u>Prodrugs of 1.I</u>

1.I.228.228; 1.I.228.229; 1.I.228.230; 1.I.228.231; 1.I.228.236; 1.I.228.237; 1.I.228.238; 1.I.228.239; 1.I.228.154; 1.I.228.157; 1.I.228.166; 1.I.228.169; 1.I.228.172; 1.I.228.175; 1.I.228.240; 1.I.228.244; 1.I.229.228; 1.I.229.229; 1.I.229.230; 1.I.229.231; 1.I.229.236; 1.I.229.237; 1.I.229.238; 1.I.229.239; 1.I.229.154; 1.I.229.157; 1.I.229.166; 1.I.229.169; 1.I.229.172; 1.I.229.175; 1.I.229.240; 1.I.229.244; 1.I.230.228; 1.I.230.229; 1.I.230.230; 1.I.230.231; 1.I.230.236; 1.I.230.237; 1.I.230.238; 1.I.230.239; 1.I.230.154; 1.I.230.157; 1.I.230.166; 1.I.230.169; 1.I.230.172; 1.I.230.175; 1.I.230.240; 1.I.230.244; 1.I.231.228; 1.I.231.229; 1.I.231.230; 1.I.231.231; 1.I.231.236; 1.I.231.237; 1.I.231.238; 1.I.231.239; 1.I.231.154; 1.I.231.157; 1.I.231.166; 1.I.231.169; 1.I.231.172; 1.I.231.175; 1.I.231.240; 1.I.231.244; 1.I.236.228; 1.I.236.229; 1.I.236.230; 1.I.236.231; 1.I.236.236; 1.I.236.237; 1.I.236.238; 1.I.236.239; 1.I.236.154; 1.I.236.157; 1.I.236.166; 1.I.236.169; 1.I.236.172; 1.I.236.175; 1.I.236.240; 1.I.236.244; 1.I.237.228; 1.I.237.229; 1.I.237.230; 1.I.237.231; 1.I.237.236; 1.I.237.237; 1.I.237.238; 1.I.237.239; 1.I.237.154; 1.I.237.157; 1.I.237.166;

1.I.237.169; 1.I.237.172; 1.I.237.175; 1.I.237.240; 1.I.237.244; 1.I.238.228; 1.I.238.229; 1.I.238.230; 1.I.238.231; 1.I.238.236; 1.I.238.237; 1.I.238.238; 1.I.238.239; 1.I.238.154; 1.I.238.157; 1.I.238.166; 1.I.238.169; 1.I.238.172; 1.I.238.175; 1.I.238.240; 1.I.238.244; 1.I.239.228; 1.I.239.229; 1.I.239.230; 1.I.239.231; 1.I.239.236; 1.I.239.237; 1.I.239.238; 1.I.239.239; 1.I.239.154; 1.I.239.157; 1.I.239.166; 1.I.239.169; 1.I.239.172; 1.I.239.175; 1.I.239.240; 1.I.239.244; 1.I.154.228; 1.I.154.229; 1.I.154.230; 1.I.154.231; 1.I.154.236; 1.I.154.237; 1.I.154.238; 1.I.154.239; 1.I.154.154; 1.I.154.157; 1.I.154.166; 1.I.154.169; 1.I.154.172; 1.I.154.175; 1.I.154.240; 1.I.154.244; 1.I.157.228; 1.I.157.229; 1.I.157.230; 1.I.157.231; 1.I.157.236; 1.I.157.237; 1.I.157.238; 1.I.157.239; 1.I.157.154; 1.I.157.157; 1.I.157.166; 1.I.157.169; 1.I.157.172; 1.I.157.175; 1.I.157.240; 1.I.157.244; 1.I.166.228; 1.I.166.229; 1.I.166.230; 1.I.166.231; 1.I.166.236; 1.I.166.237; 1.I.166.238; 1.I.166.239; 1.I.166.154; 1.I.166.157; 1.I.166.166; 1.I.166.169; 1.I.166.172; 1.I.166.175; 1.I.166.240; 1.I.166.244; 1.I.169.228; 1.I.169.229; 1.I.169.230; 1.I.169.231; 1.I.169.236; 1.I.169.237; 1.I.169.238; 1.I.169.239; 1.I.169.154; 1.I.169.157; 1.I.169.166; 1.I.169.169; 1.I.169.172; 1.I.169.175; 1.I.169.240; 1.I.169.244; 1.I.172.228; 1.I.172.229; 1.I.172.230; 1.I.172.231; 1.I.172.236; 1.I.172.237; 1.I.172.238; 1.I.172.239; 1.I.172.154; 1.I.172.157; 1.I.172.166; 1.I.172.169; 1.I.172.172; 1.I.172.175; 1.I.172.240; 1.I.172.244; 1.I.175.228; 1.I.175.229; 1.I.175.230; 1.I.175.231; 1.I.175.236; 1.I.175.237; 1.I.175.238; 1.I.175.239; 1.I.175.154; 1.I.175.157; 1.I.175.166; 1.I.175.169; 1.I.175.172; 1.I.175.175; 1.I.175.240; 1.I.175.244; 1.I.240.228; 1.I.240.229; 1.I.240.230; 1.I.240.231; 1.I.240.236; 1.I.240.237; 1.I.240.238; 1.I.240.239; 1.I.240.154; 1.I.240.157; 1.I.240.166; 1.I.240.169; 1.I.240.172; 1.I.240.175; 1.I.240.240; 1.I.240.244; 1.I.244.228; 1.I.244.229; 1.I.244.230; 1.I.244.231; 1.I.244.236; 1.I.244.237; 1.I.244.238; 1.I.244.239; 1.I.244.154; 1.I.244.157; 1.I.244.166; 1.I.244.169; 1.I.244.172; 1.I.244.175; 1.I.244.240; 1.I.244.244;

Prodrugs of 1.I

1.J.228.228; 1.J.228.229; 1.J.228.230; 1.J.228.231; 1.J.228.236; 1.J.228.237; 1.J.228.238; 1.J.228.239; 1.J.228.154; 1.J.228.157; 1.J.228.166; 1.J.228.169; 1.J.228.172; 1.J.228.175; 1.J.228.240; 1.J.228.244; 1.J.229.228; 1.J.229.229; 1.J.229.230; 1.J.229.231; 1.J.229.236; 1.J.229.237; 1.J.229.238; 1.J.229.239; 1.J.229.154; 1.J.229.157; 1.J.229.166; 1.J.229.169; 1.J.229.172; 1.J.229.175; 1.J.229.240; 1.J.229.244; 1.J.230.228; 1.J.230.229; 1.J.230.230; 1.J.230.231; 1.J.230.236; 1.J.230.237; 1.J.230.238; 1.J.230.239; 1.J.230.154; 1.J.230.157; 1.J.230.166; 1.J.230.169; 1.J.230.172; 1.J.230.175; 1.J.230.240; 1.J.230.244; 1.J.231.228; 1.J.231.229; 1.J.231.230; 1.J.231.231; 1.J.231.236; 1.J.231.237; 1.J.231.238; 1.J.231.239; 1.J.231.154; 1.J.231.157; 1.J.231.166; 1.J.231.169; 1.J.231.172; 1.J.231.175; 1.J.231.240; 1.J.231.244; 1.J.236.228; 1.J.236.229; 1.J.236.230; 1.J.236.231; 1.J.236.236; 1.J.236.237; 1.J.236.238; 1.J.236.239; 1.J.236.154; 1.J.236.157; 1.J.236.166; 1.J.236.169; 1.J.236.172; 1.J.236.175; 1.J.236.240; 1.J.236.244; 1.J.237.228; 1.J.237.229; 1.J.237.230; 1.J.237.231; 1.J.237.236; 1.J.237.237; 1.J.237.238; 1.J.237.239; 1.J.237.154; 1.J.237.157; 1.J.237.166; 1.J.237.169; 1.J.237.172; 1.J.237.175; 1.J.237.240; 1.J.237.244; 1.J.238.228; 1.J.238.229; 1.J.238.230; 1.J.238.231; 1.J.238.236; 1.J.238.237; 1.J.238.238; 1.J.238.239; 1.J.238.154; 1.J.238.157; 1.J.238.166; 1.J.238.169; 1.J.238.172; 1.J.238.175; 1.J.238.240; 1.J.238.244; 1.J.239.228; 1.J.239.229; 1.J.239.230; 1.J.239.231; 1.J.239.236; 1.J.239.237; 1.J.239.238; 1.J.239.239; 1.J.239.154; 1.J.239.157; 1.J.239.166; 1.J.239.169; 1.J.239.172; 1.J.239.175; 1.J.239.240; 1.J.239.244; 1.J.154.228; 1.J.154.229; 1.J.154.230; 1.J.154.231; 1.J.154.236; 1.J.154.237; 1.J.154.238; 1.J.154.239; 1.J.154.154; 1.J.154.157; 1.J.154.166; 1.J.154.169;

1.J.154.172; 1.J.154.175; 1.J.154.240; 1.J.154.244; 1.J.157.228; 1.J.157.229; 1.J.157.230; 1.J.157.231; 1.J.157.236; 1.J.157.237; 1.J.157.238; 1.J.157.239; 1.J.157.154; 1.J.157.157; 1.J.157.166; 1.J.157.169; 1.J.157.172; 1.J.157.175; 1.J.157.240; 1.J.157.244; 1.J.166.228; 1.J.166.229; 1.J.166.230; 1.J.166.231; 1.J.166.236; 1.J.166.237; 1.J.166.238; 1.J.166.239; 1.J.166.154; 1.J.166.157; 1.J.166.166; 1.J.166.169; 1.J.166.172; 1.J.166.175; 1.J.166.240; 1.J.166.244; 1.J.169.228; 1.J.169.229; 1.J.169.230; 1.J.169.231; 1.J.169.236; 1.J.169.237; 1.J.169.238; 1.J.169.239; 1.J.169.154; 1.J.169.157; 1.J.169.166; 1.J.169.169; 1.J.169.172; 1.J.169.175; 1.J.169.240; 1.J.169.244; 1.J.172.228; 1.J.172.229; 1.J.172.230; 1.J.172.231; 1.J.172.236; 1.J.172.237; 1.J.172.238; 1.J.172.239; 1.J.172.154; 1.J.172.157; 1.J.172.166; 1.J.172.169; 1.J.172.172; 1.J.172.175; 1.J.172.240; 1.J.172.244; 1.J.175.228; 1.J.175.229; 1.J.175.230; 1.J.175.231; 1.J.175.236; 1.J.175.237; 1.J.175.238; 1.J.175.239; 1.J.175.154; 1.J.175.157; 1.J.175.166; 1.J.175.169; 1.J.175.172; 1.J.175.175; 1.J.175.240; 1.J.175.244; 1.J.240.228; 1.J.240.229; 1.J.240.230; 1.J.240.231; 1.J.240.236; 1.J.240.237; 1.J.240.238; 1.J.240.239; 1.J.240.154; 1.J.240.157; 1.J.240.166; 1.J.240.169; 1.J.240.172; 1.J.240.175; 1.J.240.240; 1.J.240.244; 1.J.244.228; 1.J.244.229; 1.J.244.230; 1.J.244.231; 1.J.244.236; 1.J.244.237; 1.J.244.238; 1.J.244.239; 1.J.244.154; 1.J.244.157; 1.J.244.166; 1.J.244.169; 1.J.244.172; 1.J.244.175; 1.J.244.240; 1.J.244.244;

Prodrugs of 1.L

1.L.228.228; 1.L.228.229; 1.L.228.230; 1.L.228.231; 1.L.228.236; 1.L.228.237; 1.L.228.238; 1.L.228.239; 1.L.228.154; 1.L.228.157; 1.L.228.166; 1.L.228.169; 1.L.228.172; 1.L.228.175; 1.L.228.240; 1.L.228.244; 1.L.229.228; 1.L.229.229; 1.L.229.230; 1.L.229.231; 1.L.229.236; 1.L.229.237; 1.L.229.238; 1.L.229.239; 1.L.229.154; 1.L.229.157; 1.L.229.166; 1.L.229.169; 1.L.229.172; 1.L.229.175; 1.L.229.240; 1.L.229.244; 1.L.230.228; 1.L.230.229; 1.L.230.230; 1.L.230.231; 1.L.230.236; 1.L.230.237; 1.L.230.238; 1.L.230.239; 1.L.230.154; 1.L.230.157; 1.L.230.166; 1.L.230.169; 1.L.230.172; 1.L.230.175; 1.L.230.240; 1.L.230.244; 1.L.231.228; 1.L.231.229; 1.L.231.230; 1.L.231.231; 1.L.231.236; 1.L.231.237; 1.L.231.238; 1.L.231.239; 1.L.231.154; 1.L.231.157; 1.L.231.166; 1.L.231.169; 1.L.231.172; 1.L.231.175; 1.L.231.240; 1.L.231.244; 1.L.236.228; 1.L.236.229; 1.L.236.230; 1.L.236.231; 1.L.236.236; 1.L.236.237; 1.L.236.238; 1.L.236.239; 1.L.236.154; 1.L.236.157; 1.L.236.166; 1.L.236.169; 1.L.236.172; 1.L.236.175; 1.L.236.240; 1.L.236.244; 1.L.237.228; 1.L.237.229; 1.L.237.230; 1.L.237.231; 1.L.237.236; 1.L.237.237; 1.L.237.238; 1.L.237.239; 1.L.237.154; 1.L.237.157; 1.L.237.166; 1.L.237.169; 1.L.237.172; 1.L.237.175; 1.L.237.240; 1.L.237.244; 1.L.238.228; 1.L.238.229; 1.L.238.230; 1.L.238.231; 1.L.238.236; 1.L.238.237; 1.L.238.238; 1.L.238.239; 1.L.238.154; 1.L.238.157; 1.L.238.166; 1.L.238.169; 1.L.238.172; 1.L.238.175; 1.L.238.240; 1.L.238.244; 1.L.239.228; 1.L.239.229; 1.L.239.230; 1.L.239.231; 1.L.239.236; 1.L.239.237; 1.L.239.238; 1.L.239.239; 1.L.239.154; 1.L.239.157; 1.L.239.166; 1.L.239.169; 1.L.239.172; 1.L.239.175; 1.L.239.240; 1.L.239.244; 1.L.154.228; 1.L.154.229; 1.L.154.230; 1.L.154.231; 1.L.154.236; 1.L.154.237; 1.L.154.238; 1.L.154.239; 1.L.154.154; 1.L.154.157; 1.L.154.166; 1.L.154.169; 1.L.154.172; 1.L.154.175; 1.L.154.240; 1.L.154.244; 1.L.157.228; 1.L.157.229; 1.L.157.230; 1.L.157.231; 1.L.157.236; 1.L.157.237; 1.L.157.238; 1.L.157.239; 1.L.157.154; 1.L.157.157; 1.L.157.166; 1.L.157.169; 1.L.157.172; 1.L.157.175; 1.L.157.240; 1.L.157.244; 1.L.166.228; 1.L.166.229; 1.L.166.230; 1.L.166.231; 1.L.166.236; 1.L.166.237; 1.L.166.238; 1.L.166.239; 1.L.166.154; 1.L.166.157; 1.L.166.166; 1.L.166.169; 1.L.166.172; 1.L.166.175; 1.L.166.240; 1.L.166.244; 1.L.169.228; 1.L.169.229; 1.L.169.230; 1.L.169.231; 1.L.169.236; 1.L.169.237; 1.L.169.238; 1.L.169.239; 1.L.169.154; 1.L.169.157; 1.L.169.166; 1.L.169.169;

1.L.169.172; 1.L.169.175; 1.L.169.240; 1.L.169.244; 1.L.172.228; 1.L.172.229; 1.L.172.230; 1.L.172.231; 1.L.172.236; 1.L.172.237; 1.L.172.238; 1.L.172.239; 1.L.172.154; 1.L.172.157; 1.L.172.166; 1.L.172.169; 1.L.172.172; 1.L.172.175; 1.L.172.240; 1.L.172.244; 1.L.175.228; 1.L.175.229; 1.L.175.230; 1.L.175.231; 1.L.175.236; 1.L.175.237; 1.L.175.238; 1.L.175.239; 1.L.175.154; 1.L.175.157; 1.L.175.166; 1.L.175.169; 1.L.175.172; 1.L.175.175; 1.L.175.240; 1.L.175.244; 1.L.240.228; 1.L.240.229; 1.L.240.230; 1.L.240.231; 1.L.240.236; 1.L.240.237; 1.L.240.238; 1.L.240.239; 1.L.240.154; 1.L.240.157; 1.L.240.166; 1.L.240.169; 1.L.240.172; 1.L.240.175; 1.L.240.240; 1.L.240.244; 1.L.244.228; 1.L.244.229; 1.L.244.230; 1.L.244.231; 1.L.244.236; 1.L.244.237; 1.L.244.238; 1.L.244.239; 1.L.244.154; 1.L.244.157; 1.L.244.166; 1.L.244.169; 1.L.244.172; 1.L.244.175; 1.L.244.240; 1.L.244.244;

Prodrugs of 1.O

1.O.228.228; 1.O.228.229; 1.O.228.230; 1.O.228.231; 1.O.228.236; 1.O.228.237; 1.O.228.238; 1.O.228.239; 1.O.228.154; 1.O.228.157; 1.O.228.166; 1.O.228.169; 1.O.228.172; 1.O.228.175; 1.O.228.240; 1.O.228.244; 1.O.229.228; 1.O.229.229; 1.O.229.230; 1.O.229.231; 1.O.229.236; 1.O.229.237; 1.O.229.238; 1.O.229.239; 1.O.229.154; 1.O.229.157; 1.O.229.166; 1.O.229.169; 1.O.229.172; 1.O.229.175; 1.O.229.240; 1.O.229.244; 1.O.230.228; 1.O.230.229; 1.O.230.230; 1.O.230.231; 1.O.230.236; 1.O.230.237; 1.O.230.238; 1.O.230.239; 1.O.230.154; 1.O.230.157; 1.O.230.166; 1.O.230.169; 1.O.230.172; 1.O.230.175; 1.O.230.240; 1.O.230.244; 1.O.231.228; 1.O.231.229; 1.O.231.230; 1.O.231.231; 1.O.231.236; 1.O.231.237; 1.O.231.238; 1.O.231.239; 1.O.231.154; 1.O.231.157; 1.O.231.166; 1.O.231.169; 1.O.231.172; 1.O.231.175; 1.O.231.240; 1.O.231.244; 1.O.236.228; 1.O.236.229; 1.O.236.230; 1.O.236.231; 1.O.236.236; 1.O.236.237; 1.O.236.238; 1.O.236.239; 1.O.236.154; 1.O.236.157; 1.O.236.166; 1.O.236.169; 1.O.236.172; 1.O.236.175; 1.O.236.240; 1.O.236.244; 1.O.237.228; 1.O.237.229; 1.O.237.230; 1.O.237.231; 1.O.237.236; 1.O.237.237; 1.O.237.238; 1.O.237.239; 1.O.237.154; 1.O.237.157; 1.O.237.166; 1.O.237.169; 1.O.237.172; 1.O.237.175; 1.O.237.240; 1.O.237.244; 1.O.238.228; 1.O.238.229; 1.O.238.230; 1.O.238.231; 1.O.238.236; 1.O.238.237; 1.O.238.238; 1.O.238.239; 1.O.238.154; 1.O.238.157; 1.O.238.166; 1.O.238.169; 1.O.238.172; 1.O.238.175; 1.O.238.240; 1.O.238.244; 1.O.239.228; 1.O.239.229; 1.O.239.230; 1.O.239.231; 1.O.239.236; 1.O.239.237; 1.O.239.238; 1.O.239.239; 1.O.239.154; 1.O.239.157; 1.O.239.166; 1.O.239.169; 1.O.239.172; 1.O.239.175; 1.O.239.240; 1.O.239.244; 1.O.154.228; 1.O.154.229; 1.O.154.230; 1.O.154.231; 1.O.154.236; 1.O.154.237; 1.O.154.238; 1.O.154.239; 1.O.154.154; 1.O.154.157; 1.O.154.166; 1.O.154.169; 1.O.154.172; 1.O.154.175; 1.O.154.240; 1.O.154.244; 1.O.157.228; 1.O.157.229; 1.O.157.230; 1.O.157.231; 1.O.157.236; 1.O.157.237; 1.O.157.238; 1.O.157.239; 1.O.157.154; 1.O.157.157; 1.O.157.166; 1.O.157.169; 1.O.157.172; 1.O.157.175; 1.O.157.240; 1.O.157.244; 1.O.166.228; 1.O.166.229; 1.O.166.230; 1.O.166.231; 1.O.166.236; 1.O.166.237; 1.O.166.238; 1.O.166.239; 1.O.166.154; 1.O.166.157; 1.O.166.166; 1.O.166.169; 1.O.166.172; 1.O.166.175; 1.O.166.240; 1.O.166.244; 1.O.169.228; 1.O.169.229; 1.O.169.230; 1.O.169.231; 1.O.169.236; 1.O.169.237; 1.O.169.238; 1.O.169.239; 1.O.169.154; 1.O.169.157; 1.O.169.166; 1.O.169.169; 1.O.169.172; 1.O.169.175; 1.O.169.240; 1.O.169.244; 1.O.172.228; 1.O.172.229; 1.O.172.230; 1.O.172.231; 1.O.172.236; 1.O.172.237; 1.O.172.238; 1.O.172.239; 1.O.172.154; 1.O.172.157; 1.O.172.166; 1.O.172.169;

1.O.172.172; 1.O.172.175; 1.O.172.240; 1.O.172.244; 1.O.175.228; 1.O.175.229; 1.O.175.230; 1.O.175.231; 1.O.175.236; 1.O.175.237; 1.O.175.238; 1.O.175.239; 1.O.175.154; 1.O.175.157; 1.O.175.166; 1.O.175.169; 1.O.175.172; 1.O.175.175; 1.O.175.240; 1.O.175.244; 1.O.240.228; 1.O.240.229; 1.O.240.230; 1.O.240.231; 1.O.240.236; 1.O.240.237; 1.O.240.238; 1.O.240.239; 1.O.240.154; 1.O.240.157; 1.O.240.166; 1.O.240.169; 1.O.240.172; 1.O.240.175; 1.O.240.240; 1.O.240.244; 1.O.244.228; 1.O.244.229; 1.O.244.230; 1.O.244.231; 1.O.244.236; 1.O.244.237; 1.O.244.238; 1.O.244.239; 1.O.244.154; 1.O.244.157; 1.O.244.166; 1.O.244.169; 1.O.244.172; 1.O.244.175; 1.O.244.240; 1.O.244.244;

Prodrugs of 1.P

1.P.228.228; 1.P.228.229; 1.P.228.230; 1.P.228.231; 1.P.228.236; 1.P.228.237; 1.P.228.238; 1.P.228.239; 1.P.228.154; 1.P.228.157; 1.P.228.166; 1.P.228.169; 1.P.228.172; 1.P.228.175; 1.P.228.240; 1.P.228.244; 1.P.229.228; 1.P.229.229; 1.P.229.230; 1.P.229.231; 1.P.229.236; 1.P.229.237; 1.P.229.238; 1.P.229.239; 1.P.229.154; 1.P.229.157; 1.P.229.166; 1.P.229.169; 1.P.229.172; 1.P.229.175; 1.P.229.240; 1.P.229.244; 1.P.230.228; 1.P.230.229; 1.P.230.230; 1.P.230.231; 1.P.230.236; 1.P.230.237; 1.P.230.238; 1.P.230.239; 1.P.230.154; 1.P.230.157; 1.P.230.166; 1.P.230.169; 1.P.230.172; 1.P.230.175; 1.P.230.240; 1.P.230.244; 1.P.231.228; 1.P.231.229; 1.P.231.230; 1.P.231.231; 1.P.231.236; 1.P.231.237; 1.P.231.238; 1.P.231.239; 1.P.231.154; 1.P.231.157; 1.P.231.166; 1.P.231.169; 1.P.231.172; 1.P.231.175; 1.P.231.240; 1.P.231.244; 1.P.236.228; 1.P.236.229; 1.P.236.230; 1.P.236.231; 1.P.236.236; 1.P.236.237; 1.P.236.238; 1.P.236.239; 1.P.236.154; 1.P.236.157; 1.P.236.166; 1.P.236.169; 1.P.236.172; 1.P.236.175; 1.P.236.240; 1.P.236.244; 1.P.237.228; 1.P.237.229; 1.P.237.230; 1.P.237.231; 1.P.237.236; 1.P.237.237; 1.P.237.238; 1.P.237.239; 1.P.237.154; 1.P.237.157; 1.P.237.166; 1.P.237.169; 1.P.237.172; 1.P.237.175; 1.P.237.240; 1.P.237.244; 1.P.238.228; 1.P.238.229; 1.P.238.230; 1.P.238.231; 1.P.238.236; 1.P.238.237; 1.P.238.238; 1.P.238.239; 1.P.238.154; 1.P.238.157; 1.P.238.166; 1.P.238.169; 1.P.238.172; 1.P.238.175; 1.P.238.240; 1.P.238.244; 1.P.239.228; 1.P.239.229; 1.P.239.230; 1.P.239.231; 1.P.239.236; 1.P.239.237; 1.P.239.238; 1.P.239.239; 1.P.239.154; 1.P.239.157; 1.P.239.166; 1.P.239.169; 1.P.239.172; 1.P.239.175; 1.P.239.240; 1.P.239.244; 1.P.154.228; 1.P.154.229; 1.P.154.230; 1.P.154.231; 1.P.154.236; 1.P.154.237; 1.P.154.238; 1.P.154.239; 1.P.154.154; 1.P.154.157; 1.P.154.166; 1.P.154.169; 1.P.154.172; 1.P.154.175; 1.P.154.240; 1.P.154.244; 1.P.157.228; 1.P.157.229; 1.P.157.230; 1.P.157.231; 1.P.157.236; 1.P.157.237; 1.P.157.238; 1.P.157.239; 1.P.157.154; 1.P.157.157; 1.P.157.166; 1.P.157.169; 1.P.157.172; 1.P.157.175; 1.P.157.240; 1.P.157.244; 1.P.166.228; 1.P.166.229; 1.P.166.230; 1.P.166.231; 1.P.166.236; 1.P.166.237; 1.P.166.238; 1.P.166.239; 1.P.166.154; 1.P.166.157; 1.P.166.166; 1.P.166.169; 1.P.166.172; 1.P.166.175; 1.P.166.240; 1.P.166.244; 1.P.169.228; 1.P.169.229; 1.P.169.230; 1.P.169.231; 1.P.169.236; 1.P.169.237; 1.P.169.238; 1.P.169.239; 1.P.169.154; 1.P.169.157; 1.P.169.166; 1.P.169.169; 1.P.169.172; 1.P.169.175; 1.P.169.240; 1.P.169.244; 1.P.172.228; 1.P.172.229; 1.P.172.230; 1.P.172.231; 1.P.172.236; 1.P.172.237; 1.P.172.238; 1.P.172.239; 1.P.172.154; 1.P.172.157; 1.P.172.166; 1.P.172.169; 1.P.172.172; 1.P.172.175; 1.P.172.240; 1.P.172.244; 1.P.175.228; 1.P.175.229; 1.P.175.230; 1.P.175.231; 1.P.175.236; 1.P.175.237; 1.P.175.238; 1.P.175.239; 1.P.175.154; 1.P.175.157; 1.P.175.166; 1.P.175.169; 1.P.175.172; 1.P.175.175; 1.P.175.240; 1.P.175.244; 1.P.240.228; 1.P.240.229; 1.P.240.230; 1.P.240.231; 1.P.240.236; 1.P.240.237; 1.P.240.238; 1.P.240.239; 1.P.240.154; 1.P.240.157; 1.P.240.166; 1.P.240.169; 1.P.240.172; 1.P.240.175; 1.P.240.240; 1.P.240.244; 1.P.244.228; 1.P.244.229; 1.P.244.230; 1.P.244.231;

1.P.244.236; 1.P.244.237; 1.P.244.238; 1.P.244.239; 1.P.244.154; 1.P.244.157; 1.P.244.166; 1.P.244.169; 1.P.244.172; 1.P.244.175; 1.P.244.240; 1.P.244.244;

Prodrugs of 1.U

1.U.228.228; 1.U.228.229; 1.U.228.230; 1.U.228.231; 1.U.228.236; 1.U.228.237; 1.U.228.238; 1.U.228.239; 1.U.228.154; 1.U.228.157; 1.U.228.166; 1.U.228.169; 1.U.228.172; 1.U.228.175; 1.U.228.240; 1.U.228.244; 1.U.229.228; 1.U.229.229; 1.U.229.230; 1.U.229.231; 1.U.229.236; 1.U.229.237; 1.U.229.238; 1.U.229.239; 1.U.229.154; 1.U.229.157; 1.U.229.166; 1.U.229.169; 1.U.229.172; 1.U.229.175; 1.U.229.240; 1.U.229.244; 1.U.230.228; 1.U.230.229; 1.U.230.230; 1.U.230.231; 1.U.230.236; 1.U.230.237; 1.U.230.238; 1.U.230.239; 1.U.230.154; 1.U.230.157; 1.U.230.166; 1.U.230.169; 1.U.230.172; 1.U.230.175; 1.U.230.240; 1.U.230.244; 1.U.231.228; 1.U.231.229; 1.U.231.230; 1.U.231.231; 1.U.231.236; 1.U.231.237; 1.U.231.238; 1.U.231.239; 1.U.231.154; 1.U.231.157; 1.U.231.166; 1.U.231.169; 1.U.231.172; 1.U.231.175; 1.U.231.240; 1.U.231.244; 1.U.236.228; 1.U.236.229; 1.U.236.230; 1.U.236.231; 1.U.236.236; 1.U.236.237; 1.U.236.238; 1.U.236.239; 1.U.236.154; 1.U.236.157; 1.U.236.166; 1.U.236.169; 1.U.236.172; 1.U.236.175; 1.U.236.240; 1.U.236.244; 1.U.237.228; 1.U.237.229; 1.U.237.230; 1.U.237.231; 1.U.237.236; 1.U.237.237; 1.U.237.238; 1.U.237.239; 1.U.237.154; 1.U.237.157; 1.U.237.166; 1.U.237.169; 1.U.237.172; 1.U.237.175; 1.U.237.240; 1.U.237.244; 1.U.238.228; 1.U.238.229; 1.U.238.230; 1.U.238.231; 1.U.238.236; 1.U.238.237; 1.U.238.238; 1.U.238.239; 1.U.238.154; 1.U.238.157; 1.U.238.166; 1.U.238.169; 1.U.238.172; 1.U.238.175; 1.U.238.240; 1.U.238.244; 1.U.239.228; 1.U.239.229; 1.U.239.230; 1.U.239.231; 1.U.239.236; 1.U.239.237; 1.U.239.238; 1.U.239.239; 1.U.239.154; 1.U.239.157; 1.U.239.166; 1.U.239.169; 1.U.239.172; 1.U.239.175; 1.U.239.240; 1.U.239.244; 1.U.154.228; 1.U.154.229; 1.U.154.230; 1.U.154.231; 1.U.154.236; 1.U.154.237; 1.U.154.238; 1.U.154.239; 1.U.154.154; 1.U.154.157; 1.U.154.166; 1.U.154.169; 1.U.154.172; 1.U.154.175; 1.U.154.240; 1.U.154.244; 1.U.157.228; 1.U.157.229; 1.U.157.230; 1.U.157.231; 1.U.157.236; 1.U.157.237; 1.U.157.238; 1.U.157.239; 1.U.157.154; 1.U.157.157; 1.U.157.166; 1.U.157.169; 1.U.157.172; 1.U.157.175; 1.U.157.240; 1.U.157.244; 1.U.166.228; 1.U.166.229; 1.U.166.230; 1.U.166.231; 1.U.166.236; 1.U.166.237; 1.U.166.238; 1.U.166.239; 1.U.166.154; 1.U.166.157; 1.U.166.166; 1.U.166.169; 1.U.166.172; 1.U.166.175; 1.U.166.240; 1.U.166.244; 1.U.169.228; 1.U.169.229; 1.U.169.230; 1.U.169.231; 1.U.169.236; 1.U.169.237; 1.U.169.238; 1.U.169.239; 1.U.169.154; 1.U.169.157; 1.U.169.166; 1.U.169.169; 1.U.169.172; 1.U.169.175; 1.U.169.240; 1.U.169.244; 1.U.172.228; 1.U.172.229; 1.U.172.230; 1.U.172.231; 1.U.172.236; 1.U.172.237; 1.U.172.238; 1.U.172.239; 1.U.172.154; 1.U.172.157; 1.U.172.166; 1.U.172.169; 1.U.172.172; 1.U.172.175; 1.U.172.240; 1.U.172.244; 1.U.175.228; 1.U.175.229; 1.U.175.230; 1.U.175.231; 1.U.175.236; 1.U.175.237; 1.U.175.238; 1.U.175.239; 1.U.175.154; 1.U.175.157; 1.U.175.166; 1.U.175.169; 1.U.175.172; 1.U.175.175; 1.U.175.240; 1.U.175.244; 1.U.240.228; 1.U.240.229; 1.U.240.230; 1.U.240.231; 1.U.240.236; 1.U.240.237; 1.U.240.238; 1.U.240.239; 1.U.240.154; 1.U.240.157; 1.U.240.166; 1.U.240.169; 1.U.240.172; 1.U.240.175; 1.U.240.240; 1.U.240.244; 1.U.244.228; 1.U.244.229; 1.U.244.230; 1.U.244.231; 1.U.244.236; 1.U.244.237;

1.U.244.238; 1.U.244.239; 1.U.244.154; 1.U.244.157; 1.U.244.166; 1.U.244.169; 1.U.244.172; 1.U.244.175; 1.U.244.240; 1.U.244.244;

Prodrugs of 1.W

1.W.228.228; 1.W.228.229; 1.W.228.230; 1.W.228.231; 1.W.228.236; 1.W.228.237; 1.W.228.238; 1.W.228.239; 1.W.228.154; 1.W.228.157; 1.W.228.166; 1.W.228.169; 1.W.228.172; 1.W.228.175; 1.W.228.240; 1.W.228.244; 1.W.229.228; 1.W.229.229; 1.W.229.230; 1.W.229.231; 1.W.229.236; 1.W.229.237; 1.W.229.238; 1.W.229.239; 1.W.229.154; 1.W.229.157; 1.W.229.166; 1.W.229.169; 1.W.229.172; 1.W.229.175; 1.W.229.240; 1.W.229.244; 1.W.230.228; 1.W.230.229; 1.W.230.230; 1.W.230.231; 1.W.230.236; 1.W.230.237; 1.W.230.238; 1.W.230.239; 1.W.230.154; 1.W.230.157; 1.W.230.166; 1.W.230.169; 1.W.230.172; 1.W.230.175; 1.W.230.240; 1.W.230.244; 1.W.231.228; 1.W.231.229; 1.W.231.230; 1.W.231.231; 1.W.231.236; 1.W.231.237; 1.W.231.238; 1.W.231.239; 1.W.231.154; 1.W.231.157; 1.W.231.166; 1.W.231.169; 1.W.231.172; 1.W.231.175; 1.W.231.240; 1.W.231.244; 1.W.236.228; 1.W.236.229; 1.W.236.230; 1.W.236.231; 1.W.236.236; 1.W.236.237; 1.W.236.238; 1.W.236.239; 1.W.236.154; 1.W.236.157; 1.W.236.166; 1.W.236.169; 1.W.236.172; 1.W.236.175; 1.W.236.240; 1.W.236.244; 1.W.237.228; 1.W.237.229; 1.W.237.230; 1.W.237.231; 1.W.237.236; 1.W.237.237; 1.W.237.238; 1.W.237.239; 1.W.237.154; 1.W.237.157; 1.W.237.166; 1.W.237.169; 1.W.237.172; 1.W.237.175; 1.W.237.240; 1.W.237.244; 1.W.238.228; 1.W.238.229; 1.W.238.230; 1.W.238.231; 1.W.238.236; 1.W.238.237; 1.W.238.238; 1.W.238.239; 1.W.238.154; 1.W.238.157; 1.W.238.166; 1.W.238.169; 1.W.238.172; 1.W.238.175; 1.W.238.240; 1.W.238.244; 1.W.239.228; 1.W.239.229; 1.W.239.230; 1.W.239.231; 1.W.239.236; 1.W.239.237; 1.W.239.238; 1.W.239.239; 1.W.239.154; 1.W.239.157; 1.W.239.166; 1.W.239.169; 1.W.239.172; 1.W.239.175; 1.W.239.240; 1.W.239.244; 1.W.154.228; 1.W.154.229; 1.W.154.230; 1.W.154.231; 1.W.154.236; 1.W.154.237; 1.W.154.238; 1.W.154.239; 1.W.154.154; 1.W.154.157; 1.W.154.166; 1.W.154.169; 1.W.154.172; 1.W.154.175; 1.W.154.240; 1.W.154.244; 1.W.157.228; 1.W.157.229; 1.W.157.230; 1.W.157.231; 1.W.157.236; 1.W.157.237; 1.W.157.238; 1.W.157.239; 1.W.157.154; 1.W.157.157; 1.W.157.166; 1.W.157.169; 1.W.157.172; 1.W.157.175; 1.W.157.240; 1.W.157.244; 1.W.166.228; 1.W.166.229; 1.W.166.230; 1.W.166.231; 1.W.166.236; 1.W.166.237; 1.W.166.238; 1.W.166.239; 1.W.166.154; 1.W.166.157; 1.W.166.166; 1.W.166.169; 1.W.166.172; 1.W.166.175; 1.W.166.240; 1.W.166.244; 1.W.169.228; 1.W.169.229; 1.W.169.230; 1.W.169.231; 1.W.169.236; 1.W.169.237; 1.W.169.238; 1.W.169.239; 1.W.169.154; 1.W.169.157; 1.W.169.166; 1.W.169.169; 1.W.169.172; 1.W.169.175; 1.W.169.240; 1.W.169.244; 1.W.172.228; 1.W.172.229; 1.W.172.230; 1.W.172.231; 1.W.172.236; 1.W.172.237; 1.W.172.238; 1.W.172.239; 1.W.172.154; 1.W.172.157; 1.W.172.166; 1.W.172.169; 1.W.172.172; 1.W.172.175; 1.W.172.240; 1.W.172.244; 1.W.175.228; 1.W.175.229; 1.W.175.230; 1.W.175.231; 1.W.175.236; 1.W.175.237; 1.W.175.238; 1.W.175.239; 1.W.175.154; 1.W.175.157; 1.W.175.166; 1.W.175.169; 1.W.175.172; 1.W.175.175; 1.W.175.240; 1.W.175.244; 1.W.240.228; 1.W.240.229; 1.W.240.230; 1.W.240.231; 1.W.240.236; 1.W.240.237; 1.W.240.238; 1.W.240.239; 1.W.240.154; 1.W.240.157; 1.W.240.166; 1.W.240.169; 1.W.240.172; 1.W.240.175; 1.W.240.240; 1.W.240.244; 1.W.244.228; 1.W.244.229; 1.W.244.230; 1.W.244.231; 1.W.244.236; 1.W.244.237;

1.W.244.238; 1.W.244.239; 1.W.244.154; 1.W.244.157; 1.W.244.166; 1.W.244.169; 1.W.244.172; 1.W.244.175; 1.W.244.240; 1.W.244.244;

Prodrugs of 1.Y

1.Y.228.228; 1.Y.228.229; 1.Y.228.230; 1.Y.228.231; 1.Y.228.236; 1.Y.228.237; 1.Y.228.238; 1.Y.228.239; 1.Y.228.154; 1.Y.228.157; 1.Y.228.166; 1.Y.228.169; 1.Y.228.172; 1.Y.228.175; 1.Y.228.240; 1.Y.228.244; 1.Y.229.228; 1.Y.229.229; 1.Y.229.230; 1.Y.229.231; 1.Y.229.236; 1.Y.229.237; 1.Y.229.238; 1.Y.229.239; 1.Y.229.154; 1.Y.229.157; 1.Y.229.166; 1.Y.229.169; 1.Y.229.172; 1.Y.229.175; 1.Y.229.240; 1.Y.229.244; 1.Y.230.228; 1.Y.230.229; 1.Y.230.230; 1.Y.230.231; 1.Y.230.236; 1.Y.230.237; 1.Y.230.238; 1.Y.230.239; 1.Y.230.154; 1.Y.230.157; 1.Y.230.166; 1.Y.230.169; 1.Y.230.172; 1.Y.230.175; 1.Y.230.240; 1.Y.230.244; 1.Y.231.228; 1.Y.231.229; 1.Y.231.230; 1.Y.231.231; 1.Y.231.236; 1.Y.231.237; 1.Y.231.238; 1.Y.231.239; 1.Y.231.154; 1.Y.231.157; 1.Y.231.166; 1.Y.231.169; 1.Y.231.172; 1.Y.231.175; 1.Y.231.240; 1.Y.231.244; 1.Y.236.228; 1.Y.236.229; 1.Y.236.230; 1.Y.236.231; 1.Y.236.236; 1.Y.236.237; 1.Y.236.238; 1.Y.236.239; 1.Y.236.154; 1.Y.236.157; 1.Y.236.166; 1.Y.236.169; 1.Y.236.172; 1.Y.236.175; 1.Y.236.240; 1.Y.236.244; 1.Y.237.228; 1.Y.237.229; 1.Y.237.230; 1.Y.237.231; 1.Y.237.236; 1.Y.237.237; 1.Y.237.238; 1.Y.237.239; 1.Y.237.154; 1.Y.237.157; 1.Y.237.166; 1.Y.237.169; 1.Y.237.172; 1.Y.237.175; 1.Y.237.240; 1.Y.237.244; 1.Y.238.228; 1.Y.238.229; 1.Y.238.230; 1.Y.238.231; 1.Y.238.236; 1.Y.238.237; 1.Y.238.238; 1.Y.238.239; 1.Y.238.154; 1.Y.238.157; 1.Y.238.166; 1.Y.238.169; 1.Y.238.172; 1.Y.238.175; 1.Y.238.240; 1.Y.238.244; 1.Y.239.228; 1.Y.239.229; 1.Y.239.230; 1.Y.239.231; 1.Y.239.236; 1.Y.239.237; 1.Y.239.238; 1.Y.239.239; 1.Y.239.154; 1.Y.239.157; 1.Y.239.166; 1.Y.239.169; 1.Y.239.172; 1.Y.239.175; 1.Y.239.240; 1.Y.239.244; 1.Y.154.228; 1.Y.154.229; 1.Y.154.230; 1.Y.154.231; 1.Y.154.236; 1.Y.154.237; 1.Y.154.238; 1.Y.154.239; 1.Y.154.154; 1.Y.154.157; 1.Y.154.166; 1.Y.154.169; 1.Y.154.172; 1.Y.154.175; 1.Y.154.240; 1.Y.154.244; 1.Y.157.228; 1.Y.157.229; 1.Y.157.230; 1.Y.157.231; 1.Y.157.236; 1.Y.157.237; 1.Y.157.238; 1.Y.157.239; 1.Y.157.154; 1.Y.157.157; 1.Y.157.166; 1.Y.157.169; 1.Y.157.172; 1.Y.157.175; 1.Y.157.240; 1.Y.157.244; 1.Y.166.228; 1.Y.166.229; 1.Y.166.230; 1.Y.166.231; 1.Y.166.236; 1.Y.166.237; 1.Y.166.238; 1.Y.166.239; 1.Y.166.154; 1.Y.166.157; 1.Y.166.166; 1.Y.166.169; 1.Y.166.172; 1.Y.166.175; 1.Y.166.240; 1.Y.166.244; 1.Y.169.228; 1.Y.169.229; 1.Y.169.230; 1.Y.169.231; 1.Y.169.236; 1.Y.169.237; 1.Y.169.238; 1.Y.169.239; 1.Y.169.154; 1.Y.169.157; 1.Y.169.166; 1.Y.169.169; 1.Y.169.172; 1.Y.169.175; 1.Y.169.240; 1.Y.169.244; 1.Y.172.228; 1.Y.172.229; 1.Y.172.230; 1.Y.172.231; 1.Y.172.236; 1.Y.172.237; 1.Y.172.238; 1.Y.172.239; 1.Y.172.154; 1.Y.172.157; 1.Y.172.166; 1.Y.172.169; 1.Y.172.172; 1.Y.172.175; 1.Y.172.240; 1.Y.172.244; 1.Y.175.228; 1.Y.175.229; 1.Y.175.230; 1.Y.175.231; 1.Y.175.236; 1.Y.175.237; 1.Y.175.238; 1.Y.175.239; 1.Y.175.154; 1.Y.175.157; 1.Y.175.166; 1.Y.175.169; 1.Y.175.172; 1.Y.175.175; 1.Y.175.240; 1.Y.175.244; 1.Y.240.228; 1.Y.240.229; 1.Y.240.230; 1.Y.240.231; 1.Y.240.236; 1.Y.240.237; 1.Y.240.238; 1.Y.240.239; 1.Y.240.154; 1.Y.240.157; 1.Y.240.166; 1.Y.240.169; 1.Y.240.172; 1.Y.240.175; 1.Y.240.240; 1.Y.240.244; 1.Y.244.228; 1.Y.244.229; 1.Y.244.230; 1.Y.244.231; 1.Y.244.236; 1.Y.244.237;

1.Y.244.238; 1.Y.244.239; 1.Y.244.154; 1.Y.244.157; 1.Y.244.166; 1.Y.244.169; 1.Y.244.172; 1.Y.244.175; 1.Y.244.240; 1.Y.244.244;

Prodrugs of 2.B

2.B.228.228; 2.B.228.229; 2.B.228.230; 2.B.228.231; 2.B.228.236; 2.B.228.237; 2.B.228.238; 2.B.228.239; 2.B.228.154; 2.B.228.157; 2.B.228.166; 2.B.228.169; 2.B.228.172; 2.B.228.175; 2.B.228.240; 2.B.228.244; 2.B.229.228; 2.B.229.229; 2.B.229.230; 2.B.229.231; 2.B.229.236; 2.B.229.237; 2.B.229.238; 2.B.229.239; 2.B.229.154; 2.B.229.157; 2.B.229.166; 2.B.229.169; 2.B.229.172; 2.B.229.175; 2.B.229.240; 2.B.229.244; 2.B.230.228; 2.B.230.229; 2.B.230.230; 2.B.230.231; 2.B.230.236; 2.B.230.237; 2.B.230.238; 2.B.230.239; 2.B.230.154; 2.B.230.157; 2.B.230.166; 2.B.230.169; 2.B.230.172; 2.B.230.175; 2.B.230.240; 2.B.230.244; 2.B.231.228; 2.B.231.229; 2.B.231.230; 2.B.231.231; 2.B.231.236; 2.B.231.237; 2.B.231.238; 2.B.231.239; 2.B.231.154; 2.B.231.157; 2.B.231.166; 2.B.231.169; 2.B.231.172; 2.B.231.175; 2.B.231.240; 2.B.231.244; 2.B.236.228; 2.B.236.229; 2.B.236.230; 2.B.236.231; 2.B.236.236; 2.B.236.237; 2.B.236.238; 2.B.236.239; 2.B.236.154; 2.B.236.157; 2.B.236.166; 2.B.236.169; 2.B.236.172; 2.B.236.175; 2.B.236.240; 2.B.236.244; 2.B.237.228; 2.B.237.229; 2.B.237.230; 2.B.237.231; 2.B.237.236; 2.B.237.237; 2.B.237.238; 2.B.237.239; 2.B.237.154; 2.B.237.157; 2.B.237.166; 2.B.237.169; 2.B.237.172; 2.B.237.175; 2.B.237.240; 2.B.237.244; 2.B.238.228; 2.B.238.229; 2.B.238.230; 2.B.238.231; 2.B.238.236; 2.B.238.237; 2.B.238.238; 2.B.238.239; 2.B.238.154; 2.B.238.157; 2.B.238.166; 2.B.238.169; 2.B.238.172; 2.B.238.175; 2.B.238.240; 2.B.238.244; 2.B.239.228; 2.B.239.229; 2.B.239.230; 2.B.239.231; 2.B.239.236; 2.B.239.237; 2.B.239.238; 2.B.239.239; 2.B.239.154; 2.B.239.157; 2.B.239.166; 2.B.239.169; 2.B.239.172; 2.B.239.175; 2.B.239.240; 2.B.239.244; 2.B.154.228; 2.B.154.229; 2.B.154.230; 2.B.154.231; 2.B.154.236; 2.B.154.237; 2.B.154.238; 2.B.154.239; 2.B.154.154; 2.B.154.157; 2.B.154.166; 2.B.154.169; 2.B.154.172; 2.B.154.175; 2.B.154.240; 2.B.154.244; 2.B.157.228; 2.B.157.229; 2.B.157.230; 2.B.157.231; 2.B.157.236; 2.B.157.237; 2.B.157.238; 2.B.157.239; 2.B.157.154; 2.B.157.157; 2.B.157.166; 2.B.157.169; 2.B.157.172; 2.B.157.175; 2.B.157.240; 2.B.157.244; 2.B.166.228; 2.B.166.229; 2.B.166.230; 2.B.166.231; 2.B.166.236; 2.B.166.237; 2.B.166.238; 2.B.166.239; 2.B.166.154; 2.B.166.157; 2.B.166.166; 2.B.166.169; 2.B.166.172; 2.B.166.175; 2.B.166.240; 2.B.166.244; 2.B.169.228; 2.B.169.229; 2.B.169.230; 2.B.169.231; 2.B.169.236; 2.B.169.237; 2.B.169.238; 2.B.169.239; 2.B.169.154; 2.B.169.157; 2.B.169.166; 2.B.169.169; 2.B.169.172; 2.B.169.175; 2.B.169.240; 2.B.169.244; 2.B.172.228; 2.B.172.229; 2.B.172.230; 2.B.172.231; 2.B.172.236; 2.B.172.237; 2.B.172.238; 2.B.172.239; 2.B.172.154; 2.B.172.157; 2.B.172.166; 2.B.172.169; 2.B.172.172; 2.B.172.175; 2.B.172.240; 2.B.172.244; 2.B.175.228; 2.B.175.229; 2.B.175.230; 2.B.175.231; 2.B.175.236; 2.B.175.237; 2.B.175.238; 2.B.175.239; 2.B.175.154; 2.B.175.157; 2.B.175.166; 2.B.175.169; 2.B.175.172; 2.B.175.175; 2.B.175.240; 2.B.175.244; 2.B.240.228; 2.B.240.229; 2.B.240.230; 2.B.240.231; 2.B.240.236; 2.B.240.237; 2.B.240.238; 2.B.240.239; 2.B.240.154; 2.B.240.157; 2.B.240.166; 2.B.240.169; 2.B.240.172; 2.B.240.175; 2.B.240.240; 2.B.240.244; 2.B.244.228; 2.B.244.229; 2.B.244.230; 2.B.244.231; 2.B.244.236; 2.B.244.237; 2.B.244.238; 2.B.244.239; 2.B.244.154; 2.B.244.157; 2.B.244.166; 2.B.244.169; 2.B.244.172; 2.B.244.175; 2.B.244.240; 2.B.244.244;

Prodrugs of 2.D

2.D.228.228; 2.D.228.229; 2.D.228.230; 2.D.228.231; 2.D.228.236; 2.D.228.237; 2.D.228.238; 2.D.228.239; 2.D.228.154; 2.D.228.157; 2.D.228.166; 2.D.228.169; 2.D.228.172; 2.D.228.175; 2.D.228.240; 2.D.228.244; 2.D.229.228; 2.D.229.229;

2.D.229.230; 2.D.229.231; 2.D.229.236; 2.D.229.237; 2.D.229.238; 2.D.229.239; 2.D.229.154; 2.D.229.157; 2.D.229.166; 2.D.229.169; 2.D.229.172; 2.D.229.175; 2.D.229.240; 2.D.229.244; 2.D.230.228; 2.D.230.229; 2.D.230.230; 2.D.230.231; 2.D.230.236; 2.D.230.237; 2.D.230.238; 2.D.230.239; 2.D.230.154; 2.D.230.157; 2.D.230.166; 2.D.230.169; 2.D.230.172; 2.D.230.175; 2.D.230.240; 2.D.230.244; 2.D.231.228; 2.D.231.229; 2.D.231.230; 2.D.231.231; 2.D.231.236; 2.D.231.237; 2.D.231.238; 2.D.231.239; 2.D.231.154; 2.D.231.157; 2.D.231.166; 2.D.231.169; 2.D.231.172; 2.D.231.175; 2.D.231.240; 2.D.231.244; 2.D.236.228; 2.D.236.229; 2.D.236.230; 2.D.236.231; 2.D.236.236; 2.D.236.237; 2.D.236.238; 2.D.236.239; 2.D.236.154; 2.D.236.157; 2.D.236.166; 2.D.236.169; 2.D.236.172; 2.D.236.175; 2.D.236.240; 2.D.236.244; 2.D.237.228; 2.D.237.229; 2.D.237.230; 2.D.237.231; 2.D.237.236; 2.D.237.237; 2.D.237.238; 2.D.237.239; 2.D.237.154; 2.D.237.157; 2.D.237.166; 2.D.237.169; 2.D.237.172; 2.D.237.175; 2.D.237.240; 2.D.237.244; 2.D.238.228; 2.D.238.229; 2.D.238.230; 2.D.238.231; 2.D.238.236; 2.D.238.237; 2.D.238.238; 2.D.238.239; 2.D.238.154; 2.D.238.157; 2.D.238.166; 2.D.238.169; 2.D.238.172; 2.D.238.175; 2.D.238.240; 2.D.238.244; 2.D.239.228; 2.D.239.229; 2.D.239.230; 2.D.239.231; 2.D.239.236; 2.D.239.237; 2.D.239.238; 2.D.239.239; 2.D.239.154; 2.D.239.157; 2.D.239.166; 2.D.239.169; 2.D.239.172; 2.D.239.175; 2.D.239.240; 2.D.239.244; 2.D.154.228; 2.D.154.229; 2.D.154.230; 2.D.154.231; 2.D.154.236; 2.D.154.237; 2.D.154.238; 2.D.154.239; 2.D.154.154; 2.D.154.157; 2.D.154.166; 2.D.154.169; 2.D.154.172; 2.D.154.175; 2.D.154.240; 2.D.154.244; 2.D.157.228; 2.D.157.229; 2.D.157.230; 2.D.157.231; 2.D.157.236; 2.D.157.237; 2.D.157.238; 2.D.157.239; 2.D.157.154; 2.D.157.157; 2.D.157.166; 2.D.157.169; 2.D.157.172; 2.D.157.175; 2.D.157.240; 2.D.157.244; 2.D.166.228; 2.D.166.229; 2.D.166.230; 2.D.166.231; 2.D.166.236; 2.D.166.237; 2.D.166.238; 2.D.166.239; 2.D.166.154; 2.D.166.157; 2.D.166.166; 2.D.166.169; 2.D.166.172; 2.D.166.175; 2.D.166.240; 2.D.166.244; 2.D.169.228; 2.D.169.229; 2.D.169.230; 2.D.169.231; 2.D.169.236; 2.D.169.237; 2.D.169.238; 2.D.169.239; 2.D.169.154; 2.D.169.157; 2.D.169.166; 2.D.169.169; 2.D.169.172; 2.D.169.175; 2.D.169.240; 2.D.169.244; 2.D.172.228; 2.D.172.229; 2.D.172.230; 2.D.172.231; 2.D.172.236; 2.D.172.237; 2.D.172.238; 2.D.172.239; 2.D.172.154; 2.D.172.157; 2.D.172.166; 2.D.172.169; 2.D.172.172; 2.D.172.175; 2.D.172.240; 2.D.172.244; 2.D.175.228; 2.D.175.229; 2.D.175.230; 2.D.175.231; 2.D.175.236; 2.D.175.237; 2.D.175.238; 2.D.175.239; 2.D.175.154; 2.D.175.157; 2.D.175.166; 2.D.175.169; 2.D.175.172; 2.D.175.175; 2.D.175.240; 2.D.175.244; 2.D.240.228; 2.D.240.229; 2.D.240.230; 2.D.240.231; 2.D.240.236; 2.D.240.237; 2.D.240.238; 2.D.240.239; 2.D.240.154; 2.D.240.157; 2.D.240.166; 2.D.240.169; 2.D.240.172; 2.D.240.175; 2.D.240.240; 2.D.240.244; 2.D.244.228; 2.D.244.229; 2.D.244.230; 2.D.244.231; 2.D.244.236; 2.D.244.237; 2.D.244.238; 2.D.244.239; 2.D.244.154; 2.D.244.157; 2.D.244.166; 2.D.244.169; 2.D.244.172; 2.D.244.175; 2.D.244.240; 2.D.244.244;

Prodrugs of 2.E

2.E.228.228; 2.E.228.229; 2.E.228.230; 2.E.228.231; 2.E.228.236; 2.E.228.237; 2.E.228.238; 2.E.228.239; 2.E.228.154; 2.E.228.157; 2.E.228.166; 2.E.228.169; 2.E.228.172; 2.E.228.175; 2.E.228.240; 2.E.228.244; 2.E.229.228; 2.E.229.229; 2.E.229.230; 2.E.229.231; 2.E.229.236; 2.E.229.237; 2.E.229.238; 2.E.229.239; 2.E.229.154; 2.E.229.157; 2.E.229.166;

2.E.229.169; 2.E.229.172; 2.E.229.175; 2.E.229.240; 2.E.229.244; 2.E.230.228; 2.E.230.229; 2.E.230.230; 2.E.230.231; 2.E.230.236; 2.E.230.237; 2.E.230.238; 2.E.230.239; 2.E.230.154; 2.E.230.157; 2.E.230.166; 2.E.230.169; 2.E.230.172; 2.E.230.175; 2.E.230.240; 2.E.230.244; 2.E.231.228; 2.E.231.229; 2.E.231.230; 2.E.231.231; 2.E.231.236; 2.E.231.237; 2.E.231.238; 2.E.231.239; 2.E.231.154; 2.E.231.157; 2.E.231.166; 2.E.231.169; 2.E.231.172; 2.E.231.175; 2.E.231.240; 2.E.231.244; 2.E.236.228; 2.E.236.229; 2.E.236.230; 2.E.236.231; 2.E.236.236; 2.E.236.237; 2.E.236.238; 2.E.236.239; 2.E.236.154; 2.E.236.157; 2.E.236.166; 2.E.236.169; 2.E.236.172; 2.E.236.175; 2.E.236.240; 2.E.236.244; 2.E.237.228; 2.E.237.229; 2.E.237.230; 2.E.237.231; 2.E.237.236; 2.E.237.237; 2.E.237.238; 2.E.237.239; 2.E.237.154; 2.E.237.157; 2.E.237.166; 2.E.237.169; 2.E.237.172; 2.E.237.175; 2.E.237.240; 2.E.237.244; 2.E.238.228; 2.E.238.229; 2.E.238.230; 2.E.238.231; 2.E.238.236; 2.E.238.237; 2.E.238.238; 2.E.238.239; 2.E.238.154; 2.E.238.157; 2.E.238.166; 2.E.238.169; 2.E.238.172; 2.E.238.175; 2.E.238.240; 2.E.238.244; 2.E.239.228; 2.E.239.229; 2.E.239.230; 2.E.239.231; 2.E.239.236; 2.E.239.237; 2.E.239.238; 2.E.239.239; 2.E.239.154; 2.E.239.157; 2.E.239.166; 2.E.239.169; 2.E.239.172; 2.E.239.175; 2.E.239.240; 2.E.239.244; 2.E.154.228; 2.E.154.229; 2.E.154.230; 2.E.154.231; 2.E.154.236; 2.E.154.237; 2.E.154.238; 2.E.154.239; 2.E.154.154; 2.E.154.157; 2.E.154.166; 2.E.154.169; 2.E.154.172; 2.E.154.175; 2.E.154.240; 2.E.154.244; 2.E.157.228; 2.E.157.229; 2.E.157.230; 2.E.157.231; 2.E.157.236; 2.E.157.237; 2.E.157.238; 2.E.157.239; 2.E.157.154; 2.E.157.157; 2.E.157.166; 2.E.157.169; 2.E.157.172; 2.E.157.175; 2.E.157.240; 2.E.157.244; 2.E.166.228; 2.E.166.229; 2.E.166.230; 2.E.166.231; 2.E.166.236; 2.E.166.237; 2.E.166.238; 2.E.166.239; 2.E.166.154; 2.E.166.157; 2.E.166.166; 2.E.166.169; 2.E.166.172; 2.E.166.175; 2.E.166.240; 2.E.166.244; 2.E.169.228; 2.E.169.229; 2.E.169.230; 2.E.169.231; 2.E.169.236; 2.E.169.237; 2.E.169.238; 2.E.169.239; 2.E.169.154; 2.E.169.157; 2.E.169.166; 2.E.169.169; 2.E.169.172; 2.E.169.175; 2.E.169.240; 2.E.169.244; 2.E.172.228; 2.E.172.229; 2.E.172.230; 2.E.172.231; 2.E.172.236; 2.E.172.237; 2.E.172.238; 2.E.172.239; 2.E.172.154; 2.E.172.157; 2.E.172.166; 2.E.172.169; 2.E.172.172; 2.E.172.175; 2.E.172.240; 2.E.172.244; 2.E.175.228; 2.E.175.229; 2.E.175.230; 2.E.175.231; 2.E.175.236; 2.E.175.237; 2.E.175.238; 2.E.175.239; 2.E.175.154; 2.E.175.157; 2.E.175.166; 2.E.175.169; 2.E.175.172; 2.E.175.175; 2.E.175.240; 2.E.175.244; 2.E.240.228; 2.E.240.229; 2.E.240.230; 2.E.240.231; 2.E.240.236; 2.E.240.237; 2.E.240.238; 2.E.240.239; 2.E.240.154; 2.E.240.157; 2.E.240.166; 2.E.240.169; 2.E.240.172; 2.E.240.175; 2.E.240.240; 2.E.240.244; 2.E.244.228; 2.E.244.229; 2.E.244.230; 2.E.244.231; 2.E.244.236; 2.E.244.237; 2.E.244.238; 2.E.244.239; 2.E.244.154; 2.E.244.157; 2.E.244.166; 2.E.244.169; 2.E.244.172; 2.E.244.175; 2.E.244.240; 2.E.244.244;

<u>Prodrugs of 2.G</u>

2.G.228.228; 2.G.228.229; 2.G.228.230; 2.G.228.231; 2.G.228.236; 2.G.228.237; 2.G.228.238; 2.G.228.239; 2.G.228.154; 2.G.228.157; 2.G.228.166; 2.G.228.169; 2.G.228.172; 2.G.228.175; 2.G.228.240; 2.G.228.244; 2.G.229.228; 2.G.229.229; 2.G.229.230; 2.G.229.231; 2.G.229.236; 2.G.229.237; 2.G.229.238; 2.G.229.239; 2.G.229.154; 2.G.229.157; 2.G.229.166; 2.G.229.169; 2.G.229.172; 2.G.229.175; 2.G.229.240; 2.G.229.244; 2.G.230.228; 2.G.230.229; 2.G.230.230; 2.G.230.231; 2.G.230.236; 2.G.230.237; 2.G.230.238; 2.G.230.239; 2.G.230.154; 2.G.230.157; 2.G.230.166; 2.G.230.169; 2.G.230.172; 2.G.230.175; 2.G.230.240; 2.G.230.244; 2.G.231.228; 2.G.231.229; 2.G.231.230; 2.G.231.231; 2.G.231.236; 2.G.231.237; 2.G.231.238; 2.G.231.239; 2.G.231.154; 2.G.231.157; 2.G.231.166; 2.G.231.169; 2.G.231.172; 2.G.231.175; 2.G.231.240; 2.G.231.244; 2.G.236.228; 2.G.236.229;

2.G.236.230; 2.G.236.231; 2.G.236.236; 2.G.236.237; 2.G.236.238; 2.G.236.239; 2.G.236.154; 2.G.236.157; 2.G.236.166; 2.G.236.169; 2.G.236.172; 2.G.236.175; 2.G.236.240; 2.G.236.244; 2.G.237.228; 2.G.237.229; 2.G.237.230; 2.G.237.231; 2.G.237.236; 2.G.237.237; 2.G.237.238; 2.G.237.239; 2.G.237.154; 2.G.237.157; 2.G.237.166; 2.G.237.169; 2.G.237.172; 2.G.237.175; 2.G.237.240; 2.G.237.244; 2.G.238.228; 2.G.238.229; 2.G.238.230; 2.G.238.231; 2.G.238.236; 2.G.238.237; 2.G.238.238; 2.G.238.239; 2.G.238.154; 2.G.238.157; 2.G.238.166; 2.G.238.169; 2.G.238.172; 2.G.238.175; 2.G.238.240; 2.G.238.244; 2.G.239.228; 2.G.239.229; 2.G.239.230; 2.G.239.231; 2.G.239.236; 2.G.239.237; 2.G.239.238; 2.G.239.239; 2.G.239.154; 2.G.239.157; 2.G.239.166; 2.G.239.169; 2.G.239.172; 2.G.239.175; 2.G.239.240; 2.G.239.244; 2.G.154.228; 2.G.154.229; 2.G.154.230; 2.G.154.231; 2.G.154.236; 2.G.154.237; 2.G.154.238; 2.G.154.239; 2.G.154.154; 2.G.154.157; 2.G.154.166; 2.G.154.169; 2.G.154.172; 2.G.154.175; 2.G.154.240; 2.G.154.244; 2.G.157.228; 2.G.157.229; 2.G.157.230; 2.G.157.231; 2.G.157.236; 2.G.157.237; 2.G.157.238; 2.G.157.239; 2.G.157.154; 2.G.157.157; 2.G.157.166; 2.G.157.169; 2.G.157.172; 2.G.157.175; 2.G.157.240; 2.G.157.244; 2.G.166.228; 2.G.166.229; 2.G.166.230; 2.G.166.231; 2.G.166.236; 2.G.166.237; 2.G.166.238; 2.G.166.239; 2.G.166.154; 2.G.166.157; 2.G.166.166; 2.G.166.169; 2.G.166.172; 2.G.166.175; 2.G.166.240; 2.G.166.244; 2.G.169.228; 2.G.169.229; 2.G.169.230; 2.G.169.231; 2.G.169.236; 2.G.169.237; 2.G.169.238; 2.G.169.239; 2.G.169.154; 2.G.169.157; 2.G.169.166; 2.G.169.169; 2.G.169.172; 2.G.169.175; 2.G.169.240; 2.G.169.244; 2.G.172.228; 2.G.172.229; 2.G.172.230; 2.G.172.231; 2.G.172.236; 2.G.172.237; 2.G.172.238; 2.G.172.239; 2.G.172.154; 2.G.172.157; 2.G.172.166; 2.G.172.169; 2.G.172.172; 2.G.172.175; 2.G.172.240; 2.G.172.244; 2.G.175.228; 2.G.175.229; 2.G.175.230; 2.G.175.231; 2.G.175.236; 2.G.175.237; 2.G.175.238; 2.G.175.239; 2.G.175.154; 2.G.175.157; 2.G.175.166; 2.G.175.169; 2.G.175.172; 2.G.175.175; 2.G.175.240; 2.G.175.244; 2.G.240.228; 2.G.240.229; 2.G.240.230; 2.G.240.231; 2.G.240.236; 2.G.240.237; 2.G.240.238; 2.G.240.239; 2.G.240.154; 2.G.240.157; 2.G.240.166; 2.G.240.169; 2.G.240.172; 2.G.240.175; 2.G.240.240; 2.G.240.244; 2.G.244.228; 2.G.244.229; 2.G.244.230; 2.G.244.231; 2.G.244.236; 2.G.244.237; 2.G.244.238; 2.G.244.239; 2.G.244.154; 2.G.244.157; 2.G.244.166; 2.G.244.169; 2.G.244.172; 2.G.244.175; 2.G.244.240; 2.G.244.244;

Prodrugs of 2.I

2.I.228.228; 2.I.228.229; 2.I.228.230; 2.I.228.231; 2.I.228.236; 2.I.228.237; 2.I.228.238; 2.I.228.239; 2.I.228.154; 2.I.228.157; 2.I.228.166; 2.I.228.169; 2.I.228.172; 2.I.228.175; 2.I.228.240; 2.I.228.244; 2.I.229.228; 2.I.229.229; 2.I.229.230; 2.I.229.231; 2.I.229.236; 2.I.229.237; 2.I.229.238; 2.I.229.239; 2.I.229.154; 2.I.229.157; 2.I.229.166; 2.I.229.169; 2.I.229.172; 2.I.229.175; 2.I.229.240; 2.I.229.244; 2.I.230.228; 2.I.230.229; 2.I.230.230; 2.I.230.231; 2.I.230.236; 2.I.230.237; 2.I.230.238; 2.I.230.239; 2.I.230.154; 2.I.230.157; 2.I.230.166; 2.I.230.169; 2.I.230.172; 2.I.230.175; 2.I.230.240; 2.I.230.244; 2.I.231.228; 2.I.231.229; 2.I.231.230; 2.I.231.231; 2.I.231.236; 2.I.231.237; 2.I.231.238; 2.I.231.239; 2.I.231.154; 2.I.231.157; 2.I.231.166; 2.I.231.169; 2.I.231.172; 2.I.231.175; 2.I.231.240; 2.I.231.244; 2.I.236.228; 2.I.236.229; 2.I.236.230; 2.I.236.231; 2.I.236.236; 2.I.236.237; 2.I.236.238; 2.I.236.239; 2.I.236.154; 2.I.236.157; 2.I.236.166; 2.I.236.169; 2.I.236.172; 2.I.236.175; 2.I.236.240; 2.I.236.244; 2.I.237.228; 2.I.237.229; 2.I.237.230; 2.I.237.231;

2.I.237.236; 2.I.237.237; 2.I.237.238; 2.I.237.239; 2.I.237.154; 2.I.237.157; 2.I.237.166; 2.I.237.169; 2.I.237.172; 2.I.237.175; 2.I.237.240; 2.I.237.244; 2.I.238.228; 2.I.238.229; 2.I.238.230; 2.I.238.231; 2.I.238.236; 2.I.238.237; 2.I.238.238; 2.I.238.239; 2.I.238.154; 2.I.238.157; 2.I.238.166; 2.I.238.169; 2.I.238.172; 2.I.238.175; 2.I.238.240; 2.I.238.244; 2.I.239.228; 2.I.239.229; 2.I.239.230; 2.I.239.231; 2.I.239.236; 2.I.239.237; 2.I.239.238; 2.I.239.239; 2.I.239.154; 2.I.239.157; 2.I.239.166; 2.I.239.169; 2.I.239.172; 2.I.239.175; 2.I.239.240; 2.I.239.244; 2.I.154.228; 2.I.154.229; 2.I.154.230; 2.I.154.231; 2.I.154.236; 2.I.154.237; 2.I.154.238; 2.I.154.239; 2.I.154.154; 2.I.154.157; 2.I.154.166; 2.I.154.169; 2.I.154.172; 2.I.154.175; 2.I.154.240; 2.I.154.244; 2.I.157.228; 2.I.157.229; 2.I.157.230; 2.I.157.231; 2.I.157.236; 2.I.157.237; 2.I.157.238; 2.I.157.239; 2.I.157.154; 2.I.157.157; 2.I.157.166; 2.I.157.169; 2.I.157.172; 2.I.157.175; 2.I.157.240; 2.I.157.244; 2.I.166.228; 2.I.166.229; 2.I.166.230; 2.I.166.231; 2.I.166.236; 2.I.166.237; 2.I.166.238; 2.I.166.239; 2.I.166.154; 2.I.166.157; 2.I.166.166; 2.I.166.169; 2.I.166.172; 2.I.166.175; 2.I.166.240; 2.I.166.244; 2.I.169.228; 2.I.169.229; 2.I.169.230; 2.I.169.231; 2.I.169.236; 2.I.169.237; 2.I.169.238; 2.I.169.239; 2.I.169.154; 2.I.169.157; 2.I.169.166; 2.I.169.169; 2.I.169.172; 2.I.169.175; 2.I.169.240; 2.I.169.244; 2.I.172.228; 2.I.172.229; 2.I.172.230; 2.I.172.231; 2.I.172.236; 2.I.172.237; 2.I.172.238; 2.I.172.239; 2.I.172.154; 2.I.172.157; 2.I.172.166; 2.I.172.169; 2.I.172.172; 2.I.172.175; 2.I.172.240; 2.I.172.244; 2.I.175.228; 2.I.175.229; 2.I.175.230; 2.I.175.231; 2.I.175.236; 2.I.175.237; 2.I.175.238; 2.I.175.239; 2.I.175.154; 2.I.175.157; 2.I.175.166; 2.I.175.169; 2.I.175.172; 2.I.175.175; 2.I.175.240; 2.I.175.244; 2.I.240.228; 2.I.240.229; 2.I.240.230; 2.I.240.231; 2.I.240.236; 2.I.240.237; 2.I.240.238; 2.I.240.239; 2.I.240.154; 2.I.240.157; 2.I.240.166; 2.I.240.169; 2.I.240.172; 2.I.240.175; 2.I.240.240; 2.I.240.244; 2.I.244.228; 2.I.244.229; 2.I.244.230; 2.I.244.231; 2.I.244.236; 2.I.244.237; 2.I.244.238; 2.I.244.239; 2.I.244.154; 2.I.244.157; 2.I.244.166; 2.I.244.169; 2.I.244.172; 2.I.244.175; 2.I.244.240; 2.I.244.244;

Prodrugs of 2.J

2.J.228.228; 2.J.228.229; 2.J.228.230; 2.J.228.231; 2.J.228.236; 2.J.228.237; 2.J.228.238; 2.J.228.239; 2.J.228.154; 2.J.228.157; 2.J.228.166; 2.J.228.169; 2.J.228.172; 2.J.228.175; 2.J.228.240; 2.J.228.244; 2.J.229.228; 2.J.229.229; 2.J.229.230; 2.J.229.231; 2.J.229.236; 2.J.229.237; 2.J.229.238; 2.J.229.239; 2.J.229.154; 2.J.229.157; 2.J.229.166; 2.J.229.169; 2.J.229.172; 2.J.229.175; 2.J.229.240; 2.J.229.244; 2.J.230.228; 2.J.230.229; 2.J.230.230; 2.J.230.231; 2.J.230.236; 2.J.230.237; 2.J.230.238; 2.J.230.239; 2.J.230.154; 2.J.230.157; 2.J.230.166; 2.J.230.169; 2.J.230.172; 2.J.230.175; 2.J.230.240; 2.J.230.244; 2.J.231.228; 2.J.231.229; 2.J.231.230; 2.J.231.231; 2.J.231.236; 2.J.231.237; 2.J.231.238; 2.J.231.239; 2.J.231.154; 2.J.231.157; 2.J.231.166; 2.J.231.169; 2.J.231.172; 2.J.231.175; 2.J.231.240; 2.J.231.244; 2.J.236.228; 2.J.236.229; 2.J.236.230; 2.J.236.231; 2.J.236.236; 2.J.236.237; 2.J.236.238; 2.J.236.239; 2.J.236.154; 2.J.236.157; 2.J.236.166; 2.J.236.169; 2.J.236.172; 2.J.236.175; 2.J.236.240; 2.J.236.244; 2.J.237.228; 2.J.237.229; 2.J.237.230; 2.J.237.231; 2.J.237.236; 2.J.237.237; 2.J.237.238; 2.J.237.239; 2.J.237.154; 2.J.237.157; 2.J.237.166; 2.J.237.169; 2.J.237.172; 2.J.237.175; 2.J.237.240; 2.J.237.244; 2.J.238.228; 2.J.238.229; 2.J.238.230; 2.J.238.231; 2.J.238.236; 2.J.238.237; 2.J.238.238; 2.J.238.239; 2.J.238.154; 2.J.238.157; 2.J.238.166; 2.J.238.169; 2.J.238.172; 2.J.238.175; 2.J.238.240; 2.J.238.244; 2.J.239.228; 2.J.239.229; 2.J.239.230; 2.J.239.231; 2.J.239.236; 2.J.239.237; 2.J.239.238; 2.J.239.239; 2.J.239.154; 2.J.239.157; 2.J.239.166; 2.J.239.169; 2.J.239.172; 2.J.239.175; 2.J.239.240; 2.J.239.244; 2.J.154.228; 2.J.154.229; 2.J.154.230; 2.J.154.231; 2.J.154.236;

2.J.154.237; 2.J.154.238; 2.J.154.239; 2.J.154.154; 2.J.154.157; 2.J.154.166; 2.J.154.169; 2.J.154.172; 2.J.154.175; 2.J.154.240; 2.J.154.244; 2.J.157.228; 2.J.157.229; 2.J.157.230; 2.J.157.231; 2.J.157.236; 2.J.157.237; 2.J.157.238; 2.J.157.239; 2.J.157.154; 2.J.157.157; 2.J.157.166; 2.J.157.169; 2.J.157.172; 2.J.157.175; 2.J.157.240; 2.J.157.244; 2.J.166.228; 2.J.166.229; 2.J.166.230; 2.J.166.231; 2.J.166.236; 2.J.166.237; 2.J.166.238; 2.J.166.239; 2.J.166.154; 2.J.166.157; 2.J.166.166; 2.J.166.169; 2.J.166.172; 2.J.166.175; 2.J.166.240; 2.J.166.244; 2.J.169.228; 2.J.169.229; 2.J.169.230; 2.J.169.231; 2.J.169.236; 2.J.169.237; 2.J.169.238; 2.J.169.239; 2.J.169.154; 2.J.169.157; 2.J.169.166; 2.J.169.169; 2.J.169.172; 2.J.169.175; 2.J.169.240; 2.J.169.244; 2.J.172.228; 2.J.172.229; 2.J.172.230; 2.J.172.231; 2.J.172.236; 2.J.172.237; 2.J.172.238; 2.J.172.239; 2.J.172.154; 2.J.172.157; 2.J.172.166; 2.J.172.169; 2.J.172.172; 2.J.172.175; 2.J.172.240; 2.J.172.244; 2.J.175.228; 2.J.175.229; 2.J.175.230; 2.J.175.231; 2.J.175.236; 2.J.175.237; 2.J.175.238; 2.J.175.239; 2.J.175.154; 2.J.175.157; 2.J.175.166; 2.J.175.169; 2.J.175.172; 2.J.175.175; 2.J.175.240; 2.J.175.244; 2.J.240.228; 2.J.240.229; 2.J.240.230; 2.J.240.231; 2.J.240.236; 2.J.240.237; 2.J.240.238; 2.J.240.239; 2.J.240.154; 2.J.240.157; 2.J.240.166; 2.J.240.169; 2.J.240.172; 2.J.240.175; 2.J.240.240; 2.J.240.244; 2.J.244.228; 2.J.244.229; 2.J.244.230; 2.J.244.231; 2.J.244.236; 2.J.244.237; 2.J.244.238; 2.J.244.239; 2.J.244.154; 2.J.244.157; 2.J.244.166; 2.J.244.169; 2.J.244.172; 2.J.244.175; 2.J.244.240; 2.J.244.244;

<u>Prodrugs of 2.L</u>

2.L.228.228; 2.L.228.229; 2.L.228.230; 2.L.228.231; 2.L.228.236; 2.L.228.237; 2.L.228.238; 2.L.228.239; 2.L.228.154; 2.L.228.157; 2.L.228.166; 2.L.228.169; 2.L.228.172; 2.L.228.175; 2.L.228.240; 2.L.228.244; 2.L.229.228; 2.L.229.229; 2.L.229.230; 2.L.229.231; 2.L.229.236; 2.L.229.237; 2.L.229.238; 2.L.229.239; 2.L.229.154; 2.L.229.157; 2.L.229.166; 2.L.229.169; 2.L.229.172; 2.L.229.175; 2.L.229.240; 2.L.229.244; 2.L.230.228; 2.L.230.229; 2.L.230.230; 2.L.230.231; 2.L.230.236; 2.L.230.237; 2.L.230.238; 2.L.230.239; 2.L.230.154; 2.L.230.157; 2.L.230.166; 2.L.230.169; 2.L.230.172; 2.L.230.175; 2.L.230.240; 2.L.230.244; 2.L.231.228; 2.L.231.229; 2.L.231.230; 2.L.231.231; 2.L.231.236; 2.L.231.237; 2.L.231.238; 2.L.231.239; 2.L.231.154; 2.L.231.157; 2.L.231.166; 2.L.231.169; 2.L.231.172; 2.L.231.175; 2.L.231.240; 2.L.231.244; 2.L.236.228; 2.L.236.229; 2.L.236.230; 2.L.236.231; 2.L.236.236; 2.L.236.237; 2.L.236.238; 2.L.236.239; 2.L.236.154; 2.L.236.157; 2.L.236.166; 2.L.236.169; 2.L.236.172; 2.L.236.175; 2.L.236.240; 2.L.236.244; 2.L.237.228; 2.L.237.229; 2.L.237.230; 2.L.237.231; 2.L.237.236; 2.L.237.237; 2.L.237.238; 2.L.237.239; 2.L.237.154; 2.L.237.157; 2.L.237.166; 2.L.237.169; 2.L.237.172; 2.L.237.175; 2.L.237.240; 2.L.237.244; 2.L.238.228; 2.L.238.229; 2.L.238.230; 2.L.238.231; 2.L.238.236; 2.L.238.237; 2.L.238.238; 2.L.238.239; 2.L.238.154; 2.L.238.157; 2.L.238.166; 2.L.238.169; 2.L.238.172; 2.L.238.175; 2.L.238.240; 2.L.238.244; 2.L.239.228; 2.L.239.229; 2.L.239.230; 2.L.239.231; 2.L.239.236; 2.L.239.237; 2.L.239.238; 2.L.239.239; 2.L.239.154; 2.L.239.157; 2.L.239.166; 2.L.239.169; 2.L.239.172; 2.L.239.175; 2.L.239.240; 2.L.239.244; 2.L.154.228; 2.L.154.229; 2.L.154.230; 2.L.154.231; 2.L.154.236; 2.L.154.237; 2.L.154.238; 2.L.154.239; 2.L.154.154; 2.L.154.157; 2.L.154.166; 2.L.154.169; 2.L.154.172; 2.L.154.175; 2.L.154.240; 2.L.154.244; 2.L.157.228; 2.L.157.229; 2.L.157.230; 2.L.157.231; 2.L.157.236; 2.L.157.237; 2.L.157.238; 2.L.157.239; 2.L.157.154; 2.L.157.157; 2.L.157.166; 2.L.157.169; 2.L.157.172; 2.L.157.175; 2.L.157.240; 2.L.157.244; 2.L.166.228; 2.L.166.229; 2.L.166.230; 2.L.166.231; 2.L.166.236; 2.L.166.237; 2.L.166.238; 2.L.166.239; 2.L.166.154; 2.L.166.157; 2.L.166.166; 2.L.166.169; 2.L.166.172; 2.L.166.175; 2.L.166.240; 2.L.166.244; 2.L.169.228; 2.L.169.229; 2.L.169.230; 2.L.169.231; 2.L.169.236;

2.L.169.237; 2.L.169.238; 2.L.169.239; 2.L.169.154; 2.L.169.157; 2.L.169.166; 2.L.169.169; 2.L.169.172; 2.L.169.175; 2.L.169.240; 2.L.169.244; 2.L.172.228; 2.L.172.229; 2.L.172.230; 2.L.172.231; 2.L.172.236; 2.L.172.237; 2.L.172.238; 2.L.172.239; 2.L.172.154; 2.L.172.157; 2.L.172.166; 2.L.172.169; 2.L.172.172; 2.L.172.175; 2.L.172.240; 2.L.172.244; 2.L.175.228; 2.L.175.229; 2.L.175.230; 2.L.175.231; 2.L.175.236; 2.L.175.237; 2.L.175.238; 2.L.175.239; 2.L.175.154; 2.L.175.157; 2.L.175.166; 2.L.175.169; 2.L.175.172; 2.L.175.175; 2.L.175.240; 2.L.175.244; 2.L.240.228; 2.L.240.229; 2.L.240.230; 2.L.240.231; 2.L.240.236; 2.L.240.237; 2.L.240.238; 2.L.240.239; 2.L.240.154; 2.L.240.157; 2.L.240.166; 2.L.240.169; 2.L.240.172; 2.L.240.175; 2.L.240.240; 2.L.240.244; 2.L.244.228; 2.L.244.229; 2.L.244.230; 2.L.244.231; 2.L.244.236; 2.L.244.237; 2.L.244.238; 2.L.244.239; 2.L.244.154; 2.L.244.157; 2.L.244.166; 2.L.244.169; 2.L.244.172; 2.L.244.175; 2.L.244.240; 2.L.244.244;

Prodrugs of 2.O

2.O.228.228; 2.O.228.229; 2.O.228.230; 2.O.228.231; 2.O.228.236; 2.O.228.237; 2.O.228.238; 2.O.228.239; 2.O.228.154; 2.O.228.157; 2.O.228.166; 2.O.228.169; 2.O.228.172; 2.O.228.175; 2.O.228.240; 2.O.228.244; 2.O.229.228; 2.O.229.229; 2.O.229.230; 2.O.229.231; 2.O.229.236; 2.O.229.237; 2.O.229.238; 2.O.229.239; 2.O.229.154; 2.O.229.157; 2.O.229.166; 2.O.229.169; 2.O.229.172; 2.O.229.175; 2.O.229.240; 2.O.229.244; 2.O.230.228; 2.O.230.229; 2.O.230.230; 2.O.230.231; 2.O.230.236; 2.O.230.237; 2.O.230.238; 2.O.230.239; 2.O.230.154; 2.O.230.157; 2.O.230.166; 2.O.230.169; 2.O.230.172; 2.O.230.175; 2.O.230.240; 2.O.230.244; 2.O.231.228; 2.O.231.229; 2.O.231.230; 2.O.231.231; 2.O.231.236; 2.O.231.237; 2.O.231.238; 2.O.231.239; 2.O.231.154; 2.O.231.157; 2.O.231.166; 2.O.231.169; 2.O.231.172; 2.O.231.175; 2.O.231.240; 2.O.231.244; 2.O.236.228; 2.O.236.229; 2.O.236.230; 2.O.236.231; 2.O.236.236; 2.O.236.237; 2.O.236.238; 2.O.236.239; 2.O.236.154; 2.O.236.157; 2.O.236.166; 2.O.236.169; 2.O.236.172; 2.O.236.175; 2.O.236.240; 2.O.236.244; 2.O.237.228; 2.O.237.229; 2.O.237.230; 2.O.237.231; 2.O.237.236; 2.O.237.237; 2.O.237.238; 2.O.237.239; 2.O.237.154; 2.O.237.157; 2.O.237.166; 2.O.237.169; 2.O.237.172; 2.O.237.175; 2.O.237.240; 2.O.237.244; 2.O.238.228; 2.O.238.229; 2.O.238.230; 2.O.238.231; 2.O.238.236; 2.O.238.237; 2.O.238.238; 2.O.238.239; 2.O.238.154; 2.O.238.157; 2.O.238.166; 2.O.238.169; 2.O.238.172; 2.O.238.175; 2.O.238.240; 2.O.238.244; 2.O.239.228; 2.O.239.229; 2.O.239.230; 2.O.239.231; 2.O.239.236; 2.O.239.237; 2.O.239.238; 2.O.239.239; 2.O.239.154; 2.O.239.157; 2.O.239.166; 2.O.239.169; 2.O.239.172; 2.O.239.175; 2.O.239.240; 2.O.239.244; 2.O.154.228; 2.O.154.229; 2.O.154.230; 2.O.154.231; 2.O.154.236; 2.O.154.237; 2.O.154.238; 2.O.154.239; 2.O.154.154; 2.O.154.157; 2.O.154.166; 2.O.154.169; 2.O.154.172; 2.O.154.175; 2.O.154.240; 2.O.154.244; 2.O.157.228; 2.O.157.229; 2.O.157.230; 2.O.157.231; 2.O.157.236; 2.O.157.237; 2.O.157.238; 2.O.157.239; 2.O.157.154; 2.O.157.157; 2.O.157.166; 2.O.157.169; 2.O.157.172; 2.O.157.175; 2.O.157.240; 2.O.157.244; 2.O.166.228; 2.O.166.229; 2.O.166.230; 2.O.166.231; 2.O.166.236; 2.O.166.237; 2.O.166.238; 2.O.166.239; 2.O.166.154; 2.O.166.157; 2.O.166.166; 2.O.166.169; 2.O.166.172; 2.O.166.175; 2.O.166.240; 2.O.166.244; 2.O.169.228; 2.O.169.229; 2.O.169.230; 2.O.169.231; 2.O.169.236; 2.O.169.237; 2.O.169.238; 2.O.169.239; 2.O.169.154; 2.O.169.157; 2.O.169.166; 2.O.169.169; 2.O.169.172; 2.O.169.175; 2.O.169.240; 2.O.169.244; 2.O.172.228; 2.O.172.229; 2.O.172.230; 2.O.172.231; 2.O.172.236; 2.O.172.237;

2.O.172.238; 2.O.172.239; 2.O.172.154; 2.O.172.157; 2.O.172.166; 2.O.172.169; 2.O.172.172; 2.O.172.175; 2.O.172.240; 2.O.172.244; 2.O.175.228; 2.O.175.229; 2.O.175.230; 2.O.175.231; 2.O.175.236; 2.O.175.237; 2.O.175.238; 2.O.175.239; 2.O.175.154; 2.O.175.157; 2.O.175.166; 2.O.175.169; 2.O.175.172; 2.O.175.175; 2.O.175.240; 2.O.175.244; 2.O.240.228; 2.O.240.229; 2.O.240.230; 2.O.240.231; 2.O.240.236; 2.O.240.237; 2.O.240.238; 2.O.240.239; 2.O.240.154; 2.O.240.157; 2.O.240.166; 2.O.240.169; 2.O.240.172; 2.O.240.175; 2.O.240.240; 2.O.240.244; 2.O.244.228; 2.O.244.229; 2.O.244.230; 2.O.244.231; 2.O.244.236; 2.O.244.237; 2.O.244.238; 2.O.244.239; 2.O.244.154; 2.O.244.157; 2.O.244.166; 2.O.244.169; 2.O.244.172; 2.O.244.175; 2.O.244.240; 2.O.244.244;

Prodrugs of 2.P

2.P.228.228; 2.P.228.229; 2.P.228.230; 2.P.228.231; 2.P.228.236; 2.P.228.237; 2.P.228.238; 2.P.228.239; 2.P.228.154; 2.P.228.157; 2.P.228.166; 2.P.228.169; 2.P.228.172; 2.P.228.175; 2.P.228.240; 2.P.228.244; 2.P.229.228; 2.P.229.229; 2.P.229.230; 2.P.229.231; 2.P.229.236; 2.P.229.237; 2.P.229.238; 2.P.229.239; 2.P.229.154; 2.P.229.157; 2.P.229.166; 2.P.229.169; 2.P.229.172; 2.P.229.175; 2.P.229.240; 2.P.229.244; 2.P.230.228; 2.P.230.229; 2.P.230.230; 2.P.230.231; 2.P.230.236; 2.P.230.237; 2.P.230.238; 2.P.230.239; 2.P.230.154; 2.P.230.157; 2.P.230.166; 2.P.230.169; 2.P.230.172; 2.P.230.175; 2.P.230.240; 2.P.230.244; 2.P.231.228; 2.P.231.229; 2.P.231.230; 2.P.231.231; 2.P.231.236; 2.P.231.237; 2.P.231.238; 2.P.231.239; 2.P.231.154; 2.P.231.157; 2.P.231.166; 2.P.231.169; 2.P.231.172; 2.P.231.175; 2.P.231.240; 2.P.231.244; 2.P.236.228; 2.P.236.229; 2.P.236.230; 2.P.236.231; 2.P.236.236; 2.P.236.237; 2.P.236.238; 2.P.236.239; 2.P.236.154; 2.P.236.157; 2.P.236.166; 2.P.236.169; 2.P.236.172; 2.P.236.175; 2.P.236.240; 2.P.236.244; 2.P.237.228; 2.P.237.229; 2.P.237.230; 2.P.237.231; 2.P.237.236; 2.P.237.237; 2.P.237.238; 2.P.237.239; 2.P.237.154; 2.P.237.157; 2.P.237.166; 2.P.237.169; 2.P.237.172; 2.P.237.175; 2.P.237.240; 2.P.237.244; 2.P.238.228; 2.P.238.229; 2.P.238.230; 2.P.238.231; 2.P.238.236; 2.P.238.237; 2.P.238.238; 2.P.238.239; 2.P.238.154; 2.P.238.157; 2.P.238.166; 2.P.238.169; 2.P.238.172; 2.P.238.175; 2.P.238.240; 2.P.238.244; 2.P.239.228; 2.P.239.229; 2.P.239.230; 2.P.239.231; 2.P.239.236; 2.P.239.237; 2.P.239.238; 2.P.239.239; 2.P.239.154; 2.P.239.157; 2.P.239.166; 2.P.239.169; 2.P.239.172; 2.P.239.175; 2.P.239.240; 2.P.239.244; 2.P.154.228; 2.P.154.229; 2.P.154.230; 2.P.154.231; 2.P.154.236; 2.P.154.237; 2.P.154.238; 2.P.154.239; 2.P.154.154; 2.P.154.157; 2.P.154.166; 2.P.154.169; 2.P.154.172; 2.P.154.175; 2.P.154.240; 2.P.154.244; 2.P.157.228; 2.P.157.229; 2.P.157.230; 2.P.157.231; 2.P.157.236; 2.P.157.237; 2.P.157.238; 2.P.157.239; 2.P.157.154; 2.P.157.157; 2.P.157.166; 2.P.157.169; 2.P.157.172; 2.P.157.175; 2.P.157.240; 2.P.157.244; 2.P.166.228; 2.P.166.229; 2.P.166.230; 2.P.166.231; 2.P.166.236; 2.P.166.237; 2.P.166.238; 2.P.166.239; 2.P.166.154; 2.P.166.157; 2.P.166.166; 2.P.166.169; 2.P.166.172; 2.P.166.175; 2.P.166.240; 2.P.166.244; 2.P.169.228; 2.P.169.229; 2.P.169.230; 2.P.169.231; 2.P.169.236; 2.P.169.237; 2.P.169.238; 2.P.169.239; 2.P.169.154; 2.P.169.157; 2.P.169.166; 2.P.169.169; 2.P.169.172; 2.P.169.175; 2.P.169.240; 2.P.169.244; 2.P.172.228; 2.P.172.229; 2.P.172.230; 2.P.172.231; 2.P.172.236; 2.P.172.237; 2.P.172.238; 2.P.172.239; 2.P.172.154; 2.P.172.157; 2.P.172.166; 2.P.172.169; 2.P.172.172; 2.P.172.175; 2.P.172.240; 2.P.172.244; 2.P.175.228; 2.P.175.229; 2.P.175.230; 2.P.175.231; 2.P.175.236; 2.P.175.237; 2.P.175.238; 2.P.175.239; 2.P.175.154; 2.P.175.157; 2.P.175.166; 2.P.175.169; 2.P.175.172; 2.P.175.175; 2.P.175.240; 2.P.175.244; 2.P.240.228; 2.P.240.229; 2.P.240.230; 2.P.240.231; 2.P.240.236; 2.P.240.237; 2.P.240.238; 2.P.240.239; 2.P.240.154; 2.P.240.157; 2.P.240.166; 2.P.240.169; 2.P.240.172;

2.P.240.175; 2.P.240.240; 2.P.240.244; 2.P.244.228; 2.P.244.229; 2.P.244.230; 2.P.244.231; 2.P.244.236; 2.P.244.237; 2.P.244.238; 2.P.244.239; 2.P.244.154; 2.P.244.157; 2.P.244.166; 2.P.244.169; 2.P.244.172; 2.P.244.175; 2.P.244.240; 2.P.244.244;

Prodrugs of 2.U

2.U.228.228; 2.U.228.229; 2.U.228.230; 2.U.228.231; 2.U.228.236; 2.U.228.237; 2.U.228.238; 2.U.228.239; 2.U.228.154; 2.U.228.157; 2.U.228.166; 2.U.228.169; 2.U.228.172; 2.U.228.175; 2.U.228.240; 2.U.228.244; 2.U.229.228; 2.U.229.229; 2.U.229.230; 2.U.229.231; 2.U.229.236; 2.U.229.237; 2.U.229.238; 2.U.229.239; 2.U.229.154; 2.U.229.157; 2.U.229.166; 2.U.229.169; 2.U.229.172; 2.U.229.175; 2.U.229.240; 2.U.229.244; 2.U.230.228; 2.U.230.229; 2.U.230.230; 2.U.230.231; 2.U.230.236; 2.U.230.237; 2.U.230.238; 2.U.230.239; 2.U.230.154; 2.U.230.157; 2.U.230.166; 2.U.230.169; 2.U.230.172; 2.U.230.175; 2.U.230.240; 2.U.230.244; 2.U.231.228; 2.U.231.229; 2.U.231.230; 2.U.231.231; 2.U.231.236; 2.U.231.237; 2.U.231.238; 2.U.231.239; 2.U.231.154; 2.U.231.157; 2.U.231.166; 2.U.231.169; 2.U.231.172; 2.U.231.175; 2.U.231.240; 2.U.231.244; 2.U.236.228; 2.U.236.229; 2.U.236.230; 2.U.236.231; 2.U.236.236; 2.U.236.237; 2.U.236.238; 2.U.236.239; 2.U.236.154; 2.U.236.157; 2.U.236.166; 2.U.236.169; 2.U.236.172; 2.U.236.175; 2.U.236.240; 2.U.236.244; 2.U.237.228; 2.U.237.229; 2.U.237.230; 2.U.237.231; 2.U.237.236; 2.U.237.237; 2.U.237.238; 2.U.237.239; 2.U.237.154; 2.U.237.157; 2.U.237.166; 2.U.237.169; 2.U.237.172; 2.U.237.175; 2.U.237.240; 2.U.237.244; 2.U.238.228; 2.U.238.229; 2.U.238.230; 2.U.238.231; 2.U.238.236; 2.U.238.237; 2.U.238.238; 2.U.238.239; 2.U.238.154; 2.U.238.157; 2.U.238.166; 2.U.238.169; 2.U.238.172; 2.U.238.175; 2.U.238.240; 2.U.238.244; 2.U.239.228; 2.U.239.229; 2.U.239.230; 2.U.239.231; 2.U.239.236; 2.U.239.237; 2.U.239.238; 2.U.239.239; 2.U.239.154; 2.U.239.157; 2.U.239.166; 2.U.239.169; 2.U.239.172; 2.U.239.175; 2.U.239.240; 2.U.239.244; 2.U.154.228; 2.U.154.229; 2.U.154.230; 2.U.154.231; 2.U.154.236; 2.U.154.237; 2.U.154.238; 2.U.154.239; 2.U.154.154; 2.U.154.157; 2.U.154.166; 2.U.154.169; 2.U.154.172; 2.U.154.175; 2.U.154.240; 2.U.154.244; 2.U.157.228; 2.U.157.229; 2.U.157.230; 2.U.157.231; 2.U.157.236; 2.U.157.237; 2.U.157.238; 2.U.157.239; 2.U.157.154; 2.U.157.157; 2.U.157.166; 2.U.157.169; 2.U.157.172; 2.U.157.175; 2.U.157.240; 2.U.157.244; 2.U.166.228; 2.U.166.229; 2.U.166.230; 2.U.166.231; 2.U.166.236; 2.U.166.237; 2.U.166.238; 2.U.166.239; 2.U.166.154; 2.U.166.157; 2.U.166.166; 2.U.166.169; 2.U.166.172; 2.U.166.175; 2.U.166.240; 2.U.166.244; 2.U.169.228; 2.U.169.229; 2.U.169.230; 2.U.169.231; 2.U.169.236; 2.U.169.237; 2.U.169.238; 2.U.169.239; 2.U.169.154; 2.U.169.157; 2.U.169.166; 2.U.169.169; 2.U.169.172; 2.U.169.175; 2.U.169.240; 2.U.169.244; 2.U.172.228; 2.U.172.229; 2.U.172.230; 2.U.172.231; 2.U.172.236; 2.U.172.237; 2.U.172.238; 2.U.172.239; 2.U.172.154; 2.U.172.157; 2.U.172.166; 2.U.172.169; 2.U.172.172; 2.U.172.175; 2.U.172.240; 2.U.172.244; 2.U.175.228; 2.U.175.229; 2.U.175.230; 2.U.175.231; 2.U.175.236; 2.U.175.237; 2.U.175.238; 2.U.175.239; 2.U.175.154; 2.U.175.157; 2.U.175.166; 2.U.175.169; 2.U.175.172; 2.U.175.175; 2.U.175.240; 2.U.175.244; 2.U.240.228; 2.U.240.229; 2.U.240.230; 2.U.240.231; 2.U.240.236; 2.U.240.237; 2.U.240.238; 2.U.240.239; 2.U.240.154; 2.U.240.157; 2.U.240.166; 2.U.240.169; 2.U.240.172; 2.U.240.175; 2.U.240.240; 2.U.240.244; 2.U.244.228; 2.U.244.229; 2.U.244.230; 2.U.244.231; 2.U.244.236; 2.U.244.237;

2.U.244.238; 2.U.244.239; 2.U.244.154; 2.U.244.157; 2.U.244.166; 2.U.244.169; 2.U.244.172; 2.U.244.175; 2.U.244.240; 2.U.244.244;

Prodrugs of 2.W

2.W.228.228; 2.W.228.229; 2.W.228.230; 2.W.228.231; 2.W.228.236; 2.W.228.237; 2.W.228.238; 2.W.228.239; 2.W.228.154; 2.W.228.157; 2.W.228.166; 2.W.228.169; 2.W.228.172; 2.W.228.175; 2.W.228.240; 2.W.228.244; 2.W.229.228; 2.W.229.229; 2.W.229.230; 2.W.229.231; 2.W.229.236; 2.W.229.237; 2.W.229.238; 2.W.229.239; 2.W.229.154; 2.W.229.157; 2.W.229.166; 2.W.229.169; 2.W.229.172; 2.W.229.175; 2.W.229.240; 2.W.229.244; 2.W.230.228; 2.W.230.229; 2.W.230.230; 2.W.230.231; 2.W.230.236; 2.W.230.237; 2.W.230.238; 2.W.230.239; 2.W.230.154; 2.W.230.157; 2.W.230.166; 2.W.230.169; 2.W.230.172; 2.W.230.175; 2.W.230.240; 2.W.230.244; 2.W.231.228; 2.W.231.229; 2.W.231.230; 2.W.231.231; 2.W.231.236; 2.W.231.237; 2.W.231.238; 2.W.231.239; 2.W.231.154; 2.W.231.157; 2.W.231.166; 2.W.231.169; 2.W.231.172; 2.W.231.175; 2.W.231.240; 2.W.231.244; 2.W.236.228; 2.W.236.229; 2.W.236.230; 2.W.236.231; 2.W.236.236; 2.W.236.237; 2.W.236.238; 2.W.236.239; 2.W.236.154; 2.W.236.157; 2.W.236.166; 2.W.236.169; 2.W.236.172; 2.W.236.175; 2.W.236.240; 2.W.236.244; 2.W.237.228; 2.W.237.229; 2.W.237.230; 2.W.237.231; 2.W.237.236; 2.W.237.237; 2.W.237.238; 2.W.237.239; 2.W.237.154; 2.W.237.157; 2.W.237.166; 2.W.237.169; 2.W.237.172; 2.W.237.175; 2.W.237.240; 2.W.237.244; 2.W.238.228; 2.W.238.229; 2.W.238.230; 2.W.238.231; 2.W.238.236; 2.W.238.237; 2.W.238.238; 2.W.238.239; 2.W.238.154; 2.W.238.157; 2.W.238.166; 2.W.238.169; 2.W.238.172; 2.W.238.175; 2.W.238.240; 2.W.238.244; 2.W.239.228; 2.W.239.229; 2.W.239.230; 2.W.239.231; 2.W.239.236; 2.W.239.237; 2.W.239.238; 2.W.239.239; 2.W.239.154; 2.W.239.157; 2.W.239.166; 2.W.239.169; 2.W.239.172; 2.W.239.175; 2.W.239.240; 2.W.239.244; 2.W.154.228; 2.W.154.229; 2.W.154.230; 2.W.154.231; 2.W.154.236; 2.W.154.237; 2.W.154.238; 2.W.154.239; 2.W.154.154; 2.W.154.157; 2.W.154.166; 2.W.154.169; 2.W.154.172; 2.W.154.175; 2.W.154.240; 2.W.154.244; 2.W.157.228; 2.W.157.229; 2.W.157.230; 2.W.157.231; 2.W.157.236; 2.W.157.237; 2.W.157.238; 2.W.157.239; 2.W.157.154; 2.W.157.157; 2.W.157.166; 2.W.157.169; 2.W.157.172; 2.W.157.175; 2.W.157.240; 2.W.157.244; 2.W.166.228; 2.W.166.229; 2.W.166.230; 2.W.166.231; 2.W.166.236; 2.W.166.237; 2.W.166.238; 2.W.166.239; 2.W.166.154; 2.W.166.157; 2.W.166.166; 2.W.166.169; 2.W.166.172; 2.W.166.175; 2.W.166.240; 2.W.166.244; 2.W.169.228; 2.W.169.229; 2.W.169.230; 2.W.169.231; 2.W.169.236; 2.W.169.237; 2.W.169.238; 2.W.169.239; 2.W.169.154; 2.W.169.157; 2.W.169.166; 2.W.169.169; 2.W.169.172; 2.W.169.175; 2.W.169.240; 2.W.169.244; 2.W.172.228; 2.W.172.229; 2.W.172.230; 2.W.172.231; 2.W.172.236; 2.W.172.237; 2.W.172.238; 2.W.172.239; 2.W.172.154; 2.W.172.157; 2.W.172.166; 2.W.172.169; 2.W.172.172; 2.W.172.175; 2.W.172.240; 2.W.172.244; 2.W.175.228; 2.W.175.229; 2.W.175.230; 2.W.175.231; 2.W.175.236; 2.W.175.237; 2.W.175.238; 2.W.175.239; 2.W.175.154; 2.W.175.157; 2.W.175.166; 2.W.175.169; 2.W.175.172; 2.W.175.175; 2.W.175.240; 2.W.175.244; 2.W.240.228; 2.W.240.229; 2.W.240.230; 2.W.240.231; 2.W.240.236; 2.W.240.237; 2.W.240.238; 2.W.240.239; 2.W.240.154; 2.W.240.157; 2.W.240.166; 2.W.240.169; 2.W.240.172; 2.W.240.175; 2.W.240.240; 2.W.240.244; 2.W.244.228; 2.W.244.229; 2.W.244.230; 2.W.244.231; 2.W.244.236; 2.W.244.237;

2.W.244.238; 2.W.244.239; 2.W.244.154; 2.W.244.157; 2.W.244.166; 2.W.244.169; 2.W.244.172; 2.W.244.175; 2.W.244.240; 2.W.244.244;

Prodrugs of 2.Y

2.Y.228.228; 2.Y.228.229; 2.Y.228.230; 2.Y.228.231; 2.Y.228.236; 2.Y.228.237; 2.Y.228.238; 2.Y.228.239; 2.Y.228.154; 2.Y.228.157; 2.Y.228.166; 2.Y.228.169; 2.Y.228.172; 2.Y.228.175; 2.Y.228.240; 2.Y.228.244; 2.Y.229.228; 2.Y.229.229; 2.Y.229.230; 2.Y.229.231; 2.Y.229.236; 2.Y.229.237; 2.Y.229.238; 2.Y.229.239; 2.Y.229.154; 2.Y.229.157; 2.Y.229.166; 2.Y.229.169; 2.Y.229.172; 2.Y.229.175; 2.Y.229.240; 2.Y.229.244; 2.Y.230.228; 2.Y.230.229; 2.Y.230.230; 2.Y.230.231; 2.Y.230.236; 2.Y.230.237; 2.Y.230.238; 2.Y.230.239; 2.Y.230.154; 2.Y.230.157; 2.Y.230.166; 2.Y.230.169; 2.Y.230.172; 2.Y.230.175; 2.Y.230.240; 2.Y.230.244; 2.Y.231.228; 2.Y.231.229; 2.Y.231.230; 2.Y.231.231; 2.Y.231.236; 2.Y.231.237; 2.Y.231.238; 2.Y.231.239; 2.Y.231.154; 2.Y.231.157; 2.Y.231.166; 2.Y.231.169; 2.Y.231.172; 2.Y.231.175; 2.Y.231.240; 2.Y.231.244; 2.Y.236.228; 2.Y.236.229; 2.Y.236.230; 2.Y.236.231; 2.Y.236.236; 2.Y.236.237; 2.Y.236.238; 2.Y.236.239; 2.Y.236.154; 2.Y.236.157; 2.Y.236.166; 2.Y.236.169; 2.Y.236.172; 2.Y.236.175; 2.Y.236.240; 2.Y.236.244; 2.Y.237.228; 2.Y.237.229; 2.Y.237.230; 2.Y.237.231; 2.Y.237.236; 2.Y.237.237; 2.Y.237.238; 2.Y.237.239; 2.Y.237.154; 2.Y.237.157; 2.Y.237.166; 2.Y.237.169; 2.Y.237.172; 2.Y.237.175; 2.Y.237.240; 2.Y.237.244; 2.Y.238.228; 2.Y.238.229; 2.Y.238.230; 2.Y.238.231; 2.Y.238.236; 2.Y.238.237; 2.Y.238.238; 2.Y.238.239; 2.Y.238.154; 2.Y.238.157; 2.Y.238.166; 2.Y.238.169; 2.Y.238.172; 2.Y.238.175; 2.Y.238.240; 2.Y.238.244; 2.Y.239.228; 2.Y.239.229; 2.Y.239.230; 2.Y.239.231; 2.Y.239.236; 2.Y.239.237; 2.Y.239.238; 2.Y.239.239; 2.Y.239.154; 2.Y.239.157; 2.Y.239.166; 2.Y.239.169; 2.Y.239.172; 2.Y.239.175; 2.Y.239.240; 2.Y.239.244; 2.Y.154.228; 2.Y.154.229; 2.Y.154.230; 2.Y.154.231; 2.Y.154.236; 2.Y.154.237; 2.Y.154.238; 2.Y.154.239; 2.Y.154.154; 2.Y.154.157; 2.Y.154.166; 2.Y.154.169; 2.Y.154.172; 2.Y.154.175; 2.Y.154.240; 2.Y.154.244; 2.Y.157.228; 2.Y.157.229; 2.Y.157.230; 2.Y.157.231; 2.Y.157.236; 2.Y.157.237; 2.Y.157.238; 2.Y.157.239; 2.Y.157.154; 2.Y.157.157; 2.Y.157.166; 2.Y.157.169; 2.Y.157.172; 2.Y.157.175; 2.Y.157.240; 2.Y.157.244; 2.Y.166.228; 2.Y.166.229; 2.Y.166.230; 2.Y.166.231; 2.Y.166.236; 2.Y.166.237; 2.Y.166.238; 2.Y.166.239; 2.Y.166.154; 2.Y.166.157; 2.Y.166.166; 2.Y.166.169; 2.Y.166.172; 2.Y.166.175; 2.Y.166.240; 2.Y.166.244; 2.Y.169.228; 2.Y.169.229; 2.Y.169.230; 2.Y.169.231; 2.Y.169.236; 2.Y.169.237; 2.Y.169.238; 2.Y.169.239; 2.Y.169.154; 2.Y.169.157; 2.Y.169.166; 2.Y.169.169; 2.Y.169.172; 2.Y.169.175; 2.Y.169.240; 2.Y.169.244; 2.Y.172.228; 2.Y.172.229; 2.Y.172.230; 2.Y.172.231; 2.Y.172.236; 2.Y.172.237; 2.Y.172.238; 2.Y.172.239; 2.Y.172.154; 2.Y.172.157; 2.Y.172.166; 2.Y.172.169; 2.Y.172.172; 2.Y.172.175; 2.Y.172.240; 2.Y.172.244; 2.Y.175.228; 2.Y.175.229; 2.Y.175.230; 2.Y.175.231; 2.Y.175.236; 2.Y.175.237; 2.Y.175.238; 2.Y.175.239; 2.Y.175.154; 2.Y.175.157; 2.Y.175.166; 2.Y.175.169; 2.Y.175.172; 2.Y.175.175; 2.Y.175.240; 2.Y.175.244; 2.Y.240.228; 2.Y.240.229; 2.Y.240.230; 2.Y.240.231; 2.Y.240.236; 2.Y.240.237; 2.Y.240.238; 2.Y.240.239; 2.Y.240.154; 2.Y.240.157; 2.Y.240.166; 2.Y.240.169; 2.Y.240.172; 2.Y.240.175; 2.Y.240.240; 2.Y.240.244; 2.Y.244.228; 2.Y.244.229; 2.Y.244.230; 2.Y.244.231; 2.Y.244.236; 2.Y.244.237;

2.Y.244.238; 2.Y.244.239; 2.Y.244.154; 2.Y.244.157; 2.Y.244.166; 2.Y.244.169; 2.Y.244.172; 2.Y.244.175; 2.Y.244.240; 2.Y.244.244;

Prodrugs of 3.B

3.B.228.228; 3.B.228.229; 3.B.228.230; 3.B.228.231; 3.B.228.236; 3.B.228.237; 3.B.228.238; 3.B.228.239; 3.B.228.154; 3.B.228.157; 3.B.228.166; 3.B.228.169; 3.B.228.172; 3.B.228.175; 3.B.228.240; 3.B.228.244; 3.B.229.228; 3.B.229.229; 3.B.229.230; 3.B.229.231; 3.B.229.236; 3.B.229.237; 3.B.229.238; 3.B.229.239; 3.B.229.154; 3.B.229.157; 3.B.229.166; 3.B.229.169; 3.B.229.172; 3.B.229.175; 3.B.229.240; 3.B.229.244; 3.B.230.228; 3.B.230.229; 3.B.230.230; 3.B.230.231; 3.B.230.236; 3.B.230.237; 3.B.230.238; 3.B.230.239; 3.B.230.154; 3.B.230.157; 3.B.230.166; 3.B.230.169; 3.B.230.172; 3.B.230.175; 3.B.230.240; 3.B.230.244; 3.B.231.228; 3.B.231.229; 3.B.231.230; 3.B.231.231; 3.B.231.236; 3.B.231.237; 3.B.231.238; 3.B.231.239; 3.B.231.154; 3.B.231.157; 3.B.231.166; 3.B.231.169; 3.B.231.172; 3.B.231.175; 3.B.231.240; 3.B.231.244; 3.B.236.228; 3.B.236.229; 3.B.236.230; 3.B.236.231; 3.B.236.236; 3.B.236.237; 3.B.236.238; 3.B.236.239; 3.B.236.154; 3.B.236.157; 3.B.236.166; 3.B.236.169; 3.B.236.172; 3.B.236.175; 3.B.236.240; 3.B.236.244; 3.B.237.228; 3.B.237.229; 3.B.237.230; 3.B.237.231; 3.B.237.236; 3.B.237.237; 3.B.237.238; 3.B.237.239; 3.B.237.154; 3.B.237.157; 3.B.237.166; 3.B.237.169; 3.B.237.172; 3.B.237.175; 3.B.237.240; 3.B.237.244; 3.B.238.228; 3.B.238.229; 3.B.238.230; 3.B.238.231; 3.B.238.236; 3.B.238.237; 3.B.238.238; 3.B.238.239; 3.B.238.154; 3.B.238.157; 3.B.238.166; 3.B.238.169; 3.B.238.172; 3.B.238.175; 3.B.238.240; 3.B.238.244; 3.B.239.228; 3.B.239.229; 3.B.239.230; 3.B.239.231; 3.B.239.236; 3.B.239.237; 3.B.239.238; 3.B.239.239; 3.B.239.154; 3.B.239.157; 3.B.239.166; 3.B.239.169; 3.B.239.172; 3.B.239.175; 3.B.239.240; 3.B.239.244; 3.B.154.228; 3.B.154.229; 3.B.154.230; 3.B.154.231; 3.B.154.236; 3.B.154.237; 3.B.154.238; 3.B.154.239; 3.B.154.154; 3.B.154.157; 3.B.154.166; 3.B.154.169; 3.B.154.172; 3.B.154.175; 3.B.154.240; 3.B.154.244; 3.B.157.228; 3.B.157.229; 3.B.157.230; 3.B.157.231; 3.B.157.236; 3.B.157.237; 3.B.157.238; 3.B.157.239; 3.B.157.154; 3.B.157.157; 3.B.157.166; 3.B.157.169; 3.B.157.172; 3.B.157.175; 3.B.157.240; 3.B.157.244; 3.B.166.228; 3.B.166.229; 3.B.166.230; 3.B.166.231; 3.B.166.236; 3.B.166.237; 3.B.166.238; 3.B.166.239; 3.B.166.154; 3.B.166.157; 3.B.166.166; 3.B.166.169; 3.B.166.172; 3.B.166.175; 3.B.166.240; 3.B.166.244; 3.B.169.228; 3.B.169.229; 3.B.169.230; 3.B.169.231; 3.B.169.236; 3.B.169.237; 3.B.169.238; 3.B.169.239; 3.B.169.154; 3.B.169.157; 3.B.169.166; 3.B.169.169; 3.B.169.172; 3.B.169.175; 3.B.169.240; 3.B.169.244; 3.B.172.228; 3.B.172.229; 3.B.172.230; 3.B.172.231; 3.B.172.236; 3.B.172.237; 3.B.172.238; 3.B.172.239; 3.B.172.154; 3.B.172.157; 3.B.172.166; 3.B.172.169; 3.B.172.172; 3.B.172.175; 3.B.172.240; 3.B.172.244; 3.B.175.228; 3.B.175.229; 3.B.175.230; 3.B.175.231; 3.B.175.236; 3.B.175.237; 3.B.175.238; 3.B.175.239; 3.B.175.154; 3.B.175.157; 3.B.175.166; 3.B.175.169; 3.B.175.172; 3.B.175.175; 3.B.175.240; 3.B.175.244; 3.B.240.228; 3.B.240.229; 3.B.240.230; 3.B.240.231; 3.B.240.236; 3.B.240.237; 3.B.240.238; 3.B.240.239; 3.B.240.154; 3.B.240.157; 3.B.240.166; 3.B.240.169; 3.B.240.172; 3.B.240.175; 3.B.240.240; 3.B.240.244; 3.B.244.228; 3.B.244.229; 3.B.244.230; 3.B.244.231; 3.B.244.236; 3.B.244.237; 3.B.244.238; 3.B.244.239; 3.B.244.154; 3.B.244.157; 3.B.244.166; 3.B.244.169; 3.B.244.172; 3.B.244.175; 3.B.244.240; 3.B.244.244;

Prodrugs of 3.D

3.D.228.228; 3.D.228.229; 3.D.228.230; 3.D.228.231; 3.D.228.236; 3.D.228.237; 3.D.228.238; 3.D.228.239; 3.D.228.154; 3.D.228.157; 3.D.228.166; 3.D.228.169; 3.D.228.172; 3.D.228.175; 3.D.228.240; 3.D.228.244; 3.D.229.228; 3.D.229.229;

3.D.229.230; 3.D.229.231; 3.D.229.236; 3.D.229.237; 3.D.229.238; 3.D.229.239; 3.D.229.154; 3.D.229.157; 3.D.229.166; 3.D.229.169; 3.D.229.172; 3.D.229.175; 3.D.229.240; 3.D.229.244; 3.D.230.228; 3.D.230.229; 3.D.230.230; 3.D.230.231; 3.D.230.236; 3.D.230.237; 3.D.230.238; 3.D.230.239; 3.D.230.154; 3.D.230.157; 3.D.230.166; 3.D.230.169; 3.D.230.172; 3.D.230.175; 3.D.230.240; 3.D.230.244; 3.D.231.228; 3.D.231.229; 3.D.231.230; 3.D.231.231; 3.D.231.236; 3.D.231.237; 3.D.231.238; 3.D.231.239; 3.D.231.154; 3.D.231.157; 3.D.231.166; 3.D.231.169; 3.D.231.172; 3.D.231.175; 3.D.231.240; 3.D.231.244; 3.D.236.228; 3.D.236.229; 3.D.236.230; 3.D.236.231; 3.D.236.236; 3.D.236.237; 3.D.236.238; 3.D.236.239; 3.D.236.154; 3.D.236.157; 3.D.236.166; 3.D.236.169; 3.D.236.172; 3.D.236.175; 3.D.236.240; 3.D.236.244; 3.D.237.228; 3.D.237.229; 3.D.237.230; 3.D.237.231; 3.D.237.236; 3.D.237.237; 3.D.237.238; 3.D.237.239; 3.D.237.154; 3.D.237.157; 3.D.237.166; 3.D.237.169; 3.D.237.172; 3.D.237.175; 3.D.237.240; 3.D.237.244; 3.D.238.228; 3.D.238.229; 3.D.238.230; 3.D.238.231; 3.D.238.236; 3.D.238.237; 3.D.238.238; 3.D.238.239; 3.D.238.154; 3.D.238.157; 3.D.238.166; 3.D.238.169; 3.D.238.172; 3.D.238.175; 3.D.238.240; 3.D.238.244; 3.D.239.228; 3.D.239.229; 3.D.239.230; 3.D.239.231; 3.D.239.236; 3.D.239.237; 3.D.239.238; 3.D.239.239; 3.D.239.154; 3.D.239.157; 3.D.239.166; 3.D.239.169; 3.D.239.172; 3.D.239.175; 3.D.239.240; 3.D.239.244; 3.D.154.228; 3.D.154.229; 3.D.154.230; 3.D.154.231; 3.D.154.236; 3.D.154.237; 3.D.154.238; 3.D.154.239; 3.D.154.154; 3.D.154.157; 3.D.154.166; 3.D.154.169; 3.D.154.172; 3.D.154.175; 3.D.154.240; 3.D.154.244; 3.D.157.228; 3.D.157.229; 3.D.157.230; 3.D.157.231; 3.D.157.236; 3.D.157.237; 3.D.157.238; 3.D.157.239; 3.D.157.154; 3.D.157.157; 3.D.157.166; 3.D.157.169; 3.D.157.172; 3.D.157.175; 3.D.157.240; 3.D.157.244; 3.D.166.228; 3.D.166.229; 3.D.166.230; 3.D.166.231; 3.D.166.236; 3.D.166.237; 3.D.166.238; 3.D.166.239; 3.D.166.154; 3.D.166.157; 3.D.166.166; 3.D.166.169; 3.D.166.172; 3.D.166.175; 3.D.166.240; 3.D.166.244; 3.D.169.228; 3.D.169.229; 3.D.169.230; 3.D.169.231; 3.D.169.236; 3.D.169.237; 3.D.169.238; 3.D.169.239; 3.D.169.154; 3.D.169.157; 3.D.169.166; 3.D.169.169; 3.D.169.172; 3.D.169.175; 3.D.169.240; 3.D.169.244; 3.D.172.228; 3.D.172.229; 3.D.172.230; 3.D.172.231; 3.D.172.236; 3.D.172.237; 3.D.172.238; 3.D.172.239; 3.D.172.154; 3.D.172.157; 3.D.172.166; 3.D.172.169; 3.D.172.172; 3.D.172.175; 3.D.172.240; 3.D.172.244; 3.D.175.228; 3.D.175.229; 3.D.175.230; 3.D.175.231; 3.D.175.236; 3.D.175.237; 3.D.175.238; 3.D.175.239; 3.D.175.154; 3.D.175.157; 3.D.175.166; 3.D.175.169; 3.D.175.172; 3.D.175.175; 3.D.175.240; 3.D.175.244; 3.D.240.228; 3.D.240.229; 3.D.240.230; 3.D.240.231; 3.D.240.236; 3.D.240.237; 3.D.240.238; 3.D.240.239; 3.D.240.154; 3.D.240.157; 3.D.240.166; 3.D.240.169; 3.D.240.172; 3.D.240.175; 3.D.240.240; 3.D.240.244; 3.D.244.228; 3.D.244.229; 3.D.244.230; 3.D.244.231; 3.D.244.236; 3.D.244.237; 3.D.244.238; 3.D.244.239; 3.D.244.154; 3.D.244.157; 3.D.244.166; 3.D.244.169; 3.D.244.172; 3.D.244.175; 3.D.244.240; 3.D.244.244;

Prodrugs of 3.E

3.E.228.228; 3.E.228.229; 3.E.228.230; 3.E.228.231; 3.E.228.236; 3.E.228.237; 3.E.228.238; 3.E.228.239; 3.E.228.154; 3.E.228.157; 3.E.228.166; 3.E.228.169; 3.E.228.172; 3.E.228.175; 3.E.228.240; 3.E.228.244; 3.E.229.228; 3.E.229.229; 3.E.229.230; 3.E.229.231; 3.E.229.236; 3.E.229.237; 3.E.229.238; 3.E.229.239; 3.E.229.154; 3.E.229.157; 3.E.229.166;

3.E.229.169; 3.E.229.172; 3.E.229.175; 3.E.229.240; 3.E.229.244; 3.E.230.228; 3.E.230.229; 3.E.230.230; 3.E.230.231; 3.E.230.236; 3.E.230.237; 3.E.230.238; 3.E.230.239; 3.E.230.154; 3.E.230.157; 3.E.230.166; 3.E.230.169; 3.E.230.172; 3.E.230.175; 3.E.230.240; 3.E.230.244; 3.E.231.228; 3.E.231.229; 3.E.231.230; 3.E.231.231; 3.E.231.236; 3.E.231.237; 3.E.231.238; 3.E.231.239; 3.E.231.154; 3.E.231.157; 3.E.231.166; 3.E.231.169; 3.E.231.172; 3.E.231.175; 3.E.231.240; 3.E.231.244; 3.E.236.228; 3.E.236.229; 3.E.236.230; 3.E.236.231; 3.E.236.236; 3.E.236.237; 3.E.236.238; 3.E.236.239; 3.E.236.154; 3.E.236.157; 3.E.236.166; 3.E.236.169; 3.E.236.172; 3.E.236.175; 3.E.236.240; 3.E.236.244; 3.E.237.228; 3.E.237.229; 3.E.237.230; 3.E.237.231; 3.E.237.236; 3.E.237.237; 3.E.237.238; 3.E.237.239; 3.E.237.154; 3.E.237.157; 3.E.237.166; 3.E.237.169; 3.E.237.172; 3.E.237.175; 3.E.237.240; 3.E.237.244; 3.E.238.228; 3.E.238.229; 3.E.238.230; 3.E.238.231; 3.E.238.236; 3.E.238.237; 3.E.238.238; 3.E.238.239; 3.E.238.154; 3.E.238.157; 3.E.238.166; 3.E.238.169; 3.E.238.172; 3.E.238.175; 3.E.238.240; 3.E.238.244; 3.E.239.228; 3.E.239.229; 3.E.239.230; 3.E.239.231; 3.E.239.236; 3.E.239.237; 3.E.239.238; 3.E.239.239; 3.E.239.154; 3.E.239.157; 3.E.239.166; 3.E.239.169; 3.E.239.172; 3.E.239.175; 3.E.239.240; 3.E.239.244; 3.E.154.228; 3.E.154.229; 3.E.154.230; 3.E.154.231; 3.E.154.236; 3.E.154.237; 3.E.154.238; 3.E.154.239; 3.E.154.154; 3.E.154.157; 3.E.154.166; 3.E.154.169; 3.E.154.172; 3.E.154.175; 3.E.154.240; 3.E.154.244; 3.E.157.228; 3.E.157.229; 3.E.157.230; 3.E.157.231; 3.E.157.236; 3.E.157.237; 3.E.157.238; 3.E.157.239; 3.E.157.154; 3.E.157.157; 3.E.157.166; 3.E.157.169; 3.E.157.172; 3.E.157.175; 3.E.157.240; 3.E.157.244; 3.E.166.228; 3.E.166.229; 3.E.166.230; 3.E.166.231; 3.E.166.236; 3.E.166.237; 3.E.166.238; 3.E.166.239; 3.E.166.154; 3.E.166.157; 3.E.166.166; 3.E.166.169; 3.E.166.172; 3.E.166.175; 3.E.166.240; 3.E.166.244; 3.E.169.228; 3.E.169.229; 3.E.169.230; 3.E.169.231; 3.E.169.236; 3.E.169.237; 3.E.169.238; 3.E.169.239; 3.E.169.154; 3.E.169.157; 3.E.169.166; 3.E.169.169; 3.E.169.172; 3.E.169.175; 3.E.169.240; 3.E.169.244; 3.E.172.228; 3.E.172.229; 3.E.172.230; 3.E.172.231; 3.E.172.236; 3.E.172.237; 3.E.172.238; 3.E.172.239; 3.E.172.154; 3.E.172.157; 3.E.172.166; 3.E.172.169; 3.E.172.172; 3.E.172.175; 3.E.172.240; 3.E.172.244; 3.E.175.228; 3.E.175.229; 3.E.175.230; 3.E.175.231; 3.E.175.236; 3.E.175.237; 3.E.175.238; 3.E.175.239; 3.E.175.154; 3.E.175.157; 3.E.175.166; 3.E.175.169; 3.E.175.172; 3.E.175.175; 3.E.175.240; 3.E.175.244; 3.E.240.228; 3.E.240.229; 3.E.240.230; 3.E.240.231; 3.E.240.236; 3.E.240.237; 3.E.240.238; 3.E.240.239; 3.E.240.154; 3.E.240.157; 3.E.240.166; 3.E.240.169; 3.E.240.172; 3.E.240.175; 3.E.240.240; 3.E.240.244; 3.E.244.228; 3.E.244.229; 3.E.244.230; 3.E.244.231; 3.E.244.236; 3.E.244.237; 3.E.244.238; 3.E.244.239; 3.E.244.154; 3.E.244.157; 3.E.244.166; 3.E.244.169; 3.E.244.172; 3.E.244.175; 3.E.244.240; 3.E.244.244;

Prodrugs of 3.G

3.G.228.228; 3.G.228.229; 3.G.228.230; 3.G.228.231; 3.G.228.236; 3.G.228.237; 3.G.228.238; 3.G.228.239; 3.G.228.154; 3.G.228.157; 3.G.228.166; 3.G.228.169; 3.G.228.172; 3.G.228.175; 3.G.228.240; 3.G.228.244; 3.G.229.228; 3.G.229.229; 3.G.229.230; 3.G.229.231; 3.G.229.236; 3.G.229.237; 3.G.229.238; 3.G.229.239; 3.G.229.154; 3.G.229.157; 3.G.229.166; 3.G.229.169; 3.G.229.172; 3.G.229.175; 3.G.229.240; 3.G.229.244; 3.G.230.228; 3.G.230.229; 3.G.230.230; 3.G.230.231; 3.G.230.236; 3.G.230.237; 3.G.230.238; 3.G.230.239; 3.G.230.154; 3.G.230.157; 3.G.230.166; 3.G.230.169; 3.G.230.172; 3.G.230.175; 3.G.230.240; 3.G.230.244; 3.G.231.228; 3.G.231.229; 3.G.231.230; 3.G.231.231; 3.G.231.236; 3.G.231.237; 3.G.231.238; 3.G.231.239; 3.G.231.154; 3.G.231.157; 3.G.231.166; 3.G.231.169; 3.G.231.172; 3.G.231.175; 3.G.231.240; 3.G.231.244; 3.G.236.228; 3.G.236.229;

3.G.236.230; 3.G.236.231; 3.G.236.236; 3.G.236.237; 3.G.236.238; 3.G.236.239; 3.G.236.154; 3.G.236.157; 3.G.236.166; 3.G.236.169; 3.G.236.172; 3.G.236.175; 3.G.236.240; 3.G.236.244; 3.G.237.228; 3.G.237.229; 3.G.237.230; 3.G.237.231; 3.G.237.236; 3.G.237.237; 3.G.237.238; 3.G.237.239; 3.G.237.154; 3.G.237.157; 3.G.237.166; 3.G.237.169; 3.G.237.172; 3.G.237.175; 3.G.237.240; 3.G.237.244; 3.G.238.228; 3.G.238.229; 3.G.238.230; 3.G.238.231; 3.G.238.236; 3.G.238.237; 3.G.238.238; 3.G.238.239; 3.G.238.154; 3.G.238.157; 3.G.238.166; 3.G.238.169; 3.G.238.172; 3.G.238.175; 3.G.238.240; 3.G.238.244; 3.G.239.228; 3.G.239.229; 3.G.239.230; 3.G.239.231; 3.G.239.236; 3.G.239.237; 3.G.239.238; 3.G.239.239; 3.G.239.154; 3.G.239.157; 3.G.239.166; 3.G.239.169; 3.G.239.172; 3.G.239.175; 3.G.239.240; 3.G.239.244; 3.G.154.228; 3.G.154.229; 3.G.154.230; 3.G.154.231; 3.G.154.236; 3.G.154.237; 3.G.154.238; 3.G.154.239; 3.G.154.154; 3.G.154.157; 3.G.154.166; 3.G.154.169; 3.G.154.172; 3.G.154.175; 3.G.154.240; 3.G.154.244; 3.G.157.228; 3.G.157.229; 3.G.157.230; 3.G.157.231; 3.G.157.236; 3.G.157.237; 3.G.157.238; 3.G.157.239; 3.G.157.154; 3.G.157.157; 3.G.157.166; 3.G.157.169; 3.G.157.172; 3.G.157.175; 3.G.157.240; 3.G.157.244; 3.G.166.228; 3.G.166.229; 3.G.166.230; 3.G.166.231; 3.G.166.236; 3.G.166.237; 3.G.166.238; 3.G.166.239; 3.G.166.154; 3.G.166.157; 3.G.166.166; 3.G.166.169; 3.G.166.172; 3.G.166.175; 3.G.166.240; 3.G.166.244; 3.G.169.228; 3.G.169.229; 3.G.169.230; 3.G.169.231; 3.G.169.236; 3.G.169.237; 3.G.169.238; 3.G.169.239; 3.G.169.154; 3.G.169.157; 3.G.169.166; 3.G.169.169; 3.G.169.172; 3.G.169.175; 3.G.169.240; 3.G.169.244; 3.G.172.228; 3.G.172.229; 3.G.172.230; 3.G.172.231; 3.G.172.236; 3.G.172.237; 3.G.172.238; 3.G.172.239; 3.G.172.154; 3.G.172.157; 3.G.172.166; 3.G.172.169; 3.G.172.172; 3.G.172.175; 3.G.172.240; 3.G.172.244; 3.G.175.228; 3.G.175.229; 3.G.175.230; 3.G.175.231; 3.G.175.236; 3.G.175.237; 3.G.175.238; 3.G.175.239; 3.G.175.154; 3.G.175.157; 3.G.175.166; 3.G.175.169; 3.G.175.172; 3.G.175.175; 3.G.175.240; 3.G.175.244; 3.G.240.228; 3.G.240.229; 3.G.240.230; 3.G.240.231; 3.G.240.236; 3.G.240.237; 3.G.240.238; 3.G.240.239; 3.G.240.154; 3.G.240.157; 3.G.240.166; 3.G.240.169; 3.G.240.172; 3.G.240.175; 3.G.240.240; 3.G.240.244; 3.G.244.228; 3.G.244.229; 3.G.244.230; 3.G.244.231; 3.G.244.236; 3.G.244.237; 3.G.244.238; 3.G.244.239; 3.G.244.154; 3.G.244.157; 3.G.244.166; 3.G.244.169; 3.G.244.172; 3.G.244.175; 3.G.244.240; 3.G.244.244;

<u>Prodrugs of 3.I</u>

3.I.228.228; 3.I.228.229; 3.I.228.230; 3.I.228.231; 3.I.228.236; 3.I.228.237; 3.I.228.238; 3.I.228.239; 3.I.228.154; 3.I.228.157; 3.I.228.166; 3.I.228.169; 3.I.228.172; 3.I.228.175; 3.I.228.240; 3.I.228.244; 3.I.229.228; 3.I.229.229; 3.I.229.230; 3.I.229.231; 3.I.229.236; 3.I.229.237; 3.I.229.238; 3.I.229.239; 3.I.229.154; 3.I.229.157; 3.I.229.166; 3.I.229.169; 3.I.229.172; 3.I.229.175; 3.I.229.240; 3.I.229.244; 3.I.230.228; 3.I.230.229; 3.I.230.230; 3.I.230.231; 3.I.230.236; 3.I.230.237; 3.I.230.238; 3.I.230.239; 3.I.230.154; 3.I.230.157; 3.I.230.166; 3.I.230.169; 3.I.230.172; 3.I.230.175; 3.I.230.240; 3.I.230.244; 3.I.231.228; 3.I.231.229; 3.I.231.230; 3.I.231.231; 3.I.231.236; 3.I.231.237; 3.I.231.238; 3.I.231.239; 3.I.231.154; 3.I.231.157; 3.I.231.166; 3.I.231.169; 3.I.231.172; 3.I.231.175; 3.I.231.240; 3.I.231.244; 3.I.236.228; 3.I.236.229; 3.I.236.230; 3.I.236.231; 3.I.236.236; 3.I.236.237; 3.I.236.238; 3.I.236.239; 3.I.236.154; 3.I.236.157; 3.I.236.166; 3.I.236.169; 3.I.236.172; 3.I.236.175; 3.I.236.240; 3.I.236.244; 3.I.237.228; 3.I.237.229; 3.I.237.230; 3.I.237.231;

3.I.237.236; 3.I.237.237; 3.I.237.238; 3.I.237.239; 3.I.237.154; 3.I.237.157; 3.I.237.166; 3.I.237.169; 3.I.237.172; 3.I.237.175; 3.I.237.240; 3.I.237.244; 3.I.238.228; 3.I.238.229; 3.I.238.230; 3.I.238.231; 3.I.238.236; 3.I.238.237; 3.I.238.238; 3.I.238.239; 3.I.238.154; 3.I.238.157; 3.I.238.166; 3.I.238.169; 3.I.238.172; 3.I.238.175; 3.I.238.240; 3.I.238.244; 3.I.239.228; 3.I.239.229; 3.I.239.230; 3.I.239.231; 3.I.239.236; 3.I.239.237; 3.I.239.238; 3.I.239.239; 3.I.239.154; 3.I.239.157; 3.I.239.166; 3.I.239.169; 3.I.239.172; 3.I.239.175; 3.I.239.240; 3.I.239.244; 3.I.154.228; 3.I.154.229; 3.I.154.230; 3.I.154.231; 3.I.154.236; 3.I.154.237; 3.I.154.238; 3.I.154.239; 3.I.154.154; 3.I.154.157; 3.I.154.166; 3.I.154.169; 3.I.154.172; 3.I.154.175; 3.I.154.240; 3.I.154.244; 3.I.157.228; 3.I.157.229; 3.I.157.230; 3.I.157.231; 3.I.157.236; 3.I.157.237; 3.I.157.238; 3.I.157.239; 3.I.157.154; 3.I.157.157; 3.I.157.166; 3.I.157.169; 3.I.157.172; 3.I.157.175; 3.I.157.240; 3.I.157.244; 3.I.166.228; 3.I.166.229; 3.I.166.230; 3.I.166.231; 3.I.166.236; 3.I.166.237; 3.I.166.238; 3.I.166.239; 3.I.166.154; 3.I.166.157; 3.I.166.166; 3.I.166.169; 3.I.166.172; 3.I.166.175; 3.I.166.240; 3.I.166.244; 3.I.169.228; 3.I.169.229; 3.I.169.230; 3.I.169.231; 3.I.169.236; 3.I.169.237; 3.I.169.238; 3.I.169.239; 3.I.169.154; 3.I.169.157; 3.I.169.166; 3.I.169.169; 3.I.169.172; 3.I.169.175; 3.I.169.240; 3.I.169.244; 3.I.172.228; 3.I.172.229; 3.I.172.230; 3.I.172.231; 3.I.172.236; 3.I.172.237; 3.I.172.238; 3.I.172.239; 3.I.172.154; 3.I.172.157; 3.I.172.166; 3.I.172.169; 3.I.172.172; 3.I.172.175; 3.I.172.240; 3.I.172.244; 3.I.175.228; 3.I.175.229; 3.I.175.230; 3.I.175.231; 3.I.175.236; 3.I.175.237; 3.I.175.238; 3.I.175.239; 3.I.175.154; 3.I.175.157; 3.I.175.166; 3.I.175.169; 3.I.175.172; 3.I.175.175; 3.I.175.240; 3.I.175.244; 3.I.240.228; 3.I.240.229; 3.I.240.230; 3.I.240.231; 3.I.240.236; 3.I.240.237; 3.I.240.238; 3.I.240.239; 3.I.240.154; 3.I.240.157; 3.I.240.166; 3.I.240.169; 3.I.240.172; 3.I.240.175; 3.I.240.240; 3.I.240.244; 3.I.244.228; 3.I.244.229; 3.I.244.230; 3.I.244.231; 3.I.244.236; 3.I.244.237; 3.I.244.238; 3.I.244.239; 3.I.244.154; 3.I.244.157; 3.I.244.166; 3.I.244.169; 3.I.244.172; 3.I.244.175; 3.I.244.240; 3.I.244.244;

Prodrugs of 3.J

3.J.228.228; 3.J.228.229; 3.J.228.230; 3.J.228.231; 3.J.228.236; 3.J.228.237; 3.J.228.238; 3.J.228.239; 3.J.228.154; 3.J.228.157; 3.J.228.166; 3.J.228.169; 3.J.228.172; 3.J.228.175; 3.J.228.240; 3.J.228.244; 3.J.229.228; 3.J.229.229; 3.J.229.230; 3.J.229.231; 3.J.229.236; 3.J.229.237; 3.J.229.238; 3.J.229.239; 3.J.229.154; 3.J.229.157; 3.J.229.166; 3.J.229.169; 3.J.229.172; 3.J.229.175; 3.J.229.240; 3.J.229.244; 3.J.230.228; 3.J.230.229; 3.J.230.230; 3.J.230.231; 3.J.230.236; 3.J.230.237; 3.J.230.238; 3.J.230.239; 3.J.230.154; 3.J.230.157; 3.J.230.166; 3.J.230.169; 3.J.230.172; 3.J.230.175; 3.J.230.240; 3.J.230.244; 3.J.231.228; 3.J.231.229; 3.J.231.230; 3.J.231.231; 3.J.231.236; 3.J.231.237; 3.J.231.238; 3.J.231.239; 3.J.231.154; 3.J.231.157; 3.J.231.166; 3.J.231.169; 3.J.231.172; 3.J.231.175; 3.J.231.240; 3.J.231.244; 3.J.236.228; 3.J.236.229; 3.J.236.230; 3.J.236.231; 3.J.236.236; 3.J.236.237; 3.J.236.238; 3.J.236.239; 3.J.236.154; 3.J.236.157; 3.J.236.166; 3.J.236.169; 3.J.236.172; 3.J.236.175; 3.J.236.240; 3.J.236.244; 3.J.237.228; 3.J.237.229; 3.J.237.230; 3.J.237.231; 3.J.237.236; 3.J.237.237; 3.J.237.238; 3.J.237.239; 3.J.237.154; 3.J.237.157; 3.J.237.166; 3.J.237.169; 3.J.237.172; 3.J.237.175; 3.J.237.240; 3.J.237.244; 3.J.238.228; 3.J.238.229; 3.J.238.230; 3.J.238.231; 3.J.238.236; 3.J.238.237; 3.J.238.238; 3.J.238.239; 3.J.238.154; 3.J.238.157; 3.J.238.166; 3.J.238.169; 3.J.238.172; 3.J.238.175; 3.J.238.240; 3.J.238.244; 3.J.239.228; 3.J.239.229; 3.J.239.230; 3.J.239.231; 3.J.239.236; 3.J.239.237; 3.J.239.238; 3.J.239.239; 3.J.239.154; 3.J.239.157; 3.J.239.166; 3.J.239.169; 3.J.239.172; 3.J.239.175; 3.J.239.240; 3.J.239.244; 3.J.154.228; 3.J.154.229; 3.J.154.230; 3.J.154.231; 3.J.154.236;

3.J.154.237; 3.J.154.238; 3.J.154.239; 3.J.154.154; 3.J.154.157; 3.J.154.166; 3.J.154.169; 3.J.154.172; 3.J.154.175; 3.J.154.240; 3.J.154.244; 3.J.157.228; 3.J.157.229; 3.J.157.230; 3.J.157.231; 3.J.157.236; 3.J.157.237; 3.J.157.238; 3.J.157.239; 3.J.157.154; 3.J.157.157; 3.J.157.166; 3.J.157.169; 3.J.157.172; 3.J.157.175; 3.J.157.240; 3.J.157.244; 3.J.166.228; 3.J.166.229; 3.J.166.230; 3.J.166.231; 3.J.166.236; 3.J.166.237; 3.J.166.238; 3.J.166.239; 3.J.166.154; 3.J.166.157; 3.J.166.166; 3.J.166.169; 3.J.166.172; 3.J.166.175; 3.J.166.240; 3.J.166.244; 3.J.169.228; 3.J.169.229; 3.J.169.230; 3.J.169.231; 3.J.169.236; 3.J.169.237; 3.J.169.238; 3.J.169.239; 3.J.169.154; 3.J.169.157; 3.J.169.166; 3.J.169.169; 3.J.169.172; 3.J.169.175; 3.J.169.240; 3.J.169.244; 3.J.172.228; 3.J.172.229; 3.J.172.230; 3.J.172.231; 3.J.172.236; 3.J.172.237; 3.J.172.238; 3.J.172.239; 3.J.172.154; 3.J.172.157; 3.J.172.166; 3.J.172.169; 3.J.172.172; 3.J.172.175; 3.J.172.240; 3.J.172.244; 3.J.175.228; 3.J.175.229; 3.J.175.230; 3.J.175.231; 3.J.175.236; 3.J.175.237; 3.J.175.238; 3.J.175.239; 3.J.175.154; 3.J.175.157; 3.J.175.166; 3.J.175.169; 3.J.175.172; 3.J.175.175; 3.J.175.240; 3.J.175.244; 3.J.240.228; 3.J.240.229; 3.J.240.230; 3.J.240.231; 3.J.240.236; 3.J.240.237; 3.J.240.238; 3.J.240.239; 3.J.240.154; 3.J.240.157; 3.J.240.166; 3.J.240.169; 3.J.240.172; 3.J.240.175; 3.J.240.240; 3.J.240.244; 3.J.244.228; 3.J.244.229; 3.J.244.230; 3.J.244.231; 3.J.244.236; 3.J.244.237; 3.J.244.238; 3.J.244.239; 3.J.244.154; 3.J.244.157; 3.J.244.166; 3.J.244.169; 3.J.244.172; 3.J.244.175; 3.J.244.240; 3.J.244.244;

Prodrugs of 3.L

3.L.228.228; 3.L.228.229; 3.L.228.230; 3.L.228.231; 3.L.228.236; 3.L.228.237; 3.L.228.238; 3.L.228.239; 3.L.228.154; 3.L.228.157; 3.L.228.166; 3.L.228.169; 3.L.228.172; 3.L.228.175; 3.L.228.240; 3.L.228.244; 3.L.229.228; 3.L.229.229; 3.L.229.230; 3.L.229.231; 3.L.229.236; 3.L.229.237; 3.L.229.238; 3.L.229.239; 3.L.229.154; 3.L.229.157; 3.L.229.166; 3.L.229.169; 3.L.229.172; 3.L.229.175; 3.L.229.240; 3.L.229.244; 3.L.230.228; 3.L.230.229; 3.L.230.230; 3.L.230.231; 3.L.230.236; 3.L.230.237; 3.L.230.238; 3.L.230.239; 3.L.230.154; 3.L.230.157; 3.L.230.166; 3.L.230.169; 3.L.230.172; 3.L.230.175; 3.L.230.240; 3.L.230.244; 3.L.231.228; 3.L.231.229; 3.L.231.230; 3.L.231.231; 3.L.231.236; 3.L.231.237; 3.L.231.238; 3.L.231.239; 3.L.231.154; 3.L.231.157; 3.L.231.166; 3.L.231.169; 3.L.231.172; 3.L.231.175; 3.L.231.240; 3.L.231.244; 3.L.236.228; 3.L.236.229; 3.L.236.230; 3.L.236.231; 3.L.236.236; 3.L.236.237; 3.L.236.238; 3.L.236.239; 3.L.236.154; 3.L.236.157; 3.L.236.166; 3.L.236.169; 3.L.236.172; 3.L.236.175; 3.L.236.240; 3.L.236.244; 3.L.237.228; 3.L.237.229; 3.L.237.230; 3.L.237.231; 3.L.237.236; 3.L.237.237; 3.L.237.238; 3.L.237.239; 3.L.237.154; 3.L.237.157; 3.L.237.166; 3.L.237.169; 3.L.237.172; 3.L.237.175; 3.L.237.240; 3.L.237.244; 3.L.238.228; 3.L.238.229; 3.L.238.230; 3.L.238.231; 3.L.238.236; 3.L.238.237; 3.L.238.238; 3.L.238.239; 3.L.238.154; 3.L.238.157; 3.L.238.166; 3.L.238.169; 3.L.238.172; 3.L.238.175; 3.L.238.240; 3.L.238.244; 3.L.239.228; 3.L.239.229; 3.L.239.230; 3.L.239.231; 3.L.239.236; 3.L.239.237; 3.L.239.238; 3.L.239.239; 3.L.239.154; 3.L.239.157; 3.L.239.166; 3.L.239.169; 3.L.239.172; 3.L.239.175; 3.L.239.240; 3.L.239.244; 3.L.154.228; 3.L.154.229; 3.L.154.230; 3.L.154.231; 3.L.154.236; 3.L.154.237; 3.L.154.238; 3.L.154.239; 3.L.154.154; 3.L.154.157; 3.L.154.166; 3.L.154.169; 3.L.154.172; 3.L.154.175; 3.L.154.240; 3.L.154.244; 3.L.157.228; 3.L.157.229; 3.L.157.230; 3.L.157.231; 3.L.157.236; 3.L.157.237; 3.L.157.238; 3.L.157.239; 3.L.157.154; 3.L.157.157; 3.L.157.166; 3.L.157.169; 3.L.157.172; 3.L.157.175; 3.L.157.240; 3.L.157.244; 3.L.166.228; 3.L.166.229; 3.L.166.230; 3.L.166.231; 3.L.166.236; 3.L.166.237; 3.L.166.238; 3.L.166.239; 3.L.166.154; 3.L.166.157; 3.L.166.166; 3.L.166.169; 3.L.166.172; 3.L.166.175; 3.L.166.240; 3.L.166.244; 3.L.169.228; 3.L.169.229; 3.L.169.230; 3.L.169.231; 3.L.169.236;

3.L.169.237; 3.L.169.238; 3.L.169.239; 3.L.169.154; 3.L.169.157; 3.L.169.166; 3.L.169.169; 3.L.169.172; 3.L.169.175; 3.L.169.240; 3.L.169.244; 3.L.172.228; 3.L.172.229; 3.L.172.230; 3.L.172.231; 3.L.172.236; 3.L.172.237; 3.L.172.238; 3.L.172.239; 3.L.172.154; 3.L.172.157; 3.L.172.166; 3.L.172.169; 3.L.172.172; 3.L.172.175; 3.L.172.240; 3.L.172.244; 3.L.175.228; 3.L.175.229; 3.L.175.230; 3.L.175.231; 3.L.175.236; 3.L.175.237; 3.L.175.238; 3.L.175.239; 3.L.175.154; 3.L.175.157; 3.L.175.166; 3.L.175.169; 3.L.175.172; 3.L.175.175; 3.L.175.240; 3.L.175.244; 3.L.240.228; 3.L.240.229; 3.L.240.230; 3.L.240.231; 3.L.240.236; 3.L.240.237; 3.L.240.238; 3.L.240.239; 3.L.240.154; 3.L.240.157; 3.L.240.166; 3.L.240.169; 3.L.240.172; 3.L.240.175; 3.L.240.240; 3.L.240.244; 3.L.244.228; 3.L.244.229; 3.L.244.230; 3.L.244.231; 3.L.244.236; 3.L.244.237; 3.L.244.238; 3.L.244.239; 3.L.244.154; 3.L.244.157; 3.L.244.166; 3.L.244.169; 3.L.244.172; 3.L.244.175; 3.L.244.240; 3.L.244.244;

Prodrugs of 3.O

3.O.228.228; 3.O.228.229; 3.O.228.230; 3.O.228.231; 3.O.228.236; 3.O.228.237; 3.O.228.238; 3.O.228.239; 3.O.228.154; 3.O.228.157; 3.O.228.166; 3.O.228.169; 3.O.228.172; 3.O.228.175; 3.O.228.240; 3.O.228.244; 3.O.229.228; 3.O.229.229; 3.O.229.230; 3.O.229.231; 3.O.229.236; 3.O.229.237; 3.O.229.238; 3.O.229.239; 3.O.229.154; 3.O.229.157; 3.O.229.166; 3.O.229.169; 3.O.229.172; 3.O.229.175; 3.O.229.240; 3.O.229.244; 3.O.230.228; 3.O.230.229; 3.O.230.230; 3.O.230.231; 3.O.230.236; 3.O.230.237; 3.O.230.238; 3.O.230.239; 3.O.230.154; 3.O.230.157; 3.O.230.166; 3.O.230.169; 3.O.230.172; 3.O.230.175; 3.O.230.240; 3.O.230.244; 3.O.231.228; 3.O.231.229; 3.O.231.230; 3.O.231.231; 3.O.231.236; 3.O.231.237; 3.O.231.238; 3.O.231.239; 3.O.231.154; 3.O.231.157; 3.O.231.166; 3.O.231.169; 3.O.231.172; 3.O.231.175; 3.O.231.240; 3.O.231.244; 3.O.236.228; 3.O.236.229; 3.O.236.230; 3.O.236.231; 3.O.236.236; 3.O.236.237; 3.O.236.238; 3.O.236.239; 3.O.236.154; 3.O.236.157; 3.O.236.166; 3.O.236.169; 3.O.236.172; 3.O.236.175; 3.O.236.240; 3.O.236.244; 3.O.237.228; 3.O.237.229; 3.O.237.230; 3.O.237.231; 3.O.237.236; 3.O.237.237; 3.O.237.238; 3.O.237.239; 3.O.237.154; 3.O.237.157; 3.O.237.166; 3.O.237.169; 3.O.237.172; 3.O.237.175; 3.O.237.240; 3.O.237.244; 3.O.238.228; 3.O.238.229; 3.O.238.230; 3.O.238.231; 3.O.238.236; 3.O.238.237; 3.O.238.238; 3.O.238.239; 3.O.238.154; 3.O.238.157; 3.O.238.166; 3.O.238.169; 3.O.238.172; 3.O.238.175; 3.O.238.240; 3.O.238.244; 3.O.239.228; 3.O.239.229; 3.O.239.230; 3.O.239.231; 3.O.239.236; 3.O.239.237; 3.O.239.238; 3.O.239.239; 3.O.239.154; 3.O.239.157; 3.O.239.166; 3.O.239.169; 3.O.239.172; 3.O.239.175; 3.O.239.240; 3.O.239.244; 3.O.154.228; 3.O.154.229; 3.O.154.230; 3.O.154.231; 3.O.154.236; 3.O.154.237; 3.O.154.238; 3.O.154.239; 3.O.154.154; 3.O.154.157; 3.O.154.166; 3.O.154.169; 3.O.154.172; 3.O.154.175; 3.O.154.240; 3.O.154.244; 3.O.157.228; 3.O.157.229; 3.O.157.230; 3.O.157.231; 3.O.157.236; 3.O.157.237; 3.O.157.238; 3.O.157.239; 3.O.157.154; 3.O.157.157; 3.O.157.166; 3.O.157.169; 3.O.157.172; 3.O.157.175; 3.O.157.240; 3.O.157.244; 3.O.166.228; 3.O.166.229; 3.O.166.230; 3.O.166.231; 3.O.166.236; 3.O.166.237; 3.O.166.238; 3.O.166.239; 3.O.166.154; 3.O.166.157; 3.O.166.166; 3.O.166.169; 3.O.166.172; 3.O.166.175; 3.O.166.240; 3.O.166.244; 3.O.169.228; 3.O.169.229; 3.O.169.230; 3.O.169.231; 3.O.169.236; 3.O.169.237; 3.O.169.238; 3.O.169.239; 3.O.169.154; 3.O.169.157; 3.O.169.166; 3.O.169.169; 3.O.169.172; 3.O.169.175; 3.O.169.240; 3.O.169.244; 3.O.172.228; 3.O.172.229; 3.O.172.230; 3.O.172.231; 3.O.172.236; 3.O.172.237;

3.O.172.238; 3.O.172.239; 3.O.172.154; 3.O.172.157; 3.O.172.166; 3.O.172.169; 3.O.172.172; 3.O.172.175; 3.O.172.240; 3.O.172.244; 3.O.175.228; 3.O.175.229; 3.O.175.230; 3.O.175.231; 3.O.175.236; 3.O.175.237; 3.O.175.238; 3.O.175.239; 3.O.175.154; 3.O.175.157; 3.O.175.166; 3.O.175.169; 3.O.175.172; 3.O.175.175; 3.O.175.240; 3.O.175.244; 3.O.240.228; 3.O.240.229; 3.O.240.230; 3.O.240.231; 3.O.240.236; 3.O.240.237; 3.O.240.238; 3.O.240.239; 3.O.240.154; 3.O.240.157; 3.O.240.166; 3.O.240.169; 3.O.240.172; 3.O.240.175; 3.O.240.240; 3.O.240.244; 3.O.244.228; 3.O.244.229; 3.O.244.230; 3.O.244.231; 3.O.244.236; 3.O.244.237; 3.O.244.238; 3.O.244.239; 3.O.244.154; 3.O.244.157; 3.O.244.166; 3.O.244.169; 3.O.244.172; 3.O.244.175; 3.O.244.240; 3.O.244.244;

Prodrugs of 3.P

3.P.228.228; 3.P.228.229; 3.P.228.230; 3.P.228.231; 3.P.228.236; 3.P.228.237; 3.P.228.238; 3.P.228.239; 3.P.228.154; 3.P.228.157; 3.P.228.166; 3.P.228.169; 3.P.228.172; 3.P.228.175; 3.P.228.240; 3.P.228.244; 3.P.229.228; 3.P.229.229; 3.P.229.230; 3.P.229.231; 3.P.229.236; 3.P.229.237; 3.P.229.238; 3.P.229.239; 3.P.229.154; 3.P.229.157; 3.P.229.166; 3.P.229.169; 3.P.229.172; 3.P.229.175; 3.P.229.240; 3.P.229.244; 3.P.230.228; 3.P.230.229; 3.P.230.230; 3.P.230.231; 3.P.230.236; 3.P.230.237; 3.P.230.238; 3.P.230.239; 3.P.230.154; 3.P.230.157; 3.P.230.166; 3.P.230.169; 3.P.230.172; 3.P.230.175; 3.P.230.240; 3.P.230.244; 3.P.231.228; 3.P.231.229; 3.P.231.230; 3.P.231.231; 3.P.231.236; 3.P.231.237; 3.P.231.238; 3.P.231.239; 3.P.231.154; 3.P.231.157; 3.P.231.166; 3.P.231.169; 3.P.231.172; 3.P.231.175; 3.P.231.240; 3.P.231.244; 3.P.236.228; 3.P.236.229; 3.P.236.230; 3.P.236.231; 3.P.236.236; 3.P.236.237; 3.P.236.238; 3.P.236.239; 3.P.236.154; 3.P.236.157; 3.P.236.166; 3.P.236.169; 3.P.236.172; 3.P.236.175; 3.P.236.240; 3.P.236.244; 3.P.237.228; 3.P.237.229; 3.P.237.230; 3.P.237.231; 3.P.237.236; 3.P.237.237; 3.P.237.238; 3.P.237.239; 3.P.237.154; 3.P.237.157; 3.P.237.166; 3.P.237.169; 3.P.237.172; 3.P.237.175; 3.P.237.240; 3.P.237.244; 3.P.238.228; 3.P.238.229; 3.P.238.230; 3.P.238.231; 3.P.238.236; 3.P.238.237; 3.P.238.238; 3.P.238.239; 3.P.238.154; 3.P.238.157; 3.P.238.166; 3.P.238.169; 3.P.238.172; 3.P.238.175; 3.P.238.240; 3.P.238.244; 3.P.239.228; 3.P.239.229; 3.P.239.230; 3.P.239.231; 3.P.239.236; 3.P.239.237; 3.P.239.238; 3.P.239.239; 3.P.239.154; 3.P.239.157; 3.P.239.166; 3.P.239.169; 3.P.239.172; 3.P.239.175; 3.P.239.240; 3.P.239.244; 3.P.154.228; 3.P.154.229; 3.P.154.230; 3.P.154.231; 3.P.154.236; 3.P.154.237; 3.P.154.238; 3.P.154.239; 3.P.154.154; 3.P.154.157; 3.P.154.166; 3.P.154.169; 3.P.154.172; 3.P.154.175; 3.P.154.240; 3.P.154.244; 3.P.157.228; 3.P.157.229; 3.P.157.230; 3.P.157.231; 3.P.157.236; 3.P.157.237; 3.P.157.238; 3.P.157.239; 3.P.157.154; 3.P.157.157; 3.P.157.166; 3.P.157.169; 3.P.157.172; 3.P.157.175; 3.P.157.240; 3.P.157.244; 3.P.166.228; 3.P.166.229; 3.P.166.230; 3.P.166.231; 3.P.166.236; 3.P.166.237; 3.P.166.238; 3.P.166.239; 3.P.166.154; 3.P.166.157; 3.P.166.166; 3.P.166.169; 3.P.166.172; 3.P.166.175; 3.P.166.240; 3.P.166.244; 3.P.169.228; 3.P.169.229; 3.P.169.230; 3.P.169.231; 3.P.169.236; 3.P.169.237; 3.P.169.238; 3.P.169.239; 3.P.169.154; 3.P.169.157; 3.P.169.166; 3.P.169.169; 3.P.169.172; 3.P.169.175; 3.P.169.240; 3.P.169.244; 3.P.172.228; 3.P.172.229; 3.P.172.230; 3.P.172.231; 3.P.172.236; 3.P.172.237; 3.P.172.238; 3.P.172.239; 3.P.172.154; 3.P.172.157; 3.P.172.166; 3.P.172.169; 3.P.172.172; 3.P.172.175; 3.P.172.240; 3.P.172.244; 3.P.175.228; 3.P.175.229; 3.P.175.230; 3.P.175.231; 3.P.175.236; 3.P.175.237; 3.P.175.238; 3.P.175.239; 3.P.175.154; 3.P.175.157; 3.P.175.166; 3.P.175.169; 3.P.175.172; 3.P.175.175; 3.P.175.240; 3.P.175.244; 3.P.240.228; 3.P.240.229; 3.P.240.230; 3.P.240.231; 3.P.240.236; 3.P.240.237; 3.P.240.238; 3.P.240.239; 3.P.240.154; 3.P.240.157; 3.P.240.166; 3.P.240.169; 3.P.240.172;

3.P.240.175; 3.P.240.240; 3.P.240.244; 3.P.244.228; 3.P.244.229; 3.P.244.230; 3.P.244.231; 3.P.244.236; 3.P.244.237; 3.P.244.238; 3.P.244.239; 3.P.244.154; 3.P.244.157; 3.P.244.166; 3.P.244.169; 3.P.244.172; 3.P.244.175; 3.P.244.240; 3.P.244.244;

Prodrugs of 3.U

3.U.228.228; 3.U.228.229; 3.U.228.230; 3.U.228.231; 3.U.228.236; 3.U.228.237; 3.U.228.238; 3.U.228.239; 3.U.228.154; 3.U.228.157; 3.U.228.166; 3.U.228.169; 3.U.228.172; 3.U.228.175; 3.U.228.240; 3.U.228.244; 3.U.229.228; 3.U.229.229; 3.U.229.230; 3.U.229.231; 3.U.229.236; 3.U.229.237; 3.U.229.238; 3.U.229.239; 3.U.229.154; 3.U.229.157; 3.U.229.166; 3.U.229.169; 3.U.229.172; 3.U.229.175; 3.U.229.240; 3.U.229.244; 3.U.230.228; 3.U.230.229; 3.U.230.230; 3.U.230.231; 3.U.230.236; 3.U.230.237; 3.U.230.238; 3.U.230.239; 3.U.230.154; 3.U.230.157; 3.U.230.166; 3.U.230.169; 3.U.230.172; 3.U.230.175; 3.U.230.240; 3.U.230.244; 3.U.231.228; 3.U.231.229; 3.U.231.230; 3.U.231.231; 3.U.231.236; 3.U.231.237; 3.U.231.238; 3.U.231.239; 3.U.231.154; 3.U.231.157; 3.U.231.166; 3.U.231.169; 3.U.231.172; 3.U.231.175; 3.U.231.240; 3.U.231.244; 3.U.236.228; 3.U.236.229; 3.U.236.230; 3.U.236.231; 3.U.236.236; 3.U.236.237; 3.U.236.238; 3.U.236.239; 3.U.236.154; 3.U.236.157; 3.U.236.166; 3.U.236.169; 3.U.236.172; 3.U.236.175; 3.U.236.240; 3.U.236.244; 3.U.237.228; 3.U.237.229; 3.U.237.230; 3.U.237.231; 3.U.237.236; 3.U.237.237; 3.U.237.238; 3.U.237.239; 3.U.237.154; 3.U.237.157; 3.U.237.166; 3.U.237.169; 3.U.237.172; 3.U.237.175; 3.U.237.240; 3.U.237.244; 3.U.238.228; 3.U.238.229; 3.U.238.230; 3.U.238.231; 3.U.238.236; 3.U.238.237; 3.U.238.238; 3.U.238.239; 3.U.238.154; 3.U.238.157; 3.U.238.166; 3.U.238.169; 3.U.238.172; 3.U.238.175; 3.U.238.240; 3.U.238.244; 3.U.239.228; 3.U.239.229; 3.U.239.230; 3.U.239.231; 3.U.239.236; 3.U.239.237; 3.U.239.238; 3.U.239.239; 3.U.239.154; 3.U.239.157; 3.U.239.166; 3.U.239.169; 3.U.239.172; 3.U.239.175; 3.U.239.240; 3.U.239.244; 3.U.154.228; 3.U.154.229; 3.U.154.230; 3.U.154.231; 3.U.154.236; 3.U.154.237; 3.U.154.238; 3.U.154.239; 3.U.154.154; 3.U.154.157; 3.U.154.166; 3.U.154.169; 3.U.154.172; 3.U.154.175; 3.U.154.240; 3.U.154.244; 3.U.157.228; 3.U.157.229; 3.U.157.230; 3.U.157.231; 3.U.157.236; 3.U.157.237; 3.U.157.238; 3.U.157.239; 3.U.157.154; 3.U.157.157; 3.U.157.166; 3.U.157.169; 3.U.157.172; 3.U.157.175; 3.U.157.240; 3.U.157.244; 3.U.166.228; 3.U.166.229; 3.U.166.230; 3.U.166.231; 3.U.166.236; 3.U.166.237; 3.U.166.238; 3.U.166.239; 3.U.166.154; 3.U.166.157; 3.U.166.166; 3.U.166.169; 3.U.166.172; 3.U.166.175; 3.U.166.240; 3.U.166.244; 3.U.169.228; 3.U.169.229; 3.U.169.230; 3.U.169.231; 3.U.169.236; 3.U.169.237; 3.U.169.238; 3.U.169.239; 3.U.169.154; 3.U.169.157; 3.U.169.166; 3.U.169.169; 3.U.169.172; 3.U.169.175; 3.U.169.240; 3.U.169.244; 3.U.172.228; 3.U.172.229; 3.U.172.230; 3.U.172.231; 3.U.172.236; 3.U.172.237; 3.U.172.238; 3.U.172.239; 3.U.172.154; 3.U.172.157; 3.U.172.166; 3.U.172.169; 3.U.172.172; 3.U.172.175; 3.U.172.240; 3.U.172.244; 3.U.175.228; 3.U.175.229; 3.U.175.230; 3.U.175.231; 3.U.175.236; 3.U.175.237; 3.U.175.238; 3.U.175.239; 3.U.175.154; 3.U.175.157; 3.U.175.166; 3.U.175.169; 3.U.175.172; 3.U.175.175; 3.U.175.240; 3.U.175.244; 3.U.240.228; 3.U.240.229; 3.U.240.230; 3.U.240.231; 3.U.240.236; 3.U.240.237; 3.U.240.238; 3.U.240.239; 3.U.240.154; 3.U.240.157; 3.U.240.166; 3.U.240.169; 3.U.240.172; 3.U.240.175; 3.U.240.240; 3.U.240.244; 3.U.244.228; 3.U.244.229; 3.U.244.230; 3.U.244.231; 3.U.244.236; 3.U.244.237;

3.U.244.238; 3.U.244.239; 3.U.244.154; 3.U.244.157; 3.U.244.166; 3.U.244.169; 3.U.244.172; 3.U.244.175; 3.U.244.240; 3.U.244.244;

Prodrugs of 3.W

3.W.228.228; 3.W.228.229; 3.W.228.230; 3.W.228.231; 3.W.228.236; 3.W.228.237; 3.W.228.238; 3.W.228.239; 3.W.228.154; 3.W.228.157; 3.W.228.166; 3.W.228.169; 3.W.228.172; 3.W.228.175; 3.W.228.240; 3.W.228.244; 3.W.229.228; 3.W.229.229; 3.W.229.230; 3.W.229.231; 3.W.229.236; 3.W.229.237; 3.W.229.238; 3.W.229.239; 3.W.229.154; 3.W.229.157; 3.W.229.166; 3.W.229.169; 3.W.229.172; 3.W.229.175; 3.W.229.240; 3.W.229.244; 3.W.230.228; 3.W.230.229; 3.W.230.230; 3.W.230.231; 3.W.230.236; 3.W.230.237; 3.W.230.238; 3.W.230.239; 3.W.230.154; 3.W.230.157; 3.W.230.166; 3.W.230.169; 3.W.230.172; 3.W.230.175; 3.W.230.240; 3.W.230.244; 3.W.231.228; 3.W.231.229; 3.W.231.230; 3.W.231.231; 3.W.231.236; 3.W.231.237; 3.W.231.238; 3.W.231.239; 3.W.231.154; 3.W.231.157; 3.W.231.166; 3.W.231.169; 3.W.231.172; 3.W.231.175; 3.W.231.240; 3.W.231.244; 3.W.236.228; 3.W.236.229; 3.W.236.230; 3.W.236.231; 3.W.236.236; 3.W.236.237; 3.W.236.238; 3.W.236.239; 3.W.236.154; 3.W.236.157; 3.W.236.166; 3.W.236.169; 3.W.236.172; 3.W.236.175; 3.W.236.240; 3.W.236.244; 3.W.237.228; 3.W.237.229; 3.W.237.230; 3.W.237.231; 3.W.237.236; 3.W.237.237; 3.W.237.238; 3.W.237.239; 3.W.237.154; 3.W.237.157; 3.W.237.166; 3.W.237.169; 3.W.237.172; 3.W.237.175; 3.W.237.240; 3.W.237.244; 3.W.238.228; 3.W.238.229; 3.W.238.230; 3.W.238.231; 3.W.238.236; 3.W.238.237; 3.W.238.238; 3.W.238.239; 3.W.238.154; 3.W.238.157; 3.W.238.166; 3.W.238.169; 3.W.238.172; 3.W.238.175; 3.W.238.240; 3.W.238.244; 3.W.239.228; 3.W.239.229; 3.W.239.230; 3.W.239.231; 3.W.239.236; 3.W.239.237; 3.W.239.238; 3.W.239.239; 3.W.239.154; 3.W.239.157; 3.W.239.166; 3.W.239.169; 3.W.239.172; 3.W.239.175; 3.W.239.240; 3.W.239.244; 3.W.154.228; 3.W.154.229; 3.W.154.230; 3.W.154.231; 3.W.154.236; 3.W.154.237; 3.W.154.238; 3.W.154.239; 3.W.154.154; 3.W.154.157; 3.W.154.166; 3.W.154.169; 3.W.154.172; 3.W.154.175; 3.W.154.240; 3.W.154.244; 3.W.157.228; 3.W.157.229; 3.W.157.230; 3.W.157.231; 3.W.157.236; 3.W.157.237; 3.W.157.238; 3.W.157.239; 3.W.157.154; 3.W.157.157; 3.W.157.166; 3.W.157.169; 3.W.157.172; 3.W.157.175; 3.W.157.240; 3.W.157.244; 3.W.166.228; 3.W.166.229; 3.W.166.230; 3.W.166.231; 3.W.166.236; 3.W.166.237; 3.W.166.238; 3.W.166.239; 3.W.166.154; 3.W.166.157; 3.W.166.166; 3.W.166.169; 3.W.166.172; 3.W.166.175; 3.W.166.240; 3.W.166.244; 3.W.169.228; 3.W.169.229; 3.W.169.230; 3.W.169.231; 3.W.169.236; 3.W.169.237; 3.W.169.238; 3.W.169.239; 3.W.169.154; 3.W.169.157; 3.W.169.166; 3.W.169.169; 3.W.169.172; 3.W.169.175; 3.W.169.240; 3.W.169.244; 3.W.172.228; 3.W.172.229; 3.W.172.230; 3.W.172.231; 3.W.172.236; 3.W.172.237; 3.W.172.238; 3.W.172.239; 3.W.172.154; 3.W.172.157; 3.W.172.166; 3.W.172.169; 3.W.172.172; 3.W.172.175; 3.W.172.240; 3.W.172.244; 3.W.175.228; 3.W.175.229; 3.W.175.230; 3.W.175.231; 3.W.175.236; 3.W.175.237; 3.W.175.238; 3.W.175.239; 3.W.175.154; 3.W.175.157; 3.W.175.166; 3.W.175.169; 3.W.175.172; 3.W.175.175; 3.W.175.240; 3.W.175.244; 3.W.240.228; 3.W.240.229; 3.W.240.230; 3.W.240.231; 3.W.240.236; 3.W.240.237; 3.W.240.238; 3.W.240.239; 3.W.240.154; 3.W.240.157; 3.W.240.166; 3.W.240.169; 3.W.240.172; 3.W.240.175; 3.W.240.240; 3.W.240.244; 3.W.244.228; 3.W.244.229; 3.W.244.230; 3.W.244.231; 3.W.244.236; 3.W.244.237;

3.W.244.238; 3.W.244.239; 3.W.244.154; 3.W.244.157; 3.W.244.166; 3.W.244.169; 3.W.244.172; 3.W.244.175; 3.W.244.240; 3.W.244.244;

Prodrugs of 3.Y

3.Y.228.228; 3.Y.228.229; 3.Y.228.230; 3.Y.228.231; 3.Y.228.236; 3.Y.228.237; 3.Y.228.238; 3.Y.228.239; 3.Y.228.154; 3.Y.228.157; 3.Y.228.166; 3.Y.228.169; 3.Y.228.172; 3.Y.228.175; 3.Y.228.240; 3.Y.228.244; 3.Y.229.228; 3.Y.229.229; 3.Y.229.230; 3.Y.229.231; 3.Y.229.236; 3.Y.229.237; 3.Y.229.238; 3.Y.229.239; 3.Y.229.154; 3.Y.229.157; 3.Y.229.166; 3.Y.229.169; 3.Y.229.172; 3.Y.229.175; 3.Y.229.240; 3.Y.229.244; 3.Y.230.228; 3.Y.230.229; 3.Y.230.230; 3.Y.230.231; 3.Y.230.236; 3.Y.230.237; 3.Y.230.238; 3.Y.230.239; 3.Y.230.154; 3.Y.230.157; 3.Y.230.166; 3.Y.230.169; 3.Y.230.172; 3.Y.230.175; 3.Y.230.240; 3.Y.230.244; 3.Y.231.228; 3.Y.231.229; 3.Y.231.230; 3.Y.231.231; 3.Y.231.236; 3.Y.231.237; 3.Y.231.238; 3.Y.231.239; 3.Y.231.154; 3.Y.231.157; 3.Y.231.166; 3.Y.231.169; 3.Y.231.172; 3.Y.231.175; 3.Y.231.240; 3.Y.231.244; 3.Y.236.228; 3.Y.236.229; 3.Y.236.230; 3.Y.236.231; 3.Y.236.236; 3.Y.236.237; 3.Y.236.238; 3.Y.236.239; 3.Y.236.154; 3.Y.236.157; 3.Y.236.166; 3.Y.236.169; 3.Y.236.172; 3.Y.236.175; 3.Y.236.240; 3.Y.236.244; 3.Y.237.228; 3.Y.237.229; 3.Y.237.230; 3.Y.237.231; 3.Y.237.236; 3.Y.237.237; 3.Y.237.238; 3.Y.237.239; 3.Y.237.154; 3.Y.237.157; 3.Y.237.166; 3.Y.237.169; 3.Y.237.172; 3.Y.237.175; 3.Y.237.240; 3.Y.237.244; 3.Y.238.228; 3.Y.238.229; 3.Y.238.230; 3.Y.238.231; 3.Y.238.236; 3.Y.238.237; 3.Y.238.238; 3.Y.238.239; 3.Y.238.154; 3.Y.238.157; 3.Y.238.166; 3.Y.238.169; 3.Y.238.172; 3.Y.238.175; 3.Y.238.240; 3.Y.238.244; 3.Y.239.228; 3.Y.239.229; 3.Y.239.230; 3.Y.239.231; 3.Y.239.236; 3.Y.239.237; 3.Y.239.238; 3.Y.239.239; 3.Y.239.154; 3.Y.239.157; 3.Y.239.166; 3.Y.239.169; 3.Y.239.172; 3.Y.239.175; 3.Y.239.240; 3.Y.239.244; 3.Y.154.228; 3.Y.154.229; 3.Y.154.230; 3.Y.154.231; 3.Y.154.236; 3.Y.154.237; 3.Y.154.238; 3.Y.154.239; 3.Y.154.154; 3.Y.154.157; 3.Y.154.166; 3.Y.154.169; 3.Y.154.172; 3.Y.154.175; 3.Y.154.240; 3.Y.154.244; 3.Y.157.228; 3.Y.157.229; 3.Y.157.230; 3.Y.157.231; 3.Y.157.236; 3.Y.157.237; 3.Y.157.238; 3.Y.157.239; 3.Y.157.154; 3.Y.157.157; 3.Y.157.166; 3.Y.157.169; 3.Y.157.172; 3.Y.157.175; 3.Y.157.240; 3.Y.157.244; 3.Y.166.228; 3.Y.166.229; 3.Y.166.230; 3.Y.166.231; 3.Y.166.236; 3.Y.166.237; 3.Y.166.238; 3.Y.166.239; 3.Y.166.154; 3.Y.166.157; 3.Y.166.166; 3.Y.166.169; 3.Y.166.172; 3.Y.166.175; 3.Y.166.240; 3.Y.166.244; 3.Y.169.228; 3.Y.169.229; 3.Y.169.230; 3.Y.169.231; 3.Y.169.236; 3.Y.169.237; 3.Y.169.238; 3.Y.169.239; 3.Y.169.154; 3.Y.169.157; 3.Y.169.166; 3.Y.169.169; 3.Y.169.172; 3.Y.169.175; 3.Y.169.240; 3.Y.169.244; 3.Y.172.228; 3.Y.172.229; 3.Y.172.230; 3.Y.172.231; 3.Y.172.236; 3.Y.172.237; 3.Y.172.238; 3.Y.172.239; 3.Y.172.154; 3.Y.172.157; 3.Y.172.166; 3.Y.172.169; 3.Y.172.172; 3.Y.172.175; 3.Y.172.240; 3.Y.172.244; 3.Y.175.228; 3.Y.175.229; 3.Y.175.230; 3.Y.175.231; 3.Y.175.236; 3.Y.175.237; 3.Y.175.238; 3.Y.175.239; 3.Y.175.154; 3.Y.175.157; 3.Y.175.166; 3.Y.175.169; 3.Y.175.172; 3.Y.175.175; 3.Y.175.240; 3.Y.175.244; 3.Y.240.228; 3.Y.240.229; 3.Y.240.230; 3.Y.240.231; 3.Y.240.236; 3.Y.240.237; 3.Y.240.238; 3.Y.240.239; 3.Y.240.154; 3.Y.240.157; 3.Y.240.166; 3.Y.240.169; 3.Y.240.172; 3.Y.240.175; 3.Y.240.240; 3.Y.240.244; 3.Y.244.228; 3.Y.244.229; 3.Y.244.230; 3.Y.244.231; 3.Y.244.236; 3.Y.244.237;

3.Y.244.238; 3.Y.244.239; 3.Y.244.154; 3.Y.244.157; 3.Y.244.166; 3.Y.244.169; 3.Y.244.172; 3.Y.244.175; 3.Y.244.240; 3.Y.244.244;

Prodrugs of 4.B

4.B.228.228; 4.B.228.229; 4.B.228.230; 4.B.228.231; 4.B.228.236; 4.B.228.237; 4.B.228.238; 4.B.228.239; 4.B.228.154; 4.B.228.157; 4.B.228.166; 4.B.228.169; 4.B.228.172; 4.B.228.175; 4.B.228.240; 4.B.228.244; 4.B.229.228; 4.B.229.229; 4.B.229.230; 4.B.229.231; 4.B.229.236; 4.B.229.237; 4.B.229.238; 4.B.229.239; 4.B.229.154; 4.B.229.157; 4.B.229.166; 4.B.229.169; 4.B.229.172; 4.B.229.175; 4.B.229.240; 4.B.229.244; 4.B.230.228; 4.B.230.229; 4.B.230.230; 4.B.230.231; 4.B.230.236; 4.B.230.237; 4.B.230.238; 4.B.230.239; 4.B.230.154; 4.B.230.157; 4.B.230.166; 4.B.230.169; 4.B.230.172; 4.B.230.175; 4.B.230.240; 4.B.230.244; 4.B.231.228; 4.B.231.229; 4.B.231.230; 4.B.231.231; 4.B.231.236; 4.B.231.237; 4.B.231.238; 4.B.231.239; 4.B.231.154; 4.B.231.157; 4.B.231.166; 4.B.231.169; 4.B.231.172; 4.B.231.175; 4.B.231.240; 4.B.231.244; 4.B.236.228; 4.B.236.229; 4.B.236.230; 4.B.236.231; 4.B.236.236; 4.B.236.237; 4.B.236.238; 4.B.236.239; 4.B.236.154; 4.B.236.157; 4.B.236.166; 4.B.236.169; 4.B.236.172; 4.B.236.175; 4.B.236.240; 4.B.236.244; 4.B.237.228; 4.B.237.229; 4.B.237.230; 4.B.237.231; 4.B.237.236; 4.B.237.237; 4.B.237.238; 4.B.237.239; 4.B.237.154; 4.B.237.157; 4.B.237.166; 4.B.237.169; 4.B.237.172; 4.B.237.175; 4.B.237.240; 4.B.237.244; 4.B.238.228; 4.B.238.229; 4.B.238.230; 4.B.238.231; 4.B.238.236; 4.B.238.237; 4.B.238.238; 4.B.238.239; 4.B.238.154; 4.B.238.157; 4.B.238.166; 4.B.238.169; 4.B.238.172; 4.B.238.175; 4.B.238.240; 4.B.238.244; 4.B.239.228; 4.B.239.229; 4.B.239.230; 4.B.239.231; 4.B.239.236; 4.B.239.237; 4.B.239.238; 4.B.239.239; 4.B.239.154; 4.B.239.157; 4.B.239.166; 4.B.239.169; 4.B.239.172; 4.B.239.175; 4.B.239.240; 4.B.239.244; 4.B.154.228; 4.B.154.229; 4.B.154.230; 4.B.154.231; 4.B.154.236; 4.B.154.237; 4.B.154.238; 4.B.154.239; 4.B.154.154; 4.B.154.157; 4.B.154.166; 4.B.154.169; 4.B.154.172; 4.B.154.175; 4.B.154.240; 4.B.154.244; 4.B.157.228; 4.B.157.229; 4.B.157.230; 4.B.157.231; 4.B.157.236; 4.B.157.237; 4.B.157.238; 4.B.157.239; 4.B.157.154; 4.B.157.157; 4.B.157.166; 4.B.157.169; 4.B.157.172; 4.B.157.175; 4.B.157.240; 4.B.157.244; 4.B.166.228; 4.B.166.229; 4.B.166.230; 4.B.166.231; 4.B.166.236; 4.B.166.237; 4.B.166.238; 4.B.166.239; 4.B.166.154; 4.B.166.157; 4.B.166.166; 4.B.166.169; 4.B.166.172; 4.B.166.175; 4.B.166.240; 4.B.166.244; 4.B.169.228; 4.B.169.229; 4.B.169.230; 4.B.169.231; 4.B.169.236; 4.B.169.237; 4.B.169.238; 4.B.169.239; 4.B.169.154; 4.B.169.157; 4.B.169.166; 4.B.169.169; 4.B.169.172; 4.B.169.175; 4.B.169.240; 4.B.169.244; 4.B.172.228; 4.B.172.229; 4.B.172.230; 4.B.172.231; 4.B.172.236; 4.B.172.237; 4.B.172.238; 4.B.172.239; 4.B.172.154; 4.B.172.157; 4.B.172.166; 4.B.172.169; 4.B.172.172; 4.B.172.175; 4.B.172.240; 4.B.172.244; 4.B.175.228; 4.B.175.229; 4.B.175.230; 4.B.175.231; 4.B.175.236; 4.B.175.237; 4.B.175.238; 4.B.175.239; 4.B.175.154; 4.B.175.157; 4.B.175.166; 4.B.175.169; 4.B.175.172; 4.B.175.175; 4.B.175.240; 4.B.175.244; 4.B.240.228; 4.B.240.229; 4.B.240.230; 4.B.240.231; 4.B.240.236; 4.B.240.237; 4.B.240.238; 4.B.240.239; 4.B.240.154; 4.B.240.157; 4.B.240.166; 4.B.240.169; 4.B.240.172; 4.B.240.175; 4.B.240.240; 4.B.240.244; 4.B.244.228; 4.B.244.229; 4.B.244.230; 4.B.244.231; 4.B.244.236; 4.B.244.237; 4.B.244.238; 4.B.244.239; 4.B.244.154; 4.B.244.157; 4.B.244.166; 4.B.244.169; 4.B.244.172; 4.B.244.175; 4.B.244.240; 4.B.244.244;

Prodrugs of 4.D

4.D.228.228; 4.D.228.229; 4.D.228.230; 4.D.228.231; 4.D.228.236; 4.D.228.237; 4.D.228.238; 4.D.228.239; 4.D.228.154; 4.D.228.157; 4.D.228.166; 4.D.228.169; 4.D.228.172; 4.D.228.175; 4.D.228.240; 4.D.228.244; 4.D.229.228; 4.D.229.229;

4.D.229.230; 4.D.229.231; 4.D.229.236; 4.D.229.237; 4.D.229.238; 4.D.229.239; 4.D.229.154; 4.D.229.157; 4.D.229.166; 4.D.229.169; 4.D.229.172; 4.D.229.175; 4.D.229.240; 4.D.229.244; 4.D.230.228; 4.D.230.229; 4.D.230.230; 4.D.230.231; 4.D.230.236; 4.D.230.237; 4.D.230.238; 4.D.230.239; 4.D.230.154; 4.D.230.157; 4.D.230.166; 4.D.230.169; 4.D.230.172; 4.D.230.175; 4.D.230.240; 4.D.230.244; 4.D.231.228; 4.D.231.229; 4.D.231.230; 4.D.231.231; 4.D.231.236; 4.D.231.237; 4.D.231.238; 4.D.231.239; 4.D.231.154; 4.D.231.157; 4.D.231.166; 4.D.231.169; 4.D.231.172; 4.D.231.175; 4.D.231.240; 4.D.231.244; 4.D.236.228; 4.D.236.229; 4.D.236.230; 4.D.236.231; 4.D.236.236; 4.D.236.237; 4.D.236.238; 4.D.236.239; 4.D.236.154; 4.D.236.157; 4.D.236.166; 4.D.236.169; 4.D.236.172; 4.D.236.175; 4.D.236.240; 4.D.236.244; 4.D.237.228; 4.D.237.229; 4.D.237.230; 4.D.237.231; 4.D.237.236; 4.D.237.237; 4.D.237.238; 4.D.237.239; 4.D.237.154; 4.D.237.157; 4.D.237.166; 4.D.237.169; 4.D.237.172; 4.D.237.175; 4.D.237.240; 4.D.237.244; 4.D.238.228; 4.D.238.229; 4.D.238.230; 4.D.238.231; 4.D.238.236; 4.D.238.237; 4.D.238.238; 4.D.238.239; 4.D.238.154; 4.D.238.157; 4.D.238.166; 4.D.238.169; 4.D.238.172; 4.D.238.175; 4.D.238.240; 4.D.238.244; 4.D.239.228; 4.D.239.229; 4.D.239.230; 4.D.239.231; 4.D.239.236; 4.D.239.237; 4.D.239.238; 4.D.239.239; 4.D.239.154; 4.D.239.157; 4.D.239.166; 4.D.239.169; 4.D.239.172; 4.D.239.175; 4.D.239.240; 4.D.239.244; 4.D.154.228; 4.D.154.229; 4.D.154.230; 4.D.154.231; 4.D.154.236; 4.D.154.237; 4.D.154.238; 4.D.154.239; 4.D.154.154; 4.D.154.157; 4.D.154.166; 4.D.154.169; 4.D.154.172; 4.D.154.175; 4.D.154.240; 4.D.154.244; 4.D.157.228; 4.D.157.229; 4.D.157.230; 4.D.157.231; 4.D.157.236; 4.D.157.237; 4.D.157.238; 4.D.157.239; 4.D.157.154; 4.D.157.157; 4.D.157.166; 4.D.157.169; 4.D.157.172; 4.D.157.175; 4.D.157.240; 4.D.157.244; 4.D.166.228; 4.D.166.229; 4.D.166.230; 4.D.166.231; 4.D.166.236; 4.D.166.237; 4.D.166.238; 4.D.166.239; 4.D.166.154; 4.D.166.157; 4.D.166.166; 4.D.166.169; 4.D.166.172; 4.D.166.175; 4.D.166.240; 4.D.166.244; 4.D.169.228; 4.D.169.229; 4.D.169.230; 4.D.169.231; 4.D.169.236; 4.D.169.237; 4.D.169.238; 4.D.169.239; 4.D.169.154; 4.D.169.157; 4.D.169.166; 4.D.169.169; 4.D.169.172; 4.D.169.175; 4.D.169.240; 4.D.169.244; 4.D.172.228; 4.D.172.229; 4.D.172.230; 4.D.172.231; 4.D.172.236; 4.D.172.237; 4.D.172.238; 4.D.172.239; 4.D.172.154; 4.D.172.157; 4.D.172.166; 4.D.172.169; 4.D.172.172; 4.D.172.175; 4.D.172.240; 4.D.172.244; 4.D.175.228; 4.D.175.229; 4.D.175.230; 4.D.175.231; 4.D.175.236; 4.D.175.237; 4.D.175.238; 4.D.175.239; 4.D.175.154; 4.D.175.157; 4.D.175.166; 4.D.175.169; 4.D.175.172; 4.D.175.175; 4.D.175.240; 4.D.175.244; 4.D.240.228; 4.D.240.229; 4.D.240.230; 4.D.240.231; 4.D.240.236; 4.D.240.237; 4.D.240.238; 4.D.240.239; 4.D.240.154; 4.D.240.157; 4.D.240.166; 4.D.240.169; 4.D.240.172; 4.D.240.175; 4.D.240.240; 4.D.240.244; 4.D.244.228; 4.D.244.229; 4.D.244.230; 4.D.244.231; 4.D.244.236; 4.D.244.237; 4.D.244.238; 4.D.244.239; 4.D.244.154; 4.D.244.157; 4.D.244.166; 4.D.244.169; 4.D.244.172; 4.D.244.175; 4.D.244.240; 4.D.244.244;

Prodrugs of 4.E

4.E.228.228; 4.E.228.229; 4.E.228.230; 4.E.228.231; 4.E.228.236; 4.E.228.237; 4.E.228.238; 4.E.228.239; 4.E.228.154; 4.E.228.157; 4.E.228.166; 4.E.228.169; 4.E.228.172; 4.E.228.175; 4.E.228.240; 4.E.228.244; 4.E.229.228; 4.E.229.229; 4.E.229.230; 4.E.229.231; 4.E.229.236; 4.E.229.237; 4.E.229.238; 4.E.229.239; 4.E.229.154; 4.E.229.157; 4.E.229.166;

4.E.229.169; 4.E.229.172; 4.E.229.175; 4.E.229.240; 4.E.229.244; 4.E.230.228; 4.E.230.229; 4.E.230.230; 4.E.230.231; 4.E.230.236; 4.E.230.237; 4.E.230.238; 4.E.230.239; 4.E.230.154; 4.E.230.157; 4.E.230.166; 4.E.230.169; 4.E.230.172; 4.E.230.175; 4.E.230.240; 4.E.230.244; 4.E.231.228; 4.E.231.229; 4.E.231.230; 4.E.231.231; 4.E.231.236; 4.E.231.237; 4.E.231.238; 4.E.231.239; 4.E.231.154; 4.E.231.157; 4.E.231.166; 4.E.231.169; 4.E.231.172; 4.E.231.175; 4.E.231.240; 4.E.231.244; 4.E.236.228; 4.E.236.229; 4.E.236.230; 4.E.236.231; 4.E.236.236; 4.E.236.237; 4.E.236.238; 4.E.236.239; 4.E.236.154; 4.E.236.157; 4.E.236.166; 4.E.236.169; 4.E.236.172; 4.E.236.175; 4.E.236.240; 4.E.236.244; 4.E.237.228; 4.E.237.229; 4.E.237.230; 4.E.237.231; 4.E.237.236; 4.E.237.237; 4.E.237.238; 4.E.237.239; 4.E.237.154; 4.E.237.157; 4.E.237.166; 4.E.237.169; 4.E.237.172; 4.E.237.175; 4.E.237.240; 4.E.237.244; 4.E.238.228; 4.E.238.229; 4.E.238.230; 4.E.238.231; 4.E.238.236; 4.E.238.237; 4.E.238.238; 4.E.238.239; 4.E.238.154; 4.E.238.157; 4.E.238.166; 4.E.238.169; 4.E.238.172; 4.E.238.175; 4.E.238.240; 4.E.238.244; 4.E.239.228; 4.E.239.229; 4.E.239.230; 4.E.239.231; 4.E.239.236; 4.E.239.237; 4.E.239.238; 4.E.239.239; 4.E.239.154; 4.E.239.157; 4.E.239.166; 4.E.239.169; 4.E.239.172; 4.E.239.175; 4.E.239.240; 4.E.239.244; 4.E.154.228; 4.E.154.229; 4.E.154.230; 4.E.154.231; 4.E.154.236; 4.E.154.237; 4.E.154.238; 4.E.154.239; 4.E.154.154; 4.E.154.157; 4.E.154.166; 4.E.154.169; 4.E.154.172; 4.E.154.175; 4.E.154.240; 4.E.154.244; 4.E.157.228; 4.E.157.229; 4.E.157.230; 4.E.157.231; 4.E.157.236; 4.E.157.237; 4.E.157.238; 4.E.157.239; 4.E.157.154; 4.E.157.157; 4.E.157.166; 4.E.157.169; 4.E.157.172; 4.E.157.175; 4.E.157.240; 4.E.157.244; 4.E.166.228; 4.E.166.229; 4.E.166.230; 4.E.166.231; 4.E.166.236; 4.E.166.237; 4.E.166.238; 4.E.166.239; 4.E.166.154; 4.E.166.157; 4.E.166.166; 4.E.166.169; 4.E.166.172; 4.E.166.175; 4.E.166.240; 4.E.166.244; 4.E.169.228; 4.E.169.229; 4.E.169.230; 4.E.169.231; 4.E.169.236; 4.E.169.237; 4.E.169.238; 4.E.169.239; 4.E.169.154; 4.E.169.157; 4.E.169.166; 4.E.169.169; 4.E.169.172; 4.E.169.175; 4.E.169.240; 4.E.169.244; 4.E.172.228; 4.E.172.229; 4.E.172.230; 4.E.172.231; 4.E.172.236; 4.E.172.237; 4.E.172.238; 4.E.172.239; 4.E.172.154; 4.E.172.157; 4.E.172.166; 4.E.172.169; 4.E.172.172; 4.E.172.175; 4.E.172.240; 4.E.172.244; 4.E.175.228; 4.E.175.229; 4.E.175.230; 4.E.175.231; 4.E.175.236; 4.E.175.237; 4.E.175.238; 4.E.175.239; 4.E.175.154; 4.E.175.157; 4.E.175.166; 4.E.175.169; 4.E.175.172; 4.E.175.175; 4.E.175.240; 4.E.175.244; 4.E.240.228; 4.E.240.229; 4.E.240.230; 4.E.240.231; 4.E.240.236; 4.E.240.237; 4.E.240.238; 4.E.240.239; 4.E.240.154; 4.E.240.157; 4.E.240.166; 4.E.240.169; 4.E.240.172; 4.E.240.175; 4.E.240.240; 4.E.240.244; 4.E.244.228; 4.E.244.229; 4.E.244.230; 4.E.244.231; 4.E.244.236; 4.E.244.237; 4.E.244.238; 4.E.244.239; 4.E.244.154; 4.E.244.157; 4.E.244.166; 4.E.244.169; 4.E.244.172; 4.E.244.175; 4.E.244.240; 4.E.244.244;

Prodrugs of 4.G

4.G.228.228; 4.G.228.229; 4.G.228.230; 4.G.228.231; 4.G.228.236; 4.G.228.237; 4.G.228.238; 4.G.228.239; 4.G.228.154; 4.G.228.157; 4.G.228.166; 4.G.228.169; 4.G.228.172; 4.G.228.175; 4.G.228.240; 4.G.228.244; 4.G.229.228; 4.G.229.229; 4.G.229.230; 4.G.229.231; 4.G.229.236; 4.G.229.237; 4.G.229.238; 4.G.229.239; 4.G.229.154; 4.G.229.157; 4.G.229.166; 4.G.229.169; 4.G.229.172; 4.G.229.175; 4.G.229.240; 4.G.229.244; 4.G.230.228; 4.G.230.229; 4.G.230.230; 4.G.230.231; 4.G.230.236; 4.G.230.237; 4.G.230.238; 4.G.230.239; 4.G.230.154; 4.G.230.157; 4.G.230.166; 4.G.230.169; 4.G.230.172; 4.G.230.175; 4.G.230.240; 4.G.230.244; 4.G.231.228; 4.G.231.229; 4.G.231.230; 4.G.231.231; 4.G.231.236; 4.G.231.237; 4.G.231.238; 4.G.231.239; 4.G.231.154; 4.G.231.157; 4.G.231.166; 4.G.231.169; 4.G.231.172; 4.G.231.175; 4.G.231.240; 4.G.231.244; 4.G.236.228; 4.G.236.229;

4.G.236.230; 4.G.236.231; 4.G.236.236; 4.G.236.237; 4.G.236.238; 4.G.236.239; 4.G.236.154; 4.G.236.157; 4.G.236.166; 4.G.236.169; 4.G.236.172; 4.G.236.175; 4.G.236.240; 4.G.236.244; 4.G.237.228; 4.G.237.229; 4.G.237.230; 4.G.237.231; 4.G.237.236; 4.G.237.237; 4.G.237.238; 4.G.237.239; 4.G.237.154; 4.G.237.157; 4.G.237.166; 4.G.237.169; 4.G.237.172; 4.G.237.175; 4.G.237.240; 4.G.237.244; 4.G.238.228; 4.G.238.229; 4.G.238.230; 4.G.238.231; 4.G.238.236; 4.G.238.237; 4.G.238.238; 4.G.238.239; 4.G.238.154; 4.G.238.157; 4.G.238.166; 4.G.238.169; 4.G.238.172; 4.G.238.175; 4.G.238.240; 4.G.238.244; 4.G.239.228; 4.G.239.229; 4.G.239.230; 4.G.239.231; 4.G.239.236; 4.G.239.237; 4.G.239.238; 4.G.239.239; 4.G.239.154; 4.G.239.157; 4.G.239.166; 4.G.239.169; 4.G.239.172; 4.G.239.175; 4.G.239.240; 4.G.239.244; 4.G.154.228; 4.G.154.229; 4.G.154.230; 4.G.154.231; 4.G.154.236; 4.G.154.237; 4.G.154.238; 4.G.154.239; 4.G.154.154; 4.G.154.157; 4.G.154.166; 4.G.154.169; 4.G.154.172; 4.G.154.175; 4.G.154.240; 4.G.154.244; 4.G.157.228; 4.G.157.229; 4.G.157.230; 4.G.157.231; 4.G.157.236; 4.G.157.237; 4.G.157.238; 4.G.157.239; 4.G.157.154; 4.G.157.157; 4.G.157.166; 4.G.157.169; 4.G.157.172; 4.G.157.175; 4.G.157.240; 4.G.157.244; 4.G.166.228; 4.G.166.229; 4.G.166.230; 4.G.166.231; 4.G.166.236; 4.G.166.237; 4.G.166.238; 4.G.166.239; 4.G.166.154; 4.G.166.157; 4.G.166.166; 4.G.166.169; 4.G.166.172; 4.G.166.175; 4.G.166.240; 4.G.166.244; 4.G.169.228; 4.G.169.229; 4.G.169.230; 4.G.169.231; 4.G.169.236; 4.G.169.237; 4.G.169.238; 4.G.169.239; 4.G.169.154; 4.G.169.157; 4.G.169.166; 4.G.169.169; 4.G.169.172; 4.G.169.175; 4.G.169.240; 4.G.169.244; 4.G.172.228; 4.G.172.229; 4.G.172.230; 4.G.172.231; 4.G.172.236; 4.G.172.237; 4.G.172.238; 4.G.172.239; 4.G.172.154; 4.G.172.157; 4.G.172.166; 4.G.172.169; 4.G.172.172; 4.G.172.175; 4.G.172.240; 4.G.172.244; 4.G.175.228; 4.G.175.229; 4.G.175.230; 4.G.175.231; 4.G.175.236; 4.G.175.237; 4.G.175.238; 4.G.175.239; 4.G.175.154; 4.G.175.157; 4.G.175.166; 4.G.175.169; 4.G.175.172; 4.G.175.175; 4.G.175.240; 4.G.175.244; 4.G.240.228; 4.G.240.229; 4.G.240.230; 4.G.240.231; 4.G.240.236; 4.G.240.237; 4.G.240.238; 4.G.240.239; 4.G.240.154; 4.G.240.157; 4.G.240.166; 4.G.240.169; 4.G.240.172; 4.G.240.175; 4.G.240.240; 4.G.240.244; 4.G.244.228; 4.G.244.229; 4.G.244.230; 4.G.244.231; 4.G.244.236; 4.G.244.237; 4.G.244.238; 4.G.244.239; 4.G.244.154; 4.G.244.157; 4.G.244.166; 4.G.244.169; 4.G.244.172; 4.G.244.175; 4.G.244.240; 4.G.244.244;

Prodrugs of 4.I

4.I.228.228; 4.I.228.229; 4.I.228.230; 4.I.228.231; 4.I.228.236; 4.I.228.237; 4.I.228.238; 4.I.228.239; 4.I.228.154; 4.I.228.157; 4.I.228.166; 4.I.228.169; 4.I.228.172; 4.I.228.175; 4.I.228.240; 4.I.228.244; 4.I.229.228; 4.I.229.229; 4.I.229.230; 4.I.229.231; 4.I.229.236; 4.I.229.237; 4.I.229.238; 4.I.229.239; 4.I.229.154; 4.I.229.157; 4.I.229.166; 4.I.229.169; 4.I.229.172; 4.I.229.175; 4.I.229.240; 4.I.229.244; 4.I.230.228; 4.I.230.229; 4.I.230.230; 4.I.230.231; 4.I.230.236; 4.I.230.237; 4.I.230.238; 4.I.230.239; 4.I.230.154; 4.I.230.157; 4.I.230.166; 4.I.230.169; 4.I.230.172; 4.I.230.175; 4.I.230.240; 4.I.230.244; 4.I.231.228; 4.I.231.229; 4.I.231.230; 4.I.231.231; 4.I.231.236; 4.I.231.237; 4.I.231.238; 4.I.231.239; 4.I.231.154; 4.I.231.157; 4.I.231.166; 4.I.231.169; 4.I.231.172; 4.I.231.175; 4.I.231.240; 4.I.231.244; 4.I.236.228; 4.I.236.229; 4.I.236.230; 4.I.236.231; 4.I.236.236; 4.I.236.237; 4.I.236.238; 4.I.236.239; 4.I.236.154; 4.I.236.157; 4.I.236.166; 4.I.236.169; 4.I.236.172; 4.I.236.175; 4.I.236.240; 4.I.236.244; 4.I.237.228; 4.I.237.229; 4.I.237.230; 4.I.237.231;

4.I.237.236; 4.I.237.237; 4.I.237.238; 4.I.237.239; 4.I.237.154; 4.I.237.157; 4.I.237.166; 4.I.237.169; 4.I.237.172; 4.I.237.175; 4.I.237.240; 4.I.237.244; 4.I.238.228; 4.I.238.229; 4.I.238.230; 4.I.238.231; 4.I.238.236; 4.I.238.237; 4.I.238.238; 4.I.238.239; 4.I.238.154; 4.I.238.157; 4.I.238.166; 4.I.238.169; 4.I.238.172; 4.I.238.175; 4.I.238.240; 4.I.238.244; 4.I.239.228; 4.I.239.229; 4.I.239.230; 4.I.239.231; 4.I.239.236; 4.I.239.237; 4.I.239.238; 4.I.239.239; 4.I.239.154; 4.I.239.157; 4.I.239.166; 4.I.239.169; 4.I.239.172; 4.I.239.175; 4.I.239.240; 4.I.239.244; 4.I.154.228; 4.I.154.229; 4.I.154.230; 4.I.154.231; 4.I.154.236; 4.I.154.237; 4.I.154.238; 4.I.154.239; 4.I.154.154; 4.I.154.157; 4.I.154.166; 4.I.154.169; 4.I.154.172; 4.I.154.175; 4.I.154.240; 4.I.154.244; 4.I.157.228; 4.I.157.229; 4.I.157.230; 4.I.157.231; 4.I.157.236; 4.I.157.237; 4.I.157.238; 4.I.157.239; 4.I.157.154; 4.I.157.157; 4.I.157.166; 4.I.157.169; 4.I.157.172; 4.I.157.175; 4.I.157.240; 4.I.157.244; 4.I.166.228; 4.I.166.229; 4.I.166.230; 4.I.166.231; 4.I.166.236; 4.I.166.237; 4.I.166.238; 4.I.166.239; 4.I.166.154; 4.I.166.157; 4.I.166.166; 4.I.166.169; 4.I.166.172; 4.I.166.175; 4.I.166.240; 4.I.166.244; 4.I.169.228; 4.I.169.229; 4.I.169.230; 4.I.169.231; 4.I.169.236; 4.I.169.237; 4.I.169.238; 4.I.169.239; 4.I.169.154; 4.I.169.157; 4.I.169.166; 4.I.169.169; 4.I.169.172; 4.I.169.175; 4.I.169.240; 4.I.169.244; 4.I.172.228; 4.I.172.229; 4.I.172.230; 4.I.172.231; 4.I.172.236; 4.I.172.237; 4.I.172.238; 4.I.172.239; 4.I.172.154; 4.I.172.157; 4.I.172.166; 4.I.172.169; 4.I.172.172; 4.I.172.175; 4.I.172.240; 4.I.172.244; 4.I.175.228; 4.I.175.229; 4.I.175.230; 4.I.175.231; 4.I.175.236; 4.I.175.237; 4.I.175.238; 4.I.175.239; 4.I.175.154; 4.I.175.157; 4.I.175.166; 4.I.175.169; 4.I.175.172; 4.I.175.175; 4.I.175.240; 4.I.175.244; 4.I.240.228; 4.I.240.229; 4.I.240.230; 4.I.240.231; 4.I.240.236; 4.I.240.237; 4.I.240.238; 4.I.240.239; 4.I.240.154; 4.I.240.157; 4.I.240.166; 4.I.240.169; 4.I.240.172; 4.I.240.175; 4.I.240.240; 4.I.240.244; 4.I.244.228; 4.I.244.229; 4.I.244.230; 4.I.244.231; 4.I.244.236; 4.I.244.237; 4.I.244.238; 4.I.244.239; 4.I.244.154; 4.I.244.157; 4.I.244.166; 4.I.244.169; 4.I.244.172; 4.I.244.175; 4.I.244.240; 4.I.244.244;

<u>Prodrugs of 4.J</u>

4.J.228.228; 4.J.228.229; 4.J.228.230; 4.J.228.231; 4.J.228.236; 4.J.228.237; 4.J.228.238; 4.J.228.239; 4.J.228.154; 4.J.228.157; 4.J.228.166; 4.J.228.169; 4.J.228.172; 4.J.228.175; 4.J.228.240; 4.J.228.244; 4.J.229.228; 4.J.229.229; 4.J.229.230; 4.J.229.231; 4.J.229.236; 4.J.229.237; 4.J.229.238; 4.J.229.239; 4.J.229.154; 4.J.229.157; 4.J.229.166; 4.J.229.169; 4.J.229.172; 4.J.229.175; 4.J.229.240; 4.J.229.244; 4.J.230.228; 4.J.230.229; 4.J.230.230; 4.J.230.231; 4.J.230.236; 4.J.230.237; 4.J.230.238; 4.J.230.239; 4.J.230.154; 4.J.230.157; 4.J.230.166; 4.J.230.169; 4.J.230.172; 4.J.230.175; 4.J.230.240; 4.J.230.244; 4.J.231.228; 4.J.231.229; 4.J.231.230; 4.J.231.231; 4.J.231.236; 4.J.231.237; 4.J.231.238; 4.J.231.239; 4.J.231.154; 4.J.231.157; 4.J.231.166; 4.J.231.169; 4.J.231.172; 4.J.231.175; 4.J.231.240; 4.J.231.244; 4.J.236.228; 4.J.236.229; 4.J.236.230; 4.J.236.231; 4.J.236.236; 4.J.236.237; 4.J.236.238; 4.J.236.239; 4.J.236.154; 4.J.236.157; 4.J.236.166; 4.J.236.169; 4.J.236.172; 4.J.236.175; 4.J.236.240; 4.J.236.244; 4.J.237.228; 4.J.237.229; 4.J.237.230; 4.J.237.231; 4.J.237.236; 4.J.237.237; 4.J.237.238; 4.J.237.239; 4.J.237.154; 4.J.237.157; 4.J.237.166; 4.J.237.169; 4.J.237.172; 4.J.237.175; 4.J.237.240; 4.J.237.244; 4.J.238.228; 4.J.238.229; 4.J.238.230; 4.J.238.231; 4.J.238.236; 4.J.238.237; 4.J.238.238; 4.J.238.239; 4.J.238.154; 4.J.238.157; 4.J.238.166; 4.J.238.169; 4.J.238.172; 4.J.238.175; 4.J.238.240; 4.J.238.244; 4.J.239.228; 4.J.239.229; 4.J.239.230; 4.J.239.231; 4.J.239.236; 4.J.239.237; 4.J.239.238; 4.J.239.239; 4.J.239.154; 4.J.239.157; 4.J.239.166; 4.J.239.169; 4.J.239.172; 4.J.239.175; 4.J.239.240; 4.J.239.244; 4.J.154.228; 4.J.154.229; 4.J.154.230; 4.J.154.231; 4.J.154.236;

4.J.154.237; 4.J.154.238; 4.J.154.239; 4.J.154.154; 4.J.154.157; 4.J.154.166; 4.J.154.169; 4.J.154.172; 4.J.154.175; 4.J.154.240; 4.J.154.244; 4.J.157.228; 4.J.157.229; 4.J.157.230; 4.J.157.231; 4.J.157.236; 4.J.157.237; 4.J.157.238; 4.J.157.239; 4.J.157.154; 4.J.157.157; 4.J.157.166; 4.J.157.169; 4.J.157.172; 4.J.157.175; 4.J.157.240; 4.J.157.244; 4.J.166.228; 4.J.166.229; 4.J.166.230; 4.J.166.231; 4.J.166.236; 4.J.166.237; 4.J.166.238; 4.J.166.239; 4.J.166.154; 4.J.166.157; 4.J.166.166; 4.J.166.169; 4.J.166.172; 4.J.166.175; 4.J.166.240; 4.J.166.244; 4.J.169.228; 4.J.169.229; 4.J.169.230; 4.J.169.231; 4.J.169.236; 4.J.169.237; 4.J.169.238; 4.J.169.239; 4.J.169.154; 4.J.169.157; 4.J.169.166; 4.J.169.169; 4.J.169.172; 4.J.169.175; 4.J.169.240; 4.J.169.244; 4.J.172.228; 4.J.172.229; 4.J.172.230; 4.J.172.231; 4.J.172.236; 4.J.172.237; 4.J.172.238; 4.J.172.239; 4.J.172.154; 4.J.172.157; 4.J.172.166; 4.J.172.169; 4.J.172.172; 4.J.172.175; 4.J.172.240; 4.J.172.244; 4.J.175.228; 4.J.175.229; 4.J.175.230; 4.J.175.231; 4.J.175.236; 4.J.175.237; 4.J.175.238; 4.J.175.239; 4.J.175.154; 4.J.175.157; 4.J.175.166; 4.J.175.169; 4.J.175.172; 4.J.175.175; 4.J.175.240; 4.J.175.244; 4.J.240.228; 4.J.240.229; 4.J.240.230; 4.J.240.231; 4.J.240.236; 4.J.240.237; 4.J.240.238; 4.J.240.239; 4.J.240.154; 4.J.240.157; 4.J.240.166; 4.J.240.169; 4.J.240.172; 4.J.240.175; 4.J.240.240; 4.J.240.244; 4.J.244.228; 4.J.244.229; 4.J.244.230; 4.J.244.231; 4.J.244.236; 4.J.244.237; 4.J.244.238; 4.J.244.239; 4.J.244.154; 4.J.244.157; 4.J.244.166; 4.J.244.169; 4.J.244.172; 4.J.244.175; 4.J.244.240; 4.J.244.244;

Prodrugs of 4.L

4.L.228.228; 4.L.228.229; 4.L.228.230; 4.L.228.231; 4.L.228.236; 4.L.228.237; 4.L.228.238; 4.L.228.239; 4.L.228.154; 4.L.228.157; 4.L.228.166; 4.L.228.169; 4.L.228.172; 4.L.228.175; 4.L.228.240; 4.L.228.244; 4.L.229.228; 4.L.229.229; 4.L.229.230; 4.L.229.231; 4.L.229.236; 4.L.229.237; 4.L.229.238; 4.L.229.239; 4.L.229.154; 4.L.229.157; 4.L.229.166; 4.L.229.169; 4.L.229.172; 4.L.229.175; 4.L.229.240; 4.L.229.244; 4.L.230.228; 4.L.230.229; 4.L.230.230; 4.L.230.231; 4.L.230.236; 4.L.230.237; 4.L.230.238; 4.L.230.239; 4.L.230.154; 4.L.230.157; 4.L.230.166; 4.L.230.169; 4.L.230.172; 4.L.230.175; 4.L.230.240; 4.L.230.244; 4.L.231.228; 4.L.231.229; 4.L.231.230; 4.L.231.231; 4.L.231.236; 4.L.231.237; 4.L.231.238; 4.L.231.239; 4.L.231.154; 4.L.231.157; 4.L.231.166; 4.L.231.169; 4.L.231.172; 4.L.231.175; 4.L.231.240; 4.L.231.244; 4.L.236.228; 4.L.236.229; 4.L.236.230; 4.L.236.231; 4.L.236.236; 4.L.236.237; 4.L.236.238; 4.L.236.239; 4.L.236.154; 4.L.236.157; 4.L.236.166; 4.L.236.169; 4.L.236.172; 4.L.236.175; 4.L.236.240; 4.L.236.244; 4.L.237.228; 4.L.237.229; 4.L.237.230; 4.L.237.231; 4.L.237.236; 4.L.237.237; 4.L.237.238; 4.L.237.239; 4.L.237.154; 4.L.237.157; 4.L.237.166; 4.L.237.169; 4.L.237.172; 4.L.237.175; 4.L.237.240; 4.L.237.244; 4.L.238.228; 4.L.238.229; 4.L.238.230; 4.L.238.231; 4.L.238.236; 4.L.238.237; 4.L.238.238; 4.L.238.239; 4.L.238.154; 4.L.238.157; 4.L.238.166; 4.L.238.169; 4.L.238.172; 4.L.238.175; 4.L.238.240; 4.L.238.244; 4.L.239.228; 4.L.239.229; 4.L.239.230; 4.L.239.231; 4.L.239.236; 4.L.239.237; 4.L.239.238; 4.L.239.239; 4.L.239.154; 4.L.239.157; 4.L.239.166; 4.L.239.169; 4.L.239.172; 4.L.239.175; 4.L.239.240; 4.L.239.244; 4.L.154.228; 4.L.154.229; 4.L.154.230; 4.L.154.231; 4.L.154.236; 4.L.154.237; 4.L.154.238; 4.L.154.239; 4.L.154.154; 4.L.154.157; 4.L.154.166; 4.L.154.169; 4.L.154.172; 4.L.154.175; 4.L.154.240; 4.L.154.244; 4.L.157.228; 4.L.157.229; 4.L.157.230; 4.L.157.231; 4.L.157.236; 4.L.157.237; 4.L.157.238; 4.L.157.239; 4.L.157.154; 4.L.157.157; 4.L.157.166; 4.L.157.169; 4.L.157.172; 4.L.157.175; 4.L.157.240; 4.L.157.244; 4.L.166.228; 4.L.166.229; 4.L.166.230; 4.L.166.231; 4.L.166.236; 4.L.166.237; 4.L.166.238; 4.L.166.239; 4.L.166.154; 4.L.166.157; 4.L.166.166; 4.L.166.169; 4.L.166.172; 4.L.166.175; 4.L.166.240; 4.L.166.244; 4.L.169.228; 4.L.169.229; 4.L.169.230; 4.L.169.231; 4.L.169.236;

4.L.169.237; 4.L.169.238; 4.L.169.239; 4.L.169.154; 4.L.169.157; 4.L.169.166; 4.L.169.169; 4.L.169.172; 4.L.169.175; 4.L.169.240; 4.L.169.244; 4.L.172.228; 4.L.172.229; 4.L.172.230; 4.L.172.231; 4.L.172.236; 4.L.172.237; 4.L.172.238; 4.L.172.239; 4.L.172.154; 4.L.172.157; 4.L.172.166; 4.L.172.169; 4.L.172.172; 4.L.172.175; 4.L.172.240; 4.L.172.244; 4.L.175.228; 4.L.175.229; 4.L.175.230; 4.L.175.231; 4.L.175.236; 4.L.175.237; 4.L.175.238; 4.L.175.239; 4.L.175.154; 4.L.175.157; 4.L.175.166; 4.L.175.169; 4.L.175.172; 4.L.175.175; 4.L.175.240; 4.L.175.244; 4.L.240.228; 4.L.240.229; 4.L.240.230; 4.L.240.231; 4.L.240.236; 4.L.240.237; 4.L.240.238; 4.L.240.239; 4.L.240.154; 4.L.240.157; 4.L.240.166; 4.L.240.169; 4.L.240.172; 4.L.240.175; 4.L.240.240; 4.L.240.244; 4.L.244.228; 4.L.244.229; 4.L.244.230; 4.L.244.231; 4.L.244.236; 4.L.244.237; 4.L.244.238; 4.L.244.239; 4.L.244.154; 4.L.244.157; 4.L.244.166; 4.L.244.169; 4.L.244.172; 4.L.244.175; 4.L.244.240; 4.L.244.244;

Prodrugs of 4.O

4.O.228.228; 4.O.228.229; 4.O.228.230; 4.O.228.231; 4.O.228.236; 4.O.228.237; 4.O.228.238; 4.O.228.239; 4.O.228.154; 4.O.228.157; 4.O.228.166; 4.O.228.169; 4.O.228.172; 4.O.228.175; 4.O.228.240; 4.O.228.244; 4.O.229.228; 4.O.229.229; 4.O.229.230; 4.O.229.231; 4.O.229.236; 4.O.229.237; 4.O.229.238; 4.O.229.239; 4.O.229.154; 4.O.229.157; 4.O.229.166; 4.O.229.169; 4.O.229.172; 4.O.229.175; 4.O.229.240; 4.O.229.244; 4.O.230.228; 4.O.230.229; 4.O.230.230; 4.O.230.231; 4.O.230.236; 4.O.230.237; 4.O.230.238; 4.O.230.239; 4.O.230.154; 4.O.230.157; 4.O.230.166; 4.O.230.169; 4.O.230.172; 4.O.230.175; 4.O.230.240; 4.O.230.244; 4.O.231.228; 4.O.231.229; 4.O.231.230; 4.O.231.231; 4.O.231.236; 4.O.231.237; 4.O.231.238; 4.O.231.239; 4.O.231.154; 4.O.231.157; 4.O.231.166; 4.O.231.169; 4.O.231.172; 4.O.231.175; 4.O.231.240; 4.O.231.244; 4.O.236.228; 4.O.236.229; 4.O.236.230; 4.O.236.231; 4.O.236.236; 4.O.236.237; 4.O.236.238; 4.O.236.239; 4.O.236.154; 4.O.236.157; 4.O.236.166; 4.O.236.169; 4.O.236.172; 4.O.236.175; 4.O.236.240; 4.O.236.244; 4.O.237.228; 4.O.237.229; 4.O.237.230; 4.O.237.231; 4.O.237.236; 4.O.237.237; 4.O.237.238; 4.O.237.239; 4.O.237.154; 4.O.237.157; 4.O.237.166; 4.O.237.169; 4.O.237.172; 4.O.237.175; 4.O.237.240; 4.O.237.244; 4.O.238.228; 4.O.238.229; 4.O.238.230; 4.O.238.231; 4.O.238.236; 4.O.238.237; 4.O.238.238; 4.O.238.239; 4.O.238.154; 4.O.238.157; 4.O.238.166; 4.O.238.169; 4.O.238.172; 4.O.238.175; 4.O.238.240; 4.O.238.244; 4.O.239.228; 4.O.239.229; 4.O.239.230; 4.O.239.231; 4.O.239.236; 4.O.239.237; 4.O.239.238; 4.O.239.239; 4.O.239.154; 4.O.239.157; 4.O.239.166; 4.O.239.169; 4.O.239.172; 4.O.239.175; 4.O.239.240; 4.O.239.244; 4.O.154.228; 4.O.154.229; 4.O.154.230; 4.O.154.231; 4.O.154.236; 4.O.154.237; 4.O.154.238; 4.O.154.239; 4.O.154.154; 4.O.154.157; 4.O.154.166; 4.O.154.169; 4.O.154.172; 4.O.154.175; 4.O.154.240; 4.O.154.244; 4.O.157.228; 4.O.157.229; 4.O.157.230; 4.O.157.231; 4.O.157.236; 4.O.157.237; 4.O.157.238; 4.O.157.239; 4.O.157.154; 4.O.157.157; 4.O.157.166; 4.O.157.169; 4.O.157.172; 4.O.157.175; 4.O.157.240; 4.O.157.244; 4.O.166.228; 4.O.166.229; 4.O.166.230; 4.O.166.231; 4.O.166.236; 4.O.166.237; 4.O.166.238; 4.O.166.239; 4.O.166.154; 4.O.166.157; 4.O.166.166; 4.O.166.169; 4.O.166.172; 4.O.166.175; 4.O.166.240; 4.O.166.244; 4.O.169.228; 4.O.169.229; 4.O.169.230; 4.O.169.231; 4.O.169.236; 4.O.169.237; 4.O.169.238; 4.O.169.239; 4.O.169.154; 4.O.169.157; 4.O.169.166; 4.O.169.169; 4.O.169.172; 4.O.169.175; 4.O.169.240; 4.O.169.244; 4.O.172.228; 4.O.172.229; 4.O.172.230; 4.O.172.231; 4.O.172.236; 4.O.172.237;

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Prodrugs of 4.P

4.P.228.228; 4.P.228.229; 4.P.228.230; 4.P.228.231; 4.P.228.236; 4.P.228.237; 4.P.228.238; 4.P.228.239; 4.P.228.154; 4.P.228.157; 4.P.228.166; 4.P.228.169; 4.P.228.172; 4.P.228.175; 4.P.228.240; 4.P.228.244; 4.P.229.228; 4.P.229.229; 4.P.229.230; 4.P.229.231; 4.P.229.236; 4.P.229.237; 4.P.229.238; 4.P.229.239; 4.P.229.154; 4.P.229.157; 4.P.229.166; 4.P.229.169; 4.P.229.172; 4.P.229.175; 4.P.229.240; 4.P.229.244; 4.P.230.228; 4.P.230.229; 4.P.230.230; 4.P.230.231; 4.P.230.236; 4.P.230.237; 4.P.230.238; 4.P.230.239; 4.P.230.154; 4.P.230.157; 4.P.230.166; 4.P.230.169; 4.P.230.172; 4.P.230.175; 4.P.230.240; 4.P.230.244; 4.P.231.228; 4.P.231.229; 4.P.231.230; 4.P.231.231; 4.P.231.236; 4.P.231.237; 4.P.231.238; 4.P.231.239; 4.P.231.154; 4.P.231.157; 4.P.231.166; 4.P.231.169; 4.P.231.172; 4.P.231.175; 4.P.231.240; 4.P.231.244; 4.P.236.228; 4.P.236.229; 4.P.236.230; 4.P.236.231; 4.P.236.236; 4.P.236.237; 4.P.236.238; 4.P.236.239; 4.P.236.154; 4.P.236.157; 4.P.236.166; 4.P.236.169; 4.P.236.172; 4.P.236.175; 4.P.236.240; 4.P.236.244; 4.P.237.228; 4.P.237.229; 4.P.237.230; 4.P.237.231; 4.P.237.236; 4.P.237.237; 4.P.237.238; 4.P.237.239; 4.P.237.154; 4.P.237.157; 4.P.237.166; 4.P.237.169; 4.P.237.172; 4.P.237.175; 4.P.237.240; 4.P.237.244; 4.P.238.228; 4.P.238.229; 4.P.238.230; 4.P.238.231; 4.P.238.236; 4.P.238.237; 4.P.238.238; 4.P.238.239; 4.P.238.154; 4.P.238.157; 4.P.238.166; 4.P.238.169; 4.P.238.172; 4.P.238.175; 4.P.238.240; 4.P.238.244; 4.P.239.228; 4.P.239.229; 4.P.239.230; 4.P.239.231; 4.P.239.236; 4.P.239.237; 4.P.239.238; 4.P.239.239; 4.P.239.154; 4.P.239.157; 4.P.239.166; 4.P.239.169; 4.P.239.172; 4.P.239.175; 4.P.239.240; 4.P.239.244; 4.P.154.228; 4.P.154.229; 4.P.154.230; 4.P.154.231; 4.P.154.236; 4.P.154.237; 4.P.154.238; 4.P.154.239; 4.P.154.154; 4.P.154.157; 4.P.154.166; 4.P.154.169; 4.P.154.172; 4.P.154.175; 4.P.154.240; 4.P.154.244; 4.P.157.228; 4.P.157.229; 4.P.157.230; 4.P.157.231; 4.P.157.236; 4.P.157.237; 4.P.157.238; 4.P.157.239; 4.P.157.154; 4.P.157.157; 4.P.157.166; 4.P.157.169; 4.P.157.172; 4.P.157.175; 4.P.157.240; 4.P.157.244; 4.P.166.228; 4.P.166.229; 4.P.166.230; 4.P.166.231; 4.P.166.236; 4.P.166.237; 4.P.166.238; 4.P.166.239; 4.P.166.154; 4.P.166.157; 4.P.166.166; 4.P.166.169; 4.P.166.172; 4.P.166.175; 4.P.166.240; 4.P.166.244; 4.P.169.228; 4.P.169.229; 4.P.169.230; 4.P.169.231; 4.P.169.236; 4.P.169.237; 4.P.169.238; 4.P.169.239; 4.P.169.154; 4.P.169.157; 4.P.169.166; 4.P.169.169; 4.P.169.172; 4.P.169.175; 4.P.169.240; 4.P.169.244; 4.P.172.228; 4.P.172.229; 4.P.172.230; 4.P.172.231; 4.P.172.236; 4.P.172.237; 4.P.172.238; 4.P.172.239; 4.P.172.154; 4.P.172.157; 4.P.172.166; 4.P.172.169; 4.P.172.172; 4.P.172.175; 4.P.172.240; 4.P.172.244; 4.P.175.228; 4.P.175.229; 4.P.175.230; 4.P.175.231; 4.P.175.236; 4.P.175.237; 4.P.175.238; 4.P.175.239; 4.P.175.154; 4.P.175.157; 4.P.175.166; 4.P.175.169; 4.P.175.172; 4.P.175.175; 4.P.175.240; 4.P.175.244; 4.P.240.228; 4.P.240.229; 4.P.240.230; 4.P.240.231; 4.P.240.236; 4.P.240.237; 4.P.240.238; 4.P.240.239; 4.P.240.154; 4.P.240.157; 4.P.240.166; 4.P.240.169; 4.P.240.172;

4.P.240.175; 4.P.240.240; 4.P.240.244; 4.P.244.228; 4.P.244.229; 4.P.244.230; 4.P.244.231; 4.P.244.236; 4.P.244.237; 4.P.244.238; 4.P.244.239; 4.P.244.154; 4.P.244.157; 4.P.244.166; 4.P.244.169; 4.P.244.172; 4.P.244.175; 4.P.244.240; 4.P.244.244;

Prodrugs of 4.U

4.U.228.228; 4.U.228.229; 4.U.228.230; 4.U.228.231; 4.U.228.236; 4.U.228.237; 4.U.228.238; 4.U.228.239; 4.U.228.154; 4.U.228.157; 4.U.228.166; 4.U.228.169; 4.U.228.172; 4.U.228.175; 4.U.228.240; 4.U.228.244; 4.U.229.228; 4.U.229.229; 4.U.229.230; 4.U.229.231; 4.U.229.236; 4.U.229.237; 4.U.229.238; 4.U.229.239; 4.U.229.154; 4.U.229.157; 4.U.229.166; 4.U.229.169; 4.U.229.172; 4.U.229.175; 4.U.229.240; 4.U.229.244; 4.U.230.228; 4.U.230.229; 4.U.230.230; 4.U.230.231; 4.U.230.236; 4.U.230.237; 4.U.230.238; 4.U.230.239; 4.U.230.154; 4.U.230.157; 4.U.230.166; 4.U.230.169; 4.U.230.172; 4.U.230.175; 4.U.230.240; 4.U.230.244; 4.U.231.228; 4.U.231.229; 4.U.231.230; 4.U.231.231; 4.U.231.236; 4.U.231.237; 4.U.231.238; 4.U.231.239; 4.U.231.154; 4.U.231.157; 4.U.231.166; 4.U.231.169; 4.U.231.172; 4.U.231.175; 4.U.231.240; 4.U.231.244; 4.U.236.228; 4.U.236.229; 4.U.236.230; 4.U.236.231; 4.U.236.236; 4.U.236.237; 4.U.236.238; 4.U.236.239; 4.U.236.154; 4.U.236.157; 4.U.236.166; 4.U.236.169; 4.U.236.172; 4.U.236.175; 4.U.236.240; 4.U.236.244; 4.U.237.228; 4.U.237.229; 4.U.237.230; 4.U.237.231; 4.U.237.236; 4.U.237.237; 4.U.237.238; 4.U.237.239; 4.U.237.154; 4.U.237.157; 4.U.237.166; 4.U.237.169; 4.U.237.172; 4.U.237.175; 4.U.237.240; 4.U.237.244; 4.U.238.228; 4.U.238.229; 4.U.238.230; 4.U.238.231; 4.U.238.236; 4.U.238.237; 4.U.238.238; 4.U.238.239; 4.U.238.154; 4.U.238.157; 4.U.238.166; 4.U.238.169; 4.U.238.172; 4.U.238.175; 4.U.238.240; 4.U.238.244; 4.U.239.228; 4.U.239.229; 4.U.239.230; 4.U.239.231; 4.U.239.236; 4.U.239.237; 4.U.239.238; 4.U.239.239; 4.U.239.154; 4.U.239.157; 4.U.239.166; 4.U.239.169; 4.U.239.172; 4.U.239.175; 4.U.239.240; 4.U.239.244; 4.U.154.228; 4.U.154.229; 4.U.154.230; 4.U.154.231; 4.U.154.236; 4.U.154.237; 4.U.154.238; 4.U.154.239; 4.U.154.154; 4.U.154.157; 4.U.154.166; 4.U.154.169; 4.U.154.172; 4.U.154.175; 4.U.154.240; 4.U.154.244; 4.U.157.228; 4.U.157.229; 4.U.157.230; 4.U.157.231; 4.U.157.236; 4.U.157.237; 4.U.157.238; 4.U.157.239; 4.U.157.154; 4.U.157.157; 4.U.157.166; 4.U.157.169; 4.U.157.172; 4.U.157.175; 4.U.157.240; 4.U.157.244; 4.U.166.228; 4.U.166.229; 4.U.166.230; 4.U.166.231; 4.U.166.236; 4.U.166.237; 4.U.166.238; 4.U.166.239; 4.U.166.154; 4.U.166.157; 4.U.166.166; 4.U.166.169; 4.U.166.172; 4.U.166.175; 4.U.166.240; 4.U.166.244; 4.U.169.228; 4.U.169.229; 4.U.169.230; 4.U.169.231; 4.U.169.236; 4.U.169.237; 4.U.169.238; 4.U.169.239; 4.U.169.154; 4.U.169.157; 4.U.169.166; 4.U.169.169; 4.U.169.172; 4.U.169.175; 4.U.169.240; 4.U.169.244; 4.U.172.228; 4.U.172.229; 4.U.172.230; 4.U.172.231; 4.U.172.236; 4.U.172.237; 4.U.172.238; 4.U.172.239; 4.U.172.154; 4.U.172.157; 4.U.172.166; 4.U.172.169; 4.U.172.172; 4.U.172.175; 4.U.172.240; 4.U.172.244; 4.U.175.228; 4.U.175.229; 4.U.175.230; 4.U.175.231; 4.U.175.236; 4.U.175.237; 4.U.175.238; 4.U.175.239; 4.U.175.154; 4.U.175.157; 4.U.175.166; 4.U.175.169; 4.U.175.172; 4.U.175.175; 4.U.175.240; 4.U.175.244; 4.U.240.228; 4.U.240.229; 4.U.240.230; 4.U.240.231; 4.U.240.236; 4.U.240.237; 4.U.240.238; 4.U.240.239; 4.U.240.154; 4.U.240.157; 4.U.240.166; 4.U.240.169; 4.U.240.172; 4.U.240.175; 4.U.240.240; 4.U.240.244; 4.U.244.228; 4.U.244.229; 4.U.244.230; 4.U.244.231; 4.U.244.236; 4.U.244.237;

4.U.244.238; 4.U.244.239; 4.U.244.154; 4.U.244.157; 4.U.244.166; 4.U.244.169; 4.U.244.172; 4.U.244.175; 4.U.244.240; 4.U.244.244;

Prodrugs of 4.W

4.W.228.228; 4.W.228.229; 4.W.228.230; 4.W.228.231; 4.W.228.236; 4.W.228.237; 4.W.228.238; 4.W.228.239; 4.W.228.154; 4.W.228.157; 4.W.228.166; 4.W.228.169; 4.W.228.172; 4.W.228.175; 4.W.228.240; 4.W.228.244; 4.W.229.228; 4.W.229.229; 4.W.229.230; 4.W.229.231; 4.W.229.236; 4.W.229.237; 4.W.229.238; 4.W.229.239; 4.W.229.154; 4.W.229.157; 4.W.229.166; 4.W.229.169; 4.W.229.172; 4.W.229.175; 4.W.229.240; 4.W.229.244; 4.W.230.228; 4.W.230.229; 4.W.230.230; 4.W.230.231; 4.W.230.236; 4.W.230.237; 4.W.230.238; 4.W.230.239; 4.W.230.154; 4.W.230.157; 4.W.230.166; 4.W.230.169; 4.W.230.172; 4.W.230.175; 4.W.230.240; 4.W.230.244; 4.W.231.228; 4.W.231.229; 4.W.231.230; 4.W.231.231; 4.W.231.236; 4.W.231.237; 4.W.231.238; 4.W.231.239; 4.W.231.154; 4.W.231.157; 4.W.231.166; 4.W.231.169; 4.W.231.172; 4.W.231.175; 4.W.231.240; 4.W.231.244; 4.W.236.228; 4.W.236.229; 4.W.236.230; 4.W.236.231; 4.W.236.236; 4.W.236.237; 4.W.236.238; 4.W.236.239; 4.W.236.154; 4.W.236.157; 4.W.236.166; 4.W.236.169; 4.W.236.172; 4.W.236.175; 4.W.236.240; 4.W.236.244; 4.W.237.228; 4.W.237.229; 4.W.237.230; 4.W.237.231; 4.W.237.236; 4.W.237.237; 4.W.237.238; 4.W.237.239; 4.W.237.154; 4.W.237.157; 4.W.237.166; 4.W.237.169; 4.W.237.172; 4.W.237.175; 4.W.237.240; 4.W.237.244; 4.W.238.228; 4.W.238.229; 4.W.238.230; 4.W.238.231; 4.W.238.236; 4.W.238.237; 4.W.238.238; 4.W.238.239; 4.W.238.154; 4.W.238.157; 4.W.238.166; 4.W.238.169; 4.W.238.172; 4.W.238.175; 4.W.238.240; 4.W.238.244; 4.W.239.228; 4.W.239.229; 4.W.239.230; 4.W.239.231; 4.W.239.236; 4.W.239.237; 4.W.239.238; 4.W.239.239; 4.W.239.154; 4.W.239.157; 4.W.239.166; 4.W.239.169; 4.W.239.172; 4.W.239.175; 4.W.239.240; 4.W.239.244; 4.W.154.228; 4.W.154.229; 4.W.154.230; 4.W.154.231; 4.W.154.236; 4.W.154.237; 4.W.154.238; 4.W.154.239; 4.W.154.154; 4.W.154.157; 4.W.154.166; 4.W.154.169; 4.W.154.172; 4.W.154.175; 4.W.154.240; 4.W.154.244; 4.W.157.228; 4.W.157.229; 4.W.157.230; 4.W.157.231; 4.W.157.236; 4.W.157.237; 4.W.157.238; 4.W.157.239; 4.W.157.154; 4.W.157.157; 4.W.157.166; 4.W.157.169; 4.W.157.172; 4.W.157.175; 4.W.157.240; 4.W.157.244; 4.W.166.228; 4.W.166.229; 4.W.166.230; 4.W.166.231; 4.W.166.236; 4.W.166.237; 4.W.166.238; 4.W.166.239; 4.W.166.154; 4.W.166.157; 4.W.166.166; 4.W.166.169; 4.W.166.172; 4.W.166.175; 4.W.166.240; 4.W.166.244; 4.W.169.228; 4.W.169.229; 4.W.169.230; 4.W.169.231; 4.W.169.236; 4.W.169.237; 4.W.169.238; 4.W.169.239; 4.W.169.154; 4.W.169.157; 4.W.169.166; 4.W.169.169; 4.W.169.172; 4.W.169.175; 4.W.169.240; 4.W.169.244; 4.W.172.228; 4.W.172.229; 4.W.172.230; 4.W.172.231; 4.W.172.236; 4.W.172.237; 4.W.172.238; 4.W.172.239; 4.W.172.154; 4.W.172.157; 4.W.172.166; 4.W.172.169; 4.W.172.172; 4.W.172.175; 4.W.172.240; 4.W.172.244; 4.W.175.228; 4.W.175.229; 4.W.175.230; 4.W.175.231; 4.W.175.236; 4.W.175.237; 4.W.175.238; 4.W.175.239; 4.W.175.154; 4.W.175.157; 4.W.175.166; 4.W.175.169; 4.W.175.172; 4.W.175.175; 4.W.175.240; 4.W.175.244; 4.W.240.228; 4.W.240.229; 4.W.240.230; 4.W.240.231; 4.W.240.236; 4.W.240.237; 4.W.240.238; 4.W.240.239; 4.W.240.154; 4.W.240.157; 4.W.240.166; 4.W.240.169; 4.W.240.172; 4.W.240.175; 4.W.240.240; 4.W.240.244; 4.W.244.228; 4.W.244.229; 4.W.244.230; 4.W.244.231; 4.W.244.236; 4.W.244.237;

4.W.244.238; 4.W.244.239; 4.W.244.154; 4.W.244.157; 4.W.244.166; 4.W.244.169; 4.W.244.172; 4.W.244.175; 4.W.244.240; 4.W.244.244;

Prodrugs of 4.Y

4.Y.228.228; 4.Y.228.229; 4.Y.228.230; 4.Y.228.231; 4.Y.228.236; 4.Y.228.237; 4.Y.228.238; 4.Y.228.239; 4.Y.228.154; 4.Y.228.157; 4.Y.228.166; 4.Y.228.169; 4.Y.228.172; 4.Y.228.175; 4.Y.228.240; 4.Y.228.244; 4.Y.229.228; 4.Y.229.229; 4.Y.229.230; 4.Y.229.231; 4.Y.229.236; 4.Y.229.237; 4.Y.229.238; 4.Y.229.239; 4.Y.229.154; 4.Y.229.157; 4.Y.229.166; 4.Y.229.169; 4.Y.229.172; 4.Y.229.175; 4.Y.229.240; 4.Y.229.244; 4.Y.230.228; 4.Y.230.229; 4.Y.230.230; 4.Y.230.231; 4.Y.230.236; 4.Y.230.237; 4.Y.230.238; 4.Y.230.239; 4.Y.230.154; 4.Y.230.157; 4.Y.230.166; 4.Y.230.169; 4.Y.230.172; 4.Y.230.175; 4.Y.230.240; 4.Y.230.244; 4.Y.231.228; 4.Y.231.229; 4.Y.231.230; 4.Y.231.231; 4.Y.231.236; 4.Y.231.237; 4.Y.231.238; 4.Y.231.239; 4.Y.231.154; 4.Y.231.157; 4.Y.231.166; 4.Y.231.169; 4.Y.231.172; 4.Y.231.175; 4.Y.231.240; 4.Y.231.244; 4.Y.236.228; 4.Y.236.229; 4.Y.236.230; 4.Y.236.231; 4.Y.236.236; 4.Y.236.237; 4.Y.236.238; 4.Y.236.239; 4.Y.236.154; 4.Y.236.157; 4.Y.236.166; 4.Y.236.169; 4.Y.236.172; 4.Y.236.175; 4.Y.236.240; 4.Y.236.244; 4.Y.237.228; 4.Y.237.229; 4.Y.237.230; 4.Y.237.231; 4.Y.237.236; 4.Y.237.237; 4.Y.237.238; 4.Y.237.239; 4.Y.237.154; 4.Y.237.157; 4.Y.237.166; 4.Y.237.169; 4.Y.237.172; 4.Y.237.175; 4.Y.237.240; 4.Y.237.244; 4.Y.238.228; 4.Y.238.229; 4.Y.238.230; 4.Y.238.231; 4.Y.238.236; 4.Y.238.237; 4.Y.238.238; 4.Y.238.239; 4.Y.238.154; 4.Y.238.157; 4.Y.238.166; 4.Y.238.169; 4.Y.238.172; 4.Y.238.175; 4.Y.238.240; 4.Y.238.244; 4.Y.239.228; 4.Y.239.229; 4.Y.239.230; 4.Y.239.231; 4.Y.239.236; 4.Y.239.237; 4.Y.239.238; 4.Y.239.239; 4.Y.239.154; 4.Y.239.157; 4.Y.239.166; 4.Y.239.169; 4.Y.239.172; 4.Y.239.175; 4.Y.239.240; 4.Y.239.244; 4.Y.154.228; 4.Y.154.229; 4.Y.154.230; 4.Y.154.231; 4.Y.154.236; 4.Y.154.237; 4.Y.154.238; 4.Y.154.239; 4.Y.154.154; 4.Y.154.157; 4.Y.154.166; 4.Y.154.169; 4.Y.154.172; 4.Y.154.175; 4.Y.154.240; 4.Y.154.244; 4.Y.157.228; 4.Y.157.229; 4.Y.157.230; 4.Y.157.231; 4.Y.157.236; 4.Y.157.237; 4.Y.157.238; 4.Y.157.239; 4.Y.157.154; 4.Y.157.157; 4.Y.157.166; 4.Y.157.169; 4.Y.157.172; 4.Y.157.175; 4.Y.157.240; 4.Y.157.244; 4.Y.166.228; 4.Y.166.229; 4.Y.166.230; 4.Y.166.231; 4.Y.166.236; 4.Y.166.237; 4.Y.166.238; 4.Y.166.239; 4.Y.166.154; 4.Y.166.157; 4.Y.166.166; 4.Y.166.169; 4.Y.166.172; 4.Y.166.175; 4.Y.166.240; 4.Y.166.244; 4.Y.169.228; 4.Y.169.229; 4.Y.169.230; 4.Y.169.231; 4.Y.169.236; 4.Y.169.237; 4.Y.169.238; 4.Y.169.239; 4.Y.169.154; 4.Y.169.157; 4.Y.169.166; 4.Y.169.169; 4.Y.169.172; 4.Y.169.175; 4.Y.169.240; 4.Y.169.244; 4.Y.172.228; 4.Y.172.229; 4.Y.172.230; 4.Y.172.231; 4.Y.172.236; 4.Y.172.237; 4.Y.172.238; 4.Y.172.239; 4.Y.172.154; 4.Y.172.157; 4.Y.172.166; 4.Y.172.169; 4.Y.172.172; 4.Y.172.175; 4.Y.172.240; 4.Y.172.244; 4.Y.175.228; 4.Y.175.229; 4.Y.175.230; 4.Y.175.231; 4.Y.175.236; 4.Y.175.237; 4.Y.175.238; 4.Y.175.239; 4.Y.175.154; 4.Y.175.157; 4.Y.175.166; 4.Y.175.169; 4.Y.175.172; 4.Y.175.175; 4.Y.175.240; 4.Y.175.244; 4.Y.240.228; 4.Y.240.229; 4.Y.240.230; 4.Y.240.231; 4.Y.240.236; 4.Y.240.237; 4.Y.240.238; 4.Y.240.239; 4.Y.240.154; 4.Y.240.157; 4.Y.240.166; 4.Y.240.169; 4.Y.240.172; 4.Y.240.175; 4.Y.240.240; 4.Y.240.244; 4.Y.244.228; 4.Y.244.229; 4.Y.244.230; 4.Y.244.231; 4.Y.244.236; 4.Y.244.237;

4.Y.244.238; 4.Y.244.239; 4.Y.244.154; 4.Y.244.157; 4.Y.244.166; 4.Y.244.169; 4.Y.244.172; 4.Y.244.175; 4.Y.244.240; 4.Y.244.244;

Prodrugs of 5.B

5.B.228.228; 5.B.228.229; 5.B.228.230; 5.B.228.231; 5.B.228.236; 5.B.228.237; 5.B.228.238; 5.B.228.239; 5.B.228.154; 5.B.228.157; 5.B.228.166; 5.B.228.169; 5.B.228.172; 5.B.228.175; 5.B.228.240; 5.B.228.244; 5.B.229.228; 5.B.229.229; 5.B.229.230; 5.B.229.231; 5.B.229.236; 5.B.229.237; 5.B.229.238; 5.B.229.239; 5.B.229.154; 5.B.229.157; 5.B.229.166; 5.B.229.169; 5.B.229.172; 5.B.229.175; 5.B.229.240; 5.B.229.244; 5.B.230.228; 5.B.230.229; 5.B.230.230; 5.B.230.231; 5.B.230.236; 5.B.230.237; 5.B.230.238; 5.B.230.239; 5.B.230.154; 5.B.230.157; 5.B.230.166; 5.B.230.169; 5.B.230.172; 5.B.230.175; 5.B.230.240; 5.B.230.244; 5.B.231.228; 5.B.231.229; 5.B.231.230; 5.B.231.231; 5.B.231.236; 5.B.231.237; 5.B.231.238; 5.B.231.239; 5.B.231.154; 5.B.231.157; 5.B.231.166; 5.B.231.169; 5.B.231.172; 5.B.231.175; 5.B.231.240; 5.B.231.244; 5.B.236.228; 5.B.236.229; 5.B.236.230; 5.B.236.231; 5.B.236.236; 5.B.236.237; 5.B.236.238; 5.B.236.239; 5.B.236.154; 5.B.236.157; 5.B.236.166; 5.B.236.169; 5.B.236.172; 5.B.236.175; 5.B.236.240; 5.B.236.244; 5.B.237.228; 5.B.237.229; 5.B.237.230; 5.B.237.231; 5.B.237.236; 5.B.237.237; 5.B.237.238; 5.B.237.239; 5.B.237.154; 5.B.237.157; 5.B.237.166; 5.B.237.169; 5.B.237.172; 5.B.237.175; 5.B.237.240; 5.B.237.244; 5.B.238.228; 5.B.238.229; 5.B.238.230; 5.B.238.231; 5.B.238.236; 5.B.238.237; 5.B.238.238; 5.B.238.239; 5.B.238.154; 5.B.238.157; 5.B.238.166; 5.B.238.169; 5.B.238.172; 5.B.238.175; 5.B.238.240; 5.B.238.244; 5.B.239.228; 5.B.239.229; 5.B.239.230; 5.B.239.231; 5.B.239.236; 5.B.239.237; 5.B.239.238; 5.B.239.239; 5.B.239.154; 5.B.239.157; 5.B.239.166; 5.B.239.169; 5.B.239.172; 5.B.239.175; 5.B.239.240; 5.B.239.244; 5.B.154.228; 5.B.154.229; 5.B.154.230; 5.B.154.231; 5.B.154.236; 5.B.154.237; 5.B.154.238; 5.B.154.239; 5.B.154.154; 5.B.154.157; 5.B.154.166; 5.B.154.169; 5.B.154.172; 5.B.154.175; 5.B.154.240; 5.B.154.244; 5.B.157.228; 5.B.157.229; 5.B.157.230; 5.B.157.231; 5.B.157.236; 5.B.157.237; 5.B.157.238; 5.B.157.239; 5.B.157.154; 5.B.157.157; 5.B.157.166; 5.B.157.169; 5.B.157.172; 5.B.157.175; 5.B.157.240; 5.B.157.244; 5.B.166.228; 5.B.166.229; 5.B.166.230; 5.B.166.231; 5.B.166.236; 5.B.166.237; 5.B.166.238; 5.B.166.239; 5.B.166.154; 5.B.166.157; 5.B.166.166; 5.B.166.169; 5.B.166.172; 5.B.166.175; 5.B.166.240; 5.B.166.244; 5.B.169.228; 5.B.169.229; 5.B.169.230; 5.B.169.231; 5.B.169.236; 5.B.169.237; 5.B.169.238; 5.B.169.239; 5.B.169.154; 5.B.169.157; 5.B.169.166; 5.B.169.169; 5.B.169.172; 5.B.169.175; 5.B.169.240; 5.B.169.244; 5.B.172.228; 5.B.172.229; 5.B.172.230; 5.B.172.231; 5.B.172.236; 5.B.172.237; 5.B.172.238; 5.B.172.239; 5.B.172.154; 5.B.172.157; 5.B.172.166; 5.B.172.169; 5.B.172.172; 5.B.172.175; 5.B.172.240; 5.B.172.244; 5.B.175.228; 5.B.175.229; 5.B.175.230; 5.B.175.231; 5.B.175.236; 5.B.175.237; 5.B.175.238; 5.B.175.239; 5.B.175.154; 5.B.175.157; 5.B.175.166; 5.B.175.169; 5.B.175.172; 5.B.175.175; 5.B.175.240; 5.B.175.244; 5.B.240.228; 5.B.240.229; 5.B.240.230; 5.B.240.231; 5.B.240.236; 5.B.240.237; 5.B.240.238; 5.B.240.239; 5.B.240.154; 5.B.240.157; 5.B.240.166; 5.B.240.169; 5.B.240.172; 5.B.240.175; 5.B.240.240; 5.B.240.244; 5.B.244.228; 5.B.244.229; 5.B.244.230; 5.B.244.231; 5.B.244.236; 5.B.244.237; 5.B.244.238; 5.B.244.239; 5.B.244.154; 5.B.244.157; 5.B.244.166; 5.B.244.169; 5.B.244.172; 5.B.244.175; 5.B.244.240; 5.B.244.244;

Prodrugs of 5.D

5.D.228.228; 5.D.228.229; 5.D.228.230; 5.D.228.231; 5.D.228.236; 5.D.228.237; 5.D.228.238; 5.D.228.239; 5.D.228.154; 5.D.228.157; 5.D.228.166; 5.D.228.169; 5.D.228.172; 5.D.228.175; 5.D.228.240; 5.D.228.244; 5.D.229.228; 5.D.229.229;

5.D.229.230; 5.D.229.231; 5.D.229.236; 5.D.229.237; 5.D.229.238; 5.D.229.239; 5.D.229.154; 5.D.229.157; 5.D.229.166; 5.D.229.169; 5.D.229.172; 5.D.229.175; 5.D.229.240; 5.D.229.244; 5.D.230.228; 5.D.230.229; 5.D.230.230; 5.D.230.231; 5.D.230.236; 5.D.230.237; 5.D.230.238; 5.D.230.239; 5.D.230.154; 5.D.230.157; 5.D.230.166; 5.D.230.169; 5.D.230.172; 5.D.230.175; 5.D.230.240; 5.D.230.244; 5.D.231.228; 5.D.231.229; 5.D.231.230; 5.D.231.231; 5.D.231.236; 5.D.231.237; 5.D.231.238; 5.D.231.239; 5.D.231.154; 5.D.231.157; 5.D.231.166; 5.D.231.169; 5.D.231.172; 5.D.231.175; 5.D.231.240; 5.D.231.244; 5.D.236.228; 5.D.236.229; 5.D.236.230; 5.D.236.231; 5.D.236.236; 5.D.236.237; 5.D.236.238; 5.D.236.239; 5.D.236.154; 5.D.236.157; 5.D.236.166; 5.D.236.169; 5.D.236.172; 5.D.236.175; 5.D.236.240; 5.D.236.244; 5.D.237.228; 5.D.237.229; 5.D.237.230; 5.D.237.231; 5.D.237.236; 5.D.237.237; 5.D.237.238; 5.D.237.239; 5.D.237.154; 5.D.237.157; 5.D.237.166; 5.D.237.169; 5.D.237.172; 5.D.237.175; 5.D.237.240; 5.D.237.244; 5.D.238.228; 5.D.238.229; 5.D.238.230; 5.D.238.231; 5.D.238.236; 5.D.238.237; 5.D.238.238; 5.D.238.239; 5.D.238.154; 5.D.238.157; 5.D.238.166; 5.D.238.169; 5.D.238.172; 5.D.238.175; 5.D.238.240; 5.D.238.244; 5.D.239.228; 5.D.239.229; 5.D.239.230; 5.D.239.231; 5.D.239.236; 5.D.239.237; 5.D.239.238; 5.D.239.239; 5.D.239.154; 5.D.239.157; 5.D.239.166; 5.D.239.169; 5.D.239.172; 5.D.239.175; 5.D.239.240; 5.D.239.244; 5.D.154.228; 5.D.154.229; 5.D.154.230; 5.D.154.231; 5.D.154.236; 5.D.154.237; 5.D.154.238; 5.D.154.239; 5.D.154.154; 5.D.154.157; 5.D.154.166; 5.D.154.169; 5.D.154.172; 5.D.154.175; 5.D.154.240; 5.D.154.244; 5.D.157.228; 5.D.157.229; 5.D.157.230; 5.D.157.231; 5.D.157.236; 5.D.157.237; 5.D.157.238; 5.D.157.239; 5.D.157.154; 5.D.157.157; 5.D.157.166; 5.D.157.169; 5.D.157.172; 5.D.157.175; 5.D.157.240; 5.D.157.244; 5.D.166.228; 5.D.166.229; 5.D.166.230; 5.D.166.231; 5.D.166.236; 5.D.166.237; 5.D.166.238; 5.D.166.239; 5.D.166.154; 5.D.166.157; 5.D.166.166; 5.D.166.169; 5.D.166.172; 5.D.166.175; 5.D.166.240; 5.D.166.244; 5.D.169.228; 5.D.169.229; 5.D.169.230; 5.D.169.231; 5.D.169.236; 5.D.169.237; 5.D.169.238; 5.D.169.239; 5.D.169.154; 5.D.169.157; 5.D.169.166; 5.D.169.169; 5.D.169.172; 5.D.169.175; 5.D.169.240; 5.D.169.244; 5.D.172.228; 5.D.172.229; 5.D.172.230; 5.D.172.231; 5.D.172.236; 5.D.172.237; 5.D.172.238; 5.D.172.239; 5.D.172.154; 5.D.172.157; 5.D.172.166; 5.D.172.169; 5.D.172.172; 5.D.172.175; 5.D.172.240; 5.D.172.244; 5.D.175.228; 5.D.175.229; 5.D.175.230; 5.D.175.231; 5.D.175.236; 5.D.175.237; 5.D.175.238; 5.D.175.239; 5.D.175.154; 5.D.175.157; 5.D.175.166; 5.D.175.169; 5.D.175.172; 5.D.175.175; 5.D.175.240; 5.D.175.244; 5.D.240.228; 5.D.240.229; 5.D.240.230; 5.D.240.231; 5.D.240.236; 5.D.240.237; 5.D.240.238; 5.D.240.239; 5.D.240.154; 5.D.240.157; 5.D.240.166; 5.D.240.169; 5.D.240.172; 5.D.240.175; 5.D.240.240; 5.D.240.244; 5.D.244.228; 5.D.244.229; 5.D.244.230; 5.D.244.231; 5.D.244.236; 5.D.244.237; 5.D.244.238; 5.D.244.239; 5.D.244.154; 5.D.244.157; 5.D.244.166; 5.D.244.169; 5.D.244.172; 5.D.244.175; 5.D.244.240; 5.D.244.244;

Prodrugs of 5.E

5.E.228.228; 5.E.228.229; 5.E.228.230; 5.E.228.231; 5.E.228.236; 5.E.228.237; 5.E.228.238; 5.E.228.239; 5.E.228.154; 5.E.228.157; 5.E.228.166; 5.E.228.169; 5.E.228.172; 5.E.228.175; 5.E.228.240; 5.E.228.244; 5.E.229.228; 5.E.229.229; 5.E.229.230; 5.E.229.231; 5.E.229.236; 5.E.229.237; 5.E.229.238; 5.E.229.239; 5.E.229.154; 5.E.229.157; 5.E.229.166;

5.E.229.169; 5.E.229.172; 5.E.229.175; 5.E.229.240; 5.E.229.244; 5.E.230.228; 5.E.230.229; 5.E.230.230; 5.E.230.231; 5.E.230.236; 5.E.230.237; 5.E.230.238; 5.E.230.239; 5.E.230.154; 5.E.230.157; 5.E.230.166; 5.E.230.169; 5.E.230.172; 5.E.230.175; 5.E.230.240; 5.E.230.244; 5.E.231.228; 5.E.231.229; 5.E.231.230; 5.E.231.231; 5.E.231.236; 5.E.231.237; 5.E.231.238; 5.E.231.239; 5.E.231.154; 5.E.231.157; 5.E.231.166; 5.E.231.169; 5.E.231.172; 5.E.231.175; 5.E.231.240; 5.E.231.244; 5.E.236.228; 5.E.236.229; 5.E.236.230; 5.E.236.231; 5.E.236.236; 5.E.236.237; 5.E.236.238; 5.E.236.239; 5.E.236.154; 5.E.236.157; 5.E.236.166; 5.E.236.169; 5.E.236.172; 5.E.236.175; 5.E.236.240; 5.E.236.244; 5.E.237.228; 5.E.237.229; 5.E.237.230; 5.E.237.231; 5.E.237.236; 5.E.237.237; 5.E.237.238; 5.E.237.239; 5.E.237.154; 5.E.237.157; 5.E.237.166; 5.E.237.169; 5.E.237.172; 5.E.237.175; 5.E.237.240; 5.E.237.244; 5.E.238.228; 5.E.238.229; 5.E.238.230; 5.E.238.231; 5.E.238.236; 5.E.238.237; 5.E.238.238; 5.E.238.239; 5.E.238.154; 5.E.238.157; 5.E.238.166; 5.E.238.169; 5.E.238.172; 5.E.238.175; 5.E.238.240; 5.E.238.244; 5.E.239.228; 5.E.239.229; 5.E.239.230; 5.E.239.231; 5.E.239.236; 5.E.239.237; 5.E.239.238; 5.E.239.239; 5.E.239.154; 5.E.239.157; 5.E.239.166; 5.E.239.169; 5.E.239.172; 5.E.239.175; 5.E.239.240; 5.E.239.244; 5.E.154.228; 5.E.154.229; 5.E.154.230; 5.E.154.231; 5.E.154.236; 5.E.154.237; 5.E.154.238; 5.E.154.239; 5.E.154.154; 5.E.154.157; 5.E.154.166; 5.E.154.169; 5.E.154.172; 5.E.154.175; 5.E.154.240; 5.E.154.244; 5.E.157.228; 5.E.157.229; 5.E.157.230; 5.E.157.231; 5.E.157.236; 5.E.157.237; 5.E.157.238; 5.E.157.239; 5.E.157.154; 5.E.157.157; 5.E.157.166; 5.E.157.169; 5.E.157.172; 5.E.157.175; 5.E.157.240; 5.E.157.244; 5.E.166.228; 5.E.166.229; 5.E.166.230; 5.E.166.231; 5.E.166.236; 5.E.166.237; 5.E.166.238; 5.E.166.239; 5.E.166.154; 5.E.166.157; 5.E.166.166; 5.E.166.169; 5.E.166.172; 5.E.166.175; 5.E.166.240; 5.E.166.244; 5.E.169.228; 5.E.169.229; 5.E.169.230; 5.E.169.231; 5.E.169.236; 5.E.169.237; 5.E.169.238; 5.E.169.239; 5.E.169.154; 5.E.169.157; 5.E.169.166; 5.E.169.169; 5.E.169.172; 5.E.169.175; 5.E.169.240; 5.E.169.244; 5.E.172.228; 5.E.172.229; 5.E.172.230; 5.E.172.231; 5.E.172.236; 5.E.172.237; 5.E.172.238; 5.E.172.239; 5.E.172.154; 5.E.172.157; 5.E.172.166; 5.E.172.169; 5.E.172.172; 5.E.172.175; 5.E.172.240; 5.E.172.244; 5.E.175.228; 5.E.175.229; 5.E.175.230; 5.E.175.231; 5.E.175.236; 5.E.175.237; 5.E.175.238; 5.E.175.239; 5.E.175.154; 5.E.175.157; 5.E.175.166; 5.E.175.169; 5.E.175.172; 5.E.175.175; 5.E.175.240; 5.E.175.244; 5.E.240.228; 5.E.240.229; 5.E.240.230; 5.E.240.231; 5.E.240.236; 5.E.240.237; 5.E.240.238; 5.E.240.239; 5.E.240.154; 5.E.240.157; 5.E.240.166; 5.E.240.169; 5.E.240.172; 5.E.240.175; 5.E.240.240; 5.E.240.244; 5.E.244.228; 5.E.244.229; 5.E.244.230; 5.E.244.231; 5.E.244.236; 5.E.244.237; 5.E.244.238; 5.E.244.239; 5.E.244.154; 5.E.244.157; 5.E.244.166; 5.E.244.169; 5.E.244.172; 5.E.244.175; 5.E.244.240; 5.E.244.244;

Prodrugs of 5.G

5.G.228.228; 5.G.228.229; 5.G.228.230; 5.G.228.231; 5.G.228.236; 5.G.228.237; 5.G.228.238; 5.G.228.239; 5.G.228.154; 5.G.228.157; 5.G.228.166; 5.G.228.169; 5.G.228.172; 5.G.228.175; 5.G.228.240; 5.G.228.244; 5.G.229.228; 5.G.229.229; 5.G.229.230; 5.G.229.231; 5.G.229.236; 5.G.229.237; 5.G.229.238; 5.G.229.239; 5.G.229.154; 5.G.229.157; 5.G.229.166; 5.G.229.169; 5.G.229.172; 5.G.229.175; 5.G.229.240; 5.G.229.244; 5.G.230.228; 5.G.230.229; 5.G.230.230; 5.G.230.231; 5.G.230.236; 5.G.230.237; 5.G.230.238; 5.G.230.239; 5.G.230.154; 5.G.230.157; 5.G.230.166; 5.G.230.169; 5.G.230.172; 5.G.230.175; 5.G.230.240; 5.G.230.244; 5.G.231.228; 5.G.231.229; 5.G.231.230; 5.G.231.231; 5.G.231.236; 5.G.231.237; 5.G.231.238; 5.G.231.239; 5.G.231.154; 5.G.231.157; 5.G.231.166; 5.G.231.169; 5.G.231.172; 5.G.231.175; 5.G.231.240; 5.G.231.244; 5.G.236.228; 5.G.236.229;

5.G.236.230; 5.G.236.231; 5.G.236.236; 5.G.236.237; 5.G.236.238; 5.G.236.239; 5.G.236.154; 5.G.236.157; 5.G.236.166; 5.G.236.169; 5.G.236.172; 5.G.236.175; 5.G.236.240; 5.G.236.244; 5.G.237.228; 5.G.237.229; 5.G.237.230; 5.G.237.231; 5.G.237.236; 5.G.237.237; 5.G.237.238; 5.G.237.239; 5.G.237.154; 5.G.237.157; 5.G.237.166; 5.G.237.169; 5.G.237.172; 5.G.237.175; 5.G.237.240; 5.G.237.244; 5.G.238.228; 5.G.238.229; 5.G.238.230; 5.G.238.231; 5.G.238.236; 5.G.238.237; 5.G.238.238; 5.G.238.239; 5.G.238.154; 5.G.238.157; 5.G.238.166; 5.G.238.169; 5.G.238.172; 5.G.238.175; 5.G.238.240; 5.G.238.244; 5.G.239.228; 5.G.239.229; 5.G.239.230; 5.G.239.231; 5.G.239.236; 5.G.239.237; 5.G.239.238; 5.G.239.239; 5.G.239.154; 5.G.239.157; 5.G.239.166; 5.G.239.169; 5.G.239.172; 5.G.239.175; 5.G.239.240; 5.G.239.244; 5.G.154.228; 5.G.154.229; 5.G.154.230; 5.G.154.231; 5.G.154.236; 5.G.154.237; 5.G.154.238; 5.G.154.239; 5.G.154.154; 5.G.154.157; 5.G.154.166; 5.G.154.169; 5.G.154.172; 5.G.154.175; 5.G.154.240; 5.G.154.244; 5.G.157.228; 5.G.157.229; 5.G.157.230; 5.G.157.231; 5.G.157.236; 5.G.157.237; 5.G.157.238; 5.G.157.239; 5.G.157.154; 5.G.157.157; 5.G.157.166; 5.G.157.169; 5.G.157.172; 5.G.157.175; 5.G.157.240; 5.G.157.244; 5.G.166.228; 5.G.166.229; 5.G.166.230; 5.G.166.231; 5.G.166.236; 5.G.166.237; 5.G.166.238; 5.G.166.239; 5.G.166.154; 5.G.166.157; 5.G.166.166; 5.G.166.169; 5.G.166.172; 5.G.166.175; 5.G.166.240; 5.G.166.244; 5.G.169.228; 5.G.169.229; 5.G.169.230; 5.G.169.231; 5.G.169.236; 5.G.169.237; 5.G.169.238; 5.G.169.239; 5.G.169.154; 5.G.169.157; 5.G.169.166; 5.G.169.169; 5.G.169.172; 5.G.169.175; 5.G.169.240; 5.G.169.244; 5.G.172.228; 5.G.172.229; 5.G.172.230; 5.G.172.231; 5.G.172.236; 5.G.172.237; 5.G.172.238; 5.G.172.239; 5.G.172.154; 5.G.172.157; 5.G.172.166; 5.G.172.169; 5.G.172.172; 5.G.172.175; 5.G.172.240; 5.G.172.244; 5.G.175.228; 5.G.175.229; 5.G.175.230; 5.G.175.231; 5.G.175.236; 5.G.175.237; 5.G.175.238; 5.G.175.239; 5.G.175.154; 5.G.175.157; 5.G.175.166; 5.G.175.169; 5.G.175.172; 5.G.175.175; 5.G.175.240; 5.G.175.244; 5.G.240.228; 5.G.240.229; 5.G.240.230; 5.G.240.231; 5.G.240.236; 5.G.240.237; 5.G.240.238; 5.G.240.239; 5.G.240.154; 5.G.240.157; 5.G.240.166; 5.G.240.169; 5.G.240.172; 5.G.240.175; 5.G.240.240; 5.G.240.244; 5.G.244.228; 5.G.244.229; 5.G.244.230; 5.G.244.231; 5.G.244.236; 5.G.244.237; 5.G.244.238; 5.G.244.239; 5.G.244.154; 5.G.244.157; 5.G.244.166; 5.G.244.169; 5.G.244.172; 5.G.244.175; 5.G.244.240; 5.G.244.244;

Prodrugs of 5.I

5.I.228.228; 5.I.228.229; 5.I.228.230; 5.I.228.231; 5.I.228.236; 5.I.228.237; 5.I.228.238; 5.I.228.239; 5.I.228.154; 5.I.228.157; 5.I.228.166; 5.I.228.169; 5.I.228.172; 5.I.228.175; 5.I.228.240; 5.I.228.244; 5.I.229.228; 5.I.229.229; 5.I.229.230; 5.I.229.231; 5.I.229.236; 5.I.229.237; 5.I.229.238; 5.I.229.239; 5.I.229.154; 5.I.229.157; 5.I.229.166; 5.I.229.169; 5.I.229.172; 5.I.229.175; 5.I.229.240; 5.I.229.244; 5.I.230.228; 5.I.230.229; 5.I.230.230; 5.I.230.231; 5.I.230.236; 5.I.230.237; 5.I.230.238; 5.I.230.239; 5.I.230.154; 5.I.230.157; 5.I.230.166; 5.I.230.169; 5.I.230.172; 5.I.230.175; 5.I.230.240; 5.I.230.244; 5.I.231.228; 5.I.231.229; 5.I.231.230; 5.I.231.231; 5.I.231.236; 5.I.231.237; 5.I.231.238; 5.I.231.239; 5.I.231.154; 5.I.231.157; 5.I.231.166; 5.I.231.169; 5.I.231.172; 5.I.231.175; 5.I.231.240; 5.I.231.244; 5.I.236.228; 5.I.236.229; 5.I.236.230; 5.I.236.231; 5.I.236.236; 5.I.236.237; 5.I.236.238; 5.I.236.239; 5.I.236.154; 5.I.236.157; 5.I.236.166; 5.I.236.169; 5.I.236.172; 5.I.236.175; 5.I.236.240; 5.I.236.244; 5.I.237.228; 5.I.237.229; 5.I.237.230; 5.I.237.231;

5.I.237.236; 5.I.237.237; 5.I.237.238; 5.I.237.239; 5.I.237.154; 5.I.237.157; 5.I.237.166; 5.I.237.169; 5.I.237.172; 5.I.237.175; 5.I.237.240; 5.I.237.244; 5.I.238.228; 5.I.238.229; 5.I.238.230; 5.I.238.231; 5.I.238.236; 5.I.238.237; 5.I.238.238; 5.I.238.239; 5.I.238.154; 5.I.238.157; 5.I.238.166; 5.I.238.169; 5.I.238.172; 5.I.238.175; 5.I.238.240; 5.I.238.244; 5.I.239.228; 5.I.239.229; 5.I.239.230; 5.I.239.231; 5.I.239.236; 5.I.239.237; 5.I.239.238; 5.I.239.239; 5.I.239.154; 5.I.239.157; 5.I.239.166; 5.I.239.169; 5.I.239.172; 5.I.239.175; 5.I.239.240; 5.I.239.244; 5.I.154.228; 5.I.154.229; 5.I.154.230; 5.I.154.231; 5.I.154.236; 5.I.154.237; 5.I.154.238; 5.I.154.239; 5.I.154.154; 5.I.154.157; 5.I.154.166; 5.I.154.169; 5.I.154.172; 5.I.154.175; 5.I.154.240; 5.I.154.244; 5.I.157.228; 5.I.157.229; 5.I.157.230; 5.I.157.231; 5.I.157.236; 5.I.157.237; 5.I.157.238; 5.I.157.239; 5.I.157.154; 5.I.157.157; 5.I.157.166; 5.I.157.169; 5.I.157.172; 5.I.157.175; 5.I.157.240; 5.I.157.244; 5.I.166.228; 5.I.166.229; 5.I.166.230; 5.I.166.231; 5.I.166.236; 5.I.166.237; 5.I.166.238; 5.I.166.239; 5.I.166.154; 5.I.166.157; 5.I.166.166; 5.I.166.169; 5.I.166.172; 5.I.166.175; 5.I.166.240; 5.I.166.244; 5.I.169.228; 5.I.169.229; 5.I.169.230; 5.I.169.231; 5.I.169.236; 5.I.169.237; 5.I.169.238; 5.I.169.239; 5.I.169.154; 5.I.169.157; 5.I.169.166; 5.I.169.169; 5.I.169.172; 5.I.169.175; 5.I.169.240; 5.I.169.244; 5.I.172.228; 5.I.172.229; 5.I.172.230; 5.I.172.231; 5.I.172.236; 5.I.172.237; 5.I.172.238; 5.I.172.239; 5.I.172.154; 5.I.172.157; 5.I.172.166; 5.I.172.169; 5.I.172.172; 5.I.172.175; 5.I.172.240; 5.I.172.244; 5.I.175.228; 5.I.175.229; 5.I.175.230; 5.I.175.231; 5.I.175.236; 5.I.175.237; 5.I.175.238; 5.I.175.239; 5.I.175.154; 5.I.175.157; 5.I.175.166; 5.I.175.169; 5.I.175.172; 5.I.175.175; 5.I.175.240; 5.I.175.244; 5.I.240.228; 5.I.240.229; 5.I.240.230; 5.I.240.231; 5.I.240.236; 5.I.240.237; 5.I.240.238; 5.I.240.239; 5.I.240.154; 5.I.240.157; 5.I.240.166; 5.I.240.169; 5.I.240.172; 5.I.240.175; 5.I.240.240; 5.I.240.244; 5.I.244.228; 5.I.244.229; 5.I.244.230; 5.I.244.231; 5.I.244.236; 5.I.244.237; 5.I.244.238; 5.I.244.239; 5.I.244.154; 5.I.244.157; 5.I.244.166; 5.I.244.169; 5.I.244.172; 5.I.244.175; 5.I.244.240; 5.I.244.244;

Prodrugs of 5.J

5.J.228.228; 5.J.228.229; 5.J.228.230; 5.J.228.231; 5.J.228.236; 5.J.228.237; 5.J.228.238; 5.J.228.239; 5.J.228.154; 5.J.228.157; 5.J.228.166; 5.J.228.169; 5.J.228.172; 5.J.228.175; 5.J.228.240; 5.J.228.244; 5.J.229.228; 5.J.229.229; 5.J.229.230; 5.J.229.231; 5.J.229.236; 5.J.229.237; 5.J.229.238; 5.J.229.239; 5.J.229.154; 5.J.229.157; 5.J.229.166; 5.J.229.169; 5.J.229.172; 5.J.229.175; 5.J.229.240; 5.J.229.244; 5.J.230.228; 5.J.230.229; 5.J.230.230; 5.J.230.231; 5.J.230.236; 5.J.230.237; 5.J.230.238; 5.J.230.239; 5.J.230.154; 5.J.230.157; 5.J.230.166; 5.J.230.169; 5.J.230.172; 5.J.230.175; 5.J.230.240; 5.J.230.244; 5.J.231.228; 5.J.231.229; 5.J.231.230; 5.J.231.231; 5.J.231.236; 5.J.231.237; 5.J.231.238; 5.J.231.239; 5.J.231.154; 5.J.231.157; 5.J.231.166; 5.J.231.169; 5.J.231.172; 5.J.231.175; 5.J.231.240; 5.J.231.244; 5.J.236.228; 5.J.236.229; 5.J.236.230; 5.J.236.231; 5.J.236.236; 5.J.236.237; 5.J.236.238; 5.J.236.239; 5.J.236.154; 5.J.236.157; 5.J.236.166; 5.J.236.169; 5.J.236.172; 5.J.236.175; 5.J.236.240; 5.J.236.244; 5.J.237.228; 5.J.237.229; 5.J.237.230; 5.J.237.231; 5.J.237.236; 5.J.237.237; 5.J.237.238; 5.J.237.239; 5.J.237.154; 5.J.237.157; 5.J.237.166; 5.J.237.169; 5.J.237.172; 5.J.237.175; 5.J.237.240; 5.J.237.244; 5.J.238.228; 5.J.238.229; 5.J.238.230; 5.J.238.231; 5.J.238.236; 5.J.238.237; 5.J.238.238; 5.J.238.239; 5.J.238.154; 5.J.238.157; 5.J.238.166; 5.J.238.169; 5.J.238.172; 5.J.238.175; 5.J.238.240; 5.J.238.244; 5.J.239.228; 5.J.239.229; 5.J.239.230; 5.J.239.231; 5.J.239.236; 5.J.239.237; 5.J.239.238; 5.J.239.239; 5.J.239.154; 5.J.239.157; 5.J.239.166; 5.J.239.169; 5.J.239.172; 5.J.239.175; 5.J.239.240; 5.J.239.244; 5.J.154.228; 5.J.154.229; 5.J.154.230; 5.J.154.231; 5.J.154.236;

5.J.154.237; 5.J.154.238; 5.J.154.239; 5.J.154.154; 5.J.154.157; 5.J.154.166; 5.J.154.169; 5.J.154.172; 5.J.154.175; 5.J.154.240; 5.J.154.244; 5.J.157.228; 5.J.157.229; 5.J.157.230; 5.J.157.231; 5.J.157.236; 5.J.157.237; 5.J.157.238; 5.J.157.239; 5.J.157.154; 5.J.157.157; 5.J.157.166; 5.J.157.169; 5.J.157.172; 5.J.157.175; 5.J.157.240; 5.J.157.244; 5.J.166.228; 5.J.166.229; 5.J.166.230; 5.J.166.231; 5.J.166.236; 5.J.166.237; 5.J.166.238; 5.J.166.239; 5.J.166.154; 5.J.166.157; 5.J.166.166; 5.J.166.169; 5.J.166.172; 5.J.166.175; 5.J.166.240; 5.J.166.244; 5.J.169.228; 5.J.169.229; 5.J.169.230; 5.J.169.231; 5.J.169.236; 5.J.169.237; 5.J.169.238; 5.J.169.239; 5.J.169.154; 5.J.169.157; 5.J.169.166; 5.J.169.169; 5.J.169.172; 5.J.169.175; 5.J.169.240; 5.J.169.244; 5.J.172.228; 5.J.172.229; 5.J.172.230; 5.J.172.231; 5.J.172.236; 5.J.172.237; 5.J.172.238; 5.J.172.239; 5.J.172.154; 5.J.172.157; 5.J.172.166; 5.J.172.169; 5.J.172.172; 5.J.172.175; 5.J.172.240; 5.J.172.244; 5.J.175.228; 5.J.175.229; 5.J.175.230; 5.J.175.231; 5.J.175.236; 5.J.175.237; 5.J.175.238; 5.J.175.239; 5.J.175.154; 5.J.175.157; 5.J.175.166; 5.J.175.169; 5.J.175.172; 5.J.175.175; 5.J.175.240; 5.J.175.244; 5.J.240.228; 5.J.240.229; 5.J.240.230; 5.J.240.231; 5.J.240.236; 5.J.240.237; 5.J.240.238; 5.J.240.239; 5.J.240.154; 5.J.240.157; 5.J.240.166; 5.J.240.169; 5.J.240.172; 5.J.240.175; 5.J.240.240; 5.J.240.244; 5.J.244.228; 5.J.244.229; 5.J.244.230; 5.J.244.231; 5.J.244.236; 5.J.244.237; 5.J.244.238; 5.J.244.239; 5.J.244.154; 5.J.244.157; 5.J.244.166; 5.J.244.169; 5.J.244.172; 5.J.244.175; 5.J.244.240; 5.J.244.244;

Prodrugs of 5.L

5.L.228.228; 5.L.228.229; 5.L.228.230; 5.L.228.231; 5.L.228.236; 5.L.228.237; 5.L.228.238; 5.L.228.239; 5.L.228.154; 5.L.228.157; 5.L.228.166; 5.L.228.169; 5.L.228.172; 5.L.228.175; 5.L.228.240; 5.L.228.244; 5.L.229.228; 5.L.229.229; 5.L.229.230; 5.L.229.231; 5.L.229.236; 5.L.229.237; 5.L.229.238; 5.L.229.239; 5.L.229.154; 5.L.229.157; 5.L.229.166; 5.L.229.169; 5.L.229.172; 5.L.229.175; 5.L.229.240; 5.L.229.244; 5.L.230.228; 5.L.230.229; 5.L.230.230; 5.L.230.231; 5.L.230.236; 5.L.230.237; 5.L.230.238; 5.L.230.239; 5.L.230.154; 5.L.230.157; 5.L.230.166; 5.L.230.169; 5.L.230.172; 5.L.230.175; 5.L.230.240; 5.L.230.244; 5.L.231.228; 5.L.231.229; 5.L.231.230; 5.L.231.231; 5.L.231.236; 5.L.231.237; 5.L.231.238; 5.L.231.239; 5.L.231.154; 5.L.231.157; 5.L.231.166; 5.L.231.169; 5.L.231.172; 5.L.231.175; 5.L.231.240; 5.L.231.244; 5.L.236.228; 5.L.236.229; 5.L.236.230; 5.L.236.231; 5.L.236.236; 5.L.236.237; 5.L.236.238; 5.L.236.239; 5.L.236.154; 5.L.236.157; 5.L.236.166; 5.L.236.169; 5.L.236.172; 5.L.236.175; 5.L.236.240; 5.L.236.244; 5.L.237.228; 5.L.237.229; 5.L.237.230; 5.L.237.231; 5.L.237.236; 5.L.237.237; 5.L.237.238; 5.L.237.239; 5.L.237.154; 5.L.237.157; 5.L.237.166; 5.L.237.169; 5.L.237.172; 5.L.237.175; 5.L.237.240; 5.L.237.244; 5.L.238.228; 5.L.238.229; 5.L.238.230; 5.L.238.231; 5.L.238.236; 5.L.238.237; 5.L.238.238; 5.L.238.239; 5.L.238.154; 5.L.238.157; 5.L.238.166; 5.L.238.169; 5.L.238.172; 5.L.238.175; 5.L.238.240; 5.L.238.244; 5.L.239.228; 5.L.239.229; 5.L.239.230; 5.L.239.231; 5.L.239.236; 5.L.239.237; 5.L.239.238; 5.L.239.239; 5.L.239.154; 5.L.239.157; 5.L.239.166; 5.L.239.169; 5.L.239.172; 5.L.239.175; 5.L.239.240; 5.L.239.244; 5.L.154.228; 5.L.154.229; 5.L.154.230; 5.L.154.231; 5.L.154.236; 5.L.154.237; 5.L.154.238; 5.L.154.239; 5.L.154.154; 5.L.154.157; 5.L.154.166; 5.L.154.169; 5.L.154.172; 5.L.154.175; 5.L.154.240; 5.L.154.244; 5.L.157.228; 5.L.157.229; 5.L.157.230; 5.L.157.231; 5.L.157.236; 5.L.157.237; 5.L.157.238; 5.L.157.239; 5.L.157.154; 5.L.157.157; 5.L.157.166; 5.L.157.169; 5.L.157.172; 5.L.157.175; 5.L.157.240; 5.L.157.244; 5.L.166.228; 5.L.166.229; 5.L.166.230; 5.L.166.231; 5.L.166.236; 5.L.166.237; 5.L.166.238; 5.L.166.239; 5.L.166.154; 5.L.166.157; 5.L.166.166; 5.L.166.169; 5.L.166.172; 5.L.166.175; 5.L.166.240; 5.L.166.244; 5.L.169.228; 5.L.169.229; 5.L.169.230; 5.L.169.231; 5.L.169.236;

5.L.169.237; 5.L.169.238; 5.L.169.239; 5.L.169.154; 5.L.169.157; 5.L.169.166; 5.L.169.169; 5.L.169.172; 5.L.169.175; 5.L.169.240; 5.L.169.244; 5.L.172.228; 5.L.172.229; 5.L.172.230; 5.L.172.231; 5.L.172.236; 5.L.172.237; 5.L.172.238; 5.L.172.239; 5.L.172.154; 5.L.172.157; 5.L.172.166; 5.L.172.169; 5.L.172.172; 5.L.172.175; 5.L.172.240; 5.L.172.244; 5.L.175.228; 5.L.175.229; 5.L.175.230; 5.L.175.231; 5.L.175.236; 5.L.175.237; 5.L.175.238; 5.L.175.239; 5.L.175.154; 5.L.175.157; 5.L.175.166; 5.L.175.169; 5.L.175.172; 5.L.175.175; 5.L.175.240; 5.L.175.244; 5.L.240.228; 5.L.240.229; 5.L.240.230; 5.L.240.231; 5.L.240.236; 5.L.240.237; 5.L.240.238; 5.L.240.239; 5.L.240.154; 5.L.240.157; 5.L.240.166; 5.L.240.169; 5.L.240.172; 5.L.240.175; 5.L.240.240; 5.L.240.244; 5.L.244.228; 5.L.244.229; 5.L.244.230; 5.L.244.231; 5.L.244.236; 5.L.244.237; 5.L.244.238; 5.L.244.239; 5.L.244.154; 5.L.244.157; 5.L.244.166; 5.L.244.169; 5.L.244.172; 5.L.244.175; 5.L.244.240; 5.L.244.244;

Prodrugs of 5.O

5.O.228.228; 5.O.228.229; 5.O.228.230; 5.O.228.231; 5.O.228.236; 5.O.228.237; 5.O.228.238; 5.O.228.239; 5.O.228.154; 5.O.228.157; 5.O.228.166; 5.O.228.169; 5.O.228.172; 5.O.228.175; 5.O.228.240; 5.O.228.244; 5.O.229.228; 5.O.229.229; 5.O.229.230; 5.O.229.231; 5.O.229.236; 5.O.229.237; 5.O.229.238; 5.O.229.239; 5.O.229.154; 5.O.229.157; 5.O.229.166; 5.O.229.169; 5.O.229.172; 5.O.229.175; 5.O.229.240; 5.O.229.244; 5.O.230.228; 5.O.230.229; 5.O.230.230; 5.O.230.231; 5.O.230.236; 5.O.230.237; 5.O.230.238; 5.O.230.239; 5.O.230.154; 5.O.230.157; 5.O.230.166; 5.O.230.169; 5.O.230.172; 5.O.230.175; 5.O.230.240; 5.O.230.244; 5.O.231.228; 5.O.231.229; 5.O.231.230; 5.O.231.231; 5.O.231.236; 5.O.231.237; 5.O.231.238; 5.O.231.239; 5.O.231.154; 5.O.231.157; 5.O.231.166; 5.O.231.169; 5.O.231.172; 5.O.231.175; 5.O.231.240; 5.O.231.244; 5.O.236.228; 5.O.236.229; 5.O.236.230; 5.O.236.231; 5.O.236.236; 5.O.236.237; 5.O.236.238; 5.O.236.239; 5.O.236.154; 5.O.236.157; 5.O.236.166; 5.O.236.169; 5.O.236.172; 5.O.236.175; 5.O.236.240; 5.O.236.244; 5.O.237.228; 5.O.237.229; 5.O.237.230; 5.O.237.231; 5.O.237.236; 5.O.237.237; 5.O.237.238; 5.O.237.239; 5.O.237.154; 5.O.237.157; 5.O.237.166; 5.O.237.169; 5.O.237.172; 5.O.237.175; 5.O.237.240; 5.O.237.244; 5.O.238.228; 5.O.238.229; 5.O.238.230; 5.O.238.231; 5.O.238.236; 5.O.238.237; 5.O.238.238; 5.O.238.239; 5.O.238.154; 5.O.238.157; 5.O.238.166; 5.O.238.169; 5.O.238.172; 5.O.238.175; 5.O.238.240; 5.O.238.244; 5.O.239.228; 5.O.239.229; 5.O.239.230; 5.O.239.231; 5.O.239.236; 5.O.239.237; 5.O.239.238; 5.O.239.239; 5.O.239.154; 5.O.239.157; 5.O.239.166; 5.O.239.169; 5.O.239.172; 5.O.239.175; 5.O.239.240; 5.O.239.244; 5.O.154.228; 5.O.154.229; 5.O.154.230; 5.O.154.231; 5.O.154.236; 5.O.154.237; 5.O.154.238; 5.O.154.239; 5.O.154.154; 5.O.154.157; 5.O.154.166; 5.O.154.169; 5.O.154.172; 5.O.154.175; 5.O.154.240; 5.O.154.244; 5.O.157.228; 5.O.157.229; 5.O.157.230; 5.O.157.231; 5.O.157.236; 5.O.157.237; 5.O.157.238; 5.O.157.239; 5.O.157.154; 5.O.157.157; 5.O.157.166; 5.O.157.169; 5.O.157.172; 5.O.157.175; 5.O.157.240; 5.O.157.244; 5.O.166.228; 5.O.166.229; 5.O.166.230; 5.O.166.231; 5.O.166.236; 5.O.166.237; 5.O.166.238; 5.O.166.239; 5.O.166.154; 5.O.166.157; 5.O.166.166; 5.O.166.169; 5.O.166.172; 5.O.166.175; 5.O.166.240; 5.O.166.244; 5.O.169.228; 5.O.169.229; 5.O.169.230; 5.O.169.231; 5.O.169.236; 5.O.169.237; 5.O.169.238; 5.O.169.239; 5.O.169.154; 5.O.169.157; 5.O.169.166; 5.O.169.169; 5.O.169.172; 5.O.169.175; 5.O.169.240; 5.O.169.244; 5.O.172.228; 5.O.172.229; 5.O.172.230; 5.O.172.231; 5.O.172.236; 5.O.172.237;

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Prodrugs of 5.P

5.P.228.228; 5.P.228.229; 5.P.228.230; 5.P.228.231; 5.P.228.236; 5.P.228.237; 5.P.228.238; 5.P.228.239; 5.P.228.154; 5.P.228.157; 5.P.228.166; 5.P.228.169; 5.P.228.172; 5.P.228.175; 5.P.228.240; 5.P.228.244; 5.P.229.228; 5.P.229.229; 5.P.229.230; 5.P.229.231; 5.P.229.236; 5.P.229.237; 5.P.229.238; 5.P.229.239; 5.P.229.154; 5.P.229.157; 5.P.229.166; 5.P.229.169; 5.P.229.172; 5.P.229.175; 5.P.229.240; 5.P.229.244; 5.P.230.228; 5.P.230.229; 5.P.230.230; 5.P.230.231; 5.P.230.236; 5.P.230.237; 5.P.230.238; 5.P.230.239; 5.P.230.154; 5.P.230.157; 5.P.230.166; 5.P.230.169; 5.P.230.172; 5.P.230.175; 5.P.230.240; 5.P.230.244; 5.P.231.228; 5.P.231.229; 5.P.231.230; 5.P.231.231; 5.P.231.236; 5.P.231.237; 5.P.231.238; 5.P.231.239; 5.P.231.154; 5.P.231.157; 5.P.231.166; 5.P.231.169; 5.P.231.172; 5.P.231.175; 5.P.231.240; 5.P.231.244; 5.P.236.228; 5.P.236.229; 5.P.236.230; 5.P.236.231; 5.P.236.236; 5.P.236.237; 5.P.236.238; 5.P.236.239; 5.P.236.154; 5.P.236.157; 5.P.236.166; 5.P.236.169; 5.P.236.172; 5.P.236.175; 5.P.236.240; 5.P.236.244; 5.P.237.228; 5.P.237.229; 5.P.237.230; 5.P.237.231; 5.P.237.236; 5.P.237.237; 5.P.237.238; 5.P.237.239; 5.P.237.154; 5.P.237.157; 5.P.237.166; 5.P.237.169; 5.P.237.172; 5.P.237.175; 5.P.237.240; 5.P.237.244; 5.P.238.228; 5.P.238.229; 5.P.238.230; 5.P.238.231; 5.P.238.236; 5.P.238.237; 5.P.238.238; 5.P.238.239; 5.P.238.154; 5.P.238.157; 5.P.238.166; 5.P.238.169; 5.P.238.172; 5.P.238.175; 5.P.238.240; 5.P.238.244; 5.P.239.228; 5.P.239.229; 5.P.239.230; 5.P.239.231; 5.P.239.236; 5.P.239.237; 5.P.239.238; 5.P.239.239; 5.P.239.154; 5.P.239.157; 5.P.239.166; 5.P.239.169; 5.P.239.172; 5.P.239.175; 5.P.239.240; 5.P.239.244; 5.P.154.228; 5.P.154.229; 5.P.154.230; 5.P.154.231; 5.P.154.236; 5.P.154.237; 5.P.154.238; 5.P.154.239; 5.P.154.154; 5.P.154.157; 5.P.154.166; 5.P.154.169; 5.P.154.172; 5.P.154.175; 5.P.154.240; 5.P.154.244; 5.P.157.228; 5.P.157.229; 5.P.157.230; 5.P.157.231; 5.P.157.236; 5.P.157.237; 5.P.157.238; 5.P.157.239; 5.P.157.154; 5.P.157.157; 5.P.157.166; 5.P.157.169; 5.P.157.172; 5.P.157.175; 5.P.157.240; 5.P.157.244; 5.P.166.228; 5.P.166.229; 5.P.166.230; 5.P.166.231; 5.P.166.236; 5.P.166.237; 5.P.166.238; 5.P.166.239; 5.P.166.154; 5.P.166.157; 5.P.166.166; 5.P.166.169; 5.P.166.172; 5.P.166.175; 5.P.166.240; 5.P.166.244; 5.P.169.228; 5.P.169.229; 5.P.169.230; 5.P.169.231; 5.P.169.236; 5.P.169.237; 5.P.169.238; 5.P.169.239; 5.P.169.154; 5.P.169.157; 5.P.169.166; 5.P.169.169; 5.P.169.172; 5.P.169.175; 5.P.169.240; 5.P.169.244; 5.P.172.228; 5.P.172.229; 5.P.172.230; 5.P.172.231; 5.P.172.236; 5.P.172.237; 5.P.172.238; 5.P.172.239; 5.P.172.154; 5.P.172.157; 5.P.172.166; 5.P.172.169; 5.P.172.172; 5.P.172.175; 5.P.172.240; 5.P.172.244; 5.P.175.228; 5.P.175.229; 5.P.175.230; 5.P.175.231; 5.P.175.236; 5.P.175.237; 5.P.175.238; 5.P.175.239; 5.P.175.154; 5.P.175.157; 5.P.175.166; 5.P.175.169; 5.P.175.172; 5.P.175.175; 5.P.175.240; 5.P.175.244; 5.P.240.228; 5.P.240.229; 5.P.240.230; 5.P.240.231; 5.P.240.236; 5.P.240.237; 5.P.240.238; 5.P.240.239; 5.P.240.154; 5.P.240.157; 5.P.240.166; 5.P.240.169; 5.P.240.172;

5.P.240.175; 5.P.240.240; 5.P.240.244; 5.P.244.228; 5.P.244.229; 5.P.244.230; 5.P.244.231; 5.P.244.236; 5.P.244.237; 5.P.244.238; 5.P.244.239; 5.P.244.154; 5.P.244.157; 5.P.244.166; 5.P.244.169; 5.P.244.172; 5.P.244.175; 5.P.244.240; 5.P.244.244;

Prodrugs of 5.U

5.U.228.228; 5.U.228.229; 5.U.228.230; 5.U.228.231; 5.U.228.236; 5.U.228.237; 5.U.228.238; 5.U.228.239; 5.U.228.154; 5.U.228.157; 5.U.228.166; 5.U.228.169; 5.U.228.172; 5.U.228.175; 5.U.228.240; 5.U.228.244; 5.U.229.228; 5.U.229.229; 5.U.229.230; 5.U.229.231; 5.U.229.236; 5.U.229.237; 5.U.229.238; 5.U.229.239; 5.U.229.154; 5.U.229.157; 5.U.229.166; 5.U.229.169; 5.U.229.172; 5.U.229.175; 5.U.229.240; 5.U.229.244; 5.U.230.228; 5.U.230.229; 5.U.230.230; 5.U.230.231; 5.U.230.236; 5.U.230.237; 5.U.230.238; 5.U.230.239; 5.U.230.154; 5.U.230.157; 5.U.230.166; 5.U.230.169; 5.U.230.172; 5.U.230.175; 5.U.230.240; 5.U.230.244; 5.U.231.228; 5.U.231.229; 5.U.231.230; 5.U.231.231; 5.U.231.236; 5.U.231.237; 5.U.231.238; 5.U.231.239; 5.U.231.154; 5.U.231.157; 5.U.231.166; 5.U.231.169; 5.U.231.172; 5.U.231.175; 5.U.231.240; 5.U.231.244; 5.U.236.228; 5.U.236.229; 5.U.236.230; 5.U.236.231; 5.U.236.236; 5.U.236.237; 5.U.236.238; 5.U.236.239; 5.U.236.154; 5.U.236.157; 5.U.236.166; 5.U.236.169; 5.U.236.172; 5.U.236.175; 5.U.236.240; 5.U.236.244; 5.U.237.228; 5.U.237.229; 5.U.237.230; 5.U.237.231; 5.U.237.236; 5.U.237.237; 5.U.237.238; 5.U.237.239; 5.U.237.154; 5.U.237.157; 5.U.237.166; 5.U.237.169; 5.U.237.172; 5.U.237.175; 5.U.237.240; 5.U.237.244; 5.U.238.228; 5.U.238.229; 5.U.238.230; 5.U.238.231; 5.U.238.236; 5.U.238.237; 5.U.238.238; 5.U.238.239; 5.U.238.154; 5.U.238.157; 5.U.238.166; 5.U.238.169; 5.U.238.172; 5.U.238.175; 5.U.238.240; 5.U.238.244; 5.U.239.228; 5.U.239.229; 5.U.239.230; 5.U.239.231; 5.U.239.236; 5.U.239.237; 5.U.239.238; 5.U.239.239; 5.U.239.154; 5.U.239.157; 5.U.239.166; 5.U.239.169; 5.U.239.172; 5.U.239.175; 5.U.239.240; 5.U.239.244; 5.U.154.228; 5.U.154.229; 5.U.154.230; 5.U.154.231; 5.U.154.236; 5.U.154.237; 5.U.154.238; 5.U.154.239; 5.U.154.154; 5.U.154.157; 5.U.154.166; 5.U.154.169; 5.U.154.172; 5.U.154.175; 5.U.154.240; 5.U.154.244; 5.U.157.228; 5.U.157.229; 5.U.157.230; 5.U.157.231; 5.U.157.236; 5.U.157.237; 5.U.157.238; 5.U.157.239; 5.U.157.154; 5.U.157.157; 5.U.157.166; 5.U.157.169; 5.U.157.172; 5.U.157.175; 5.U.157.240; 5.U.157.244; 5.U.166.228; 5.U.166.229; 5.U.166.230; 5.U.166.231; 5.U.166.236; 5.U.166.237; 5.U.166.238; 5.U.166.239; 5.U.166.154; 5.U.166.157; 5.U.166.166; 5.U.166.169; 5.U.166.172; 5.U.166.175; 5.U.166.240; 5.U.166.244; 5.U.169.228; 5.U.169.229; 5.U.169.230; 5.U.169.231; 5.U.169.236; 5.U.169.237; 5.U.169.238; 5.U.169.239; 5.U.169.154; 5.U.169.157; 5.U.169.166; 5.U.169.169; 5.U.169.172; 5.U.169.175; 5.U.169.240; 5.U.169.244; 5.U.172.228; 5.U.172.229; 5.U.172.230; 5.U.172.231; 5.U.172.236; 5.U.172.237; 5.U.172.238; 5.U.172.239; 5.U.172.154; 5.U.172.157; 5.U.172.166; 5.U.172.169; 5.U.172.172; 5.U.172.175; 5.U.172.240; 5.U.172.244; 5.U.175.228; 5.U.175.229; 5.U.175.230; 5.U.175.231; 5.U.175.236; 5.U.175.237; 5.U.175.238; 5.U.175.239; 5.U.175.154; 5.U.175.157; 5.U.175.166; 5.U.175.169; 5.U.175.172; 5.U.175.175; 5.U.175.240; 5.U.175.244; 5.U.240.228; 5.U.240.229; 5.U.240.230; 5.U.240.231; 5.U.240.236; 5.U.240.237; 5.U.240.238; 5.U.240.239; 5.U.240.154; 5.U.240.157; 5.U.240.166; 5.U.240.169; 5.U.240.172; 5.U.240.175; 5.U.240.240; 5.U.240.244; 5.U.244.228; 5.U.244.229; 5.U.244.230; 5.U.244.231; 5.U.244.236; 5.U.244.237;

5.U.244.238; 5.U.244.239; 5.U.244.154; 5.U.244.157; 5.U.244.166; 5.U.244.169; 5.U.244.172; 5.U.244.175; 5.U.244.240; 5.U.244.244;

Prodrugs of 5.W

5.W.228.228; 5.W.228.229; 5.W.228.230; 5.W.228.231; 5.W.228.236; 5.W.228.237; 5.W.228.238; 5.W.228.239; 5.W.228.154; 5.W.228.157; 5.W.228.166; 5.W.228.169; 5.W.228.172; 5.W.228.175; 5.W.228.240; 5.W.228.244; 5.W.229.228; 5.W.229.229; 5.W.229.230; 5.W.229.231; 5.W.229.236; 5.W.229.237; 5.W.229.238; 5.W.229.239; 5.W.229.154; 5.W.229.157; 5.W.229.166; 5.W.229.169; 5.W.229.172; 5.W.229.175; 5.W.229.240; 5.W.229.244; 5.W.230.228; 5.W.230.229; 5.W.230.230; 5.W.230.231; 5.W.230.236; 5.W.230.237; 5.W.230.238; 5.W.230.239; 5.W.230.154; 5.W.230.157; 5.W.230.166; 5.W.230.169; 5.W.230.172; 5.W.230.175; 5.W.230.240; 5.W.230.244; 5.W.231.228; 5.W.231.229; 5.W.231.230; 5.W.231.231; 5.W.231.236; 5.W.231.237; 5.W.231.238; 5.W.231.239; 5.W.231.154; 5.W.231.157; 5.W.231.166; 5.W.231.169; 5.W.231.172; 5.W.231.175; 5.W.231.240; 5.W.231.244; 5.W.236.228; 5.W.236.229; 5.W.236.230; 5.W.236.231; 5.W.236.236; 5.W.236.237; 5.W.236.238; 5.W.236.239; 5.W.236.154; 5.W.236.157; 5.W.236.166; 5.W.236.169; 5.W.236.172; 5.W.236.175; 5.W.236.240; 5.W.236.244; 5.W.237.228; 5.W.237.229; 5.W.237.230; 5.W.237.231; 5.W.237.236; 5.W.237.237; 5.W.237.238; 5.W.237.239; 5.W.237.154; 5.W.237.157; 5.W.237.166; 5.W.237.169; 5.W.237.172; 5.W.237.175; 5.W.237.240; 5.W.237.244; 5.W.238.228; 5.W.238.229; 5.W.238.230; 5.W.238.231; 5.W.238.236; 5.W.238.237; 5.W.238.238; 5.W.238.239; 5.W.238.154; 5.W.238.157; 5.W.238.166; 5.W.238.169; 5.W.238.172; 5.W.238.175; 5.W.238.240; 5.W.238.244; 5.W.239.228; 5.W.239.229; 5.W.239.230; 5.W.239.231; 5.W.239.236; 5.W.239.237; 5.W.239.238; 5.W.239.239; 5.W.239.154; 5.W.239.157; 5.W.239.166; 5.W.239.169; 5.W.239.172; 5.W.239.175; 5.W.239.240; 5.W.239.244; 5.W.154.228; 5.W.154.229; 5.W.154.230; 5.W.154.231; 5.W.154.236; 5.W.154.237; 5.W.154.238; 5.W.154.239; 5.W.154.154; 5.W.154.157; 5.W.154.166; 5.W.154.169; 5.W.154.172; 5.W.154.175; 5.W.154.240; 5.W.154.244; 5.W.157.228; 5.W.157.229; 5.W.157.230; 5.W.157.231; 5.W.157.236; 5.W.157.237; 5.W.157.238; 5.W.157.239; 5.W.157.154; 5.W.157.157; 5.W.157.166; 5.W.157.169; 5.W.157.172; 5.W.157.175; 5.W.157.240; 5.W.157.244; 5.W.166.228; 5.W.166.229; 5.W.166.230; 5.W.166.231; 5.W.166.236; 5.W.166.237; 5.W.166.238; 5.W.166.239; 5.W.166.154; 5.W.166.157; 5.W.166.166; 5.W.166.169; 5.W.166.172; 5.W.166.175; 5.W.166.240; 5.W.166.244; 5.W.169.228; 5.W.169.229; 5.W.169.230; 5.W.169.231; 5.W.169.236; 5.W.169.237; 5.W.169.238; 5.W.169.239; 5.W.169.154; 5.W.169.157; 5.W.169.166; 5.W.169.169; 5.W.169.172; 5.W.169.175; 5.W.169.240; 5.W.169.244; 5.W.172.228; 5.W.172.229; 5.W.172.230; 5.W.172.231; 5.W.172.236; 5.W.172.237; 5.W.172.238; 5.W.172.239; 5.W.172.154; 5.W.172.157; 5.W.172.166; 5.W.172.169; 5.W.172.172; 5.W.172.175; 5.W.172.240; 5.W.172.244; 5.W.175.228; 5.W.175.229; 5.W.175.230; 5.W.175.231; 5.W.175.236; 5.W.175.237; 5.W.175.238; 5.W.175.239; 5.W.175.154; 5.W.175.157; 5.W.175.166; 5.W.175.169; 5.W.175.172; 5.W.175.175; 5.W.175.240; 5.W.175.244; 5.W.240.228; 5.W.240.229; 5.W.240.230; 5.W.240.231; 5.W.240.236; 5.W.240.237; 5.W.240.238; 5.W.240.239; 5.W.240.154; 5.W.240.157; 5.W.240.166; 5.W.240.169; 5.W.240.172; 5.W.240.175; 5.W.240.240; 5.W.240.244; 5.W.244.228; 5.W.244.229; 5.W.244.230; 5.W.244.231; 5.W.244.236; 5.W.244.237;

5.W.244.238; 5.W.244.239; 5.W.244.154; 5.W.244.157; 5.W.244.166; 5.W.244.169; 5.W.244.172; 5.W.244.175; 5.W.244.240; 5.W.244.244;

Prodrugs of 5.Y

5.Y.228.228; 5.Y.228.229; 5.Y.228.230; 5.Y.228.231; 5.Y.228.236; 5.Y.228.237; 5.Y.228.238; 5.Y.228.239; 5.Y.228.154; 5.Y.228.157; 5.Y.228.166; 5.Y.228.169; 5.Y.228.172; 5.Y.228.175; 5.Y.228.240; 5.Y.228.244; 5.Y.229.228; 5.Y.229.229; 5.Y.229.230; 5.Y.229.231; 5.Y.229.236; 5.Y.229.237; 5.Y.229.238; 5.Y.229.239; 5.Y.229.154; 5.Y.229.157; 5.Y.229.166; 5.Y.229.169; 5.Y.229.172; 5.Y.229.175; 5.Y.229.240; 5.Y.229.244; 5.Y.230.228; 5.Y.230.229; 5.Y.230.230; 5.Y.230.231; 5.Y.230.236; 5.Y.230.237; 5.Y.230.238; 5.Y.230.239; 5.Y.230.154; 5.Y.230.157; 5.Y.230.166; 5.Y.230.169; 5.Y.230.172; 5.Y.230.175; 5.Y.230.240; 5.Y.230.244; 5.Y.231.228; 5.Y.231.229; 5.Y.231.230; 5.Y.231.231; 5.Y.231.236; 5.Y.231.237; 5.Y.231.238; 5.Y.231.239; 5.Y.231.154; 5.Y.231.157; 5.Y.231.166; 5.Y.231.169; 5.Y.231.172; 5.Y.231.175; 5.Y.231.240; 5.Y.231.244; 5.Y.236.228; 5.Y.236.229; 5.Y.236.230; 5.Y.236.231; 5.Y.236.236; 5.Y.236.237; 5.Y.236.238; 5.Y.236.239; 5.Y.236.154; 5.Y.236.157; 5.Y.236.166; 5.Y.236.169; 5.Y.236.172; 5.Y.236.175; 5.Y.236.240; 5.Y.236.244; 5.Y.237.228; 5.Y.237.229; 5.Y.237.230; 5.Y.237.231; 5.Y.237.236; 5.Y.237.237; 5.Y.237.238; 5.Y.237.239; 5.Y.237.154; 5.Y.237.157; 5.Y.237.166; 5.Y.237.169; 5.Y.237.172; 5.Y.237.175; 5.Y.237.240; 5.Y.237.244; 5.Y.238.228; 5.Y.238.229; 5.Y.238.230; 5.Y.238.231; 5.Y.238.236; 5.Y.238.237; 5.Y.238.238; 5.Y.238.239; 5.Y.238.154; 5.Y.238.157; 5.Y.238.166; 5.Y.238.169; 5.Y.238.172; 5.Y.238.175; 5.Y.238.240; 5.Y.238.244; 5.Y.239.228; 5.Y.239.229; 5.Y.239.230; 5.Y.239.231; 5.Y.239.236; 5.Y.239.237; 5.Y.239.238; 5.Y.239.239; 5.Y.239.154; 5.Y.239.157; 5.Y.239.166; 5.Y.239.169; 5.Y.239.172; 5.Y.239.175; 5.Y.239.240; 5.Y.239.244; 5.Y.154.228; 5.Y.154.229; 5.Y.154.230; 5.Y.154.231; 5.Y.154.236; 5.Y.154.237; 5.Y.154.238; 5.Y.154.239; 5.Y.154.154; 5.Y.154.157; 5.Y.154.166; 5.Y.154.169; 5.Y.154.172; 5.Y.154.175; 5.Y.154.240; 5.Y.154.244; 5.Y.157.228; 5.Y.157.229; 5.Y.157.230; 5.Y.157.231; 5.Y.157.236; 5.Y.157.237; 5.Y.157.238; 5.Y.157.239; 5.Y.157.154; 5.Y.157.157; 5.Y.157.166; 5.Y.157.169; 5.Y.157.172; 5.Y.157.175; 5.Y.157.240; 5.Y.157.244; 5.Y.166.228; 5.Y.166.229; 5.Y.166.230; 5.Y.166.231; 5.Y.166.236; 5.Y.166.237; 5.Y.166.238; 5.Y.166.239; 5.Y.166.154; 5.Y.166.157; 5.Y.166.166; 5.Y.166.169; 5.Y.166.172; 5.Y.166.175; 5.Y.166.240; 5.Y.166.244; 5.Y.169.228; 5.Y.169.229; 5.Y.169.230; 5.Y.169.231; 5.Y.169.236; 5.Y.169.237; 5.Y.169.238; 5.Y.169.239; 5.Y.169.154; 5.Y.169.157; 5.Y.169.166; 5.Y.169.169; 5.Y.169.172; 5.Y.169.175; 5.Y.169.240; 5.Y.169.244; 5.Y.172.228; 5.Y.172.229; 5.Y.172.230; 5.Y.172.231; 5.Y.172.236; 5.Y.172.237; 5.Y.172.238; 5.Y.172.239; 5.Y.172.154; 5.Y.172.157; 5.Y.172.166; 5.Y.172.169; 5.Y.172.172; 5.Y.172.175; 5.Y.172.240; 5.Y.172.244; 5.Y.175.228; 5.Y.175.229; 5.Y.175.230; 5.Y.175.231; 5.Y.175.236; 5.Y.175.237; 5.Y.175.238; 5.Y.175.239; 5.Y.175.154; 5.Y.175.157; 5.Y.175.166; 5.Y.175.169; 5.Y.175.172; 5.Y.175.175; 5.Y.175.240; 5.Y.175.244; 5.Y.240.228; 5.Y.240.229; 5.Y.240.230; 5.Y.240.231; 5.Y.240.236; 5.Y.240.237; 5.Y.240.238; 5.Y.240.239; 5.Y.240.154; 5.Y.240.157; 5.Y.240.166; 5.Y.240.169; 5.Y.240.172; 5.Y.240.175; 5.Y.240.240; 5.Y.240.244; 5.Y.244.228; 5.Y.244.229; 5.Y.244.230; 5.Y.244.231; 5.Y.244.236; 5.Y.244.237;

5.Y.244.238; 5.Y.244.239; 5.Y.244.154; 5.Y.244.157; 5.Y.244.166; 5.Y.244.169; 5.Y.244.172; 5.Y.244.175; 5.Y.244.240; 5.Y.244.244;

Prodrugs of 6.B

6.B.228.228; 6.B.228.229; 6.B.228.230; 6.B.228.231; 6.B.228.236; 6.B.228.237; 6.B.228.238; 6.B.228.239; 6.B.228.154; 6.B.228.157; 6.B.228.166; 6.B.228.169; 6.B.228.172; 6.B.228.175; 6.B.228.240; 6.B.228.244; 6.B.229.228; 6.B.229.229; 6.B.229.230; 6.B.229.231; 6.B.229.236; 6.B.229.237; 6.B.229.238; 6.B.229.239; 6.B.229.154; 6.B.229.157; 6.B.229.166; 6.B.229.169; 6.B.229.172; 6.B.229.175; 6.B.229.240; 6.B.229.244; 6.B.230.228; 6.B.230.229; 6.B.230.230; 6.B.230.231; 6.B.230.236; 6.B.230.237; 6.B.230.238; 6.B.230.239; 6.B.230.154; 6.B.230.157; 6.B.230.166; 6.B.230.169; 6.B.230.172; 6.B.230.175; 6.B.230.240; 6.B.230.244; 6.B.231.228; 6.B.231.229; 6.B.231.230; 6.B.231.231; 6.B.231.236; 6.B.231.237; 6.B.231.238; 6.B.231.239; 6.B.231.154; 6.B.231.157; 6.B.231.166; 6.B.231.169; 6.B.231.172; 6.B.231.175; 6.B.231.240; 6.B.231.244; 6.B.236.228; 6.B.236.229; 6.B.236.230; 6.B.236.231; 6.B.236.236; 6.B.236.237; 6.B.236.238; 6.B.236.239; 6.B.236.154; 6.B.236.157; 6.B.236.166; 6.B.236.169; 6.B.236.172; 6.B.236.175; 6.B.236.240; 6.B.236.244; 6.B.237.228; 6.B.237.229; 6.B.237.230; 6.B.237.231; 6.B.237.236; 6.B.237.237; 6.B.237.238; 6.B.237.239; 6.B.237.154; 6.B.237.157; 6.B.237.166; 6.B.237.169; 6.B.237.172; 6.B.237.175; 6.B.237.240; 6.B.237.244; 6.B.238.228; 6.B.238.229; 6.B.238.230; 6.B.238.231; 6.B.238.236; 6.B.238.237; 6.B.238.238; 6.B.238.239; 6.B.238.154; 6.B.238.157; 6.B.238.166; 6.B.238.169; 6.B.238.172; 6.B.238.175; 6.B.238.240; 6.B.238.244; 6.B.239.228; 6.B.239.229; 6.B.239.230; 6.B.239.231; 6.B.239.236; 6.B.239.237; 6.B.239.238; 6.B.239.239; 6.B.239.154; 6.B.239.157; 6.B.239.166; 6.B.239.169; 6.B.239.172; 6.B.239.175; 6.B.239.240; 6.B.239.244; 6.B.154.228; 6.B.154.229; 6.B.154.230; 6.B.154.231; 6.B.154.236; 6.B.154.237; 6.B.154.238; 6.B.154.239; 6.B.154.154; 6.B.154.157; 6.B.154.166; 6.B.154.169; 6.B.154.172; 6.B.154.175; 6.B.154.240; 6.B.154.244; 6.B.157.228; 6.B.157.229; 6.B.157.230; 6.B.157.231; 6.B.157.236; 6.B.157.237; 6.B.157.238; 6.B.157.239; 6.B.157.154; 6.B.157.157; 6.B.157.166; 6.B.157.169; 6.B.157.172; 6.B.157.175; 6.B.157.240; 6.B.157.244; 6.B.166.228; 6.B.166.229; 6.B.166.230; 6.B.166.231; 6.B.166.236; 6.B.166.237; 6.B.166.238; 6.B.166.239; 6.B.166.154; 6.B.166.157; 6.B.166.166; 6.B.166.169; 6.B.166.172; 6.B.166.175; 6.B.166.240; 6.B.166.244; 6.B.169.228; 6.B.169.229; 6.B.169.230; 6.B.169.231; 6.B.169.236; 6.B.169.237; 6.B.169.238; 6.B.169.239; 6.B.169.154; 6.B.169.157; 6.B.169.166; 6.B.169.169; 6.B.169.172; 6.B.169.175; 6.B.169.240; 6.B.169.244; 6.B.172.228; 6.B.172.229; 6.B.172.230; 6.B.172.231; 6.B.172.236; 6.B.172.237; 6.B.172.238; 6.B.172.239; 6.B.172.154; 6.B.172.157; 6.B.172.166; 6.B.172.169; 6.B.172.172; 6.B.172.175; 6.B.172.240; 6.B.172.244; 6.B.175.228; 6.B.175.229; 6.B.175.230; 6.B.175.231; 6.B.175.236; 6.B.175.237; 6.B.175.238; 6.B.175.239; 6.B.175.154; 6.B.175.157; 6.B.175.166; 6.B.175.169; 6.B.175.172; 6.B.175.175; 6.B.175.240; 6.B.175.244; 6.B.240.228; 6.B.240.229; 6.B.240.230; 6.B.240.231; 6.B.240.236; 6.B.240.237; 6.B.240.238; 6.B.240.239; 6.B.240.154; 6.B.240.157; 6.B.240.166; 6.B.240.169; 6.B.240.172; 6.B.240.175; 6.B.240.240; 6.B.240.244; 6.B.244.228; 6.B.244.229; 6.B.244.230; 6.B.244.231; 6.B.244.236; 6.B.244.237; 6.B.244.238; 6.B.244.239; 6.B.244.154; 6.B.244.157; 6.B.244.166; 6.B.244.169; 6.B.244.172; 6.B.244.175; 6.B.244.240; 6.B.244.244;

Prodrugs of 6.D

6.D.228.228; 6.D.228.229; 6.D.228.230; 6.D.228.231; 6.D.228.236; 6.D.228.237; 6.D.228.238; 6.D.228.239; 6.D.228.154; 6.D.228.157; 6.D.228.166; 6.D.228.169; 6.D.228.172; 6.D.228.175; 6.D.228.240; 6.D.228.244; 6.D.229.228; 6.D.229.229;

6.D.229.230; 6.D.229.231; 6.D.229.236; 6.D.229.237; 6.D.229.238; 6.D.229.239; 6.D.229.154; 6.D.229.157; 6.D.229.166; 6.D.229.169; 6.D.229.172; 6.D.229.175; 6.D.229.240; 6.D.229.244; 6.D.230.228; 6.D.230.229; 6.D.230.230; 6.D.230.231; 6.D.230.236; 6.D.230.237; 6.D.230.238; 6.D.230.239; 6.D.230.154; 6.D.230.157; 6.D.230.166; 6.D.230.169; 6.D.230.172; 6.D.230.175; 6.D.230.240; 6.D.230.244; 6.D.231.228; 6.D.231.229; 6.D.231.230; 6.D.231.231; 6.D.231.236; 6.D.231.237; 6.D.231.238; 6.D.231.239; 6.D.231.154; 6.D.231.157; 6.D.231.166; 6.D.231.169; 6.D.231.172; 6.D.231.175; 6.D.231.240; 6.D.231.244; 6.D.236.228; 6.D.236.229; 6.D.236.230; 6.D.236.231; 6.D.236.236; 6.D.236.237; 6.D.236.238; 6.D.236.239; 6.D.236.154; 6.D.236.157; 6.D.236.166; 6.D.236.169; 6.D.236.172; 6.D.236.175; 6.D.236.240; 6.D.236.244; 6.D.237.228; 6.D.237.229; 6.D.237.230; 6.D.237.231; 6.D.237.236; 6.D.237.237; 6.D.237.238; 6.D.237.239; 6.D.237.154; 6.D.237.157; 6.D.237.166; 6.D.237.169; 6.D.237.172; 6.D.237.175; 6.D.237.240; 6.D.237.244; 6.D.238.228; 6.D.238.229; 6.D.238.230; 6.D.238.231; 6.D.238.236; 6.D.238.237; 6.D.238.238; 6.D.238.239; 6.D.238.154; 6.D.238.157; 6.D.238.166; 6.D.238.169; 6.D.238.172; 6.D.238.175; 6.D.238.240; 6.D.238.244; 6.D.239.228; 6.D.239.229; 6.D.239.230; 6.D.239.231; 6.D.239.236; 6.D.239.237; 6.D.239.238; 6.D.239.239; 6.D.239.154; 6.D.239.157; 6.D.239.166; 6.D.239.169; 6.D.239.172; 6.D.239.175; 6.D.239.240; 6.D.239.244; 6.D.154.228; 6.D.154.229; 6.D.154.230; 6.D.154.231; 6.D.154.236; 6.D.154.237; 6.D.154.238; 6.D.154.239; 6.D.154.154; 6.D.154.157; 6.D.154.166; 6.D.154.169; 6.D.154.172; 6.D.154.175; 6.D.154.240; 6.D.154.244; 6.D.157.228; 6.D.157.229; 6.D.157.230; 6.D.157.231; 6.D.157.236; 6.D.157.237; 6.D.157.238; 6.D.157.239; 6.D.157.154; 6.D.157.157; 6.D.157.166; 6.D.157.169; 6.D.157.172; 6.D.157.175; 6.D.157.240; 6.D.157.244; 6.D.166.228; 6.D.166.229; 6.D.166.230; 6.D.166.231; 6.D.166.236; 6.D.166.237; 6.D.166.238; 6.D.166.239; 6.D.166.154; 6.D.166.157; 6.D.166.166; 6.D.166.169; 6.D.166.172; 6.D.166.175; 6.D.166.240; 6.D.166.244; 6.D.169.228; 6.D.169.229; 6.D.169.230; 6.D.169.231; 6.D.169.236; 6.D.169.237; 6.D.169.238; 6.D.169.239; 6.D.169.154; 6.D.169.157; 6.D.169.166; 6.D.169.169; 6.D.169.172; 6.D.169.175; 6.D.169.240; 6.D.169.244; 6.D.172.228; 6.D.172.229; 6.D.172.230; 6.D.172.231; 6.D.172.236; 6.D.172.237; 6.D.172.238; 6.D.172.239; 6.D.172.154; 6.D.172.157; 6.D.172.166; 6.D.172.169; 6.D.172.172; 6.D.172.175; 6.D.172.240; 6.D.172.244; 6.D.175.228; 6.D.175.229; 6.D.175.230; 6.D.175.231; 6.D.175.236; 6.D.175.237; 6.D.175.238; 6.D.175.239; 6.D.175.154; 6.D.175.157; 6.D.175.166; 6.D.175.169; 6.D.175.172; 6.D.175.175; 6.D.175.240; 6.D.175.244; 6.D.240.228; 6.D.240.229; 6.D.240.230; 6.D.240.231; 6.D.240.236; 6.D.240.237; 6.D.240.238; 6.D.240.239; 6.D.240.154; 6.D.240.157; 6.D.240.166; 6.D.240.169; 6.D.240.172; 6.D.240.175; 6.D.240.240; 6.D.240.244; 6.D.244.228; 6.D.244.229; 6.D.244.230; 6.D.244.231; 6.D.244.236; 6.D.244.237; 6.D.244.238; 6.D.244.239; 6.D.244.154; 6.D.244.157; 6.D.244.166; 6.D.244.169; 6.D.244.172; 6.D.244.175; 6.D.244.240; 6.D.244.244;

<u>Prodrugs of 6.E</u>

6.E.228.228; 6.E.228.229; 6.E.228.230; 6.E.228.231; 6.E.228.236; 6.E.228.237; 6.E.228.238; 6.E.228.239; 6.E.228.154; 6.E.228.157; 6.E.228.166; 6.E.228.169; 6.E.228.172; 6.E.228.175; 6.E.228.240; 6.E.228.244; 6.E.229.228; 6.E.229.229; 6.E.229.230; 6.E.229.231; 6.E.229.236; 6.E.229.237; 6.E.229.238; 6.E.229.239; 6.E.229.154; 6.E.229.157; 6.E.229.166;

6.E.229.169; 6.E.229.172; 6.E.229.175; 6.E.229.240; 6.E.229.244; 6.E.230.228; 6.E.230.229; 6.E.230.230; 6.E.230.231; 6.E.230.236; 6.E.230.237; 6.E.230.238; 6.E.230.239; 6.E.230.154; 6.E.230.157; 6.E.230.166; 6.E.230.169; 6.E.230.172; 6.E.230.175; 6.E.230.240; 6.E.230.244; 6.E.231.228; 6.E.231.229; 6.E.231.230; 6.E.231.231; 6.E.231.236; 6.E.231.237; 6.E.231.238; 6.E.231.239; 6.E.231.154; 6.E.231.157; 6.E.231.166; 6.E.231.169; 6.E.231.172; 6.E.231.175; 6.E.231.240; 6.E.231.244; 6.E.236.228; 6.E.236.229; 6.E.236.230; 6.E.236.231; 6.E.236.236; 6.E.236.237; 6.E.236.238; 6.E.236.239; 6.E.236.154; 6.E.236.157; 6.E.236.166; 6.E.236.169; 6.E.236.172; 6.E.236.175; 6.E.236.240; 6.E.236.244; 6.E.237.228; 6.E.237.229; 6.E.237.230; 6.E.237.231; 6.E.237.236; 6.E.237.237; 6.E.237.238; 6.E.237.239; 6.E.237.154; 6.E.237.157; 6.E.237.166; 6.E.237.169; 6.E.237.172; 6.E.237.175; 6.E.237.240; 6.E.237.244; 6.E.238.228; 6.E.238.229; 6.E.238.230; 6.E.238.231; 6.E.238.236; 6.E.238.237; 6.E.238.238; 6.E.238.239; 6.E.238.154; 6.E.238.157; 6.E.238.166; 6.E.238.169; 6.E.238.172; 6.E.238.175; 6.E.238.240; 6.E.238.244; 6.E.239.228; 6.E.239.229; 6.E.239.230; 6.E.239.231; 6.E.239.236; 6.E.239.237; 6.E.239.238; 6.E.239.239; 6.E.239.154; 6.E.239.157; 6.E.239.166; 6.E.239.169; 6.E.239.172; 6.E.239.175; 6.E.239.240; 6.E.239.244; 6.E.154.228; 6.E.154.229; 6.E.154.230; 6.E.154.231; 6.E.154.236; 6.E.154.237; 6.E.154.238; 6.E.154.239; 6.E.154.154; 6.E.154.157; 6.E.154.166; 6.E.154.169; 6.E.154.172; 6.E.154.175; 6.E.154.240; 6.E.154.244; 6.E.157.228; 6.E.157.229; 6.E.157.230; 6.E.157.231; 6.E.157.236; 6.E.157.237; 6.E.157.238; 6.E.157.239; 6.E.157.154; 6.E.157.157; 6.E.157.166; 6.E.157.169; 6.E.157.172; 6.E.157.175; 6.E.157.240; 6.E.157.244; 6.E.166.228; 6.E.166.229; 6.E.166.230; 6.E.166.231; 6.E.166.236; 6.E.166.237; 6.E.166.238; 6.E.166.239; 6.E.166.154; 6.E.166.157; 6.E.166.166; 6.E.166.169; 6.E.166.172; 6.E.166.175; 6.E.166.240; 6.E.166.244; 6.E.169.228; 6.E.169.229; 6.E.169.230; 6.E.169.231; 6.E.169.236; 6.E.169.237; 6.E.169.238; 6.E.169.239; 6.E.169.154; 6.E.169.157; 6.E.169.166; 6.E.169.169; 6.E.169.172; 6.E.169.175; 6.E.169.240; 6.E.169.244; 6.E.172.228; 6.E.172.229; 6.E.172.230; 6.E.172.231; 6.E.172.236; 6.E.172.237; 6.E.172.238; 6.E.172.239; 6.E.172.154; 6.E.172.157; 6.E.172.166; 6.E.172.169; 6.E.172.172; 6.E.172.175; 6.E.172.240; 6.E.172.244; 6.E.175.228; 6.E.175.229; 6.E.175.230; 6.E.175.231; 6.E.175.236; 6.E.175.237; 6.E.175.238; 6.E.175.239; 6.E.175.154; 6.E.175.157; 6.E.175.166; 6.E.175.169; 6.E.175.172; 6.E.175.175; 6.E.175.240; 6.E.175.244; 6.E.240.228; 6.E.240.229; 6.E.240.230; 6.E.240.231; 6.E.240.236; 6.E.240.237; 6.E.240.238; 6.E.240.239; 6.E.240.154; 6.E.240.157; 6.E.240.166; 6.E.240.169; 6.E.240.172; 6.E.240.175; 6.E.240.240; 6.E.240.244; 6.E.244.228; 6.E.244.229; 6.E.244.230; 6.E.244.231; 6.E.244.236; 6.E.244.237; 6.E.244.238; 6.E.244.239; 6.E.244.154; 6.E.244.157; 6.E.244.166; 6.E.244.169; 6.E.244.172; 6.E.244.175; 6.E.244.240; 6.E.244.244;

<u>Prodrugs of 6.G</u>

6.G.228.228; 6.G.228.229; 6.G.228.230; 6.G.228.231; 6.G.228.236; 6.G.228.237; 6.G.228.238; 6.G.228.239; 6.G.228.154; 6.G.228.157; 6.G.228.166; 6.G.228.169; 6.G.228.172; 6.G.228.175; 6.G.228.240; 6.G.228.244; 6.G.229.228; 6.G.229.229; 6.G.229.230; 6.G.229.231; 6.G.229.236; 6.G.229.237; 6.G.229.238; 6.G.229.239; 6.G.229.154; 6.G.229.157; 6.G.229.166; 6.G.229.169; 6.G.229.172; 6.G.229.175; 6.G.229.240; 6.G.229.244; 6.G.230.228; 6.G.230.229; 6.G.230.230; 6.G.230.231; 6.G.230.236; 6.G.230.237; 6.G.230.238; 6.G.230.239; 6.G.230.154; 6.G.230.157; 6.G.230.166; 6.G.230.169; 6.G.230.172; 6.G.230.175; 6.G.230.240; 6.G.230.244; 6.G.231.228; 6.G.231.229; 6.G.231.230; 6.G.231.231; 6.G.231.236; 6.G.231.237; 6.G.231.238; 6.G.231.239; 6.G.231.154; 6.G.231.157; 6.G.231.166; 6.G.231.169; 6.G.231.172; 6.G.231.175; 6.G.231.240; 6.G.231.244; 6.G.236.228; 6.G.236.229;

6.G.236.230; 6.G.236.231; 6.G.236.236; 6.G.236.237; 6.G.236.238; 6.G.236.239; 6.G.236.154; 6.G.236.157; 6.G.236.166; 6.G.236.169; 6.G.236.172; 6.G.236.175; 6.G.236.240; 6.G.236.244; 6.G.237.228; 6.G.237.229; 6.G.237.230; 6.G.237.231; 6.G.237.236; 6.G.237.237; 6.G.237.238; 6.G.237.239; 6.G.237.154; 6.G.237.157; 6.G.237.166; 6.G.237.169; 6.G.237.172; 6.G.237.175; 6.G.237.240; 6.G.237.244; 6.G.238.228; 6.G.238.229; 6.G.238.230; 6.G.238.231; 6.G.238.236; 6.G.238.237; 6.G.238.238; 6.G.238.239; 6.G.238.154; 6.G.238.157; 6.G.238.166; 6.G.238.169; 6.G.238.172; 6.G.238.175; 6.G.238.240; 6.G.238.244; 6.G.239.228; 6.G.239.229; 6.G.239.230; 6.G.239.231; 6.G.239.236; 6.G.239.237; 6.G.239.238; 6.G.239.239; 6.G.239.154; 6.G.239.157; 6.G.239.166; 6.G.239.169; 6.G.239.172; 6.G.239.175; 6.G.239.240; 6.G.239.244; 6.G.154.228; 6.G.154.229; 6.G.154.230; 6.G.154.231; 6.G.154.236; 6.G.154.237; 6.G.154.238; 6.G.154.239; 6.G.154.154; 6.G.154.157; 6.G.154.166; 6.G.154.169; 6.G.154.172; 6.G.154.175; 6.G.154.240; 6.G.154.244; 6.G.157.228; 6.G.157.229; 6.G.157.230; 6.G.157.231; 6.G.157.236; 6.G.157.237; 6.G.157.238; 6.G.157.239; 6.G.157.154; 6.G.157.157; 6.G.157.166; 6.G.157.169; 6.G.157.172; 6.G.157.175; 6.G.157.240; 6.G.157.244; 6.G.166.228; 6.G.166.229; 6.G.166.230; 6.G.166.231; 6.G.166.236; 6.G.166.237; 6.G.166.238; 6.G.166.239; 6.G.166.154; 6.G.166.157; 6.G.166.166; 6.G.166.169; 6.G.166.172; 6.G.166.175; 6.G.166.240; 6.G.166.244; 6.G.169.228; 6.G.169.229; 6.G.169.230; 6.G.169.231; 6.G.169.236; 6.G.169.237; 6.G.169.238; 6.G.169.239; 6.G.169.154; 6.G.169.157; 6.G.169.166; 6.G.169.169; 6.G.169.172; 6.G.169.175; 6.G.169.240; 6.G.169.244; 6.G.172.228; 6.G.172.229; 6.G.172.230; 6.G.172.231; 6.G.172.236; 6.G.172.237; 6.G.172.238; 6.G.172.239; 6.G.172.154; 6.G.172.157; 6.G.172.166; 6.G.172.169; 6.G.172.172; 6.G.172.175; 6.G.172.240; 6.G.172.244; 6.G.175.228; 6.G.175.229; 6.G.175.230; 6.G.175.231; 6.G.175.236; 6.G.175.237; 6.G.175.238; 6.G.175.239; 6.G.175.154; 6.G.175.157; 6.G.175.166; 6.G.175.169; 6.G.175.172; 6.G.175.175; 6.G.175.240; 6.G.175.244; 6.G.240.228; 6.G.240.229; 6.G.240.230; 6.G.240.231; 6.G.240.236; 6.G.240.237; 6.G.240.238; 6.G.240.239; 6.G.240.154; 6.G.240.157; 6.G.240.166; 6.G.240.169; 6.G.240.172; 6.G.240.175; 6.G.240.240; 6.G.240.244; 6.G.244.228; 6.G.244.229; 6.G.244.230; 6.G.244.231; 6.G.244.236; 6.G.244.237; 6.G.244.238; 6.G.244.239; 6.G.244.154; 6.G.244.157; 6.G.244.166; 6.G.244.169; 6.G.244.172; 6.G.244.175; 6.G.244.240; 6.G.244.244;

<u>Prodrugs of 6.I</u>

6.I.228.228; 6.I.228.229; 6.I.228.230; 6.I.228.231; 6.I.228.236; 6.I.228.237; 6.I.228.238; 6.I.228.239; 6.I.228.154; 6.I.228.157; 6.I.228.166; 6.I.228.169; 6.I.228.172; 6.I.228.175; 6.I.228.240; 6.I.228.244; 6.I.229.228; 6.I.229.229; 6.I.229.230; 6.I.229.231; 6.I.229.236; 6.I.229.237; 6.I.229.238; 6.I.229.239; 6.I.229.154; 6.I.229.157; 6.I.229.166; 6.I.229.169; 6.I.229.172; 6.I.229.175; 6.I.229.240; 6.I.229.244; 6.I.230.228; 6.I.230.229; 6.I.230.230; 6.I.230.231; 6.I.230.236; 6.I.230.237; 6.I.230.238; 6.I.230.239; 6.I.230.154; 6.I.230.157; 6.I.230.166; 6.I.230.169; 6.I.230.172; 6.I.230.175; 6.I.230.240; 6.I.230.244; 6.I.231.228; 6.I.231.229; 6.I.231.230; 6.I.231.231; 6.I.231.236; 6.I.231.237; 6.I.231.238; 6.I.231.239; 6.I.231.154; 6.I.231.157; 6.I.231.166; 6.I.231.169; 6.I.231.172; 6.I.231.175; 6.I.231.240; 6.I.231.244; 6.I.236.228; 6.I.236.229; 6.I.236.230; 6.I.236.231; 6.I.236.236; 6.I.236.237; 6.I.236.238; 6.I.236.239; 6.I.236.154; 6.I.236.157; 6.I.236.166; 6.I.236.169; 6.I.236.172; 6.I.236.175; 6.I.236.240; 6.I.236.244; 6.I.237.228; 6.I.237.229; 6.I.237.230; 6.I.237.231;

6.I.237.236; 6.I.237.237; 6.I.237.238; 6.I.237.239; 6.I.237.154; 6.I.237.157; 6.I.237.166; 6.I.237.169; 6.I.237.172; 6.I.237.175; 6.I.237.240; 6.I.237.244; 6.I.238.228; 6.I.238.229; 6.I.238.230; 6.I.238.231; 6.I.238.236; 6.I.238.237; 6.I.238.238; 6.I.238.239; 6.I.238.154; 6.I.238.157; 6.I.238.166; 6.I.238.169; 6.I.238.172; 6.I.238.175; 6.I.238.240; 6.I.238.244; 6.I.239.228; 6.I.239.229; 6.I.239.230; 6.I.239.231; 6.I.239.236; 6.I.239.237; 6.I.239.238; 6.I.239.239; 6.I.239.154; 6.I.239.157; 6.I.239.166; 6.I.239.169; 6.I.239.172; 6.I.239.175; 6.I.239.240; 6.I.239.244; 6.I.154.228; 6.I.154.229; 6.I.154.230; 6.I.154.231; 6.I.154.236; 6.I.154.237; 6.I.154.238; 6.I.154.239; 6.I.154.154; 6.I.154.157; 6.I.154.166; 6.I.154.169; 6.I.154.172; 6.I.154.175; 6.I.154.240; 6.I.154.244; 6.I.157.228; 6.I.157.229; 6.I.157.230; 6.I.157.231; 6.I.157.236; 6.I.157.237; 6.I.157.238; 6.I.157.239; 6.I.157.154; 6.I.157.157; 6.I.157.166; 6.I.157.169; 6.I.157.172; 6.I.157.175; 6.I.157.240; 6.I.157.244; 6.I.166.228; 6.I.166.229; 6.I.166.230; 6.I.166.231; 6.I.166.236; 6.I.166.237; 6.I.166.238; 6.I.166.239; 6.I.166.154; 6.I.166.157; 6.I.166.166; 6.I.166.169; 6.I.166.172; 6.I.166.175; 6.I.166.240; 6.I.166.244; 6.I.169.228; 6.I.169.229; 6.I.169.230; 6.I.169.231; 6.I.169.236; 6.I.169.237; 6.I.169.238; 6.I.169.239; 6.I.169.154; 6.I.169.157; 6.I.169.166; 6.I.169.169; 6.I.169.172; 6.I.169.175; 6.I.169.240; 6.I.169.244; 6.I.172.228; 6.I.172.229; 6.I.172.230; 6.I.172.231; 6.I.172.236; 6.I.172.237; 6.I.172.238; 6.I.172.239; 6.I.172.154; 6.I.172.157; 6.I.172.166; 6.I.172.169; 6.I.172.172; 6.I.172.175; 6.I.172.240; 6.I.172.244; 6.I.175.228; 6.I.175.229; 6.I.175.230; 6.I.175.231; 6.I.175.236; 6.I.175.237; 6.I.175.238; 6.I.175.239; 6.I.175.154; 6.I.175.157; 6.I.175.166; 6.I.175.169; 6.I.175.172; 6.I.175.175; 6.I.175.240; 6.I.175.244; 6.I.240.228; 6.I.240.229; 6.I.240.230; 6.I.240.231; 6.I.240.236; 6.I.240.237; 6.I.240.238; 6.I.240.239; 6.I.240.154; 6.I.240.157; 6.I.240.166; 6.I.240.169; 6.I.240.172; 6.I.240.175; 6.I.240.240; 6.I.240.244; 6.I.244.228; 6.I.244.229; 6.I.244.230; 6.I.244.231; 6.I.244.236; 6.I.244.237; 6.I.244.238; 6.I.244.239; 6.I.244.154; 6.I.244.157; 6.I.244.166; 6.I.244.169; 6.I.244.172; 6.I.244.175; 6.I.244.240; 6.I.244.244;

<u>Prodrugs of 6.I</u>

6.J.228.228; 6.J.228.229; 6.J.228.230; 6.J.228.231; 6.J.228.236; 6.J.228.237; 6.J.228.238; 6.J.228.239; 6.J.228.154; 6.J.228.157; 6.J.228.166; 6.J.228.169; 6.J.228.172; 6.J.228.175; 6.J.228.240; 6.J.228.244; 6.J.229.228; 6.J.229.229; 6.J.229.230; 6.J.229.231; 6.J.229.236; 6.J.229.237; 6.J.229.238; 6.J.229.239; 6.J.229.154; 6.J.229.157; 6.J.229.166; 6.J.229.169; 6.J.229.172; 6.J.229.175; 6.J.229.240; 6.J.229.244; 6.J.230.228; 6.J.230.229; 6.J.230.230; 6.J.230.231; 6.J.230.236; 6.J.230.237; 6.J.230.238; 6.J.230.239; 6.J.230.154; 6.J.230.157; 6.J.230.166; 6.J.230.169; 6.J.230.172; 6.J.230.175; 6.J.230.240; 6.J.230.244; 6.J.231.228; 6.J.231.229; 6.J.231.230; 6.J.231.231; 6.J.231.236; 6.J.231.237; 6.J.231.238; 6.J.231.239; 6.J.231.154; 6.J.231.157; 6.J.231.166; 6.J.231.169; 6.J.231.172; 6.J.231.175; 6.J.231.240; 6.J.231.244; 6.J.236.228; 6.J.236.229; 6.J.236.230; 6.J.236.231; 6.J.236.236; 6.J.236.237; 6.J.236.238; 6.J.236.239; 6.J.236.154; 6.J.236.157; 6.J.236.166; 6.J.236.169; 6.J.236.172; 6.J.236.175; 6.J.236.240; 6.J.236.244; 6.J.237.228; 6.J.237.229; 6.J.237.230; 6.J.237.231; 6.J.237.236; 6.J.237.237; 6.J.237.238; 6.J.237.239; 6.J.237.154; 6.J.237.157; 6.J.237.166; 6.J.237.169; 6.J.237.172; 6.J.237.175; 6.J.237.240; 6.J.237.244; 6.J.238.228; 6.J.238.229; 6.J.238.230; 6.J.238.231; 6.J.238.236; 6.J.238.237; 6.J.238.238; 6.J.238.239; 6.J.238.154; 6.J.238.157; 6.J.238.166; 6.J.238.169; 6.J.238.172; 6.J.238.175; 6.J.238.240; 6.J.238.244; 6.J.239.228; 6.J.239.229; 6.J.239.230; 6.J.239.231; 6.J.239.236; 6.J.239.237; 6.J.239.238; 6.J.239.239; 6.J.239.154; 6.J.239.157; 6.J.239.166; 6.J.239.169; 6.J.239.172; 6.J.239.175; 6.J.239.240; 6.J.239.244; 6.J.154.228; 6.J.154.229; 6.J.154.230; 6.J.154.231; 6.J.154.236;

6.J.154.237; 6.J.154.238; 6.J.154.239; 6.J.154.154; 6.J.154.157; 6.J.154.166; 6.J.154.169; 6.J.154.172; 6.J.154.175; 6.J.154.240; 6.J.154.244; 6.J.157.228; 6.J.157.229; 6.J.157.230; 6.J.157.231; 6.J.157.236; 6.J.157.237; 6.J.157.238; 6.J.157.239; 6.J.157.154; 6.J.157.157; 6.J.157.166; 6.J.157.169; 6.J.157.172; 6.J.157.175; 6.J.157.240; 6.J.157.244; 6.J.166.228; 6.J.166.229; 6.J.166.230; 6.J.166.231; 6.J.166.236; 6.J.166.237; 6.J.166.238; 6.J.166.239; 6.J.166.154; 6.J.166.157; 6.J.166.166; 6.J.166.169; 6.J.166.172; 6.J.166.175; 6.J.166.240; 6.J.166.244; 6.J.169.228; 6.J.169.229; 6.J.169.230; 6.J.169.231; 6.J.169.236; 6.J.169.237; 6.J.169.238; 6.J.169.239; 6.J.169.154; 6.J.169.157; 6.J.169.166; 6.J.169.169; 6.J.169.172; 6.J.169.175; 6.J.169.240; 6.J.169.244; 6.J.172.228; 6.J.172.229; 6.J.172.230; 6.J.172.231; 6.J.172.236; 6.J.172.237; 6.J.172.238; 6.J.172.239; 6.J.172.154; 6.J.172.157; 6.J.172.166; 6.J.172.169; 6.J.172.172; 6.J.172.175; 6.J.172.240; 6.J.172.244; 6.J.175.228; 6.J.175.229; 6.J.175.230; 6.J.175.231; 6.J.175.236; 6.J.175.237; 6.J.175.238; 6.J.175.239; 6.J.175.154; 6.J.175.157; 6.J.175.166; 6.J.175.169; 6.J.175.172; 6.J.175.175; 6.J.175.240; 6.J.175.244; 6.J.240.228; 6.J.240.229; 6.J.240.230; 6.J.240.231; 6.J.240.236; 6.J.240.237; 6.J.240.238; 6.J.240.239; 6.J.240.154; 6.J.240.157; 6.J.240.166; 6.J.240.169; 6.J.240.172; 6.J.240.175; 6.J.240.240; 6.J.240.244; 6.J.244.228; 6.J.244.229; 6.J.244.230; 6.J.244.231; 6.J.244.236; 6.J.244.237; 6.J.244.238; 6.J.244.239; 6.J.244.154; 6.J.244.157; 6.J.244.166; 6.J.244.169; 6.J.244.172; 6.J.244.175; 6.J.244.240; 6.J.244.244;

<u>Prodrugs of 6.L</u>

6.L.228.228; 6.L.228.229; 6.L.228.230; 6.L.228.231; 6.L.228.236; 6.L.228.237; 6.L.228.238; 6.L.228.239; 6.L.228.154; 6.L.228.157; 6.L.228.166; 6.L.228.169; 6.L.228.172; 6.L.228.175; 6.L.228.240; 6.L.228.244; 6.L.229.228; 6.L.229.229; 6.L.229.230; 6.L.229.231; 6.L.229.236; 6.L.229.237; 6.L.229.238; 6.L.229.239; 6.L.229.154; 6.L.229.157; 6.L.229.166; 6.L.229.169; 6.L.229.172; 6.L.229.175; 6.L.229.240; 6.L.229.244; 6.L.230.228; 6.L.230.229; 6.L.230.230; 6.L.230.231; 6.L.230.236; 6.L.230.237; 6.L.230.238; 6.L.230.239; 6.L.230.154; 6.L.230.157; 6.L.230.166; 6.L.230.169; 6.L.230.172; 6.L.230.175; 6.L.230.240; 6.L.230.244; 6.L.231.228; 6.L.231.229; 6.L.231.230; 6.L.231.231; 6.L.231.236; 6.L.231.237; 6.L.231.238; 6.L.231.239; 6.L.231.154; 6.L.231.157; 6.L.231.166; 6.L.231.169; 6.L.231.172; 6.L.231.175; 6.L.231.240; 6.L.231.244; 6.L.236.228; 6.L.236.229; 6.L.236.230; 6.L.236.231; 6.L.236.236; 6.L.236.237; 6.L.236.238; 6.L.236.239; 6.L.236.154; 6.L.236.157; 6.L.236.166; 6.L.236.169; 6.L.236.172; 6.L.236.175; 6.L.236.240; 6.L.236.244; 6.L.237.228; 6.L.237.229; 6.L.237.230; 6.L.237.231; 6.L.237.236; 6.L.237.237; 6.L.237.238; 6.L.237.239; 6.L.237.154; 6.L.237.157; 6.L.237.166; 6.L.237.169; 6.L.237.172; 6.L.237.175; 6.L.237.240; 6.L.237.244; 6.L.238.228; 6.L.238.229; 6.L.238.230; 6.L.238.231; 6.L.238.236; 6.L.238.237; 6.L.238.238; 6.L.238.239; 6.L.238.154; 6.L.238.157; 6.L.238.166; 6.L.238.169; 6.L.238.172; 6.L.238.175; 6.L.238.240; 6.L.238.244; 6.L.239.228; 6.L.239.229; 6.L.239.230; 6.L.239.231; 6.L.239.236; 6.L.239.237; 6.L.239.238; 6.L.239.239; 6.L.239.154; 6.L.239.157; 6.L.239.166; 6.L.239.169; 6.L.239.172; 6.L.239.175; 6.L.239.240; 6.L.239.244; 6.L.154.228; 6.L.154.229; 6.L.154.230; 6.L.154.231; 6.L.154.236; 6.L.154.237; 6.L.154.238; 6.L.154.239; 6.L.154.154; 6.L.154.157; 6.L.154.166; 6.L.154.169; 6.L.154.172; 6.L.154.175; 6.L.154.240; 6.L.154.244; 6.L.157.228; 6.L.157.229; 6.L.157.230; 6.L.157.231; 6.L.157.236; 6.L.157.237; 6.L.157.238; 6.L.157.239; 6.L.157.154; 6.L.157.157; 6.L.157.166; 6.L.157.169; 6.L.157.172; 6.L.157.175; 6.L.157.240; 6.L.157.244; 6.L.166.228; 6.L.166.229; 6.L.166.230; 6.L.166.231; 6.L.166.236; 6.L.166.237; 6.L.166.238; 6.L.166.239; 6.L.166.154; 6.L.166.157; 6.L.166.166; 6.L.166.169; 6.L.166.172; 6.L.166.175; 6.L.166.240; 6.L.166.244; 6.L.169.228; 6.L.169.229; 6.L.169.230; 6.L.169.231; 6.L.169.236;

6.L.169.237; 6.L.169.238; 6.L.169.239; 6.L.169.154; 6.L.169.157; 6.L.169.166; 6.L.169.169; 6.L.169.172; 6.L.169.175; 6.L.169.240; 6.L.169.244; 6.L.172.228; 6.L.172.229; 6.L.172.230; 6.L.172.231; 6.L.172.236; 6.L.172.237; 6.L.172.238; 6.L.172.239; 6.L.172.154; 6.L.172.157; 6.L.172.166; 6.L.172.169; 6.L.172.172; 6.L.172.175; 6.L.172.240; 6.L.172.244; 6.L.175.228; 6.L.175.229; 6.L.175.230; 6.L.175.231; 6.L.175.236; 6.L.175.237; 6.L.175.238; 6.L.175.239; 6.L.175.154; 6.L.175.157; 6.L.175.166; 6.L.175.169; 6.L.175.172; 6.L.175.175; 6.L.175.240; 6.L.175.244; 6.L.240.228; 6.L.240.229; 6.L.240.230; 6.L.240.231; 6.L.240.236; 6.L.240.237; 6.L.240.238; 6.L.240.239; 6.L.240.154; 6.L.240.157; 6.L.240.166; 6.L.240.169; 6.L.240.172; 6.L.240.175; 6.L.240.240; 6.L.240.244; 6.L.244.228; 6.L.244.229; 6.L.244.230; 6.L.244.231; 6.L.244.236; 6.L.244.237; 6.L.244.238; 6.L.244.239; 6.L.244.154; 6.L.244.157; 6.L.244.166; 6.L.244.169; 6.L.244.172; 6.L.244.175; 6.L.244.240; 6.L.244.244;

Prodrugs of 6.O

6.O.228.228; 6.O.228.229; 6.O.228.230; 6.O.228.231; 6.O.228.236; 6.O.228.237; 6.O.228.238; 6.O.228.239; 6.O.228.154; 6.O.228.157; 6.O.228.166; 6.O.228.169; 6.O.228.172; 6.O.228.175; 6.O.228.240; 6.O.228.244; 6.O.229.228; 6.O.229.229; 6.O.229.230; 6.O.229.231; 6.O.229.236; 6.O.229.237; 6.O.229.238; 6.O.229.239; 6.O.229.154; 6.O.229.157; 6.O.229.166; 6.O.229.169; 6.O.229.172; 6.O.229.175; 6.O.229.240; 6.O.229.244; 6.O.230.228; 6.O.230.229; 6.O.230.230; 6.O.230.231; 6.O.230.236; 6.O.230.237; 6.O.230.238; 6.O.230.239; 6.O.230.154; 6.O.230.157; 6.O.230.166; 6.O.230.169; 6.O.230.172; 6.O.230.175; 6.O.230.240; 6.O.230.244; 6.O.231.228; 6.O.231.229; 6.O.231.230; 6.O.231.231; 6.O.231.236; 6.O.231.237; 6.O.231.238; 6.O.231.239; 6.O.231.154; 6.O.231.157; 6.O.231.166; 6.O.231.169; 6.O.231.172; 6.O.231.175; 6.O.231.240; 6.O.231.244; 6.O.236.228; 6.O.236.229; 6.O.236.230; 6.O.236.231; 6.O.236.236; 6.O.236.237; 6.O.236.238; 6.O.236.239; 6.O.236.154; 6.O.236.157; 6.O.236.166; 6.O.236.169; 6.O.236.172; 6.O.236.175; 6.O.236.240; 6.O.236.244; 6.O.237.228; 6.O.237.229; 6.O.237.230; 6.O.237.231; 6.O.237.236; 6.O.237.237; 6.O.237.238; 6.O.237.239; 6.O.237.154; 6.O.237.157; 6.O.237.166; 6.O.237.169; 6.O.237.172; 6.O.237.175; 6.O.237.240; 6.O.237.244; 6.O.238.228; 6.O.238.229; 6.O.238.230; 6.O.238.231; 6.O.238.236; 6.O.238.237; 6.O.238.238; 6.O.238.239; 6.O.238.154; 6.O.238.157; 6.O.238.166; 6.O.238.169; 6.O.238.172; 6.O.238.175; 6.O.238.240; 6.O.238.244; 6.O.239.228; 6.O.239.229; 6.O.239.230; 6.O.239.231; 6.O.239.236; 6.O.239.237; 6.O.239.238; 6.O.239.239; 6.O.239.154; 6.O.239.157; 6.O.239.166; 6.O.239.169; 6.O.239.172; 6.O.239.175; 6.O.239.240; 6.O.239.244; 6.O.154.228; 6.O.154.229; 6.O.154.230; 6.O.154.231; 6.O.154.236; 6.O.154.237; 6.O.154.238; 6.O.154.239; 6.O.154.154; 6.O.154.157; 6.O.154.166; 6.O.154.169; 6.O.154.172; 6.O.154.175; 6.O.154.240; 6.O.154.244; 6.O.157.228; 6.O.157.229; 6.O.157.230; 6.O.157.231; 6.O.157.236; 6.O.157.237; 6.O.157.238; 6.O.157.239; 6.O.157.154; 6.O.157.157; 6.O.157.166; 6.O.157.169; 6.O.157.172; 6.O.157.175; 6.O.157.240; 6.O.157.244; 6.O.166.228; 6.O.166.229; 6.O.166.230; 6.O.166.231; 6.O.166.236; 6.O.166.237; 6.O.166.238; 6.O.166.239; 6.O.166.154; 6.O.166.157; 6.O.166.166; 6.O.166.169; 6.O.166.172; 6.O.166.175; 6.O.166.240; 6.O.166.244; 6.O.169.228; 6.O.169.229; 6.O.169.230; 6.O.169.231; 6.O.169.236; 6.O.169.237; 6.O.169.238; 6.O.169.239; 6.O.169.154; 6.O.169.157; 6.O.169.166; 6.O.169.169; 6.O.169.172; 6.O.169.175; 6.O.169.240; 6.O.169.244; 6.O.172.228; 6.O.172.229; 6.O.172.230; 6.O.172.231; 6.O.172.236; 6.O.172.237;

6.O.172.238; 6.O.172.239; 6.O.172.154; 6.O.172.157; 6.O.172.166; 6.O.172.169; 6.O.172.172; 6.O.172.175; 6.O.172.240; 6.O.172.244; 6.O.175.228; 6.O.175.229; 6.O.175.230; 6.O.175.231; 6.O.175.236; 6.O.175.237; 6.O.175.238; 6.O.175.239; 6.O.175.154; 6.O.175.157; 6.O.175.166; 6.O.175.169; 6.O.175.172; 6.O.175.175; 6.O.175.240; 6.O.175.244; 6.O.240.228; 6.O.240.229; 6.O.240.230; 6.O.240.231; 6.O.240.236; 6.O.240.237; 6.O.240.238; 6.O.240.239; 6.O.240.154; 6.O.240.157; 6.O.240.166; 6.O.240.169; 6.O.240.172; 6.O.240.175; 6.O.240.240; 6.O.240.244; 6.O.244.228; 6.O.244.229; 6.O.244.230; 6.O.244.231; 6.O.244.236; 6.O.244.237; 6.O.244.238; 6.O.244.239; 6.O.244.154; 6.O.244.157; 6.O.244.166; 6.O.244.169; 6.O.244.172; 6.O.244.175; 6.O.244.240; 6.O.244.244;

Prodrugs of 6.P

6.P.228.228; 6.P.228.229; 6.P.228.230; 6.P.228.231; 6.P.228.236; 6.P.228.237; 6.P.228.238; 6.P.228.239; 6.P.228.154; 6.P.228.157; 6.P.228.166; 6.P.228.169; 6.P.228.172; 6.P.228.175; 6.P.228.240; 6.P.228.244; 6.P.229.228; 6.P.229.229; 6.P.229.230; 6.P.229.231; 6.P.229.236; 6.P.229.237; 6.P.229.238; 6.P.229.239; 6.P.229.154; 6.P.229.157; 6.P.229.166; 6.P.229.169; 6.P.229.172; 6.P.229.175; 6.P.229.240; 6.P.229.244; 6.P.230.228; 6.P.230.229; 6.P.230.230; 6.P.230.231; 6.P.230.236; 6.P.230.237; 6.P.230.238; 6.P.230.239; 6.P.230.154; 6.P.230.157; 6.P.230.166; 6.P.230.169; 6.P.230.172; 6.P.230.175; 6.P.230.240; 6.P.230.244; 6.P.231.228; 6.P.231.229; 6.P.231.230; 6.P.231.231; 6.P.231.236; 6.P.231.237; 6.P.231.238; 6.P.231.239; 6.P.231.154; 6.P.231.157; 6.P.231.166; 6.P.231.169; 6.P.231.172; 6.P.231.175; 6.P.231.240; 6.P.231.244; 6.P.236.228; 6.P.236.229; 6.P.236.230; 6.P.236.231; 6.P.236.236; 6.P.236.237; 6.P.236.238; 6.P.236.239; 6.P.236.154; 6.P.236.157; 6.P.236.166; 6.P.236.169; 6.P.236.172; 6.P.236.175; 6.P.236.240; 6.P.236.244; 6.P.237.228; 6.P.237.229; 6.P.237.230; 6.P.237.231; 6.P.237.236; 6.P.237.237; 6.P.237.238; 6.P.237.239; 6.P.237.154; 6.P.237.157; 6.P.237.166; 6.P.237.169; 6.P.237.172; 6.P.237.175; 6.P.237.240; 6.P.237.244; 6.P.238.228; 6.P.238.229; 6.P.238.230; 6.P.238.231; 6.P.238.236; 6.P.238.237; 6.P.238.238; 6.P.238.239; 6.P.238.154; 6.P.238.157; 6.P.238.166; 6.P.238.169; 6.P.238.172; 6.P.238.175; 6.P.238.240; 6.P.238.244; 6.P.239.228; 6.P.239.229; 6.P.239.230; 6.P.239.231; 6.P.239.236; 6.P.239.237; 6.P.239.238; 6.P.239.239; 6.P.239.154; 6.P.239.157; 6.P.239.166; 6.P.239.169; 6.P.239.172; 6.P.239.175; 6.P.239.240; 6.P.239.244; 6.P.154.228; 6.P.154.229; 6.P.154.230; 6.P.154.231; 6.P.154.236; 6.P.154.237; 6.P.154.238; 6.P.154.239; 6.P.154.154; 6.P.154.157; 6.P.154.166; 6.P.154.169; 6.P.154.172; 6.P.154.175; 6.P.154.240; 6.P.154.244; 6.P.157.228; 6.P.157.229; 6.P.157.230; 6.P.157.231; 6.P.157.236; 6.P.157.237; 6.P.157.238; 6.P.157.239; 6.P.157.154; 6.P.157.157; 6.P.157.166; 6.P.157.169; 6.P.157.172; 6.P.157.175; 6.P.157.240; 6.P.157.244; 6.P.166.228; 6.P.166.229; 6.P.166.230; 6.P.166.231; 6.P.166.236; 6.P.166.237; 6.P.166.238; 6.P.166.239; 6.P.166.154; 6.P.166.157; 6.P.166.166; 6.P.166.169; 6.P.166.172; 6.P.166.175; 6.P.166.240; 6.P.166.244; 6.P.169.228; 6.P.169.229; 6.P.169.230; 6.P.169.231; 6.P.169.236; 6.P.169.237; 6.P.169.238; 6.P.169.239; 6.P.169.154; 6.P.169.157; 6.P.169.166; 6.P.169.169; 6.P.169.172; 6.P.169.175; 6.P.169.240; 6.P.169.244; 6.P.172.228; 6.P.172.229; 6.P.172.230; 6.P.172.231; 6.P.172.236; 6.P.172.237; 6.P.172.238; 6.P.172.239; 6.P.172.154; 6.P.172.157; 6.P.172.166; 6.P.172.169; 6.P.172.172; 6.P.172.175; 6.P.172.240; 6.P.172.244; 6.P.175.228; 6.P.175.229; 6.P.175.230; 6.P.175.231; 6.P.175.236; 6.P.175.237; 6.P.175.238; 6.P.175.239; 6.P.175.154; 6.P.175.157; 6.P.175.166; 6.P.175.169; 6.P.175.172; 6.P.175.175; 6.P.175.240; 6.P.175.244; 6.P.240.228; 6.P.240.229; 6.P.240.230; 6.P.240.231; 6.P.240.236; 6.P.240.237; 6.P.240.238; 6.P.240.239; 6.P.240.154; 6.P.240.157; 6.P.240.166; 6.P.240.169; 6.P.240.172;

6.P.240.175; 6.P.240.240; 6.P.240.244; 6.P.244.228; 6.P.244.229; 6.P.244.230; 6.P.244.231; 6.P.244.236; 6.P.244.237; 6.P.244.238; 6.P.244.239; 6.P.244.154; 6.P.244.157; 6.P.244.166; 6.P.244.169; 6.P.244.172; 6.P.244.175; 6.P.244.240; 6.P.244.244;

Prodrugs of 6.U

6.U.228.228; 6.U.228.229; 6.U.228.230; 6.U.228.231; 6.U.228.236; 6.U.228.237; 6.U.228.238; 6.U.228.239; 6.U.228.154; 6.U.228.157; 6.U.228.166; 6.U.228.169; 6.U.228.172; 6.U.228.175; 6.U.228.240; 6.U.228.244; 6.U.229.228; 6.U.229.229; 6.U.229.230; 6.U.229.231; 6.U.229.236; 6.U.229.237; 6.U.229.238; 6.U.229.239; 6.U.229.154; 6.U.229.157; 6.U.229.166; 6.U.229.169; 6.U.229.172; 6.U.229.175; 6.U.229.240; 6.U.229.244; 6.U.230.228; 6.U.230.229; 6.U.230.230; 6.U.230.231; 6.U.230.236; 6.U.230.237; 6.U.230.238; 6.U.230.239; 6.U.230.154; 6.U.230.157; 6.U.230.166; 6.U.230.169; 6.U.230.172; 6.U.230.175; 6.U.230.240; 6.U.230.244; 6.U.231.228; 6.U.231.229; 6.U.231.230; 6.U.231.231; 6.U.231.236; 6.U.231.237; 6.U.231.238; 6.U.231.239; 6.U.231.154; 6.U.231.157; 6.U.231.166; 6.U.231.169; 6.U.231.172; 6.U.231.175; 6.U.231.240; 6.U.231.244; 6.U.236.228; 6.U.236.229; 6.U.236.230; 6.U.236.231; 6.U.236.236; 6.U.236.237; 6.U.236.238; 6.U.236.239; 6.U.236.154; 6.U.236.157; 6.U.236.166; 6.U.236.169; 6.U.236.172; 6.U.236.175; 6.U.236.240; 6.U.236.244; 6.U.237.228; 6.U.237.229; 6.U.237.230; 6.U.237.231; 6.U.237.236; 6.U.237.237; 6.U.237.238; 6.U.237.239; 6.U.237.154; 6.U.237.157; 6.U.237.166; 6.U.237.169; 6.U.237.172; 6.U.237.175; 6.U.237.240; 6.U.237.244; 6.U.238.228; 6.U.238.229; 6.U.238.230; 6.U.238.231; 6.U.238.236; 6.U.238.237; 6.U.238.238; 6.U.238.239; 6.U.238.154; 6.U.238.157; 6.U.238.166; 6.U.238.169; 6.U.238.172; 6.U.238.175; 6.U.238.240; 6.U.238.244; 6.U.239.228; 6.U.239.229; 6.U.239.230; 6.U.239.231; 6.U.239.236; 6.U.239.237; 6.U.239.238; 6.U.239.239; 6.U.239.154; 6.U.239.157; 6.U.239.166; 6.U.239.169; 6.U.239.172; 6.U.239.175; 6.U.239.240; 6.U.239.244; 6.U.154.228; 6.U.154.229; 6.U.154.230; 6.U.154.231; 6.U.154.236; 6.U.154.237; 6.U.154.238; 6.U.154.239; 6.U.154.154; 6.U.154.157; 6.U.154.166; 6.U.154.169; 6.U.154.172; 6.U.154.175; 6.U.154.240; 6.U.154.244; 6.U.157.228; 6.U.157.229; 6.U.157.230; 6.U.157.231; 6.U.157.236; 6.U.157.237; 6.U.157.238; 6.U.157.239; 6.U.157.154; 6.U.157.157; 6.U.157.166; 6.U.157.169; 6.U.157.172; 6.U.157.175; 6.U.157.240; 6.U.157.244; 6.U.166.228; 6.U.166.229; 6.U.166.230; 6.U.166.231; 6.U.166.236; 6.U.166.237; 6.U.166.238; 6.U.166.239; 6.U.166.154; 6.U.166.157; 6.U.166.166; 6.U.166.169; 6.U.166.172; 6.U.166.175; 6.U.166.240; 6.U.166.244; 6.U.169.228; 6.U.169.229; 6.U.169.230; 6.U.169.231; 6.U.169.236; 6.U.169.237; 6.U.169.238; 6.U.169.239; 6.U.169.154; 6.U.169.157; 6.U.169.166; 6.U.169.169; 6.U.169.172; 6.U.169.175; 6.U.169.240; 6.U.169.244; 6.U.172.228; 6.U.172.229; 6.U.172.230; 6.U.172.231; 6.U.172.236; 6.U.172.237; 6.U.172.238; 6.U.172.239; 6.U.172.154; 6.U.172.157; 6.U.172.166; 6.U.172.169; 6.U.172.172; 6.U.172.175; 6.U.172.240; 6.U.172.244; 6.U.175.228; 6.U.175.229; 6.U.175.230; 6.U.175.231; 6.U.175.236; 6.U.175.237; 6.U.175.238; 6.U.175.239; 6.U.175.154; 6.U.175.157; 6.U.175.166; 6.U.175.169; 6.U.175.172; 6.U.175.175; 6.U.175.240; 6.U.175.244; 6.U.240.228; 6.U.240.229; 6.U.240.230; 6.U.240.231; 6.U.240.236; 6.U.240.237; 6.U.240.238; 6.U.240.239; 6.U.240.154; 6.U.240.157; 6.U.240.166; 6.U.240.169; 6.U.240.172; 6.U.240.175; 6.U.240.240; 6.U.240.244; 6.U.244.228; 6.U.244.229; 6.U.244.230; 6.U.244.231; 6.U.244.236; 6.U.244.237;

6.U.244.238; 6.U.244.239; 6.U.244.154; 6.U.244.157; 6.U.244.166; 6.U.244.169; 6.U.244.172; 6.U.244.175; 6.U.244.240; 6.U.244.244;

Prodrugs of 6.W

6.W.228.228; 6.W.228.229; 6.W.228.230; 6.W.228.231; 6.W.228.236; 6.W.228.237; 6.W.228.238; 6.W.228.239; 6.W.228.154; 6.W.228.157; 6.W.228.166; 6.W.228.169; 6.W.228.172; 6.W.228.175; 6.W.228.240; 6.W.228.244; 6.W.229.228; 6.W.229.229; 6.W.229.230; 6.W.229.231; 6.W.229.236; 6.W.229.237; 6.W.229.238; 6.W.229.239; 6.W.229.154; 6.W.229.157; 6.W.229.166; 6.W.229.169; 6.W.229.172; 6.W.229.175; 6.W.229.240; 6.W.229.244; 6.W.230.228; 6.W.230.229; 6.W.230.230; 6.W.230.231; 6.W.230.236; 6.W.230.237; 6.W.230.238; 6.W.230.239; 6.W.230.154; 6.W.230.157; 6.W.230.166; 6.W.230.169; 6.W.230.172; 6.W.230.175; 6.W.230.240; 6.W.230.244; 6.W.231.228; 6.W.231.229; 6.W.231.230; 6.W.231.231; 6.W.231.236; 6.W.231.237; 6.W.231.238; 6.W.231.239; 6.W.231.154; 6.W.231.157; 6.W.231.166; 6.W.231.169; 6.W.231.172; 6.W.231.175; 6.W.231.240; 6.W.231.244; 6.W.236.228; 6.W.236.229; 6.W.236.230; 6.W.236.231; 6.W.236.236; 6.W.236.237; 6.W.236.238; 6.W.236.239; 6.W.236.154; 6.W.236.157; 6.W.236.166; 6.W.236.169; 6.W.236.172; 6.W.236.175; 6.W.236.240; 6.W.236.244; 6.W.237.228; 6.W.237.229; 6.W.237.230; 6.W.237.231; 6.W.237.236; 6.W.237.237; 6.W.237.238; 6.W.237.239; 6.W.237.154; 6.W.237.157; 6.W.237.166; 6.W.237.169; 6.W.237.172; 6.W.237.175; 6.W.237.240; 6.W.237.244; 6.W.238.228; 6.W.238.229; 6.W.238.230; 6.W.238.231; 6.W.238.236; 6.W.238.237; 6.W.238.238; 6.W.238.239; 6.W.238.154; 6.W.238.157; 6.W.238.166; 6.W.238.169; 6.W.238.172; 6.W.238.175; 6.W.238.240; 6.W.238.244; 6.W.239.228; 6.W.239.229; 6.W.239.230; 6.W.239.231; 6.W.239.236; 6.W.239.237; 6.W.239.238; 6.W.239.239; 6.W.239.154; 6.W.239.157; 6.W.239.166; 6.W.239.169; 6.W.239.172; 6.W.239.175; 6.W.239.240; 6.W.239.244; 6.W.154.228; 6.W.154.229; 6.W.154.230; 6.W.154.231; 6.W.154.236; 6.W.154.237; 6.W.154.238; 6.W.154.239; 6.W.154.154; 6.W.154.157; 6.W.154.166; 6.W.154.169; 6.W.154.172; 6.W.154.175; 6.W.154.240; 6.W.154.244; 6.W.157.228; 6.W.157.229; 6.W.157.230; 6.W.157.231; 6.W.157.236; 6.W.157.237; 6.W.157.238; 6.W.157.239; 6.W.157.154; 6.W.157.157; 6.W.157.166; 6.W.157.169; 6.W.157.172; 6.W.157.175; 6.W.157.240; 6.W.157.244; 6.W.166.228; 6.W.166.229; 6.W.166.230; 6.W.166.231; 6.W.166.236; 6.W.166.237; 6.W.166.238; 6.W.166.239; 6.W.166.154; 6.W.166.157; 6.W.166.166; 6.W.166.169; 6.W.166.172; 6.W.166.175; 6.W.166.240; 6.W.166.244; 6.W.169.228; 6.W.169.229; 6.W.169.230; 6.W.169.231; 6.W.169.236; 6.W.169.237; 6.W.169.238; 6.W.169.239; 6.W.169.154; 6.W.169.157; 6.W.169.166; 6.W.169.169; 6.W.169.172; 6.W.169.175; 6.W.169.240; 6.W.169.244; 6.W.172.228; 6.W.172.229; 6.W.172.230; 6.W.172.231; 6.W.172.236; 6.W.172.237; 6.W.172.238; 6.W.172.239; 6.W.172.154; 6.W.172.157; 6.W.172.166; 6.W.172.169; 6.W.172.172; 6.W.172.175; 6.W.172.240; 6.W.172.244; 6.W.175.228; 6.W.175.229; 6.W.175.230; 6.W.175.231; 6.W.175.236; 6.W.175.237; 6.W.175.238; 6.W.175.239; 6.W.175.154; 6.W.175.157; 6.W.175.166; 6.W.175.169; 6.W.175.172; 6.W.175.175; 6.W.175.240; 6.W.175.244; 6.W.240.228; 6.W.240.229; 6.W.240.230; 6.W.240.231; 6.W.240.236; 6.W.240.237; 6.W.240.238; 6.W.240.239; 6.W.240.154; 6.W.240.157; 6.W.240.166; 6.W.240.169; 6.W.240.172; 6.W.240.175; 6.W.240.240; 6.W.240.244; 6.W.244.228; 6.W.244.229; 6.W.244.230; 6.W.244.231; 6.W.244.236; 6.W.244.237;

6.W.244.238; 6.W.244.239; 6.W.244.154; 6.W.244.157; 6.W.244.166; 6.W.244.169; 6.W.244.172; 6.W.244.175; 6.W.244.240; 6.W.244.244;

Prodrugs of 6.Y

6.Y.228.228; 6.Y.228.229; 6.Y.228.230; 6.Y.228.231; 6.Y.228.236; 6.Y.228.237; 6.Y.228.238; 6.Y.228.239; 6.Y.228.154; 6.Y.228.157; 6.Y.228.166; 6.Y.228.169; 6.Y.228.172; 6.Y.228.175; 6.Y.228.240; 6.Y.228.244; 6.Y.229.228; 6.Y.229.229; 6.Y.229.230; 6.Y.229.231; 6.Y.229.236; 6.Y.229.237; 6.Y.229.238; 6.Y.229.239; 6.Y.229.154; 6.Y.229.157; 6.Y.229.166; 6.Y.229.169; 6.Y.229.172; 6.Y.229.175; 6.Y.229.240; 6.Y.229.244; 6.Y.230.228; 6.Y.230.229; 6.Y.230.230; 6.Y.230.231; 6.Y.230.236; 6.Y.230.237; 6.Y.230.238; 6.Y.230.239; 6.Y.230.154; 6.Y.230.157; 6.Y.230.166; 6.Y.230.169; 6.Y.230.172; 6.Y.230.175; 6.Y.230.240; 6.Y.230.244; 6.Y.231.228; 6.Y.231.229; 6.Y.231.230; 6.Y.231.231; 6.Y.231.236; 6.Y.231.237; 6.Y.231.238; 6.Y.231.239; 6.Y.231.154; 6.Y.231.157; 6.Y.231.166; 6.Y.231.169; 6.Y.231.172; 6.Y.231.175; 6.Y.231.240; 6.Y.231.244; 6.Y.236.228; 6.Y.236.229; 6.Y.236.230; 6.Y.236.231; 6.Y.236.236; 6.Y.236.237; 6.Y.236.238; 6.Y.236.239; 6.Y.236.154; 6.Y.236.157; 6.Y.236.166; 6.Y.236.169; 6.Y.236.172; 6.Y.236.175; 6.Y.236.240; 6.Y.236.244; 6.Y.237.228; 6.Y.237.229; 6.Y.237.230; 6.Y.237.231; 6.Y.237.236; 6.Y.237.237; 6.Y.237.238; 6.Y.237.239; 6.Y.237.154; 6.Y.237.157; 6.Y.237.166; 6.Y.237.169; 6.Y.237.172; 6.Y.237.175; 6.Y.237.240; 6.Y.237.244; 6.Y.238.228; 6.Y.238.229; 6.Y.238.230; 6.Y.238.231; 6.Y.238.236; 6.Y.238.237; 6.Y.238.238; 6.Y.238.239; 6.Y.238.154; 6.Y.238.157; 6.Y.238.166; 6.Y.238.169; 6.Y.238.172; 6.Y.238.175; 6.Y.238.240; 6.Y.238.244; 6.Y.239.228; 6.Y.239.229; 6.Y.239.230; 6.Y.239.231; 6.Y.239.236; 6.Y.239.237; 6.Y.239.238; 6.Y.239.239; 6.Y.239.154; 6.Y.239.157; 6.Y.239.166; 6.Y.239.169; 6.Y.239.172; 6.Y.239.175; 6.Y.239.240; 6.Y.239.244; 6.Y.154.228; 6.Y.154.229; 6.Y.154.230; 6.Y.154.231; 6.Y.154.236; 6.Y.154.237; 6.Y.154.238; 6.Y.154.239; 6.Y.154.154; 6.Y.154.157; 6.Y.154.166; 6.Y.154.169; 6.Y.154.172; 6.Y.154.175; 6.Y.154.240; 6.Y.154.244; 6.Y.157.228; 6.Y.157.229; 6.Y.157.230; 6.Y.157.231; 6.Y.157.236; 6.Y.157.237; 6.Y.157.238; 6.Y.157.239; 6.Y.157.154; 6.Y.157.157; 6.Y.157.166; 6.Y.157.169; 6.Y.157.172; 6.Y.157.175; 6.Y.157.240; 6.Y.157.244; 6.Y.166.228; 6.Y.166.229; 6.Y.166.230; 6.Y.166.231; 6.Y.166.236; 6.Y.166.237; 6.Y.166.238; 6.Y.166.239; 6.Y.166.154; 6.Y.166.157; 6.Y.166.166; 6.Y.166.169; 6.Y.166.172; 6.Y.166.175; 6.Y.166.240; 6.Y.166.244; 6.Y.169.228; 6.Y.169.229; 6.Y.169.230; 6.Y.169.231; 6.Y.169.236; 6.Y.169.237; 6.Y.169.238; 6.Y.169.239; 6.Y.169.154; 6.Y.169.157; 6.Y.169.166; 6.Y.169.169; 6.Y.169.172; 6.Y.169.175; 6.Y.169.240; 6.Y.169.244; 6.Y.172.228; 6.Y.172.229; 6.Y.172.230; 6.Y.172.231; 6.Y.172.236; 6.Y.172.237; 6.Y.172.238; 6.Y.172.239; 6.Y.172.154; 6.Y.172.157; 6.Y.172.166; 6.Y.172.169; 6.Y.172.172; 6.Y.172.175; 6.Y.172.240; 6.Y.172.244; 6.Y.175.228; 6.Y.175.229; 6.Y.175.230; 6.Y.175.231; 6.Y.175.236; 6.Y.175.237; 6.Y.175.238; 6.Y.175.239; 6.Y.175.154; 6.Y.175.157; 6.Y.175.166; 6.Y.175.169; 6.Y.175.172; 6.Y.175.175; 6.Y.175.240; 6.Y.175.244; 6.Y.240.228; 6.Y.240.229; 6.Y.240.230; 6.Y.240.231; 6.Y.240.236; 6.Y.240.237; 6.Y.240.238; 6.Y.240.239; 6.Y.240.154; 6.Y.240.157; 6.Y.240.166; 6.Y.240.169; 6.Y.240.172; 6.Y.240.175; 6.Y.240.240; 6.Y.240.244; 6.Y.244.228; 6.Y.244.229; 6.Y.244.230; 6.Y.244.231; 6.Y.244.236; 6.Y.244.237; 6.Y.244.238; 6.Y.244.239; 6.Y.244.154; 6.Y.244.157; 6.Y.244.166; 6.Y.244.169; 6.Y.244.172; 6.Y.244.175; 6.Y.244.240; 6.Y.244.244;

Prodrugs of 7.AH

7.AH.4.157; 7.AH.4.158; 7.AH.4.196; 7.AH.4.223; 7.AH.4.240; 7.AH.4.244; 7.AH.4.243; 7.AH.4.247; 7.AH.5.157; 7.AH.5.158; 7.AH.5.196; 7.AH.5.223; 7.AH.5.240; 7.AH.5.244; 7.AH.5.243; 7.AH.5.247; 7.AH.7.157; 7.AH.7.158; 7.AH.7.196; 7.AH.7.223; 7.AH.7.240; 7.AH.7.244; 7.AH.7.243; 7.AH.7.247; 7.AH.15.157; 7.AH.15.158; 7.AH.15.196; 7.AH.15.223; 7.AH.15.240; 7.AH.15.244; 7.AH.15.243; 7.AH.15.247; 7.AH.16.157; 7.AH.16.158; 7.AH.16.196; 7.AH.16.223; 7.AH.16.240; 7.AH.16.244; 7.AH.16.243; 7.AH.16.247; 7.AH.18.157; 7.AH.18.158; 7.AH.18.196; 7.AH.18.223; 7.AH.18.240; 7.AH.18.244; 7.AH.18.243; 7.AH.18.247; 7.AH.26.157; 7.AH.26.158; 7.AH.26.196; 7.AH.26.223; 7.AH.26.240; 7.AH.26.244; 7.AH.26.243; 7.AH.26.247; 7.AH.27.157; 7.AH.27.158; 7.AH.27.196; 7.AH.27.223; 7.AH.27.240; 7.AH.27.244; 7.AH.27.243; 7.AH.27.247; 7.AH.29.157; 7.AH.29.158; 7.AH.29.196; 7.AH.29.223; 7.AH.29.240; 7.AH.29.244; 7.AH.29.243; 7.AH.29.247; 7.AH.54.157; 7.AH.54.158; 7.AH.54.196; 7.AH.54.223; 7.AH.54.240; 7.AH.54.244; 7.AH.54.243; 7.AH.54.247; 7.AH.55.157; 7.AH.55.158; 7.AH.55.196; 7.AH.55.223; 7.AH.55.240; 7.AH.55.244; 7.AH.55.243; 7.AH.55.247; 7.AH.56.157; 7.AH.56.158; 7.AH.56.196; 7.AH.56.223; 7.AH.56.240; 7.AH.56.244; 7.AH.56.243; 7.AH.56.247; 7.AH.157.157; 7.AH.157.158; 7.AH.157.196; 7.AH.157.223; 7.AH.157.240; 7.AH.157.244; 7.AH.157.243; 7.AH.157.247; 7.AH.196.157; 7.AH.196.158; 7.AH.196.196; 7.AH.196.223; 7.AH.196.240; 7.AH.196.244; 7.AH.196.243; 7.AH.196.247; 7.AH.223.157; 7.AH.223.158; 7.AH.223.196; 7.AH.223.223; 7.AH.223.240; 7.AH.223.244; 7.AH.223.243; 7.AH.223.247; 7.AH.240.157; 7.AH.240.158; 7.AH.240.196; 7.AH.240.223; 7.AH.240.240; 7.AH.240.244; 7.AH.240.243; 7.AH.240.247; 7.AH.244.157; 7.AH.244.158; 7.AH.244.196; 7.AH.244.223; 7.AH.244.240; 7.AH.244.244; 7.AH.244.243; 7.AH.244.247; 7.AH.247.157; 7.AH.247.158; 7.AH.247.196; 7.AH.247.223; 7.AH.247.240; 7.AH.247.244; 7.AH.247.243; 7.AH.247.247;

Prodrugs of 7.AJ

7.AJ.4.157; 7.AJ.4.158; 7.AJ.4.196; 7.AJ.4.223; 7.AJ.4.240; 7.AJ.4.244; 7.AJ.4.243; 7.AJ.4.247; 7.AJ.5.157; 7.AJ.5.158; 7.AJ.5.196; 7.AJ.5.223; 7.AJ.5.240; 7.AJ.5.244; 7.AJ.5.243; 7.AJ.5.247; 7.AJ.7.157; 7.AJ.7.158; 7.AJ.7.196; 7.AJ.7.223; 7.AJ.7.240; 7.AJ.7.244; 7.AJ.7.243; 7.AJ.7.247; 7.AJ.15.157; 7.AJ.15.158; 7.AJ.15.196; 7.AJ.15.223; 7.AJ.15.240; 7.AJ.15.244; 7.AJ.15.243; 7.AJ.15.247; 7.AJ.16.157; 7.AJ.16.158; 7.AJ.16.196; 7.AJ.16.223; 7.AJ.16.240; 7.AJ.16.244; 7.AJ.16.243; 7.AJ.16.247; 7.AJ.18.157; 7.AJ.18.158; 7.AJ.18.196; 7.AJ.18.223; 7.AJ.18.240; 7.AJ.18.244; 7.AJ.18.243; 7.AJ.18.247; 7.AJ.26.157; 7.AJ.26.158; 7.AJ.26.196; 7.AJ.26.223; 7.AJ.26.240; 7.AJ.26.244; 7.AJ.26.243; 7.AJ.26.247; 7.AJ.27.157; 7.AJ.27.158; 7.AJ.27.196; 7.AJ.27.223; 7.AJ.27.240; 7.AJ.27.244; 7.AJ.27.243; 7.AJ.27.247; 7.AJ.29.157; 7.AJ.29.158; 7.AJ.29.196; 7.AJ.29.223; 7.AJ.29.240; 7.AJ.29.244; 7.AJ.29.243; 7.AJ.29.247; 7.AJ.54.157; 7.AJ.54.158; 7.AJ.54.196; 7.AJ.54.223; 7.AJ.54.240; 7.AJ.54.244; 7.AJ.54.243; 7.AJ.54.247; 7.AJ.55.157; 7.AJ.55.158; 7.AJ.55.196; 7.AJ.55.223; 7.AJ.55.240; 7.AJ.55.244; 7.AJ.55.243; 7.AJ.55.247; 7.AJ.56.157; 7.AJ.56.158; 7.AJ.56.196; 7.AJ.56.223; 7.AJ.56.240; 7.AJ.56.244; 7.AJ.56.243; 7.AJ.56.247; 7.AJ.157.157; 7.AJ.157.158; 7.AJ.157.196; 7.AJ.157.223; 7.AJ.157.240; 7.AJ.157.244; 7.AJ.157.243; 7.AJ.157.247; 7.AJ.196.157; 7.AJ.196.158; 7.AJ.196.196; 7.AJ.196.223; 7.AJ.196.240; 7.AJ.196.244; 7.AJ.196.243; 7.AJ.196.247; 7.AJ.223.157; 7.AJ.223.158; 7.AJ.223.196; 7.AJ.223.223; 7.AJ.223.240; 7.AJ.223.244; 7.AJ.223.243; 7.AJ.223.247; 7.AJ.240.157; 7.AJ.240.158; 7.AJ.240.196; 7.AJ.240.223; 7.AJ.240.240; 7.AJ.240.244; 7.AJ.240.243; 7.AJ.240.247; 7.AJ.244.157; 7.AJ.244.158; 7.AJ.244.196; 7.AJ.244.223; 7.AJ.244.240;

7.AJ.244.244; 7.AJ.244.243; 7.AJ.244.247; 7.AJ.247.157; 7.AJ.247.158; 7.AJ.247.196; 7.AJ.247.223; 7.AJ.247.240; 7.AJ.247.244; 7.AJ.247.243; 7.AJ.247.247;

Prodrugs of 7.AN

7.AN.4.157; 7.AN.4.158; 7.AN.4.196; 7.AN.4.223; 7.AN.4.240; 7.AN.4.244; 7.AN.4.243; 7.AN.4.247; 7.AN.5.157; 7.AN.5.158; 7.AN.5.196; 7.AN.5.223; 7.AN.5.240; 7.AN.5.244; 7.AN.5.243; 7.AN.5.247; 7.AN.7.157; 7.AN.7.158; 7.AN.7.196; 7.AN.7.223; 7.AN.7.240; 7.AN.7.244; 7.AN.7.243; 7.AN.7.247; 7.AN.15.157; 7.AN.15.158; 7.AN.15.196; 7.AN.15.223; 7.AN.15.240; 7.AN.15.244; 7.AN.15.243; 7.AN.15.247; 7.AN.16.157; 7.AN.16.158; 7.AN.16.196; 7.AN.16.223; 7.AN.16.240; 7.AN.16.244; 7.AN.16.243; 7.AN.16.247; 7.AN.18.157; 7.AN.18.158; 7.AN.18.196; 7.AN.18.223; 7.AN.18.240; 7.AN.18.244; 7.AN.18.243; 7.AN.18.247; 7.AN.26.157; 7.AN.26.158; 7.AN.26.196; 7.AN.26.223; 7.AN.26.240; 7.AN.26.244; 7.AN.26.243; 7.AN.26.247; 7.AN.27.157; 7.AN.27.158; 7.AN.27.196; 7.AN.27.223; 7.AN.27.240; 7.AN.27.244; 7.AN.27.243; 7.AN.27.247; 7.AN.29.157; 7.AN.29.158; 7.AN.29.196; 7.AN.29.223; 7.AN.29.240; 7.AN.29.244; 7.AN.29.243; 7.AN.29.247; 7.AN.54.157; 7.AN.54.158; 7.AN.54.196; 7.AN.54.223; 7.AN.54.240; 7.AN.54.244; 7.AN.54.243; 7.AN.54.247; 7.AN.55.157; 7.AN.55.158; 7.AN.55.196; 7.AN.55.223; 7.AN.55.240; 7.AN.55.244; 7.AN.55.243; 7.AN.55.247; 7.AN.56.157; 7.AN.56.158; 7.AN.56.196; 7.AN.56.223; 7.AN.56.240; 7.AN.56.244; 7.AN.56.243; 7.AN.56.247; 7.AN.157.157; 7.AN.157.158; 7.AN.157.196; 7.AN.157.223; 7.AN.157.240; 7.AN.157.244; 7.AN.157.243; 7.AN.157.247; 7.AN.196.157; 7.AN.196.158; 7.AN.196.196; 7.AN.196.223; 7.AN.196.240; 7.AN.196.244; 7.AN.196.243; 7.AN.196.247; 7.AN.223.157; 7.AN.223.158; 7.AN.223.196; 7.AN.223.223; 7.AN.223.240; 7.AN.223.244; 7.AN.223.243; 7.AN.223.247; 7.AN.240.157; 7.AN.240.158; 7.AN.240.196; 7.AN.240.223; 7.AN.240.240; 7.AN.240.244; 7.AN.240.243; 7.AN.240.247; 7.AN.244.157; 7.AN.244.158; 7.AN.244.196; 7.AN.244.223; 7.AN.244.240; 7.AN.244.244; 7.AN.244.243; 7.AN.244.247; 7.AN.247.157; 7.AN.247.158; 7.AN.247.196; 7.AN.247.223; 7.AN.247.240; 7.AN.247.244; 7.AN.247.243; 7.AN.247.247;

Prodrugs of 7.AP

7.AP.4.157; 7.AP.4.158; 7.AP.4.196; 7.AP.4.223; 7.AP.4.240; 7.AP.4.244; 7.AP.4.243; 7.AP.4.247; 7.AP.5.157; 7.AP.5.158; 7.AP.5.196; 7.AP.5.223; 7.AP.5.240; 7.AP.5.244; 7.AP.5.243; 7.AP.5.247; 7.AP.7.157; 7.AP.7.158; 7.AP.7.196; 7.AP.7.223; 7.AP.7.240; 7.AP.7.244; 7.AP.7.243; 7.AP.7.247; 7.AP.15.157; 7.AP.15.158; 7.AP.15.196; 7.AP.15.223; 7.AP.15.240; 7.AP.15.244; 7.AP.15.243; 7.AP.15.247; 7.AP.16.157; 7.AP.16.158; 7.AP.16.196; 7.AP.16.223; 7.AP.16.240; 7.AP.16.244; 7.AP.16.243; 7.AP.16.247; 7.AP.18.157; 7.AP.18.158; 7.AP.18.196; 7.AP.18.223; 7.AP.18.240; 7.AP.18.244; 7.AP.18.243; 7.AP.18.247; 7.AP.26.157; 7.AP.26.158; 7.AP.26.196; 7.AP.26.223; 7.AP.26.240; 7.AP.26.244; 7.AP.26.243; 7.AP.26.247; 7.AP.27.157; 7.AP.27.158; 7.AP.27.196; 7.AP.27.223; 7.AP.27.240; 7.AP.27.244; 7.AP.27.243; 7.AP.27.247; 7.AP.29.157; 7.AP.29.158; 7.AP.29.196; 7.AP.29.223; 7.AP.29.240; 7.AP.29.244; 7.AP.29.243; 7.AP.29.247; 7.AP.54.157; 7.AP.54.158; 7.AP.54.196; 7.AP.54.223; 7.AP.54.240; 7.AP.54.244; 7.AP.54.243; 7.AP.54.247; 7.AP.55.157; 7.AP.55.158; 7.AP.55.196; 7.AP.55.223; 7.AP.55.240; 7.AP.55.244; 7.AP.55.243; 7.AP.55.247; 7.AP.56.157; 7.AP.56.158; 7.AP.56.196; 7.AP.56.223; 7.AP.56.240; 7.AP.56.244; 7.AP.56.243; 7.AP.56.247; 7.AP.157.157; 7.AP.157.158; 7.AP.157.196; 7.AP.157.223; 7.AP.157.240; 7.AP.157.244; 7.AP.157.243; 7.AP.157.247; 7.AP.196.157; 7.AP.196.158; 7.AP.196.196; 7.AP.196.223; 7.AP.196.240; 7.AP.196.244; 7.AP.196.243; 7.AP.196.247;

7.AP.223.157; 7.AP.223.158; 7.AP.223.196; 7.AP.223.223; 7.AP.223.240; 7.AP.223.244; 7.AP.223.243; 7.AP.223.247; 7.AP.240.157; 7.AP.240.158; 7.AP.240.196; 7.AP.240.223; 7.AP.240.240; 7.AP.240.244; 7.AP.240.243; 7.AP.240.247; 7.AP.244.157; 7.AP.244.158; 7.AP.244.196; 7.AP.244.223; 7.AP.244.240; 7.AP.244.244; 7.AP.244.243; 7.AP.244.247; 7.AP.247.157; 7.AP.247.158; 7.AP.247.196; 7.AP.247.223; 7.AP.247.240; 7.AP.247.244; 7.AP.247.243; 7.AP.247.247;

Prodrugs of 7.AZ

7.AZ.4.157; 7.AZ.4.158; 7.AZ.4.196; 7.AZ.4.223; 7.AZ.4.240; 7.AZ.4.244; 7.AZ.4.243; 7.AZ.4.247; 7.AZ.5.157; 7.AZ.5.158; 7.AZ.5.196; 7.AZ.5.223; 7.AZ.5.240; 7.AZ.5.244; 7.AZ.5.243; 7.AZ.5.247; 7.AZ.7.157; 7.AZ.7.158; 7.AZ.7.196; 7.AZ.7.223; 7.AZ.7.240; 7.AZ.7.244; 7.AZ.7.243; 7.AZ.7.247; 7.AZ.15.157; 7.AZ.15.158; 7.AZ.15.196; 7.AZ.15.223; 7.AZ.15.240; 7.AZ.15.244; 7.AZ.15.243; 7.AZ.15.247; 7.AZ.16.157; 7.AZ.16.158; 7.AZ.16.196; 7.AZ.16.223; 7.AZ.16.240; 7.AZ.16.244; 7.AZ.16.243; 7.AZ.16.247; 7.AZ.18.157; 7.AZ.18.158; 7.AZ.18.196; 7.AZ.18.223; 7.AZ.18.240; 7.AZ.18.244; 7.AZ.18.243; 7.AZ.18.247; 7.AZ.26.157; 7.AZ.26.158; 7.AZ.26.196; 7.AZ.26.223; 7.AZ.26.240; 7.AZ.26.244; 7.AZ.26.243; 7.AZ.26.247; 7.AZ.27.157; 7.AZ.27.158; 7.AZ.27.196; 7.AZ.27.223; 7.AZ.27.240; 7.AZ.27.244; 7.AZ.27.243; 7.AZ.27.247; 7.AZ.29.157; 7.AZ.29.158; 7.AZ.29.196; 7.AZ.29.223; 7.AZ.29.240; 7.AZ.29.244; 7.AZ.29.243; 7.AZ.29.247; 7.AZ.54.157; 7.AZ.54.158; 7.AZ.54.196; 7.AZ.54.223; 7.AZ.54.240; 7.AZ.54.244; 7.AZ.54.243; 7.AZ.54.247; 7.AZ.55.157; 7.AZ.55.158; 7.AZ.55.196; 7.AZ.55.223; 7.AZ.55.240; 7.AZ.55.244; 7.AZ.55.243; 7.AZ.55.247; 7.AZ.56.157; 7.AZ.56.158; 7.AZ.56.196; 7.AZ.56.223; 7.AZ.56.240; 7.AZ.56.244; 7.AZ.56.243; 7.AZ.56.247; 7.AZ.157.157; 7.AZ.157.158; 7.AZ.157.196; 7.AZ.157.223; 7.AZ.157.240; 7.AZ.157.244; 7.AZ.157.243; 7.AZ.157.247; 7.AZ.196.157; 7.AZ.196.158; 7.AZ.196.196; 7.AZ.196.223; 7.AZ.196.240; 7.AZ.196.244; 7.AZ.196.243; 7.AZ.196.247; 7.AZ.223.157; 7.AZ.223.158; 7.AZ.223.196; 7.AZ.223.223; 7.AZ.223.240; 7.AZ.223.244; 7.AZ.223.243; 7.AZ.223.247; 7.AZ.240.157; 7.AZ.240.158; 7.AZ.240.196; 7.AZ.240.223; 7.AZ.240.240; 7.AZ.240.244; 7.AZ.240.243; 7.AZ.240.247; 7.AZ.244.157; 7.AZ.244.158; 7.AZ.244.196; 7.AZ.244.223; 7.AZ.244.240; 7.AZ.244.244; 7.AZ.244.243; 7.AZ.244.247; 7.AZ.247.157; 7.AZ.247.158; 7.AZ.247.196; 7.AZ.247.223; 7.AZ.247.240; 7.AZ.247.244; 7.AZ.247.243; 7.AZ.247.247;

Prodrugs of 7.BF

7.BF.4.157; 7.BF.4.158; 7.BF.4.196; 7.BF.4.223; 7.BF.4.240; 7.BF.4.244; 7.BF.4.243; 7.BF.4.247; 7.BF.5.157; 7.BF.5.158; 7.BF.5.196; 7.BF.5.223; 7.BF.5.240; 7.BF.5.244; 7.BF.5.243; 7.BF.5.247; 7.BF.7.157; 7.BF.7.158; 7.BF.7.196; 7.BF.7.223; 7.BF.7.240; 7.BF.7.244; 7.BF.7.243; 7.BF.7.247; 7.BF.15.157; 7.BF.15.158; 7.BF.15.196; 7.BF.15.223; 7.BF.15.240; 7.BF.15.244; 7.BF.15.243; 7.BF.15.247; 7.BF.16.157; 7.BF.16.158; 7.BF.16.196; 7.BF.16.223; 7.BF.16.240; 7.BF.16.244; 7.BF.16.243; 7.BF.16.247; 7.BF.18.157; 7.BF.18.158; 7.BF.18.196; 7.BF.18.223; 7.BF.18.240; 7.BF.18.244; 7.BF.18.243; 7.BF.18.247; 7.BF.26.157; 7.BF.26.158; 7.BF.26.196; 7.BF.26.223; 7.BF.26.240; 7.BF.26.244; 7.BF.26.243; 7.BF.26.247; 7.BF.27.157; 7.BF.27.158; 7.BF.27.196; 7.BF.27.223; 7.BF.27.240; 7.BF.27.244; 7.BF.27.243; 7.BF.27.247; 7.BF.29.157; 7.BF.29.158; 7.BF.29.196; 7.BF.29.223; 7.BF.29.240; 7.BF.29.244; 7.BF.29.243; 7.BF.29.247; 7.BF.54.157; 7.BF.54.158; 7.BF.54.196; 7.BF.54.223; 7.BF.54.240; 7.BF.54.244; 7.BF.54.243; 7.BF.54.247; 7.BF.55.157; 7.BF.55.158; 7.BF.55.196; 7.BF.55.223; 7.BF.55.240; 7.BF.55.244; 7.BF.55.243; 7.BF.55.247;

7.BF.56.157; 7.BF.56.158; 7.BF.56.196; 7.BF.56.223; 7.BF.56.240; 7.BF.56.244; 7.BF.56.243; 7.BF.56.247; 7.BF.157.157; 7.BF.157.158; 7.BF.157.196; 7.BF.157.223; 7.BF.157.240; 7.BF.157.244; 7.BF.157.243; 7.BF.157.247; 7.BF.196.157; 7.BF.196.158; 7.BF.196.196; 7.BF.196.223; 7.BF.196.240; 7.BF.196.244; 7.BF.196.243; 7.BF.196.247; 7.BF.223.157; 7.BF.223.158; 7.BF.223.196; 7.BF.223.223; 7.BF.223.240; 7.BF.223.244; 7.BF.223.243; 7.BF.223.247; 7.BF.240.157; 7.BF.240.158; 7.BF.240.196; 7.BF.240.223; 7.BF.240.240; 7.BF.240.244; 7.BF.240.243; 7.BF.240.247; 7.BF.244.157; 7.BF.244.158; 7.BF.244.196; 7.BF.244.223; 7.BF.244.240; 7.BF.244.244; 7.BF.244.243; 7.BF.244.247; 7.BF.247.157; 7.BF.247.158; 7.BF.247.196; 7.BF.247.223; 7.BF.247.240; 7.BF.247.244; 7.BF.247.243; 7.BF.247.247;

Prodrugs of 7.CI

7.CI.4.157; 7.CI.4.158; 7.CI.4.196; 7.CI.4.223; 7.CI.4.240; 7.CI.4.244; 7.CI.4.243; 7.CI.4.247; 7.CI.5.157; 7.CI.5.158; 7.CI.5.196; 7.CI.5.223; 7.CI.5.240; 7.CI.5.244; 7.CI.5.243; 7.CI.5.247; 7.CI.7.157; 7.CI.7.158; 7.CI.7.196; 7.CI.7.223; 7.CI.7.240; 7.CI.7.244; 7.CI.7.243; 7.CI.7.247; 7.CI.15.157; 7.CI.15.158; 7.CI.15.196; 7.CI.15.223; 7.CI.15.240; 7.CI.15.244; 7.CI.15.243; 7.CI.15.247; 7.CI.16.157; 7.CI.16.158; 7.CI.16.196; 7.CI.16.223; 7.CI.16.240; 7.CI.16.244; 7.CI.16.243; 7.CI.16.247; 7.CI.18.157; 7.CI.18.158; 7.CI.18.196; 7.CI.18.223; 7.CI.18.240; 7.CI.18.244; 7.CI.18.243; 7.CI.18.247; 7.CI.26.157; 7.CI.26.158; 7.CI.26.196; 7.CI.26.223; 7.CI.26.240; 7.CI.26.244; 7.CI.26.243; 7.CI.26.247; 7.CI.27.157; 7.CI.27.158; 7.CI.27.196; 7.CI.27.223; 7.CI.27.240; 7.CI.27.244; 7.CI.27.243; 7.CI.27.247; 7.CI.29.157; 7.CI.29.158; 7.CI.29.196; 7.CI.29.223; 7.CI.29.240; 7.CI.29.244; 7.CI.29.243; 7.CI.29.247; 7.CI.54.157; 7.CI.54.158; 7.CI.54.196; 7.CI.54.223; 7.CI.54.240; 7.CI.54.244; 7.CI.54.243; 7.CI.54.247; 7.CI.55.157; 7.CI.55.158; 7.CI.55.196; 7.CI.55.223; 7.CI.55.240; 7.CI.55.244; 7.CI.55.243; 7.CI.55.247; 7.CI.56.157; 7.CI.56.158; 7.CI.56.196; 7.CI.56.223; 7.CI.56.240; 7.CI.56.244; 7.CI.56.243; 7.CI.56.247; 7.CI.157.157; 7.CI.157.158; 7.CI.157.196; 7.CI.157.223; 7.CI.157.240; 7.CI.157.244; 7.CI.157.243; 7.CI.157.247; 7.CI.196.157; 7.CI.196.158; 7.CI.196.196; 7.CI.196.223; 7.CI.196.240; 7.CI.196.244; 7.CI.196.243; 7.CI.196.247; 7.CI.223.157; 7.CI.223.158; 7.CI.223.196; 7.CI.223.223; 7.CI.223.240; 7.CI.223.244; 7.CI.223.243; 7.CI.223.247; 7.CI.240.157; 7.CI.240.158; 7.CI.240.196; 7.CI.240.223; 7.CI.240.240; 7.CI.240.244; 7.CI.240.243; 7.CI.240.247; 7.CI.244.157; 7.CI.244.158; 7.CI.244.196; 7.CI.244.223; 7.CI.244.240; 7.CI.244.244; 7.CI.244.243; 7.CI.244.247; 7.CI.247.157; 7.CI.247.158; 7.CI.247.196; 7.CI.247.223; 7.CI.247.240; 7.CI.247.244; 7.CI.247.243; 7.CI.247.247;

Prodrugs of 7.CO

7.CO.4.157; 7.CO.4.158; 7.CO.4.196; 7.CO.4.223; 7.CO.4.240; 7.CO.4.244; 7.CO.4.243; 7.CO.4.247; 7.CO.5.157; 7.CO.5.158; 7.CO.5.196; 7.CO.5.223; 7.CO.5.240; 7.CO.5.244; 7.CO.5.243; 7.CO.5.247; 7.CO.7.157; 7.CO.7.158; 7.CO.7.196; 7.CO.7.223; 7.CO.7.240; 7.CO.7.244; 7.CO.7.243; 7.CO.7.247; 7.CO.15.157; 7.CO.15.158; 7.CO.15.196; 7.CO.15.223; 7.CO.15.240; 7.CO.15.244; 7.CO.15.243; 7.CO.15.247; 7.CO.16.157; 7.CO.16.158; 7.CO.16.196; 7.CO.16.223; 7.CO.16.240; 7.CO.16.244; 7.CO.16.243; 7.CO.16.247; 7.CO.18.157; 7.CO.18.158; 7.CO.18.196; 7.CO.18.223; 7.CO.18.240; 7.CO.18.244; 7.CO.18.243; 7.CO.18.247; 7.CO.26.157; 7.CO.26.158; 7.CO.26.196; 7.CO.26.223; 7.CO.26.240; 7.CO.26.244; 7.CO.26.243; 7.CO.26.247; 7.CO.27.157; 7.CO.27.158; 7.CO.27.196; 7.CO.27.223; 7.CO.27.240; 7.CO.27.244; 7.CO.27.243; 7.CO.27.247; 7.CO.29.157; 7.CO.29.158; 7.CO.29.196; 7.CO.29.223; 7.CO.29.240; 7.CO.29.244; 7.CO.29.243; 7.CO.29.247; 7.CO.54.157; 7.CO.54.158; 7.CO.54.196;

7.CO.54.223; 7.CO.54.240; 7.CO.54.244; 7.CO.54.243; 7.CO.54.247; 7.CO.55.157; 7.CO.55.158; 7.CO.55.196; 7.CO.55.223; 7.CO.55.240; 7.CO.55.244; 7.CO.55.243; 7.CO.55.247; 7.CO.56.157; 7.CO.56.158; 7.CO.56.196; 7.CO.56.223; 7.CO.56.240; 7.CO.56.244; 7.CO.56.243; 7.CO.56.247; 7.CO.157.157; 7.CO.157.158; 7.CO.157.196; 7.CO.157.223; 7.CO.157.240; 7.CO.157.244; 7.CO.157.243; 7.CO.157.247; 7.CO.196.157; 7.CO.196.158; 7.CO.196.196; 7.CO.196.223; 7.CO.196.240; 7.CO.196.244; 7.CO.196.243; 7.CO.196.247; 7.CO.223.157; 7.CO.223.158; 7.CO.223.196; 7.CO.223.223; 7.CO.223.240; 7.CO.223.244; 7.CO.223.243; 7.CO.223.247; 7.CO.240.157; 7.CO.240.158; 7.CO.240.196; 7.CO.240.223; 7.CO.240.240; 7.CO.240.244; 7.CO.240.243; 7.CO.240.247; 7.CO.244.157; 7.CO.244.158; 7.CO.244.196; 7.CO.244.223; 7.CO.244.240; 7.CO.244.244; 7.CO.244.243; 7.CO.244.247; 7.CO.4.157; 7.CO.4.158; 7.CO.4.196; 7.CO.4.223; 7.CO.4.240; 7.CO.4.244; 7.CO.4.243; 7.CO.4.247;

Prodrugs of 8.AH

8.AH.4.157; 8.AH.4.158; 8.AH.4.196; 8.AH.4.223; 8.AH.4.240; 8.AH.4.244; 8.AH.4.243; 8.AH.4.247; 8.AH.5.157; 8.AH.5.158; 8.AH.5.196; 8.AH.5.223; 8.AH.5.240; 8.AH.5.244; 8.AH.5.243; 8.AH.5.247; 8.AH.7.157; 8.AH.7.158; 8.AH.7.196; 8.AH.7.223; 8.AH.7.240; 8.AH.7.244; 8.AH.7.243; 8.AH.7.247; 8.AH.15.157; 8.AH.15.158; 8.AH.15.196; 8.AH.15.223; 8.AH.15.240; 8.AH.15.244; 8.AH.15.243; 8.AH.15.247; 8.AH.16.157; 8.AH.16.158; 8.AH.16.196; 8.AH.16.223; 8.AH.16.240; 8.AH.16.244; 8.AH.16.243; 8.AH.16.247; 8.AH.18.157; 8.AH.18.158; 8.AH.18.196; 8.AH.18.223; 8.AH.18.240; 8.AH.18.244; 8.AH.18.243; 8.AH.18.247; 8.AH.26.157; 8.AH.26.158; 8.AH.26.196; 8.AH.26.223; 8.AH.26.240; 8.AH.26.244; 8.AH.26.243; 8.AH.26.247; 8.AH.27.157; 8.AH.27.158; 8.AH.27.196; 8.AH.27.223; 8.AH.27.240; 8.AH.27.244; 8.AH.27.243; 8.AH.27.247; 8.AH.29.157; 8.AH.29.158; 8.AH.29.196; 8.AH.29.223; 8.AH.29.240; 8.AH.29.244; 8.AH.29.243; 8.AH.29.247; 8.AH.54.157; 8.AH.54.158; 8.AH.54.196; 8.AH.54.223; 8.AH.54.240; 8.AH.54.244; 8.AH.54.243; 8.AH.54.247; 8.AH.55.157; 8.AH.55.158; 8.AH.55.196; 8.AH.55.223; 8.AH.55.240; 8.AH.55.244; 8.AH.55.243; 8.AH.55.247; 8.AH.56.157; 8.AH.56.158; 8.AH.56.196; 8.AH.56.223; 8.AH.56.240; 8.AH.56.244; 8.AH.56.243; 8.AH.56.247; 8.AH.157.157; 8.AH.157.158; 8.AH.157.196; 8.AH.157.223; 8.AH.157.240; 8.AH.157.244; 8.AH.157.243; 8.AH.157.247; 8.AH.196.157; 8.AH.196.158; 8.AH.196.196; 8.AH.196.223; 8.AH.196.240; 8.AH.196.244; 8.AH.196.243; 8.AH.196.247; 8.AH.223.157; 8.AH.223.158; 8.AH.223.196; 8.AH.223.223; 8.AH.223.240; 8.AH.223.244; 8.AH.223.243; 8.AH.223.247; 8.AH.240.157; 8.AH.240.158; 8.AH.240.196; 8.AH.240.223; 8.AH.240.240; 8.AH.240.244; 8.AH.240.243; 8.AH.240.247; 8.AH.244.157; 8.AH.244.158; 8.AH.244.196; 8.AH.244.223; 8.AH.244.240; 8.AH.244.244; 8.AH.244.243; 8.AH.244.247; 8.AH.247.157; 8.AH.247.158; 8.AH.247.196; 8.AH.247.223; 8.AH.247.240; 8.AH.247.244; 8.AH.247.243; 8.AH.247.247;

Prodrugs of 8.AI

8.AJ.4.157; 8.AJ.4.158; 8.AJ.4.196; 8.AJ.4.223; 8.AJ.4.240; 8.AJ.4.244; 8.AJ.4.243; 8.AJ.4.247; 8.AJ.5.157; 8.AJ.5.158; 8.AJ.5.196; 8.AJ.5.223; 8.AJ.5.240; 8.AJ.5.244; 8.AJ.5.243; 8.AJ.5.247; 8.AJ.7.157; 8.AJ.7.158; 8.AJ.7.196; 8.AJ.7.223; 8.AJ.7.240; 8.AJ.7.244; 8.AJ.7.243; 8.AJ.7.247; 8.AJ.15.157; 8.AJ.15.158; 8.AJ.15.196; 8.AJ.15.223; 8.AJ.15.240; 8.AJ.15.244; 8.AJ.15.243; 8.AJ.15.247; 8.AJ.16.157; 8.AJ.16.158; 8.AJ.16.196; 8.AJ.16.223; 8.AJ.16.240; 8.AJ.16.244; 8.AJ.16.243; 8.AJ.16.247; 8.AJ.18.157; 8.AJ.18.158; 8.AJ.18.196; 8.AJ.18.223; 8.AJ.18.240; 8.AJ.18.244; 8.AJ.18.243; 8.AJ.18.247; 8.AJ.26.157; 8.AJ.26.158; 8.AJ.26.196; 8.AJ.26.223; 8.AJ.26.240; 8.AJ.26.244; 8.AJ.26.243; 8.AJ.26.247;

8.AJ.27.157; 8.AJ.27.158; 8.AJ.27.196; 8.AJ.27.223; 8.AJ.27.240; 8.AJ.27.244; 8.AJ.27.243; 8.AJ.27.247; 8.AJ.29.157; 8.AJ.29.158; 8.AJ.29.196; 8.AJ.29.223; 8.AJ.29.240; 8.AJ.29.244; 8.AJ.29.243; 8.AJ.29.247; 8.AJ.54.157; 8.AJ.54.158; 8.AJ.54.196; 8.AJ.54.223; 8.AJ.54.240; 8.AJ.54.244; 8.AJ.54.243; 8.AJ.54.247; 8.AJ.55.157; 8.AJ.55.158; 8.AJ.55.196; 8.AJ.55.223; 8.AJ.55.240; 8.AJ.55.244; 8.AJ.55.243; 8.AJ.55.247; 8.AJ.56.157; 8.AJ.56.158; 8.AJ.56.196; 8.AJ.56.223; 8.AJ.56.240; 8.AJ.56.244; 8.AJ.56.243; 8.AJ.56.247; 8.AJ.157.157; 8.AJ.157.158; 8.AJ.157.196; 8.AJ.157.223; 8.AJ.157.240; 8.AJ.157.244; 8.AJ.157.243; 8.AJ.157.247; 8.AJ.196.157; 8.AJ.196.158; 8.AJ.196.196; 8.AJ.196.223; 8.AJ.196.240; 8.AJ.196.244; 8.AJ.196.243; 8.AJ.196.247; 8.AJ.223.157; 8.AJ.223.158; 8.AJ.223.196; 8.AJ.223.223; 8.AJ.223.240; 8.AJ.223.244; 8.AJ.223.243; 8.AJ.223.247; 8.AJ.240.157; 8.AJ.240.158; 8.AJ.240.196; 8.AJ.240.223; 8.AJ.240.240; 8.AJ.240.244; 8.AJ.240.243; 8.AJ.240.247; 8.AJ.244.157; 8.AJ.244.158; 8.AJ.244.196; 8.AJ.244.223; 8.AJ.244.240; 8.AJ.244.244; 8.AJ.244.243; 8.AJ.244.247; 8.AJ.247.157; 8.AJ.247.158; 8.AJ.247.196; 8.AJ.247.223; 8.AJ.247.240; 8.AJ.247.244; 8.AJ.247.243; 8.AJ.247.247;

Prodrugs of 8.AN

8.AN.4.157; 8.AN.4.158; 8.AN.4.196; 8.AN.4.223; 8.AN.4.240; 8.AN.4.244; 8.AN.4.243; 8.AN.4.247; 8.AN.5.157; 8.AN.5.158; 8.AN.5.196; 8.AN.5.223; 8.AN.5.240; 8.AN.5.244; 8.AN.5.243; 8.AN.5.247; 8.AN.7.157; 8.AN.7.158; 8.AN.7.196; 8.AN.7.223; 8.AN.7.240; 8.AN.7.244; 8.AN.7.243; 8.AN.7.247; 8.AN.15.157; 8.AN.15.158; 8.AN.15.196; 8.AN.15.223; 8.AN.15.240; 8.AN.15.244; 8.AN.15.243; 8.AN.15.247; 8.AN.16.157; 8.AN.16.158; 8.AN.16.196; 8.AN.16.223; 8.AN.16.240; 8.AN.16.244; 8.AN.16.243; 8.AN.16.247; 8.AN.18.157; 8.AN.18.158; 8.AN.18.196; 8.AN.18.223; 8.AN.18.240; 8.AN.18.244; 8.AN.18.243; 8.AN.18.247; 8.AN.26.157; 8.AN.26.158; 8.AN.26.196; 8.AN.26.223; 8.AN.26.240; 8.AN.26.244; 8.AN.26.243; 8.AN.26.247; 8.AN.27.157; 8.AN.27.158; 8.AN.27.196; 8.AN.27.223; 8.AN.27.240; 8.AN.27.244; 8.AN.27.243; 8.AN.27.247; 8.AN.29.157; 8.AN.29.158; 8.AN.29.196; 8.AN.29.223; 8.AN.29.240; 8.AN.29.244; 8.AN.29.243; 8.AN.29.247; 8.AN.54.157; 8.AN.54.158; 8.AN.54.196; 8.AN.54.223; 8.AN.54.240; 8.AN.54.244; 8.AN.54.243; 8.AN.54.247; 8.AN.55.157; 8.AN.55.158; 8.AN.55.196; 8.AN.55.223; 8.AN.55.240; 8.AN.55.244; 8.AN.55.243; 8.AN.55.247; 8.AN.56.157; 8.AN.56.158; 8.AN.56.196; 8.AN.56.223; 8.AN.56.240; 8.AN.56.244; 8.AN.56.243; 8.AN.56.247; 8.AN.157.157; 8.AN.157.158; 8.AN.157.196; 8.AN.157.223; 8.AN.157.240; 8.AN.157.244; 8.AN.157.243; 8.AN.157.247; 8.AN.196.157; 8.AN.196.158; 8.AN.196.196; 8.AN.196.223; 8.AN.196.240; 8.AN.196.244; 8.AN.196.243; 8.AN.196.247; 8.AN.223.157; 8.AN.223.158; 8.AN.223.196; 8.AN.223.223; 8.AN.223.240; 8.AN.223.244; 8.AN.223.243; 8.AN.223.247; 8.AN.240.157; 8.AN.240.158; 8.AN.240.196; 8.AN.240.223; 8.AN.240.240; 8.AN.240.244; 8.AN.240.243; 8.AN.240.247; 8.AN.244.157; 8.AN.244.158; 8.AN.244.196; 8.AN.244.223; 8.AN.244.240; 8.AN.244.244; 8.AN.244.243; 8.AN.244.247; 8.AN.247.157; 8.AN.247.158; 8.AN.247.196; 8.AN.247.223; 8.AN.247.240; 8.AN.247.244; 8.AN.247.243; 8.AN.247.247;

Prodrugs of 8.AP

8.AP.4.157; 8.AP.4.158; 8.AP.4.196; 8.AP.4.223; 8.AP.4.240; 8.AP.4.244; 8.AP.4.243; 8.AP.4.247; 8.AP.5.157; 8.AP.5.158; 8.AP.5.196; 8.AP.5.223; 8.AP.5.240; 8.AP.5.244; 8.AP.5.243; 8.AP.5.247; 8.AP.7.157; 8.AP.7.158; 8.AP.7.196; 8.AP.7.223; 8.AP.7.240; 8.AP.7.244; 8.AP.7.243; 8.AP.7.247; 8.AP.15.157; 8.AP.15.158; 8.AP.15.196; 8.AP.15.223; 8.AP.15.240; 8.AP.15.244; 8.AP.15.243; 8.AP.15.247; 8.AP.16.157; 8.AP.16.158; 8.AP.16.196; 8.AP.16.223; 8.AP.16.240; 8.AP.16.244; 8.AP.16.243; 8.AP.16.247;

8.AP.18.157; 8.AP.18.158; 8.AP.18.196; 8.AP.18.223; 8.AP.18.240; 8.AP.18.244; 8.AP.18.243; 8.AP.18.247; 8.AP.26.157; 8.AP.26.158; 8.AP.26.196; 8.AP.26.223; 8.AP.26.240; 8.AP.26.244; 8.AP.26.243; 8.AP.26.247; 8.AP.27.157; 8.AP.27.158; 8.AP.27.196; 8.AP.27.223; 8.AP.27.240; 8.AP.27.244; 8.AP.27.243; 8.AP.27.247; 8.AP.29.157; 8.AP.29.158; 8.AP.29.196; 8.AP.29.223; 8.AP.29.240; 8.AP.29.244; 8.AP.29.243; 8.AP.29.247; 8.AP.54.157; 8.AP.54.158; 8.AP.54.196; 8.AP.54.223; 8.AP.54.240; 8.AP.54.244; 8.AP.54.243; 8.AP.54.247; 8.AP.55.157; 8.AP.55.158; 8.AP.55.196; 8.AP.55.223; 8.AP.55.240; 8.AP.55.244; 8.AP.55.243; 8.AP.55.247; 8.AP.56.157; 8.AP.56.158; 8.AP.56.196; 8.AP.56.223; 8.AP.56.240; 8.AP.56.244; 8.AP.56.243; 8.AP.56.247; 8.AP.157.157; 8.AP.157.158; 8.AP.157.196; 8.AP.157.223; 8.AP.157.240; 8.AP.157.244; 8.AP.157.243; 8.AP.157.247; 8.AP.196.157; 8.AP.196.158; 8.AP.196.196; 8.AP.196.223; 8.AP.196.240; 8.AP.196.244; 8.AP.196.243; 8.AP.196.247; 8.AP.223.157; 8.AP.223.158; 8.AP.223.196; 8.AP.223.223; 8.AP.223.240; 8.AP.223.244; 8.AP.223.243; 8.AP.223.247; 8.AP.240.157; 8.AP.240.158; 8.AP.240.196; 8.AP.240.223; 8.AP.240.240; 8.AP.240.244; 8.AP.240.243; 8.AP.240.247; 8.AP.244.157; 8.AP.244.158; 8.AP.244.196; 8.AP.244.223; 8.AP.244.240; 8.AP.244.244; 8.AP.244.243; 8.AP.244.247; 8.AP.247.157; 8.AP.247.158; 8.AP.247.196; 8.AP.247.223; 8.AP.247.240; 8.AP.247.244; 8.AP.247.243; 8.AP.247.247;

Prodrugs of 8.AZ

8.AZ.4.157; 8.AZ.4.158; 8.AZ.4.196; 8.AZ.4.223; 8.AZ.4.240; 8.AZ.4.244; 8.AZ.4.243; 8.AZ.4.247; 8.AZ.5.157; 8.AZ.5.158; 8.AZ.5.196; 8.AZ.5.223; 8.AZ.5.240; 8.AZ.5.244; 8.AZ.5.243; 8.AZ.5.247; 8.AZ.7.157; 8.AZ.7.158; 8.AZ.7.196; 8.AZ.7.223; 8.AZ.7.240; 8.AZ.7.244; 8.AZ.7.243; 8.AZ.7.247; 8.AZ.15.157; 8.AZ.15.158; 8.AZ.15.196; 8.AZ.15.223; 8.AZ.15.240; 8.AZ.15.244; 8.AZ.15.243; 8.AZ.15.247; 8.AZ.16.157; 8.AZ.16.158; 8.AZ.16.196; 8.AZ.16.223; 8.AZ.16.240; 8.AZ.16.244; 8.AZ.16.243; 8.AZ.16.247; 8.AZ.18.157; 8.AZ.18.158; 8.AZ.18.196; 8.AZ.18.223; 8.AZ.18.240; 8.AZ.18.244; 8.AZ.18.243; 8.AZ.18.247; 8.AZ.26.157; 8.AZ.26.158; 8.AZ.26.196; 8.AZ.26.223; 8.AZ.26.240; 8.AZ.26.244; 8.AZ.26.243; 8.AZ.26.247; 8.AZ.27.157; 8.AZ.27.158; 8.AZ.27.196; 8.AZ.27.223; 8.AZ.27.240; 8.AZ.27.244; 8.AZ.27.243; 8.AZ.27.247; 8.AZ.29.157; 8.AZ.29.158; 8.AZ.29.196; 8.AZ.29.223; 8.AZ.29.240; 8.AZ.29.244; 8.AZ.29.243; 8.AZ.29.247; 8.AZ.54.157; 8.AZ.54.158; 8.AZ.54.196; 8.AZ.54.223; 8.AZ.54.240; 8.AZ.54.244; 8.AZ.54.243; 8.AZ.54.247; 8.AZ.55.157; 8.AZ.55.158; 8.AZ.55.196; 8.AZ.55.223; 8.AZ.55.240; 8.AZ.55.244; 8.AZ.55.243; 8.AZ.55.247; 8.AZ.56.157; 8.AZ.56.158; 8.AZ.56.196; 8.AZ.56.223; 8.AZ.56.240; 8.AZ.56.244; 8.AZ.56.243; 8.AZ.56.247; 8.AZ.157.157; 8.AZ.157.158; 8.AZ.157.196; 8.AZ.157.223; 8.AZ.157.240; 8.AZ.157.244; 8.AZ.157.243; 8.AZ.157.247; 8.AZ.196.157; 8.AZ.196.158; 8.AZ.196.196; 8.AZ.196.223; 8.AZ.196.240; 8.AZ.196.244; 8.AZ.196.243; 8.AZ.196.247; 8.AZ.223.157; 8.AZ.223.158; 8.AZ.223.196; 8.AZ.223.223; 8.AZ.223.240; 8.AZ.223.244; 8.AZ.223.243; 8.AZ.223.247; 8.AZ.240.157; 8.AZ.240.158; 8.AZ.240.196; 8.AZ.240.223; 8.AZ.240.240; 8.AZ.240.244; 8.AZ.240.243; 8.AZ.240.247; 8.AZ.244.157; 8.AZ.244.158; 8.AZ.244.196; 8.AZ.244.223; 8.AZ.244.240; 8.AZ.244.244; 8.AZ.244.243; 8.AZ.244.247; 8.AZ.247.157; 8.AZ.247.158; 8.AZ.247.196; 8.AZ.247.223; 8.AZ.247.240; 8.AZ.247.244; 8.AZ.247.243; 8.AZ.247.247;

Prodrugs of 8.BF

8.BF.4.157; 8.BF.4.158; 8.BF.4.196; 8.BF.4.223; 8.BF.4.240; 8.BF.4.244; 8.BF.4.243; 8.BF.4.247; 8.BF.5.157; 8.BF.5.158; 8.BF.5.196; 8.BF.5.223; 8.BF.5.240; 8.BF.5.244;

8.BF.5.243; 8.BF.5.247; 8.BF.7.157; 8.BF.7.158; 8.BF.7.196; 8.BF.7.223; 8.BF.7.240; 8.BF.7.244; 8.BF.7.243; 8.BF.7.247; 8.BF.15.157; 8.BF.15.158; 8.BF.15.196; 8.BF.15.223; 8.BF.15.240; 8.BF.15.244; 8.BF.15.243; 8.BF.15.247; 8.BF.16.157; 8.BF.16.158; 8.BF.16.196; 8.BF.16.223; 8.BF.16.240; 8.BF.16.244; 8.BF.16.243; 8.BF.16.247; 8.BF.18.157; 8.BF.18.158; 8.BF.18.196; 8.BF.18.223; 8.BF.18.240; 8.BF.18.244; 8.BF.18.243; 8.BF.18.247; 8.BF.26.157; 8.BF.26.158; 8.BF.26.196; 8.BF.26.223; 8.BF.26.240; 8.BF.26.244; 8.BF.26.243; 8.BF.26.247; 8.BF.27.157; 8.BF.27.158; 8.BF.27.196; 8.BF.27.223; 8.BF.27.240; 8.BF.27.244; 8.BF.27.243; 8.BF.27.247; 8.BF.29.157; 8.BF.29.158; 8.BF.29.196; 8.BF.29.223; 8.BF.29.240; 8.BF.29.244; 8.BF.29.243; 8.BF.29.247; 8.BF.54.157; 8.BF.54.158; 8.BF.54.196; 8.BF.54.223; 8.BF.54.240; 8.BF.54.244; 8.BF.54.243; 8.BF.54.247; 8.BF.55.157; 8.BF.55.158; 8.BF.55.196; 8.BF.55.223; 8.BF.55.240; 8.BF.55.244; 8.BF.55.243; 8.BF.55.247; 8.BF.56.157; 8.BF.56.158; 8.BF.56.196; 8.BF.56.223; 8.BF.56.240; 8.BF.56.244; 8.BF.56.243; 8.BF.56.247; 8.BF.157.157; 8.BF.157.158; 8.BF.157.196; 8.BF.157.223; 8.BF.157.240; 8.BF.157.244; 8.BF.157.243; 8.BF.157.247; 8.BF.196.157; 8.BF.196.158; 8.BF.196.196; 8.BF.196.223; 8.BF.196.240; 8.BF.196.244; 8.BF.196.243; 8.BF.196.247; 8.BF.223.157; 8.BF.223.158; 8.BF.223.196; 8.BF.223.223; 8.BF.223.240; 8.BF.223.244; 8.BF.223.243; 8.BF.223.247; 8.BF.240.157; 8.BF.240.158; 8.BF.240.196; 8.BF.240.223; 8.BF.240.240; 8.BF.240.244; 8.BF.240.243; 8.BF.240.247; 8.BF.244.157; 8.BF.244.158; 8.BF.244.196; 8.BF.244.223; 8.BF.244.240; 8.BF.244.244; 8.BF.244.243; 8.BF.244.247; 8.BF.247.157; 8.BF.247.158; 8.BF.247.196; 8.BF.247.223; 8.BF.247.240; 8.BF.247.244; 8.BF.247.243; 8.BF.247.247;

Prodrugs of 8.CI

8.CI.4.157; 8.CI.4.158; 8.CI.4.196; 8.CI.4.223; 8.CI.4.240; 8.CI.4.244; 8.CI.4.243; 8.CI.4.247; 8.CI.5.157; 8.CI.5.158; 8.CI.5.196; 8.CI.5.223; 8.CI.5.240; 8.CI.5.244; 8.CI.5.243; 8.CI.5.247; 8.CI.7.157; 8.CI.7.158; 8.CI.7.196; 8.CI.7.223; 8.CI.7.240; 8.CI.7.244; 8.CI.7.243; 8.CI.7.247; 8.CI.15.157; 8.CI.15.158; 8.CI.15.196; 8.CI.15.223; 8.CI.15.240; 8.CI.15.244; 8.CI.15.243; 8.CI.15.247; 8.CI.16.157; 8.CI.16.158; 8.CI.16.196; 8.CI.16.223; 8.CI.16.240; 8.CI.16.244; 8:CI.16.243; 8.CI.16.247; 8.CI.18.157; 8.CI.18.158; 8.CI.18.196; 8.CI.18.223; 8.CI.18.240; 8.CI.18.244; 8.CI.18.243; 8.CI.18.247; 8.CI.26.157; 8.CI.26.158; 8.CI.26.196; 8.CI.26.223; 8.CI.26.240; 8.CI.26.244; 8.CI.26.243; 8.CI.26.247; 8.CI.27.157; 8.CI.27.158; 8.CI.27.196; 8.CI.27.223; 8.CI.27.240; 8.CI.27.244; 8.CI.27.243; 8.CI.27.247; 8.CI.29.157; 8.CI.29.158; 8.CI.29.196; 8.CI.29.223; 8.CI.29.240; 8.CI.29.244; 8.CI.29.243; 8.CI.29.247; 8.CI.54.157; 8.CI.54.158; 8.CI.54.196; 8.CI.54.223; 8.CI.54.240; 8.CI.54.244; 8.CI.54.243; 8.CI.54.247; 8.CI.55.157; 8.CI.55.158; 8.CI.55.196; 8.CI.55.223; 8.CI.55.240; 8.CI.55.244; 8.CI.55.243; 8.CI.55.247; 8.CI.56.157; 8.CI.56.158; 8.CI.56.196; 8.CI.56.223; 8.CI.56.240; 8.CI.56.244; 8.CI.56.243; 8.CI.56.247; 8.CI.157.157; 8.CI.157.158; 8.CI.157.196; 8.CI.157.223; 8.CI.157.240; 8.CI.157.244; 8.CI.157.243; 8.CI.157.247; 8.CI.196.157; 8.CI.196.158; 8.CI.196.196; 8.CI.196.223; 8.CI.196.240; 8.CI.196.244; 8.CI.196.243; 8.CI.196.247; 8.CI.223.157; 8.CI.223.158; 8.CI.223.196; 8.CI.223.223; 8.CI.223.240; 8.CI.223.244; 8.CI.223.243; 8.CI.223.247; 8.CI.240.157; 8.CI.240.158; 8.CI.240.196; 8.CI.240.223; 8.CI.240.240; 8.CI.240.244; 8.CI.240.243; 8.CI.240.247; 8.CI.244.157; 8.CI.244.158; 8.CI.244.196; 8.CI.244.223; 8.CI.244.240; 8.CI.244.244; 8.CI.244.243; 8.CI.244.247; 8.CI.247.157; 8.CI.247.158; 8.CI.247.196; 8.CI.247.223; 8.CI.247.240; 8.CI.247.244; 8.CI.247.243; 8.CI.247.247;

Prodrugs of 8.CO

8.CO.4.157; 8.CO.4.158; 8.CO.4.196; 8.CO.4.223; 8.CO.4.240; 8.CO.4.244; 8.CO.4.243; 8.CO.4.247; 8.CO.5.157; 8.CO.5.158; 8.CO.5.196; 8.CO.5.223; 8.CO.5.240; 8.CO.5.244; 8.CO.5.243; 8.CO.5.247; 8.CO.7.157; 8.CO.7.158; 8.CO.7.196; 8.CO.7.223; 8.CO.7.240; 8.CO.7.244; 8.CO.7.243; 8.CO.7.247; 8.CO.15.157; 8.CO.15.158; 8.CO.15.196; 8.CO.15.223; 8.CO.15.240; 8.CO.15.244; 8.CO.15.243; 8.CO.15.247; 8.CO.16.157; 8.CO.16.158; 8.CO.16.196; 8.CO.16.223; 8.CO.16.240; 8.CO.16.244; 8.CO.16.243; 8.CO.16.247; 8.CO.18.157; 8.CO.18.158; 8.CO.18.196; 8.CO.18.223; 8.CO.18.240; 8.CO.18.244; 8.CO.18.243; 8.CO.18.247; 8.CO.26.157; 8.CO.26.158; 8.CO.26.196; 8.CO.26.223; 8.CO.26.240; 8.CO.26.244; 8.CO.26.243; 8.CO.26.247; 8.CO.27.157; 8.CO.27.158; 8.CO.27.196; 8.CO.27.223; 8.CO.27.240; 8.CO.27.244; 8.CO.27.243; 8.CO.27.247; 8.CO.29.157; 8.CO.29.158; 8.CO.29.196; 8.CO.29.223; 8.CO.29.240; 8.CO.29.244; 8.CO.29.243; 8.CO.29.247; 8.CO.54.157; 8.CO.54.158; 8.CO.54.196; 8.CO.54.223; 8.CO.54.240; 8.CO.54.244; 8.CO.54.243; 8.CO.54.247; 8.CO.55.157; 8.CO.55.158; 8.CO.55.196; 8.CO.55.223; 8.CO.55.240; 8.CO.55.244; 8.CO.55.243; 8.CO.55.247; 8.CO.56.157; 8.CO.56.158; 8.CO.56.196; 8.CO.56.223; 8.CO.56.240; 8.CO.56.244; 8.CO.56.243; 8.CO.56.247; 8.CO.157.157; 8.CO.157.158; 8.CO.157.196; 8.CO.157.223; 8.CO.157.240; 8.CO.157.244; 8.CO.157.243; 8.CO.157.247; 8.CO.196.157; 8.CO.196.158; 8.CO.196.196; 8.CO.196.223; 8.CO.196.240; 8.CO.196.244; 8.CO.196.243; 8.CO.196.247; 8.CO.223.157; 8.CO.223.158; 8.CO.223.196; 8.CO.223.223; 8.CO.223.240; 8.CO.223.244; 8.CO.223.243; 8.CO.223.247; 8.CO.240.157; 8.CO.240.158; 8.CO.240.196; 8.CO.240.223; 8.CO.240.240; 8.CO.240.244; 8.CO.240.243; 8.CO.240.247; 8.CO.244.157; 8.CO.244.158; 8.CO.244.196; 8.CO.244.223; 8.CO.244.240; 8.CO.244.244; 8.CO.244.243; 8.CO.244.247; 8.CO.247.157; 8.CO.247.158; 8.CO.247.196; 8.CO.247.223; 8.CO.247.240; 8.CO.247.244; 8.CO.247.243; 8.CO.247.247;

Prodrugs of 9.AH

9.AH.4.157; 9.AH.4.158; 9.AH.4.196; 9.AH.4.223; 9.AH.4.240; 9.AH.4.244; 9.AH.4.243; 9.AH.4.247; 9.AH.5.157; 9.AH.5.158; 9.AH.5.196; 9.AH.5.223; 9.AH.5.240; 9.AH.5.244; 9.AH.5.243; 9.AH.5.247; 9.AH.7.157; 9.AH.7.158; 9.AH.7.196; 9.AH.7.223; 9.AH.7.240; 9.AH.7.244; 9.AH.7.243; 9.AH.7.247; 9.AH.15.157; 9.AH.15.158; 9.AH.15.196; 9.AH.15.223; 9.AH.15.240; 9.AH.15.244; 9.AH.15.243; 9.AH.15.247; 9.AH.16.157; 9.AH.16.158; 9.AH.16.196; 9.AH.16.223; 9.AH.16.240; 9.AH.16.244; 9.AH.16.243; 9.AH.16.247; 9.AH.18.157; 9.AH.18.158; 9.AH.18.196; 9.AH.18.223; 9.AH.18.240; 9.AH.18.244; 9.AH.18.243; 9.AH.18.247; 9.AH.26.157; 9.AH.26.158; 9.AH.26.196; 9.AH.26.223; 9.AH.26.240; 9.AH.26.244; 9.AH.26.243; 9.AH.26.247; 9.AH.27.157; 9.AH.27.158; 9.AH.27.196; 9.AH.27.223; 9.AH.27.240; 9.AH.27.244; 9.AH.27.243; 9.AH.27.247; 9.AH.29.157; 9.AH.29.158; 9.AH.29.196; 9.AH.29.223; 9.AH.29.240; 9.AH.29.244; 9.AH.29.243; 9.AH.29.247; 9.AH.54.157; 9.AH.54.158; 9.AH.54.196; 9.AH.54.223; 9.AH.54.240; 9.AH.54.244; 9.AH.54.243; 9.AH.54.247; 9.AH.55.157; 9.AH.55.158; 9.AH.55.196; 9.AH.55.223; 9.AH.55.240; 9.AH.55.244; 9.AH.55.243; 9.AH.55.247; 9.AH.56.157; 9.AH.56.158; 9.AH.56.196; 9.AH.56.223; 9.AH.56.240; 9.AH.56.244; 9.AH.56.243; 9.AH.56.247; 9.AH.157.157; 9.AH.157.158; 9.AH.157.196; 9.AH.157.223; 9.AH.157.240; 9.AH.157.244; 9.AH.157.243; 9.AH.157.247; 9.AH.196.157; 9.AH.196.158; 9.AH.196.196; 9.AH.196.223; 9.AH.196.240; 9.AH.196.244; 9.AH.196.243; 9.AH.196.247; 9.AH.223.157; 9.AH.223.158; 9.AH.223.196; 9.AH.223.223; 9.AH.223.240; 9.AH.223.244; 9.AH.223.243; 9.AH.223.247; 9.AH.240.157; 9.AH.240.158; 9.AH.240.196; 9.AH.240.223; 9.AH.240.240; 9.AH.240.244; 9.AH.240.243; 9.AH.240.247; 9.AH.244.157; 9.AH.244.158; 9.AH.244.196; 9.AH.244.223; 9.AH.244.240; 9.AH.244.244; 9.AH.244.243;

9.AH.244.247; 9.AH.247.157; 9.AH.247.158; 9.AH.247.196; 9.AH.247.223; 9.AH.247.240; 9.AH.247.244; 9.AH.247.243; 9.AH.247.247;

Prodrugs of 9.AJ

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Prodrugs of 9.AN

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Prodrugs of 9.AP

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Prodrugs of 9.AZ

9.AZ.4.157; 9.AZ.4.158; 9.AZ.4.196; 9.AZ.4.223; 9.AZ.4.240; 9.AZ.4.244; 9.AZ.4.243; 9.AZ.4.247; 9.AZ.5.157; 9.AZ.5.158; 9.AZ.5.196; 9.AZ.5.223; 9.AZ.5.240; 9.AZ.5.244; 9.AZ.5.243; 9.AZ.5.247; 9.AZ.7.157; 9.AZ.7.158; 9.AZ.7.196; 9.AZ.7.223; 9.AZ.7.240; 9.AZ.7.244; 9.AZ.7.243; 9.AZ.7.247; 9.AZ.15.157; 9.AZ.15.158; 9.AZ.15.196; 9.AZ.15.223; 9.AZ.15.240; 9.AZ.15.244; 9.AZ.15.243; 9.AZ.15.247; 9.AZ.16.157; 9.AZ.16.158; 9.AZ.16.196; 9.AZ.16.223; 9.AZ.16.240; 9.AZ.16.244; 9.AZ.16.243; 9.AZ.16.247; 9.AZ.18.157; 9.AZ.18.158; 9.AZ.18.196; 9.AZ.18.223; 9.AZ.18.240; 9.AZ.18.244; 9.AZ.18.243; 9.AZ.18.247; 9.AZ.26.157; 9.AZ.26.158; 9.AZ.26.196; 9.AZ.26.223; 9.AZ.26.240; 9.AZ.26.244; 9.AZ.26.243; 9.AZ.26.247; 9.AZ.27.157; 9.AZ.27.158; 9.AZ.27.196; 9.AZ.27.223; 9.AZ.27.240; 9.AZ.27.244; 9.AZ.27.243; 9.AZ.27.247; 9.AZ.29.157; 9.AZ.29.158; 9.AZ.29.196; 9.AZ.29.223; 9.AZ.29.240; 9.AZ.29.244; 9.AZ.29.243; 9.AZ.29.247; 9.AZ.54.157; 9.AZ.54.158; 9.AZ.54.196; 9.AZ.54.223; 9.AZ.54.240; 9.AZ.54.244; 9.AZ.54.243; 9.AZ.54.247; 9.AZ.55.157; 9.AZ.55.158; 9.AZ.55.196; 9.AZ.55.223; 9.AZ.55.240; 9.AZ.55.244; 9.AZ.55.243; 9.AZ.55.247; 9.AZ.56.157; 9.AZ.56.158; 9.AZ.56.196; 9.AZ.56.223; 9.AZ.56.240; 9.AZ.56.244; 9.AZ.56.243; 9.AZ.56.247; 9.AZ.157.157; 9.AZ.157.158; 9.AZ.157.196; 9.AZ.157.223;

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Prodrugs of 9.BF

9.BF.4.157; 9.BF.4.158; 9.BF.4.196; 9.BF.4.223; 9.BF.4.240; 9.BF.4.244; 9.BF.4.243; 9.BF.4.247; 9.BF.5.157; 9.BF.5.158; 9.BF.5.196; 9.BF.5.223; 9.BF.5.240; 9.BF.5.244; 9.BF.5.243; 9.BF.5.247; 9.BF.7.157; 9.BF.7.158; 9.BF.7.196; 9.BF.7.223; 9.BF.7.240; 9.BF.7.244; 9.BF.7.243; 9.BF.7.247; 9.BF.15.157; 9.BF.15.158; 9.BF.15.196; 9.BF.15.223; 9.BF.15.240; 9.BF.15.244; 9.BF.15.243; 9.BF.15.247; 9.BF.16.157; 9.BF.16.158; 9.BF.16.196; 9.BF.16.223; 9.BF.16.240; 9.BF.16.244; 9.BF.16.243; 9.BF.16.247; 9.BF.18.157; 9.BF.18.158; 9.BF.18.196; 9.BF.18.223; 9.BF.18.240; 9.BF.18.244; 9.BF.18.243; 9.BF.18.247; 9.BF.26.157; 9.BF.26.158; 9.BF.26.196; 9.BF.26.223; 9.BF.26.240; 9.BF.26.244; 9.BF.26.243; 9.BF.26.247; 9.BF.27.157; 9.BF.27.158; 9.BF.27.196; 9.BF.27.223; 9.BF.27.240; 9.BF.27.244; 9.BF.27.243; 9.BF.27.247; 9.BF.29.157; 9.BF.29.158; 9.BF.29.196; 9.BF.29.223; 9.BF.29.240; 9.BF.29.244; 9.BF.29.243; 9.BF.29.247; 9.BF.54.157; 9.BF.54.158; 9.BF.54.196; 9.BF.54.223; 9.BF.54.240; 9.BF.54.244; 9.BF.54.243; 9.BF.54.247; 9.BF.55.157; 9.BF.55.158; 9.BF.55.196; 9.BF.55.223; 9.BF.55.240; 9.BF.55.244; 9.BF.55.243; 9.BF.55.247; 9.BF.56.157; 9.BF.56.158; 9.BF.56.196; 9.BF.56.223; 9.BF.56.240; 9.BF.56.244; 9.BF.56.243; 9.BF.56.247; 9.BF.157.157; 9.BF.157.158; 9.BF.157.196; 9.BF.157.223; 9.BF.157.240; 9.BF.157.244; 9.BF.157.243; 9.BF.157.247; 9.BF.196.157; 9.BF.196.158; 9.BF.196.196; 9.BF.196.223; 9.BF.196.240; 9.BF.196.244; 9.BF.196.243; 9.BF.196.247; 9.BF.223.157; 9.BF.223.158; 9.BF.223.196; 9.BF.223.223; 9.BF.223.240; 9.BF.223.244; 9.BF.223.243; 9.BF.223.247; 9.BF.240.157; 9.BF.240.158; 9.BF.240.196; 9.BF.240.223; 9.BF.240.240; 9.BF.240.244; 9.BF.240.243; 9.BF.240.247; 9.BF.244.157; 9.BF.244.158; 9.BF.244.196; 9.BF.244.223; 9.BF.244.240; 9.BF.244.244; 9.BF.244.243; 9.BF.244.247; 9.BF.247.157; 9.BF.247.158; 9.BF.247.196; 9.BF.247.223; 9.BF.247.240; 9.BF.247.244; 9.BF.247.243; 9.BF.247.247;

Prodrugs of 9.CI

9.CI.4.157; 9.CI.4.158; 9.CI.4.196; 9.CI.4.223; 9.CI.4.240; 9.CI.4.244; 9.CI.4.243; 9.CI.4.247; 9.CI.5.157; 9.CI.5.158; 9.CI.5.196; 9.CI.5.223; 9.CI.5.240; 9.CI.5.244; 9.CI.5.243; 9.CI.5.247; 9.CI.7.157; 9.CI.7.158; 9.CI.7.196; 9.CI.7.223; 9.CI.7.240; 9.CI.7.244; 9.CI.7.243; 9.CI.7.247; 9.CI.15.157; 9.CI.15.158; 9.CI.15.196; 9.CI.15.223; 9.CI.15.240; 9.CI.15.244; 9.CI.15.243; 9.CI.15.247; 9.CI.16.157; 9.CI.16.158; 9.CI.16.196; 9.CI.16.223; 9.CI.16.240; 9.CI.16.244; 9.CI.16.243; 9.CI.16.247; 9.CI.18.157; 9.CI.18.158; 9.CI.18.196; 9.CI.18.223; 9.CI.18.240; 9.CI.18.244; 9.CI.18.243; 9.CI.18.247; 9.CI.26.157; 9.CI.26.158; 9.CI.26.196; 9.CI.26.223; 9.CI.26.240; 9.CI.26.244; 9.CI.26.243; 9.CI.26.247; 9.CI.27.157; 9.CI.27.158; 9.CI.27.196; 9.CI.27.223; 9.CI.27.240; 9.CI.27.244; 9.CI.27.243; 9.CI.27.247; 9.CI.29.157; 9.CI.29.158; 9.CI.29.196; 9.CI.29.223; 9.CI.29.240; 9.CI.29.244; 9.CI.29.243; 9.CI.29.247; 9.CI.54.157; 9.CI.54.158; 9.CI.54.196; 9.CI.54.223; 9.CI.54.240; 9.CI.54.244; 9.CI.54.243; 9.CI.54.247; 9.CI.55.157; 9.CI.55.158; 9.CI.55.196; 9.CI.55.223;

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Prodrugs of 9.CO

9.CO.4.157; 9.CO.4.158; 9.CO.4.196; 9.CO.4.223; 9.CO.4.240; 9.CO.4.244; 9.CO.4.243; 9.CO.4.247; 9.CO.5.157; 9.CO.5.158; 9.CO.5.196; 9.CO.5.223; 9.CO.5.240; 9.CO.5.244; 9.CO.5.243; 9.CO.5.247; 9.CO.7.157; 9.CO.7.158; 9.CO.7.196; 9.CO.7.223; 9.CO.7.240; 9.CO.7.244; 9.CO.7.243; 9.CO.7.247; 9.CO.15.157; 9.CO.15.158; 9.CO.15.196; 9.CO.15.223; 9.CO.15.240; 9.CO.15.244; 9.CO.15.243; 9.CO.15.247; 9.CO.16.157; 9.CO.16.158; 9.CO.16.196; 9.CO.16.223; 9.CO.16.240; 9.CO.16.244; 9.CO.16.243; 9.CO.16.247; 9.CO.18.157; 9.CO.18.158; 9.CO.18.196; 9.CO.18.223; 9.CO.18.240; 9.CO.18.244; 9.CO.18.243; 9.CO.18.247; 9.CO.26.157; 9.CO.26.158; 9.CO.26.196; 9.CO.26.223; 9.CO.26.240; 9.CO.26.244; 9.CO.26.243; 9.CO.26.247; 9.CO.27.157; 9.CO.27.158; 9.CO.27.196; 9.CO.27.223; 9.CO.27.240; 9.CO.27.244; 9.CO.27.243; 9.CO.27.247; 9.CO.29.157; 9.CO.29.158; 9.CO.29.196; 9.CO.29.223; 9.CO.29.240; 9.CO.29.244; 9.CO.29.243; 9.CO.29.247; 9.CO.54.157; 9.CO.54.158; 9.CO.54.196; 9.CO.54.223; 9.CO.54.240; 9.CO.54.244; 9.CO.54.243; 9.CO.54.247; 9.CO.55.157; 9.CO.55.158; 9.CO.55.196; 9.CO.55.223; 9.CO.55.240; 9.CO.55.244; 9.CO.55.243; 9.CO.55.247; 9.CO.56.157; 9.CO.56.158; 9.CO.56.196; 9.CO.56.223; 9.CO.56.240; 9.CO.56.244; 9.CO.56.243; 9.CO.56.247; 9.CO.157.157; 9.CO.157.158; 9.CO.157.196; 9.CO.157.223; 9.CO.157.240; 9.CO.157.244; 9.CO.157.243; 9.CO.157.247; 9.CO.196.157; 9.CO.196.158; 9.CO.196.196; 9.CO.196.223; 9.CO.196.240; 9.CO.196.244; 9.CO.196.243; 9.CO.196.247; 9.CO.223.157; 9.CO.223.158; 9.CO.223.196; 9.CO.223.223; 9.CO.223.240; 9.CO.223.244; 9.CO.223.243; 9.CO.223.247; 9.CO.240.157; 9.CO.240.158; 9.CO.240.196; 9.CO.240.223; 9.CO.240.240; 9.CO.240.244; 9.CO.240.243; 9.CO.240.247; 9.CO.244.157; 9.CO.244.158; 9.CO.244.196; 9.CO.244.223; 9.CO.244.240; 9.CO.244.244; 9.CO.244.243; 9.CO.244.247; 9.CO.247.157; 9.CO.247.158; 9.CO.247.196; 9.CO.247.223; 9.CO.247.240; 9.CO.247.244; 9.CO.247.243; 9.CO.247.247;

Prodrugs of 10.AH

10.AH.4.157; 10.AH.4.158; 10.AH.4.196; 10.AH.4.223; 10.AH.4.240; 10.AH.4.244; 10.AH.4.243; 10.AH.4.247; 10.AH.5.157; 10.AH.5.158; 10.AH.5.196; 10.AH.5.223; 10.AH.5.240; 10.AH.5.244; 10.AH.5.243; 10.AH.5.247; 10.AH.7.157; 10.AH.7.158; 10.AH.7.196; 10.AH.7.223; 10.AH.7.240; 10.AH.7.244; 10.AH.7.243; 10.AH.7.247; 10.AH.15.157; 10.AH.15.158; 10.AH.15.196; 10.AH.15.223; 10.AH.15.240; 10.AH.15.244; 10.AH.15.243; 10.AH.15.247; 10.AH.16.157; 10.AH.16.158; 10.AH.16.196; 10.AH.16.223; 10.AH.16.240; 10.AH.16.244; 10.AH.16.243; 10.AH.16.247; 10.AH.18.157; 10.AH.18.158; 10.AH.18.196; 10.AH.18.223; 10.AH.18.240; 10.AH.18.244; 10.AH.18.243; 10.AH.18.247; 10.AH.26.157; 10.AH.26.158; 10.AH.26.196; 10.AH.26.223; 10.AH.26.240; 10.AH.26.244; 10.AH.26.243; 10.AH.26.247; 10.AH.27.157; 10.AH.27.158; 10.AH.27.196; 10.AH.27.223;

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Prodrugs of 10.AJ

10.AJ.4.157; 10.AJ.4.158; 10.AJ.4.196; 10.AJ.4.223; 10.AJ.4.240; 10.AJ.4.244; 10.AJ.4.243; 10.AJ.4.247; 10.AJ.5.157; 10.AJ.5.158; 10.AJ.5.196; 10.AJ.5.223; 10.AJ.5.240; 10.AJ.5.244; 10.AJ.5.243; 10.AJ.5.247; 10.AJ.7.157; 10.AJ.7.158; 10.AJ.7.196; 10.AJ.7.223; 10.AJ.7.240; 10.AJ.7.244; 10.AJ.7.243; 10.AJ.7.247; 10.AJ.15.157; 10.AJ.15.158; 10.AJ.15.196; 10.AJ.15.223; 10.AJ.15.240; 10.AJ.15.244; 10.AJ.15.243; 10.AJ.15.247; 10.AJ.16.157; 10.AJ.16.158; 10.AJ.16.196; 10.AJ.16.223; 10.AJ.16.240; 10.AJ.16.244; 10.AJ.16.243; 10.AJ.16.247; 10.AJ.18.157; 10.AJ.18.158; 10.AJ.18.196; 10.AJ.18.223; 10.AJ.18.240; 10.AJ.18.244; 10.AJ.18.243; 10.AJ.18.247; 10.AJ.26.157; 10.AJ.26.158; 10.AJ.26.196; 10.AJ.26.223; 10.AJ.26.240; 10.AJ.26.244; 10.AJ.26.243; 10.AJ.26.247; 10.AJ.27.157; 10.AJ.27.158; 10.AJ.27.196; 10.AJ.27.223; 10.AJ.27.240; 10.AJ.27.244; 10.AJ.27.243; 10.AJ.27.247; 10.AJ.29.157; 10.AJ.29.158; 10.AJ.29.196; 10.AJ.29.223; 10.AJ.29.240; 10.AJ.29.244; 10.AJ.29.243; 10.AJ.29.247; 10.AJ.54.157; 10.AJ.54.158; 10.AJ.54.196; 10.AJ.54.223; 10.AJ.54.240; 10.AJ.54.244; 10.AJ.54.243; 10.AJ.54.247; 10.AJ.55.157; 10.AJ.55.158; 10.AJ.55.196; 10.AJ.55.223; 10.AJ.55.240; 10.AJ.55.244; 10.AJ.55.243; 10.AJ.55.247; 10.AJ.56.157; 10.AJ.56.158; 10.AJ.56.196; 10.AJ.56.223; 10.AJ.56.240; 10.AJ.56.244; 10.AJ.56.243; 10.AJ.56.247; 10.AJ.157.157; 10.AJ.157.158; 10.AJ.157.196; 10.AJ.157.223; 10.AJ.157.240; 10.AJ.157.244; 10.AJ.157.243; 10.AJ.157.247; 10.AJ.196.157; 10.AJ.196.158; 10.AJ.196.196; 10.AJ.196.223; 10.AJ.196.240; 10.AJ.196.244; 10.AJ.196.243; 10.AJ.196.247; 10.AJ.223.157; 10.AJ.223.158; 10.AJ.223.196; 10.AJ.223.223; 10.AJ.223.240; 10.AJ.223.244; 10.AJ.223.243; 10.AJ.223.247; 10.AJ.240.157; 10.AJ.240.158; 10.AJ.240.196; 10.AJ.240.223; 10.AJ.240.240; 10.AJ.240.244; 10.AJ.240.243; 10.AJ.240.247; 10.AJ.244.157; 10.AJ.244.158; 10.AJ.244.196; 10.AJ.244.223; 10.AJ.244.240; 10.AJ.244.244; 10.AJ.244.243; 10.AJ.244.247; 10.AJ.247.157; 10.AJ.247.158; 10.AJ.247.196; 10.AJ.247.223; 10.AJ.247.240; 10.AJ.247.244; 10.AJ.247.243; 10.AJ.247.247;

Prodrugs of 10.AN

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Prodrugs of 10.AP

10.AP.4.157; 10.AP.4.158; 10.AP.4.196; 10.AP.4.223; 10.AP.4.240; 10.AP.4.244; 10.AP.4.243; 10.AP.4.247; 10.AP.5.157; 10.AP.5.158; 10.AP.5.196; 10.AP.5.223; 10.AP.5.240; 10.AP.5.244; 10.AP.5.243; 10.AP.5.247; 10.AP.7.157; 10.AP.7.158; 10.AP.7.196; 10.AP.7.223; 10.AP.7.240; 10.AP.7.244; 10.AP.7.243; 10.AP.7.247; 10.AP.15.157; 10.AP.15.158; 10.AP.15.196; 10.AP.15.223; 10.AP.15.240; 10.AP.15.244; 10.AP.15.243; 10.AP.15.247; 10.AP.16.157; 10.AP.16.158; 10.AP.16.196; 10.AP.16.223; 10.AP.16.240; 10.AP.16.244; 10.AP.16.243; 10.AP.16.247; 10.AP.18.157; 10.AP.18.158; 10.AP.18.196; 10.AP.18.223; 10.AP.18.240; 10.AP.18.244; 10.AP.18.243; 10.AP.18.247; 10.AP.26.157; 10.AP.26.158; 10.AP.26.196; 10.AP.26.223; 10.AP.26.240; 10.AP.26.244; 10.AP.26.243; 10.AP.26.247; 10.AP.27.157; 10.AP.27.158; 10.AP.27.196; 10.AP.27.223; 10.AP.27.240; 10.AP.27.244; 10.AP.27.243; 10.AP.27.247; 10.AP.29.157; 10.AP.29.158; 10.AP.29.196; 10.AP.29.223; 10.AP.29.240; 10.AP.29.244; 10.AP.29.243; 10.AP.29.247; 10.AP.54.157; 10.AP.54.158; 10.AP.54.196; 10.AP.54.223; 10.AP.54.240; 10.AP.54.244; 10.AP.54.243; 10.AP.54.247; 10.AP.55.157; 10.AP.55.158; 10.AP.55.196; 10.AP.55.223; 10.AP.55.240; 10.AP.55.244; 10.AP.55.243; 10.AP.55.247; 10.AP.56.157; 10.AP.56.158; 10.AP.56.196; 10.AP.56.223; 10.AP.56.240; 10.AP.56.244; 10.AP.56.243; 10.AP.56.247; 10.AP.157.157; 10.AP.157.158; 10.AP.157.196; 10.AP.157.223; 10.AP.157.240; 10.AP.157.244; 10.AP.157.243; 10.AP.157.247; 10.AP.196.157; 10.AP.196.158; 10.AP.196.196; 10.AP.196.223; 10.AP.196.240; 10.AP.196.244; 10.AP.196.243; 10.AP.196.247; 10.AP.223.157; 10.AP.223.158; 10.AP.223.196; 10.AP.223.223; 10.AP.223.240; 10.AP.223.244; 10.AP.223.243; 10.AP.223.247; 10.AP.240.157; 10.AP.240.158; 10.AP.240.196; 10.AP.240.223; 10.AP.240.240; 10.AP.240.244;

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Prodrugs of 10.AZ

10.AZ.4.157; 10.AZ.4.158; 10.AZ.4.196; 10.AZ.4.223; 10.AZ.4.240; 10.AZ.4.244; 10.AZ.4.243; 10.AZ.4.247; 10.AZ.5.157; 10.AZ.5.158; 10.AZ.5.196; 10.AZ.5.223; 10.AZ.5.240; 10.AZ.5.244; 10.AZ.5.243; 10.AZ.5.247; 10.AZ.7.157; 10.AZ.7.158; 10.AZ.7.196; 10.AZ.7.223; 10.AZ.7.240; 10.AZ.7.244; 10.AZ.7.243; 10.AZ.7.247; 10.AZ.15.157; 10.AZ.15.158; 10.AZ.15.196; 10.AZ.15.223; 10.AZ.15.240; 10.AZ.15.244; 10.AZ.15.243; 10.AZ.15.247; 10.AZ.16.157; 10.AZ.16.158; 10.AZ.16.196; 10.AZ.16.223; 10.AZ.16.240; 10.AZ.16.244; 10.AZ.16.243; 10.AZ.16.247; 10.AZ.18.157; 10.AZ.18.158; 10.AZ.18.196; 10.AZ.18.223; 10.AZ.18.240; 10.AZ.18.244; 10.AZ.18.243; 10.AZ.18.247; 10.AZ.26.157; 10.AZ.26.158; 10.AZ.26.196; 10.AZ.26.223; 10.AZ.26.240; 10.AZ.26.244; 10.AZ.26.243; 10.AZ.26.247; 10.AZ.27.157; 10.AZ.27.158; 10.AZ.27.196; 10.AZ.27.223; 10.AZ.27.240; 10.AZ.27.244; 10.AZ.27.243; 10.AZ.27.247; 10.AZ.29.157; 10.AZ.29.158; 10.AZ.29.196; 10.AZ.29.223; 10.AZ.29.240; 10.AZ.29.244; 10.AZ.29.243; 10.AZ.29.247; 10.AZ.54.157; 10.AZ.54.158; 10.AZ.54.196; 10.AZ.54.223; 10.AZ.54.240; 10.AZ.54.244; 10.AZ.54.243; 10.AZ.54.247; 10.AZ.55.157; 10.AZ.55.158; 10.AZ.55.196; 10.AZ.55.223; 10.AZ.55.240; 10.AZ.55.244; 10.AZ.55.243; 10.AZ.55.247; 10.AZ.56.157; 10.AZ.56.158; 10.AZ.56.196; 10.AZ.56.223; 10.AZ.56.240; 10.AZ.56.244; 10.AZ.56.243; 10.AZ.56.247; 10.AZ.157.157; 10.AZ.157.158; 10.AZ.157.196; 10.AZ.157.223; 10.AZ.157.240; 10.AZ.157.244; 10.AZ.157.243; 10.AZ.157.247; 10.AZ.196.157; 10.AZ.196.158; 10.AZ.196.196; 10.AZ.196.223; 10.AZ.196.240; 10.AZ.196.244; 10.AZ.196.243; 10.AZ.196.247; 10.AZ.223.157; 10.AZ.223.158; 10.AZ.223.196; 10.AZ.223.223; 10.AZ.223.240; 10.AZ.223.244; 10.AZ.223.243; 10.AZ.223.247; 10.AZ.240.157; 10.AZ.240.158; 10.AZ.240.196; 10.AZ.240.223; 10.AZ.240.240; 10.AZ.240.244; 10.AZ.240.243; 10.AZ.240.247; 10.AZ.244.157; 10.AZ.244.158; 10.AZ.244.196; 10.AZ.244.223; 10.AZ.244.240; 10.AZ.244.244; 10.AZ.244.243; 10.AZ.244.247; 10.AZ.247.157; 10.AZ.247.158; 10.AZ.247.196; 10.AZ.247.223; 10.AZ.247.240; 10.AZ.247.244; 10.AZ.247.243; 10.AZ.247.247;

Prodrugs of 10.BF

10.BF.4.157; 10.BF.4.158; 10.BF.4.196; 10.BF.4.223; 10.BF.4.240; 10.BF.4.244; 10.BF.4.243; 10.BF.4.247; 10.BF.5.157; 10.BF.5.158; 10.BF.5.196; 10.BF.5.223; 10.BF.5.240; 10.BF.5.244; 10.BF.5.243; 10.BF.5.247; 10.BF.7.157; 10.BF.7.158; 10.BF.7.196; 10.BF.7.223; 10.BF.7.240; 10.BF.7.244; 10.BF.7.243; 10.BF.7.247; 10.BF.15.157; 10.BF.15.158; 10.BF.15.196; 10.BF.15.223; 10.BF.15.240; 10.BF.15.244; 10.BF.15.243; 10.BF.15.247; 10.BF.16.157; 10.BF.16.158; 10.BF.16.196; 10.BF.16.223; 10.BF.16.240; 10.BF.16.244; 10.BF.16.243; 10.BF.16.247; 10.BF.18.157; 10.BF.18.158; 10.BF.18.196; 10.BF.18.223; 10.BF.18.240; 10.BF.18.244; 10.BF.18.243; 10.BF.18.247; 10.BF.26.157; 10.BF.26.158; 10.BF.26.196; 10.BF.26.223; 10.BF.26.240; 10.BF.26.244; 10.BF.26.243; 10.BF.26.247; 10.BF.27.157; 10.BF.27.158; 10.BF.27.196; 10.BF.27.223; 10.BF.27.240; 10.BF.27.244; 10.BF.27.243; 10.BF.27.247; 10.BF.29.157; 10.BF.29.158; 10.BF.29.196; 10.BF.29.223; 10.BF.29.240; 10.BF.29.244; 10.BF.29.243; 10.BF.29.247; 10.BF.54.157; 10.BF.54.158; 10.BF.54.196; 10.BF.54.223; 10.BF.54.240; 10.BF.54.244; 10.BF.54.243; 10.BF.54.247; 10.BF.55.157; 10.BF.55.158; 10.BF.55.196; 10.BF.55.223;

10.BF.55.240; 10.BF.55.244; 10.BF.55.243; 10.BF.55.247; 10.BF.56.157; 10.BF.56.158; 10.BF.56.196; 10.BF.56.223; 10.BF.56.240; 10.BF.56.244; 10.BF.56.243; 10.BF.56.247; 10.BF.157.157; 10.BF.157.158; 10.BF.157.196; 10.BF.157.223; 10.BF.157.240; 10.BF.157.244; 10.BF.157.243; 10.BF.157.247; 10.BF.196.157; 10.BF.196.158; 10.BF.196.196; 10.BF.196.223; 10.BF.196.240; 10.BF.196.244; 10.BF.196.243; 10.BF.196.247; 10.BF.223.157; 10.BF.223.158; 10.BF.223.196; 10.BF.223.223; 10.BF.223.240; 10.BF.223.244; 10.BF.223.243; 10.BF.223.247; 10.BF.240.157; 10.BF.240.158; 10.BF.240.196; 10.BF.240.223; 10.BF.240.240; 10.BF.240.244; 10.BF.240.243; 10.BF.240.247; 10.BF.244.157; 10.BF.244.158; 10.BF.244.196; 10.BF.244.223; 10.BF.244.240; 10.BF.244.244; 10.BF.244.243; 10.BF.244.247; 10.BF.247.157; 10.BF.247.158; 10.BF.247.196; 10.BF.247.223; 10.BF.247.240; 10.BF.247.244; 10.BF.247.243; 10.BF.247.247;

Prodrugs of 10.CI

10.CI.4.157; 10.CI.4.158; 10.CI.4.196; 10.CI.4.223; 10.CI.4.240; 10.CI.4.244; 10.CI.4.243; 10.CI.4.247; 10.CI.5.157; 10.CI.5.158; 10.CI.5.196; 10.CI.5.223; 10.CI.5.240; 10.CI.5.244; 10.CI.5.243; 10.CI.5.247; 10.CI.7.157; 10.CI.7.158; 10.CI.7.196; 10.CI.7.223; 10.CI.7.240; 10.CI.7.244; 10.CI.7.243; 10.CI.7.247; 10.CI.15.157; 10.CI.15.158; 10.CI.15.196; 10.CI.15.223; 10.CI.15.240; 10.CI.15.244; 10.CI.15.243; 10.CI.15.247; 10.CI.16.157; 10.CI.16.158; 10.CI.16.196; 10.CI.16.223; 10.CI.16.240; 10.CI.16.244; 10.CI.16.243; 10.CI.16.247; 10.CI.18.157; 10.CI.18.158; 10.CI.18.196; 10.CI.18.223; 10.CI.18.240; 10.CI.18.244; 10.CI.18.243; 10.CI.18.247; 10.CI.26.157; 10.CI.26.158; 10.CI.26.196; 10.CI.26.223; 10.CI.26.240; 10.CI.26.244; 10.CI.26.243; 10.CI.26.247; 10.CI.27.157; 10.CI.27.158; 10.CI.27.196; 10.CI.27.223; 10.CI.27.240; 10.CI.27.244; 10.CI.27.243; 10.CI.27.247; 10.CI.29.157; 10.CI.29.158; 10.CI.29.196; 10.CI.29.223; 10.CI.29.240; 10.CI.29.244; 10.CI.29.243; 10.CI.29.247; 10.CI.54.157; 10.CI.54.158; 10.CI.54.196; 10.CI.54.223; 10.CI.54.240; 10.CI.54.244; 10.CI.54.243; 10.CI.54.247; 10.CI.55.157; 10.CI.55.158; 10.CI.55.196; 10.CI.55.223; 10.CI.55.240; 10.CI.55.244; 10.CI.55.243; 10.CI.55.247; 10.CI.56.157; 10.CI.56.158; 10.CI.56.196; 10.CI.56.223; 10.CI.56.240; 10.CI.56.244; 10.CI.56.243; 10.CI.56.247; 10.CI.157.157; 10.CI.157.158; 10.CI.157.196; 10.CI.157.223; 10.CI.157.240; 10.CI.157.244; 10.CI.157.243; 10.CI.157.247; 10.CI.196.157; 10.CI.196.158; 10.CI.196.196; 10.CI.196.223; 10.CI.196.240; 10.CI.196.244; 10.CI.196.243; 10.CI.196.247; 10.CI.223.157; 10.CI.223.158; 10.CI.223.196; 10.CI.223.223; 10.CI.223.240; 10.CI.223.244; 10.CI.223.243; 10.CI.223.247; 10.CI.240.157; 10.CI.240.158; 10.CI.240.196; 10.CI.240.223; 10.CI.240.240; 10.CI.240.244; 10.CI.240.243; 10.CI.240.247; 10.CI.244.157; 10.CI.244.158; 10.CI.244.196; 10.CI.244.223; 10.CI.244.240; 10.CI.244.244; 10.CI.244.243; 10.CI.244.247; 10.CI.247.157; 10.CI.247.158; 10.CI.247.196; 10.CI.247.223; 10.CI.247.240; 10.CI.247.244; 10.CI.247.243; 10.CI.247.247;

Prodrugs of 10.CO

10.CO.4.157; 10.CO.4.158; 10.CO.4.196; 10.CO.4.223; 10.CO.4.240; 10.CO.4.244; 10.CO.4.243; 10.CO.4.247; 10.CO.5.157; 10.CO.5.158; 10.CO.5.196; 10.CO.5.223; 10.CO.5.240; 10.CO.5.244; 10.CO.5.243; 10.CO.5.247; 10.CO.7.157; 10.CO.7.158; 10.CO.7.196; 10.CO.7.223; 10.CO.7.240; 10.CO.7.244; 10.CO.7.243; 10.CO.7.247; 10.CO.15.157; 10.CO.15.158; 10.CO.15.196; 10.CO.15.223; 10.CO.15.240; 10.CO.15.244; 10.CO.15.243; 10.CO.15.247; 10.CO.16.157; 10.CO.16.158; 10.CO.16.196; 10.CO.16.223; 10.CO.16.240; 10.CO.16.244; 10.CO.16.243; 10.CO.16.247; 10.CO.18.157; 10.CO.18.158; 10.CO.18.196; 10.CO.18.223; 10.CO.18.240; 10.CO.18.244; 10.CO.18.243; 10.CO.18.247;

10.CO.26.157; 10.CO.26.158; 10.CO.26.196; 10.CO.26.223; 10.CO.26.240; 10.CO.26.244; 10.CO.26.243; 10.CO.26.247; 10.CO.27.157; 10.CO.27.158; 10.CO.27.196; 10.CO.27.223; 10.CO.27.240; 10.CO.27.244; 10.CO.27.243; 10.CO.27.247; 10.CO.29.157; 10.CO.29.158; 10.CO.29.196; 10.CO.29.223; 10.CO.29.240; 10.CO.29.244; 10.CO.29.243; 10.CO.29.247; 10.CO.54.157; 10.CO.54.158; 10.CO.54.196; 10.CO.54.223; 10.CO.54.240; 10.CO.54.244; 10.CO.54.243; 10.CO.54.247; 10.CO.55.157; 10.CO.55.158; 10.CO.55.196; 10.CO.55.223; 10.CO.55.240; 10.CO.55.244; 10.CO.55.243; 10.CO.55.247; 10.CO.56.157; 10.CO.56.158; 10.CO.56.196; 10.CO.56.223; 10.CO.56.240; 10.CO.56.244; 10.CO.56.243; 10.CO.56.247; 10.CO.157.157; 10.CO.157.158; 10.CO.157.196; 10.CO.157.223; 10.CO.157.240; 10.CO.157.244; 10.CO.157.243; 10.CO.157.247; 10.CO.196.157; 10.CO.196.158; 10.CO.196.196; 10.CO.196.223; 10.CO.196.240; 10.CO.196.244; 10.CO.196.243; 10.CO.196.247; 10.CO.223.157; 10.CO.223.158; 10.CO.223.196; 10.CO.223.223; 10.CO.223.240; 10.CO.223.244; 10.CO.223.243; 10.CO.223.247; 10.CO.240.157; 10.CO.240.158; 10.CO.240.196; 10.CO.240.223; 10.CO.240.240; 10.CO.240.244; 10.CO.240.243; 10.CO.240.247; 10.CO.244.157; 10.CO.244.158; 10.CO.244.196; 10.CO.244.223; 10.CO.244.240; 10.CO.244.244; 10.CO.244.243; 10.CO.244.247; 10.CO.247.157; 10.CO.247.158; 10.CO.247.196; 10.CO.247.223; 10.CO.247.240; 10.CO.247.244; 10.CO.247.243; 10.CO.247.247;

Prodrugs of 11.AH

11.AH.4.157; 11.AH.4.158; 11.AH.4.196; 11.AH.4.223; 11.AH.4.240; 11.AH.4.244; 11.AH.4.243; 11.AH.4.247; 11.AH.5.157; 11.AH.5.158; 11.AH.5.196; 11.AH.5.223; 11.AH.5.240; 11.AH.5.244; 11.AH.5.243; 11.AH.5.247; 11.AH.7.157; 11.AH.7.158; 11.AH.7.196; 11.AH.7.223; 11.AH.7.240; 11.AH.7.244; 11.AH.7.243; 11.AH.7.247; 11.AH.15.157; 11.AH.15.158; 11.AH.15.196; 11.AH.15.223; 11.AH.15.240; 11.AH.15.244; 11.AH.15.243; 11.AH.15.247; 11.AH.16.157; 11.AH.16.158; 11.AH.16.196; 11.AH.16.223; 11.AH.16.240; 11.AH.16.244; 11.AH.16.243; 11.AH.16.247; 11.AH.18.157; 11.AH.18.158; 11.AH.18.196; 11.AH.18.223; 11.AH.18.240; 11.AH.18.244; 11.AH.18.243; 11.AH.18.247; 11.AH.26.157; 11.AH.26.158; 11.AH.26.196; 11.AH.26.223; 11.AH.26.240; 11.AH.26.244; 11.AH.26.243; 11.AH.26.247; 11.AH.27.157; 11.AH.27.158; 11.AH.27.196; 11.AH.27.223; 11.AH.27.240; 11.AH.27.244; 11.AH.27.243; 11.AH.27.247; 11.AH.29.157; 11.AH.29.158; 11.AH.29.196; 11.AH.29.223; 11.AH.29.240; 11.AH.29.244; 11.AH.29.243; 11.AH.29.247; 11.AH.54.157; 11.AH.54.158; 11.AH.54.196; 11.AH.54.223; 11.AH.54.240; 11.AH.54.244; 11.AH.54.243; 11.AH.54.247; 11.AH.55.157; 11.AH.55.158; 11.AH.55.196; 11.AH.55.223; 11.AH.55.240; 11.AH.55.244; 11.AH.55.243; 11.AH.55.247; 11.AH.56.157; 11.AH.56.158; 11.AH.56.196; 11.AH.56.223; 11.AH.56.240; 11.AH.56.244; 11.AH.56.243; 11.AH.56.247; 11.AH.157.157; 11.AH.157.158; 11.AH.157.196; 11.AH.157.223; 11.AH.157.240; 11.AH.157.244; 11.AH.157.243; 11.AH.157.247; 11.AH.196.157; 11.AH.196.158; 11.AH.196.196; 11.AH.196.223; 11.AH.196.240; 11.AH.196.244; 11.AH.196.243; 11.AH.196.247; 11.AH.223.157; 11.AH.223.158; 11.AH.223.196; 11.AH.223.223; 11.AH.223.240; 11.AH.223.244; 11.AH.223.243; 11.AH.223.247; 11.AH.240.157; 11.AH.240.158; 11.AH.240.196; 11.AH.240.223; 11.AH.240.240; 11.AH.240.244; 11.AH.240.243; 11.AH.240.247; 11.AH.244.157; 11.AH.244.158; 11.AH.244.196; 11.AH.244.223; 11.AH.244.240; 11.AH.244.244; 11.AH.244.243; 11.AH.244.247; 11.AH.247.157; 11.AH.247.158; 11.AH.247.196; 11.AH.247.223; 11.AH.247.240; 11.AH.247.244; 11.AH.247.243; 11.AH.247.247;

Prodrugs of 11.AJ

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Prodrugs of 11.AN

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Prodrugs of 11.AP

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Prodrugs of 11.AZ

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Prodrugs of 11.BF

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Prodrugs of 11.CI

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Prodrugs of 11.CO

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Prodrugs of 12.AH

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Prodrugs of 12.AJ

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Prodrugs of 12.AN

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Prodrugs of 12.AP

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Prodrugs of 12.AZ

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Prodrugs of 12.BF

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Prodrugs of 12.CI

12.CI.4.157; 12.CI.4.158; 12.CI.4.196; 12.CI.4.223; 12.CI.4.240; 12.CI.4.244; 12.CI.4.243; 12.CI.4.247; 12.CI.5.157; 12.CI.5.158; 12.CI.5.196; 12.CI.5.223; 12.CI.5.240; 12.CI.5.244; 12.CI.5.243; 12.CI.5.247; 12.CI.7.157; 12.CI.7.158; 12.CI.7.196; 12.CI.7.223; 12.CI.7.240; 12.CI.7.244; 12.CI.7.243; 12.CI.7.247; 12.CI.15.157; 12.CI.15.158; 12.CI.15.196; 12.CI.15.223; 12.CI.15.240; 12.CI.15.244; 12.CI.15.243; 12.CI.15.247; 12.CI.16.157; 12.CI.16.158; 12.CI.16.196; 12.CI.16.223; 12.CI.16.240; 12.CI.16.244; 12.CI.16.243; 12.CI.16.247; 12.CI.18.157; 12.CI.18.158; 12.CI.18.196; 12.CI.18.223; 12.CI.18.240; 12.CI.18.244; 12.CI.18.243; 12.CI.18.247; 12.CI.26.157; 12.CI.26.158; 12.CI.26.196; 12.CI.26.223; 12.CI.26.240; 12.CI.26.244; 12.CI.26.243; 12.CI.26.247; 12.CI.27.157; 12.CI.27.158; 12.CI.27.196; 12.CI.27.223; 12.CI.27.240; 12.CI.27.244; 12.CI.27.243; 12.CI.27.247; 12.CI.29.157; 12.CI.29.158; 12.CI.29.196; 12.CI.29.223; 12.CI.29.240; 12.CI.29.244; 12.CI.29.243; 12.CI.29.247; 12.CI.54.157; 12.CI.54.158; 12.CI.54.196; 12.CI.54.223; 12.CI.54.240; 12.CI.54.244; 12.CI.54.243; 12.CI.54.247; 12.CI.55.157; 12.CI.55.158; 12.CI.55.196; 12.CI.55.223; 12.CI.55.240; 12.CI.55.244; 12.CI.55.243; 12.CI.55.247; 12.CI.56.157; 12.CI.56.158; 12.CI.56.196; 12.CI.56.223; 12.CI.56.240; 12.CI.56.244; 12.CI.56.243; 12.CI.56.247; 12.CI.157.157; 12.CI.157.158; 12.CI.157.196; 12.CI.157.223; 12.CI.157.240; 12.CI.157.244; 12.CI.157.243; 12.CI.157.247; 12.CI.196.157; 12.CI.196.158; 12.CI.196.196; 12.CI.196.223; 12.CI.196.240; 12.CI.196.244; 12.CI.196.243; 12.CI.196.247; 12.CI.223.157; 12.CI.223.158; 12.CI.223.196; 12.CI.223.223; 12.CI.223.240; 12.CI.223.244; 12.CI.223.243; 12.CI.223.247; 12.CI.240.157; 12.CI.240.158; 12.CI.240.196; 12.CI.240.223; 12.CI.240.240; 12.CI.240.244; 12.CI.240.243; 12.CI.240.247; 12.CI.244.157; 12.CI.244.158; 12.CI.244.196; 12.CI.244.223; 12.CI.244.240; 12.CI.244.244;

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Prodrugs of 12.CO

12.CO.4.157; 12.CO.4.158; 12.CO.4.196; 12.CO.4.223; 12.CO.4.240; 12.CO.4.244; 12.CO.4.243; 12.CO.4.247; 12.CO.5.157; 12.CO.5.158; 12.CO.5.196; 12.CO.5.223; 12.CO.5.240; 12.CO.5.244; 12.CO.5.243; 12.CO.5.247; 12.CO.7.157; 12.CO.7.158; 12.CO.7.196; 12.CO.7.223; 12.CO.7.240; 12.CO.7.244; 12.CO.7.243; 12.CO.7.247; 12.CO.15.157; 12.CO.15.158; 12.CO.15.196; 12.CO.15.223; 12.CO.15.240; 12.CO.15.244; 12.CO.15.243; 12.CO.15.247; 12.CO.16.157; 12.CO.16.158; 12.CO.16.196; 12.CO.16.223; 12.CO.16.240; 12.CO.16.244; 12.CO.16.243; 12.CO.16.247; 12.CO.18.157; 12.CO.18.158; 12.CO.18.196; 12.CO.18.223; 12.CO.18.240; 12.CO.18.244; 12.CO.18.243; 12.CO.18.247; 12.CO.26.157; 12.CO.26.158; 12.CO.26.196; 12.CO.26.223; 12.CO.26.240; 12.CO.26.244; 12.CO.26.243; 12.CO.26.247; 12.CO.27.157; 12.CO.27.158; 12.CO.27.196; 12.CO.27.223; 12.CO.27.240; 12.CO.27.244; 12.CO.27.243; 12.CO.27.247; 12.CO.29.157; 12.CO.29.158; 12.CO.29.196; 12.CO.29.223; 12.CO.29.240; 12.CO.29.244; 12.CO.29.243; 12.CO.29.247; 12.CO.54.157; 12.CO.54.158; 12.CO.54.196; 12.CO.54.223; 12.CO.54.240; 12.CO.54.244; 12.CO.54.243; 12.CO.54.247; 12.CO.55.157; 12.CO.55.158; 12.CO.55.196; 12.CO.55.223; 12.CO.55.240; 12.CO.55.244; 12.CO.55.243; 12.CO.55.247; 12.CO.56.157; 12.CO.56.158; 12.CO.56.196; 12.CO.56.223; 12.CO.56.240; 12.CO.56.244; 12.CO.56.243; 12.CO.56.247; 12.CO.157.157; 12.CO.157.158; 12.CO.157.196; 12.CO.157.223; 12.CO.157.240; 12.CO.157.244; 12.CO.157.243; 12.CO.157.247; 12.CO.196.157; 12.CO.196.158; 12.CO.196.196; 12.CO.196.223; 12.CO.196.240; 12.CO.196.244; 12.CO.196.243; 12.CO.196.247; 12.CO.223.157; 12.CO.223.158; 12.CO.223.196; 12.CO.223.223; 12.CO.223.240; 12.CO.223.244; 12.CO.223.243; 12.CO.223.247; 12.CO.240.157; 12.CO.240.158; 12.CO.240.196; 12.CO.240.223; 12.CO.240.240; 12.CO.240.244; 12.CO.240.243; 12.CO.240.247; 12.CO.244.157; 12.CO.244.158; 12.CO.244.196; 12.CO.244.223; 12.CO.244.240; 12.CO.244.244; 12.CO.244.243; 12.CO.244.247; 12.CO.247.157; 12.CO.247.158; 12.CO.247.196; 12.CO.247.223; 12.CO.247.240; 12.CO.247.244; 12.CO.247.243; 12.CO.247.247.

Prodrugs of 13.B

13.B.228.228; 13.B.228.229; 13.B.228.230; 13.B.228.231; 13.B.228.236; 13.B.228.237; 13.B.228.238; 13.B.228.239; 13.B.228.154; 13.B.228.157; 13.B.228.166; 13.B.228.169; 13.B.228.172; 13.B.228.175; 13.B.228.240; 13.B.228.244; 13.B.229.228; 13.B.229.229; 13.B.229.230; 13.B.229.231; 13.B.229.236; 13.B.229.237; 13.B.229.238; 13.B.229.239; 13.B.229.154; 13.B.229.157; 13.B.229.166; 13.B.229.169; 13.B.229.172; 13.B.229.175; 13.B.229.240; 13.B.229.244; 13.B.230.228; 13.B.230.229; 13.B.230.230; 13.B.230.231; 13.B.230.236; 13.B.230.237; 13.B.230.238; 13.B.230.239; 13.B.230.154; 13.B.230.157; 13.B.230.166; 13.B.230.169; 13.B.230.172; 13.B.230.175; 13.B.230.240; 13.B.230.244; 13.B.231.228; 13.B.231.229; 13.B.231.230; 13.B.231.231; 13.B.231.236; 13.B.231.237; 13.B.231.238; 13.B.231.239; 13.B.231.154; 13.B.231.157; 13.B.231.166; 13.B.231.169; 13.B.231.172; 13.B.231.175; 13.B.231.240; 13.B.231.244; 13.B.236.228; 13.B.236.229; 13.B.236.230; 13.B.236.231; 13.B.236.236; 13.B.236.237; 13.B.236.238; 13.B.236.239; 13.B.236.154; 13.B.236.157; 13.B.236.166; 13.B.236.169; 13.B.236.172; 13.B.236.175; 13.B.236.240; 13.B.236.244; 13.B.237.228; 13.B.237.229; 13.B.237.230; 13.B.237.231; 13.B.237.236; 13.B.237.237; 13.B.237.238; 13.B.237.239; 13.B.237.154; 13.B.237.157; 13.B.237.166; 13.B.237.169; 13.B.237.172; 13.B.237.175; 13.B.237.240; 13.B.237.244; 13.B.238.228; 13.B.238.229; 13.B.238.230; 13.B.238.231; 13.B.238.236; 13.B.238.237; 13.B.238.238; 13.B.238.239; 13.B.238.154; 13.B.238.157; 13.B.238.166; 13.B.238.169; 13.B.238.172; 13.B.238.175; 13.B.238.240; 13.B.238.244; 13.B.239.228; 13.B.239.229; 13.B.239.230; 13.B.239.231; 13.B.239.236; 13.B.239.237; 13.B.239.238; 13.B.239.239; 13.B.239.154; 13.B.239.157; 13.B.239.166; 13.B.239.169; 13.B.239.172; 13.B.239.175; 13.B.239.240; 13.B.239.244; 13.B.154.228; 13.B.154.229; 13.B.154.230; 13.B.154.231; 13.B.154.236; 13.B.154.237; 13.B.154.238; 13.B.154.239; 13.B.154.154; 13.B.154.157; 13.B.154.166; 13.B.154.169; 13.B.154.172; 13.B.154.175; 13.B.154.240; 13.B.154.244; 13.B.157.228; 13.B.157.229; 13.B.157.230; 13.B.157.231; 13.B.157.236; 13.B.157.237; 13.B.157.238; 13.B.157.239; 13.B.157.154; 13.B.157.157; 13.B.157.166; 13.B.157.169; 13.B.157.172; 13.B.157.175; 13.B.157.240; 13.B.157.244; 13.B.166.228; 13.B.166.229; 13.B.166.230; 13.B.166.231; 13.B.166.236; 13.B.166.237; 13.B.166.238; 13.B.166.239; 13.B.166.154; 13.B.166.157; 13.B.166.166; 13.B.166.169; 13.B.166.172; 13.B.166.175; 13.B.166.240; 13.B.166.244; 13.B.169.228; 13.B.169.229; 13.B.169.230; 13.B.169.231; 13.B.169.236; 13.B.169.237; 13.B.169.238; 13.B.169.239; 13.B.169.154; 13.B.169.157; 13.B.169.166; 13.B.169.169; 13.B.169.172; 13.B.169.175; 13.B.169.240; 13.B.169.244; 13.B.172.228; 13.B.172.229; 13.B.172.230; 13.B.172.231; 13.B.172.236; 13.B.172.237; 13.B.172.238; 13.B.172.239; 13.B.172.154; 13.B.172.157; 13.B.172.166; 13.B.172.169; 13.B.172.172; 13.B.172.175; 13.B.172.240; 13.B.172.244; 13.B.175.228; 13.B.175.229; 13.B.175.230; 13.B.175.231; 13.B.175.236; 13.B.175.237; 13.B.175.238; 13.B.175.239; 13.B.175.154; 13.B.175.157; 13.B.175.166; 13.B.175.169; 13.B.175.172; 13.B.175.175; 13.B.175.240; 13.B.175.244; 13.B.240.228; 13.B.240.229; 13.B.240.230; 13.B.240.231; 13.B.240.236; 13.B.240.237; 13.B.240.238; 13.B.240.239; 13.B.240.154; 13.B.240.157; 13.B.240.166; 13.B.240.169; 13.B.240.172; 13.B.240.175; 13.B.240.240; 13.B.240.244; 13.B.244.228; 13.B.244.229; 13.B.244.230; 13.B.244.231; 13.B.244.236; 13.B.244.237; 13.B.244.238; 13.B.244.239; 13.B.244.154; 13.B.244.157; 13.B.244.166; 13.B.244.169; 13.B.244.172; 13.B.244.175; 13.B.244.240; 13.B.244.244;

Prodrugs of 13.D

13.D.228.228; 13.D.228.229; 13.D.228.230; 13.D.228.231; 13.D.228.236; 13.D.228.237; 13.D.228.238; 13.D.228.239; 13.D.228.154; 13.D.228.157; 13.D.228.166; 13.D.228.169; 13.D.228.172; 13.D.228.175; 13.D.228.240; 13.D.228.244; 13.D.229.228; 13.D.229.229; 13.D.229.230; 13.D.229.231; 13.D.229.236; 13.D.229.237; 13.D.229.238; 13.D.229.239; 13.D.229.154; 13.D.229.157; 13.D.229.166; 13.D.229.169; 13.D.229.172; 13.D.229.175; 13.D.229.240; 13.D.229.244; 13.D.230.228; 13.D.230.229; 13.D.230.230; 13.D.230.231; 13.D.230.236; 13.D.230.237; 13.D.230.238; 13.D.230.239; 13.D.230.154; 13.D.230.157; 13.D.230.166; 13.D.230.169; 13.D.230.172; 13.D.230.175; 13.D.230.240; 13.D.230.244; 13.D.231.228; 13.D.231.229; 13.D.231.230; 13.D.231.231; 13.D.231.236; 13.D.231.237; 13.D.231.238; 13.D.231.239; 13.D.231.154; 13.D.231.157; 13.D.231.166; 13.D.231.169; 13.D.231.172; 13.D.231.175; 13.D.231.240; 13.D.231.244; 13.D.236.228; 13.D.236.229; 13.D.236.230; 13.D.236.231; 13.D.236.236; 13.D.236.237; 13.D.236.238; 13.D.236.239; 13.D.236.154; 13.D.236.157; 13.D.236.166; 13.D.236.169; 13.D.236.172; 13.D.236.175; 13.D.236.240; 13.D.236.244; 13.D.237.228; 13.D.237.229; 13.D.237.230; 13.D.237.231; 13.D.237.236; 13.D.237.237; 13.D.237.238; 13.D.237.239; 13.D.237.154; 13.D.237.157; 13.D.237.166; 13.D.237.169; 13.D.237.172; 13.D.237.175; 13.D.237.240; 13.D.237.244; 13.D.238.228; 13.D.238.229; 13.D.238.230; 13.D.238.231; 13.D.238.236; 13.D.238.237; 13.D.238.238; 13.D.238.239; 13.D.238.154; 13.D.238.157; 13.D.238.166; 13.D.238.169; 13.D.238.172; 13.D.238.175; 13.D.238.240; 13.D.238.244; 13.D.239.228; 13.D.239.229; 13.D.239.230; 13.D.239.231; 13.D.239.236; 13.D.239.237; 13.D.239.238; 13.D.239.239; 13.D.239.154; 13.D.239.157; 13.D.239.166; 13.D.239.169; 13.D.239.172; 13.D.239.175; 13.D.239.240; 13.D.239.244; 13.D.154.228; 13.D.154.229; 13.D.154.230; 13.D.154.231; 13.D.154.236; 13.D.154.237; 13.D.154.238; 13.D.154.239; 13.D.154.154; 13.D.154.157; 13.D.154.166; 13.D.154.169; 13.D.154.172; 13.D.154.175; 13.D.154.240; 13.D.154.244; 13.D.157.228; 13.D.157.229; 13.D.157.230; 13.D.157.231; 13.D.157.236; 13.D.157.237; 13.D.157.238; 13.D.157.239; 13.D.157.154; 13.D.157.157; 13.D.157.166; 13.D.157.169; 13.D.157.172; 13.D.157.175; 13.D.157.240; 13.D.157.244; 13.D.166.228; 13.D.166.229; 13.D.166.230; 13.D.166.231; 13.D.166.236; 13.D.166.237; 13.D.166.238; 13.D.166.239; 13.D.166.154; 13.D.166.157; 13.D.166.166; 13.D.166.169; 13.D.166.172; 13.D.166.175; 13.D.166.240; 13.D.166.244; 13.D.169.228; 13.D.169.229; 13.D.169.230; 13.D.169.231; 13.D.169.236; 13.D.169.237; 13.D.169.238; 13.D.169.239; 13.D.169.154; 13.D.169.157; 13.D.169.166; 13.D.169.169; 13.D.169.172; 13.D.169.175; 13.D.169.240; 13.D.169.244; 13.D.172.228; 13.D.172.229; 13.D.172.230; 13.D.172.231; 13.D.172.236; 13.D.172.237; 13.D.172.238; 13.D.172.239; 13.D.172.154; 13.D.172.157; 13.D.172.166; 13.D.172.169; 13.D.172.172; 13.D.172.175; 13.D.172.240; 13.D.172.244; 13.D.175.228; 13.D.175.229; 13.D.175.230; 13.D.175.231; 13.D.175.236; 13.D.175.237; 13.D.175.238; 13.D.175.239; 13.D.175.154; 13.D.175.157; 13.D.175.166; 13.D.175.169; 13.D.175.172; 13.D.175.175; 13.D.175.240; 13.D.175.244; 13.D.240.228; 13.D.240.229; 13.D.240.230; 13.D.240.231; 13.D.240.236; 13.D.240.237; 13.D.240.238; 13.D.240.239; 13.D.240.154; 13.D.240.157; 13.D.240.166; 13.D.240.169; 13.D.240.172; 13.D.240.175; 13.D.240.240; 13.D.240.244; 13.D.244.228; 13.D.244.229; 13.D.244.230; 13.D.244.231; 13.D.244.236; 13.D.244.237; 13.D.244.238; 13.D.244.239; 13.D.244.154; 13.D.244.157; 13.D.244.166; 13.D.244.169; 13.D.244.172; 13.D.244.175; 13.D.244.240; 13.D.244.244;

Prodrugs of 13.E

13.E.228.228; 13.E.228.229; 13.E.228.230; 13.E.228.231; 13.E.228.236; 13.E.228.237; 13.E.228.238; 13.E.228.239; 13.E.228.154; 13.E.228.157; 13.E.228.166; 13.E.228.169; 13.E.228.172; 13.E.228.175; 13.E.228.240; 13.E.228.244; 13.E.229.228; 13.E.229.229; 13.E.229.230; 13.E.229.231; 13.E.229.236; 13.E.229.237; 13.E.229.238; 13.E.229.239; 13.E.229.154; 13.E.229.157; 13.E.229.166; 13.E.229.169; 13.E.229.172; 13.E.229.175; 13.E.229.240; 13.E.229.244; 13.E.230.228; 13.E.230.229; 13.E.230.230; 13.E.230.231; 13.E.230.236; 13.E.230.237; 13.E.230.238; 13.E.230.239; 13.E.230.154; 13.E.230.157; 13.E.230.166; 13.E.230.169; 13.E.230.172; 13.E.230.175; 13.E.230.240; 13.E.230.244; 13.E.231.228; 13.E.231.229; 13.E.231.230; 13.E.231.231; 13.E.231.236; 13.E.231.237; 13.E.231.238; 13.E.231.239; 13.E.231.154; 13.E.231.157; 13.E.231.166; 13.E.231.169; 13.E.231.172; 13.E.231.175; 13.E.231.240; 13.E.231.244; 13.E.236.228; 13.E.236.229; 13.E.236.230; 13.E.236.231; 13.E.236.236; 13.E.236.237; 13.E.236.238; 13.E.236.239; 13.E.236.154; 13.E.236.157; 13.E.236.166; 13.E.236.169; 13.E.236.172; 13.E.236.175; 13.E.236.240; 13.E.236.244; 13.E.237.228; 13.E.237.229; 13.E.237.230; 13.E.237.231; 13.E.237.236; 13.E.237.237; 13.E.237.238; 13.E.237.239; 13.E.237.154; 13.E.237.157; 13.E.237.166; 13.E.237.169; 13.E.237.172; 13.E.237.175; 13.E.237.240; 13.E.237.244; 13.E.238.228; 13.E.238.229; 13.E.238.230; 13.E.238.231; 13.E.238.236; 13.E.238.237; 13.E.238.238; 13.E.238.239; 13.E.238.154; 13.E.238.157; 13.E.238.166; 13.E.238.169; 13.E.238.172; 13.E.238.175; 13.E.238.240; 13.E.238.244; 13.E.239.228; 13.E.239.229; 13.E.239.230; 13.E.239.231; 13.E.239.236; 13.E.239.237; 13.E.239.238; 13.E.239.239; 13.E.239.154; 13.E.239.157; 13.E.239.166; 13.E.239.169; 13.E.239.172; 13.E.239.175; 13.E.239.240; 13.E.239.244; 13.E.154.228; 13.E.154.229; 13.E.154.230; 13.E.154.231; 13.E.154.236; 13.E.154.237; 13.E.154.238; 13.E.154.239; 13.E.154.154; 13.E.154.157; 13.E.154.166; 13.E.154.169; 13.E.154.172; 13.E.154.175; 13.E.154.240; 13.E.154.244; 13.E.157.228; 13.E.157.229; 13.E.157.230; 13.E.157.231; 13.E.157.236; 13.E.157.237; 13.E.157.238; 13.E.157.239; 13.E.157.154; 13.E.157.157; 13.E.157.166; 13.E.157.169; 13.E.157.172; 13.E.157.175; 13.E.157.240; 13.E.157.244; 13.E.166.228; 13.E.166.229; 13.E.166.230; 13.E.166.231; 13.E.166.236; 13.E.166.237; 13.E.166.238; 13.E.166.239; 13.E.166.154; 13.E.166.157; 13.E.166.166; 13.E.166.169; 13.E.166.172; 13.E.166.175; 13.E.166.240; 13.E.166.244; 13.E.169.228; 13.E.169.229; 13.E.169.230; 13.E.169.231; 13.E.169.236; 13.E.169.237; 13.E.169.238; 13.E.169.239; 13.E.169.154; 13.E.169.157; 13.E.169.166; 13.E.169.169; 13.E.169.172; 13.E.169.175; 13.E.169.240; 13.E.169.244; 13.E.172.228; 13.E.172.229; 13.E.172.230; 13.E.172.231; 13.E.172.236; 13.E.172.237; 13.E.172.238; 13.E.172.239; 13.E.172.154; 13.E.172.157; 13.E.172.166; 13.E.172.169; 13.E.172.172; 13.E.172.175; 13.E.172.240; 13.E.172.244; 13.E.175.228; 13.E.175.229; 13.E.175.230; 13.E.175.231; 13.E.175.236; 13.E.175.237; 13.E.175.238; 13.E.175.239; 13.E.175.154; 13.E.175.157; 13.E.175.166; 13.E.175.169; 13.E.175.172; 13.E.175.175; 13.E.175.240; 13.E.175.244; 13.E.240.228; 13.E.240.229; 13.E.240.230; 13.E.240.231; 13.E.240.236; 13.E.240.237; 13.E.240.238; 13.E.240.239; 13.E.240.154; 13.E.240.157; 13.E.240.166; 13.E.240.169; 13.E.240.172; 13.E.240.175; 13.E.240.240; 13.E.240.244; 13.E.244.228; 13.E.244.229; 13.E.244.230; 13.E.244.231; 13.E.244.236; 13.E.244.237; 13.E.244.238; 13.E.244.239; 13.E.244.154; 13.E.244.157; 13.E.244.166; 13.E.244.169; 13.E.244.172; 13.E.244.175; 13.E.244.240; 13.E.244.244;

Prodrugs of 13.G

13.G.228.228; 13.G.228.229; 13.G.228.230; 13.G.228.231; 13.G.228.236; 13.G.228.237; 13.G.228.238; 13.G.228.239; 13.G.228.154; 13.G.228.157; 13.G.228.166; 13.G.228.169; 13.G.228.172; 13.G.228.175; 13.G.228.240; 13.G.228.244; 13.G.229.228; 13.G.229.229; 13.G.229.230; 13.G.229.231; 13.G.229.236; 13.G.229.237; 13.G.229.238; 13.G.229.239; 13.G.229.154; 13.G.229.157; 13.G.229.166; 13.G.229.169; 13.G.229.172; 13.G.229.175; 13.G.229.240; 13.G.229.244; 13.G.230.228; 13.G.230.229; 13.G.230.230; 13.G.230.231; 13.G.230.236; 13.G.230.237; 13.G.230.238; 13.G.230.239; 13.G.230.154; 13.G.230.157; 13.G.230.166; 13.G.230.169; 13.G.230.172; 13.G.230.175; 13.G.230.240; 13.G.230.244; 13.G.231.228; 13.G.231.229; 13.G.231.230; 13.G.231.231; 13.G.231.236; 13.G.231.237; 13.G.231.238; 13.G.231.239; 13.G.231.154; 13.G.231.157; 13.G.231.166; 13.G.231.169; 13.G.231.172; 13.G.231.175; 13.G.231.240; 13.G.231.244; 13.G.236.228; 13.G.236.229; 13.G.236.230; 13.G.236.231; 13.G.236.236; 13.G.236.237; 13.G.236.238; 13.G.236.239; 13.G.236.154; 13.G.236.157; 13.G.236.166; 13.G.236.169; 13.G.236.172; 13.G.236.175; 13.G.236.240; 13.G.236.244; 13.G.237.228; 13.G.237.229; 13.G.237.230; 13.G.237.231; 13.G.237.236; 13.G.237.237; 13.G.237.238; 13.G.237.239; 13.G.237.154; 13.G.237.157; 13.G.237.166; 13.G.237.169; 13.G.237.172; 13.G.237.175; 13.G.237.240; 13.G.237.244; 13.G.238.228; 13.G.238.229; 13.G.238.230; 13.G.238.231; 13.G.238.236; 13.G.238.237; 13.G.238.238; 13.G.238.239; 13.G.238.154; 13.G.238.157; 13.G.238.166; 13.G.238.169; 13.G.238.172; 13.G.238.175; 13.G.238.240; 13.G.238.244; 13.G.239.228; 13.G.239.229; 13.G.239.230; 13.G.239.231; 13.G.239.236; 13.G.239.237; 13.G.239.238; 13.G.239.239; 13.G.239.154; 13.G.239.157; 13.G.239.166; 13.G.239.169; 13.G.239.172; 13.G.239.175; 13.G.239.240; 13.G.239.244; 13.G.154.228; 13.G.154.229; 13.G.154.230; 13.G.154.231; 13.G.154.236; 13.G.154.237; 13.G.154.238; 13.G.154.239; 13.G.154.154; 13.G.154.157; 13.G.154.166; 13.G.154.169; 13.G.154.172; 13.G.154.175; 13.G.154.240; 13.G.154.244; 13.G.157.228; 13.G.157.229; 13.G.157.230; 13.G.157.231; 13.G.157.236; 13.G.157.237; 13.G.157.238; 13.G.157.239; 13.G.157.154; 13.G.157.157; 13.G.157.166; 13.G.157.169; 13.G.157.172; 13.G.157.175; 13.G.157.240; 13.G.157.244; 13.G.166.228; 13.G.166.229; 13.G.166.230; 13.G.166.231; 13.G.166.236; 13.G.166.237; 13.G.166.238; 13.G.166.239; 13.G.166.154; 13.G.166.157; 13.G.166.166; 13.G.166.169; 13.G.166.172; 13.G.166.175; 13.G.166.240; 13.G.166.244; 13.G.169.228; 13.G.169.229; 13.G.169.230; 13.G.169.231; 13.G.169.236; 13.G.169.237; 13.G.169.238; 13.G.169.239; 13.G.169.154; 13.G.169.157; 13.G.169.166; 13.G.169.169; 13.G.169.172; 13.G.169.175; 13.G.169.240; 13.G.169.244; 13.G.172.228; 13.G.172.229; 13.G.172.230; 13.G.172.231; 13.G.172.236; 13.G.172.237; 13.G.172.238; 13.G.172.239; 13.G.172.154; 13.G.172.157; 13.G.172.166; 13.G.172.169; 13.G.172.172; 13.G.172.175; 13.G.172.240; 13.G.172.244; 13.G.175.228; 13.G.175.229; 13.G.175.230; 13.G.175.231; 13.G.175.236; 13.G.175.237; 13.G.175.238; 13.G.175.239; 13.G.175.154; 13.G.175.157; 13.G.175.166; 13.G.175.169; 13.G.175.172; 13.G.175.175; 13.G.175.240; 13.G.175.244; 13.G.240.228; 13.G.240.229; 13.G.240.230; 13.G.240.231; 13.G.240.236; 13.G.240.237; 13.G.240.238; 13.G.240.239; 13.G.240.154; 13.G.240.157; 13.G.240.166; 13.G.240.169; 13.G.240.172; 13.G.240.175; 13.G.240.240; 13.G.240.244; 13.G.244.228; 13.G.244.229; 13.G.244.230; 13.G.244.231; 13.G.244.236; 13.G.244.237; 13.G.244.238; 13.G.244.239; 13.G.244.154; 13.G.244.157; 13.G.244.166; 13.G.244.169; 13.G.244.172; 13.G.244.175; 13.G.244.240; 13.G.244.244;

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13.I.228.228; 13.I.228.229; 13.I.228.230; 13.I.228.231; 13.I.228.236; 13.I.228.237; 13.I.228.238; 13.I.228.239; 13.I.228.154; 13.I.228.157; 13.I.228.166; 13.I.228.169; 13.I.228.172; 13.I.228.175; 13.I.228.240; 13.I.228.244; 13.I.229.228; 13.I.229.229; 13.I.229.230; 13.I.229.231; 13.I.229.236; 13.I.229.237; 13.I.229.238; 13.I.229.239; 13.I.229.154; 13.I.229.157; 13.I.229.166; 13.I.229.169; 13.I.229.172; 13.I.229.175; 13.I.229.240; 13.I.229.244; 13.I.230.228; 13.I.230.229; 13.I.230.230; 13.I.230.231; 13.I.230.236; 13.I.230.237; 13.I.230.238; 13.I.230.239; 13.I.230.154; 13.I.230.157; 13.I.230.166; 13.I.230.169; 13.I.230.172; 13.I.230.175; 13.I.230.240; 13.I.230.244; 13.I.231.228; 13.I.231.229; 13.I.231.230; 13.I.231.231; 13.I.231.236; 13.I.231.237; 13.I.231.238; 13.I.231.239; 13.I.231.154; 13.I.231.157; 13.I.231.166; 13.I.231.169; 13.I.231.172; 13.I.231.175; 13.I.231.240; 13.I.231.244; 13.I.236.228; 13.I.236.229; 13.I.236.230; 13.I.236.231; 13.I.236.236; 13.I.236.237; 13.I.236.238; 13.I.236.239; 13.I.236.154; 13.I.236.157; 13.I.236.166; 13.I.236.169; 13.I.236.172; 13.I.236.175; 13.I.236.240; 13.I.236.244; 13.I.237.228; 13.I.237.229; 13.I.237.230; 13.I.237.231; 13.I.237.236; 13.I.237.237; 13.I.237.238; 13.I.237.239; 13.I.237.154; 13.I.237.157; 13.I.237.166; 13.I.237.169; 13.I.237.172; 13.I.237.175; 13.I.237.240; 13.I.237.244; 13.I.238.228; 13.I.238.229; 13.I.238.230; 13.I.238.231; 13.I.238.236; 13.I.238.237; 13.I.238.238; 13.I.238.239; 13.I.238.154; 13.I.238.157; 13.I.238.166; 13.I.238.169; 13.I.238.172; 13.I.238.175; 13.I.238.240; 13.I.238.244; 13.I.239.228; 13.I.239.229; 13.I.239.230; 13.I.239.231; 13.I.239.236; 13.I.239.237; 13.I.239.238; 13.I.239.239; 13.I.239.154; 13.I.239.157; 13.I.239.166; 13.I.239.169; 13.I.239.172; 13.I.239.175; 13.I.239.240; 13.I.239.244; 13.I.154.228; 13.I.154.229; 13.I.154.230; 13.I.154.231; 13.I.154.236; 13.I.154.237; 13.I.154.238; 13.I.154.239; 13.I.154.154; 13.I.154.157; 13.I.154.166; 13.I.154.169; 13.I.154.172; 13.I.154.175; 13.I.154.240; 13.I.154.244; 13.I.157.228; 13.I.157.229; 13.I.157.230; 13.I.157.231; 13.I.157.236; 13.I.157.237; 13.I.157.238; 13.I.157.239; 13.I.157.154; 13.I.157.157; 13.I.157.166; 13.I.157.169; 13.I.157.172; 13.I.157.175; 13.I.157.240; 13.I.157.244; 13.I.166.228; 13.I.166.229; 13.I.166.230; 13.I.166.231; 13.I.166.236; 13.I.166.237; 13.I.166.238; 13.I.166.239; 13.I.166.154; 13.I.166.157; 13.I.166.166; 13.I.166.169; 13.I.166.172; 13.I.166.175; 13.I.166.240; 13.I.166.244; 13.I.169.228; 13.I.169.229; 13.I.169.230; 13.I.169.231; 13.I.169.236; 13.I.169.237; 13.I.169.238; 13.I.169.239; 13.I.169.154; 13.I.169.157; 13.I.169.166; 13.I.169.169; 13.I.169.172; 13.I.169.175; 13.I.169.240; 13.I.169.244; 13.I.172.228; 13.I.172.229; 13.I.172.230; 13.I.172.231; 13.I.172.236; 13.I.172.237; 13.I.172.238; 13.I.172.239; 13.I.172.154; 13.I.172.157; 13.I.172.166; 13.I.172.169; 13.I.172.172; 13.I.172.175; 13.I.172.240; 13.I.172.244; 13.I.175.228; 13.I.175.229; 13.I.175.230; 13.I.175.231; 13.I.175.236; 13.I.175.237; 13.I.175.238; 13.I.175.239; 13.I.175.154; 13.I.175.157; 13.I.175.166; 13.I.175.169; 13.I.175.172; 13.I.175.175; 13.I.175.240; 13.I.175.244; 13.I.240.228; 13.I.240.229; 13.I.240.230; 13.I.240.231; 13.I.240.236; 13.I.240.237; 13.I.240.238; 13.I.240.239; 13.I.240.154; 13.I.240.157; 13.I.240.166; 13.I.240.169; 13.I.240.172; 13.I.240.175; 13.I.240.240; 13.I.240.244; 13.I.244.228; 13.I.244.229; 13.I.244.230; 13.I.244.231; 13.I.244.236; 13.I.244.237; 13.I.244.238; 13.I.244.239; 13.I.244.154; 13.I.244.157; 13.I.244.166; 13.I.244.169; 13.I.244.172; 13.I.244.175; 13.I.244.240; 13.I.244.244;

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13.J.228.228; 13.J.228.229; 13.J.228.230; 13.J.228.231; 13.J.228.236; 13.J.228.237; 13.J.228.238; 13.J.228.239; 13.J.228.154; 13.J.228.157; 13.J.228.166; 13.J.228.169; 13.J.228.172; 13.J.228.175; 13.J.228.240; 13.J.228.244; 13.J.229.228; 13.J.229.229; 13.J.229.230; 13.J.229.231; 13.J.229.236; 13.J.229.237; 13.J.229.238; 13.J.229.239; 13.J.229.154; 13.J.229.157; 13.J.229.166; 13.J.229.169; 13.J.229.172; 13.J.229.175; 13.J.229.240; 13.J.229.244; 13.J.230.228; 13.J.230.229; 13.J.230.230; 13.J.230.231; 13.J.230.236; 13.J.230.237; 13.J.230.238; 13.J.230.239; 13.J.230.154; 13.J.230.157; 13.J.230.166; 13.J.230.169; 13.J.230.172; 13.J.230.175; 13.J.230.240; 13.J.230.244; 13.J.231.228; 13.J.231.229; 13.J.231.230; 13.J.231.231; 13.J.231.236; 13.J.231.237; 13.J.231.238; 13.J.231.239; 13.J.231.154; 13.J.231.157; 13.J.231.166; 13.J.231.169; 13.J.231.172; 13.J.231.175; 13.J.231.240; 13.J.231.244; 13.J.236.228; 13.J.236.229; 13.J.236.230; 13.J.236.231; 13.J.236.236; 13.J.236.237; 13.J.236.238; 13.J.236.239; 13.J.236.154; 13.J.236.157; 13.J.236.166; 13.J.236.169; 13.J.236.172; 13.J.236.175; 13.J.236.240; 13.J.236.244; 13.J.237.228; 13.J.237.229; 13.J.237.230; 13.J.237.231; 13.J.237.236; 13.J.237.237; 13.J.237.238; 13.J.237.239; 13.J.237.154; 13.J.237.157; 13.J.237.166; 13.J.237.169; 13.J.237.172; 13.J.237.175; 13.J.237.240; 13.J.237.244; 13.J.238.228; 13.J.238.229; 13.J.238.230; 13.J.238.231; 13.J.238.236; 13.J.238.237; 13.J.238.238; 13.J.238.239; 13.J.238.154; 13.J.238.157; 13.J.238.166; 13.J.238.169; 13.J.238.172; 13.J.238.175; 13.J.238.240; 13.J.238.244; 13.J.239.228; 13.J.239.229; 13.J.239.230; 13.J.239.231; 13.J.239.236; 13.J.239.237; 13.J.239.238; 13.J.239.239; 13.J.239.154; 13.J.239.157; 13.J.239.166; 13.J.239.169; 13.J.239.172; 13.J.239.175; 13.J.239.240; 13.J.239.244; 13.J.154.228; 13.J.154.229; 13.J.154.230; 13.J.154.231; 13.J.154.236; 13.J.154.237; 13.J.154.238; 13.J.154.239; 13.J.154.154; 13.J.154.157; 13.J.154.166; 13.J.154.169; 13.J.154.172; 13.J.154.175; 13.J.154.240; 13.J.154.244; 13.J.157.228; 13.J.157.229; 13.J.157.230; 13.J.157.231; 13.J.157.236; 13.J.157.237; 13.J.157.238; 13.J.157.239; 13.J.157.154; 13.J.157.157; 13.J.157.166; 13.J.157.169; 13.J.157.172; 13.J.157.175; 13.J.157.240; 13.J.157.244; 13.J.166.228; 13.J.166.229; 13.J.166.230; 13.J.166.231; 13.J.166.236; 13.J.166.237; 13.J.166.238; 13.J.166.239; 13.J.166.154; 13.J.166.157; 13.J.166.166; 13.J.166.169; 13.J.166.172; 13.J.166.175; 13.J.166.240; 13.J.166.244; 13.J.169.228; 13.J.169.229; 13.J.169.230; 13.J.169.231; 13.J.169.236; 13.J.169.237; 13.J.169.238; 13.J.169.239; 13.J.169.154; 13.J.169.157; 13.J.169.166; 13.J.169.169; 13.J.169.172; 13.J.169.175; 13.J.169.240; 13.J.169.244; 13.J.172.228; 13.J.172.229; 13.J.172.230; 13.J.172.231; 13.J.172.236; 13.J.172.237; 13.J.172.238; 13.J.172.239; 13.J.172.154; 13.J.172.157; 13.J.172.166; 13.J.172.169; 13.J.172.172; 13.J.172.175; 13.J.172.240; 13.J.172.244; 13.J.175.228; 13.J.175.229; 13.J.175.230; 13.J.175.231; 13.J.175.236; 13.J.175.237; 13.J.175.238; 13.J.175.239; 13.J.175.154; 13.J.175.157; 13.J.175.166; 13.J.175.169; 13.J.175.172; 13.J.175.175; 13.J.175.240; 13.J.175.244; 13.J.240.228; 13.J.240.229; 13.J.240.230; 13.J.240.231; 13.J.240.236; 13.J.240.237; 13.J.240.238; 13.J.240.239; 13.J.240.154; 13.J.240.157; 13.J.240.166; 13.J.240.169; 13.J.240.172; 13.J.240.175; 13.J.240.240; 13.J.240.244; 13.J.244.228; 13.J.244.229; 13.J.244.230; 13.J.244.231; 13.J.244.236; 13.J.244.237; 13.J.244.238; 13.J.244.239; 13.J.244.154; 13.J.244.157; 13.J.244.166; 13.J.244.169; 13.J.244.172; 13.J.244.175; 13.J.244.240; 13.J.244.244;

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13.U.228.228; 13.U.228.229; 13.U.228.230; 13.U.228.231; 13.U.228.236; 13.U.228.237; 13.U.228.238; 13.U.228.239; 13.U.228.154; 13.U.228.157; 13.U.228.166; 13.U.228.169; 13.U.228.172; 13.U.228.175; 13.U.228.240; 13.U.228.244; 13.U.229.228; 13.U.229.229; 13.U.229.230; 13.U.229.231; 13.U.229.236; 13.U.229.237; 13.U.229.238; 13.U.229.239; 13.U.229.154; 13.U.229.157; 13.U.229.166; 13.U.229.169; 13.U.229.172; 13.U.229.175; 13.U.229.240; 13.U.229.244; 13.U.230.228; 13.U.230.229; 13.U.230.230; 13.U.230.231; 13.U.230.236; 13.U.230.237; 13.U.230.238; 13.U.230.239; 13.U.230.154; 13.U.230.157; 13.U.230.166; 13.U.230.169; 13.U.230.172; 13.U.230.175; 13.U.230.240; 13.U.230.244; 13.U.231.228; 13.U.231.229; 13.U.231.230; 13.U.231.231; 13.U.231.236; 13.U.231.237; 13.U.231.238; 13.U.231.239; 13.U.231.154; 13.U.231.157; 13.U.231.166; 13.U.231.169; 13.U.231.172; 13.U.231.175; 13.U.231.240; 13.U.231.244; 13.U.236.228; 13.U.236.229; 13.U.236.230; 13.U.236.231; 13.U.236.236; 13.U.236.237; 13.U.236.238; 13.U.236.239; 13.U.236.154; 13.U.236.157; 13.U.236.166; 13.U.236.169; 13.U.236.172; 13.U.236.175; 13.U.236.240; 13.U.236.244; 13.U.237.228; 13.U.237.229; 13.U.237.230; 13.U.237.231; 13.U.237.236; 13.U.237.237; 13.U.237.238; 13.U.237.239; 13.U.237.154; 13.U.237.157; 13.U.237.166; 13.U.237.169; 13.U.237.172; 13.U.237.175; 13.U.237.240; 13.U.237.244; 13.U.238.228; 13.U.238.229; 13.U.238.230; 13.U.238.231; 13.U.238.236; 13.U.238.237; 13.U.238.238; 13.U.238.239; 13.U.238.154; 13.U.238.157; 13.U.238.166; 13.U.238.169; 13.U.238.172; 13.U.238.175; 13.U.238.240; 13.U.238.244; 13.U.239.228; 13.U.239.229; 13.U.239.230; 13.U.239.231; 13.U.239.236; 13.U.239.237; 13.U.239.238; 13.U.239.239; 13.U.239.154; 13.U.239.157; 13.U.239.166; 13.U.239.169; 13.U.239.172; 13.U.239.175; 13.U.239.240; 13.U.239.244; 13.U.154.228; 13.U.154.229; 13.U.154.230; 13.U.154.231; 13.U.154.236; 13.U.154.237; 13.U.154.238; 13.U.154.239; 13.U.154.154; 13.U.154.157; 13.U.154.166; 13.U.154.169; 13.U.154.172; 13.U.154.175; 13.U.154.240; 13.U.154.244; 13.U.157.228; 13.U.157.229; 13.U.157.230; 13.U.157.231; 13.U.157.236; 13.U.157.237; 13.U.157.238; 13.U.157.239; 13.U.157.154; 13.U.157.157; 13.U.157.166; 13.U.157.169; 13.U.157.172; 13.U.157.175; 13.U.157.240; 13.U.157.244; 13.U.166.228; 13.U.166.229; 13.U.166.230; 13.U.166.231; 13.U.166.236; 13.U.166.237; 13.U.166.238; 13.U.166.239; 13.U.166.154; 13.U.166.157; 13.U.166.166; 13.U.166.169; 13.U.166.172; 13.U.166.175; 13.U.166.240; 13.U.166.244; 13.U.169.228; 13.U.169.229; 13.U.169.230; 13.U.169.231; 13.U.169.236; 13.U.169.237; 13.U.169.238; 13.U.169.239; 13.U.169.154; 13.U.169.157; 13.U.169.166; 13.U.169.169; 13.U.169.172; 13.U.169.175; 13.U.169.240; 13.U.169.244; 13.U.172.228; 13.U.172.229; 13.U.172.230; 13.U.172.231; 13.U.172.236; 13.U.172.237; 13.U.172.238; 13.U.172.239; 13.U.172.154; 13.U.172.157; 13.U.172.166; 13.U.172.169; 13.U.172.172; 13.U.172.175; 13.U.172.240; 13.U.172.244; 13.U.175.228; 13.U.175.229; 13.U.175.230; 13.U.175.231; 13.U.175.236; 13.U.175.237; 13.U.175.238; 13.U.175.239; 13.U.175.154; 13.U.175.157; 13.U.175.166; 13.U.175.169; 13.U.175.172; 13.U.175.175; 13.U.175.240; 13.U.175.244; 13.U.240.228; 13.U.240.229; 13.U.240.230; 13.U.240.231; 13.U.240.236; 13.U.240.237; 13.U.240.238; 13.U.240.239; 13.U.240.154; 13.U.240.157; 13.U.240.166; 13.U.240.169; 13.U.240.172; 13.U.240.175; 13.U.240.240; 13.U.240.244; 13.U.244.228; 13.U.244.229; 13.U.244.230; 13.U.244.231; 13.U.244.236; 13.U.244.237; 13.U.244.238; 13.U.244.239; 13.U.244.154; 13.U.244.157; 13.U.244.166; 13.U.244.169; 13.U.244.172; 13.U.244.175; 13.U.244.240; 13.U.244.244;

Prodrugs of 13.W

13.W.228.228; 13.W.228.229; 13.W.228.230; 13.W.228.231; 13.W.228.236; 13.W.228.237; 13.W.228.238; 13.W.228.239; 13.W.228.154; 13.W.228.157; 13.W.228.166; 13.W.228.169; 13.W.228.172; 13.W.228.175; 13.W.228.240; 13.W.228.244; 13.W.229.228; 13.W.229.229; 13.W.229.230; 13.W.229.231; 13.W.229.236; 13.W.229.237; 13.W.229.238; 13.W.229.239; 13.W.229.154; 13.W.229.157; 13.W.229.166; 13.W.229.169; 13.W.229.172; 13.W.229.175; 13.W.229.240; 13.W.229.244; 13.W.230.228; 13.W.230.229; 13.W.230.230; 13.W.230.231; 13.W.230.236; 13.W.230.237; 13.W.230.238; 13.W.230.239; 13.W.230.154; 13.W.230.157; 13.W.230.166; 13.W.230.169; 13.W.230.172; 13.W.230.175; 13.W.230.240; 13.W.230.244; 13.W.231.228; 13.W.231.229; 13.W.231.230; 13.W.231.231; 13.W.231.236; 13.W.231.237; 13.W.231.238; 13.W.231.239; 13.W.231.154; 13.W.231.157; 13.W.231.166; 13.W.231.169; 13.W.231.172; 13.W.231.175; 13.W.231.240; 13.W.231.244; 13.W.236.228; 13.W.236.229; 13.W.236.230; 13.W.236.231; 13.W.236.236; 13.W.236.237; 13.W.236.238; 13.W.236.239; 13.W.236.154; 13.W.236.157; 13.W.236.166; 13.W.236.169; 13.W.236.172; 13.W.236.175; 13.W.236.240; 13.W.236.244; 13.W.237.228; 13.W.237.229; 13.W.237.230; 13.W.237.231; 13.W.237.236; 13.W.237.237; 13.W.237.238; 13.W.237.239; 13.W.237.154; 13.W.237.157; 13.W.237.166; 13.W.237.169; 13.W.237.172; 13.W.237.175; 13.W.237.240; 13.W.237.244; 13.W.238.228; 13.W.238.229; 13.W.238.230; 13.W.238.231; 13.W.238.236; 13.W.238.237; 13.W.238.238; 13.W.238.239; 13.W.238.154; 13.W.238.157; 13.W.238.166; 13.W.238.169; 13.W.238.172; 13.W.238.175; 13.W.238.240; 13.W.238.244; 13.W.239.228; 13.W.239.229; 13.W.239.230; 13.W.239.231; 13.W.239.236; 13.W.239.237; 13.W.239.238; 13.W.239.239; 13.W.239.154; 13.W.239.157; 13.W.239.166; 13.W.239.169; 13.W.239.172; 13.W.239.175; 13.W.239.240; 13.W.239.244; 13.W.154.228; 13.W.154.229; 13.W.154.230; 13.W.154.231; 13.W.154.236; 13.W.154.237; 13.W.154.238; 13.W.154.239; 13.W.154.154; 13.W.154.157; 13.W.154.166; 13.W.154.169; 13.W.154.172; 13.W.154.175; 13.W.154.240; 13.W.154.244; 13.W.157.228; 13.W.157.229; 13.W.157.230; 13.W.157.231; 13.W.157.236; 13.W.157.237; 13.W.157.238; 13.W.157.239; 13.W.157.154; 13.W.157.157; 13.W.157.166; 13.W.157.169; 13.W.157.172; 13.W.157.175; 13.W.157.240; 13.W.157.244; 13.W.166.228; 13.W.166.229; 13.W.166.230; 13.W.166.231; 13.W.166.236; 13.W.166.237; 13.W.166.238; 13.W.166.239; 13.W.166.154; 13.W.166.157; 13.W.166.166; 13.W.166.169; 13.W.166.172; 13.W.166.175; 13.W.166.240; 13.W.166.244; 13.W.169.228; 13.W.169.229; 13.W.169.230; 13.W.169.231; 13.W.169.236; 13.W.169.237; 13.W.169.238; 13.W.169.239; 13.W.169.154; 13.W.169.157; 13.W.169.166; 13.W.169.169; 13.W.169.172; 13.W.169.175; 13.W.169.240; 13.W.169.244; 13.W.172.228; 13.W.172.229; 13.W.172.230; 13.W.172.231; 13.W.172.236; 13.W.172.237; 13.W.172.238; 13.W.172.239; 13.W.172.154; 13.W.172.157; 13.W.172.166; 13.W.172.169; 13.W.172.172; 13.W.172.175; 13.W.172.240; 13.W.172.244; 13.W.175.228; 13.W.175.229; 13.W.175.230; 13.W.175.231; 13.W.175.236; 13.W.175.237; 13.W.175.238; 13.W.175.239; 13.W.175.154; 13.W.175.157; 13.W.175.166; 13.W.175.169; 13.W.175.172; 13.W.175.175; 13.W.175.240; 13.W.175.244; 13.W.240.228; 13.W.240.229; 13.W.240.230; 13.W.240.231; 13.W.240.236; 13.W.240.237; 13.W.240.238; 13.W.240.239; 13.W.240.154; 13.W.240.157; 13.W.240.166; 13.W.240.169; 13.W.240.172; 13.W.240.175; 13.W.240.240; 13.W.240.244; 13.W.244.228; 13.W.244.229; 13.W.244.230; 13.W.244.231; 13.W.244.236; 13.W.244.237; 13.W.244.238; 13.W.244.239; 13.W.244.154; 13.W.244.157; 13.W.244.166; 13.W.244.169; 13.W.244.172; 13.W.244.175; 13.W.244.240; 13.W.244.244;

Prodrugs of 13.Y

13.Y.228.228; 13.Y.228.229; 13.Y.228.230; 13.Y.228.231; 13.Y.228.236; 13.Y.228.237; 13.Y.228.238; 13.Y.228.239; 13.Y.228.154; 13.Y.228.157; 13.Y.228.166; 13.Y.228.169; 13.Y.228.172; 13.Y.228.175; 13.Y.228.240; 13.Y.228.244; 13.Y.229.228; 13.Y.229.229; 13.Y.229.230; 13.Y.229.231; 13.Y.229.236; 13.Y.229.237; 13.Y.229.238; 13.Y.229.239; 13.Y.229.154; 13.Y.229.157; 13.Y.229.166; 13.Y.229.169; 13.Y.229.172; 13.Y.229.175; 13.Y.229.240; 13.Y.229.244; 13.Y.230.228; 13.Y.230.229; 13.Y.230.230; 13.Y.230.231; 13.Y.230.236; 13.Y.230.237; 13.Y.230.238; 13.Y.230.239; 13.Y.230.154; 13.Y.230.157; 13.Y.230.166; 13.Y.230.169; 13.Y.230.172; 13.Y.230.175; 13.Y.230.240; 13.Y.230.244; 13.Y.231.228; 13.Y.231.229; 13.Y.231.230; 13.Y.231.231; 13.Y.231.236; 13.Y.231.237; 13.Y.231.238; 13.Y.231.239; 13.Y.231.154; 13.Y.231.157; 13.Y.231.166; 13.Y.231.169; 13.Y.231.172; 13.Y.231.175; 13.Y.231.240; 13.Y.231.244; 13.Y.236.228; 13.Y.236.229; 13.Y.236.230; 13.Y.236.231; 13.Y.236.236; 13.Y.236.237; 13.Y.236.238; 13.Y.236.239; 13.Y.236.154; 13.Y.236.157; 13.Y.236.166; 13.Y.236.169; 13.Y.236.172; 13.Y.236.175; 13.Y.236.240; 13.Y.236.244; 13.Y.237.228; 13.Y.237.229; 13.Y.237.230; 13.Y.237.231; 13.Y.237.236; 13.Y.237.237; 13.Y.237.238; 13.Y.237.239; 13.Y.237.154; 13.Y.237.157; 13.Y.237.166; 13.Y.237.169; 13.Y.237.172; 13.Y.237.175; 13.Y.237.240; 13.Y.237.244; 13.Y.238.228; 13.Y.238.229; 13.Y.238.230; 13.Y.238.231; 13.Y.238.236; 13.Y.238.237; 13.Y.238.238; 13.Y.238.239; 13.Y.238.154; 13.Y.238.157; 13.Y.238.166; 13.Y.238.169; 13.Y.238.172; 13.Y.238.175; 13.Y.238.240; 13.Y.238.244; 13.Y.239.228; 13.Y.239.229; 13.Y.239.230; 13.Y.239.231; 13.Y.239.236; 13.Y.239.237; 13.Y.239.238; 13.Y.239.239; 13.Y.239.154; 13.Y.239.157; 13.Y.239.166; 13.Y.239.169; 13.Y.239.172; 13.Y.239.175; 13.Y.239.240; 13.Y.239.244; 13.Y.154.228; 13.Y.154.229; 13.Y.154.230; 13.Y.154.231; 13.Y.154.236; 13.Y.154.237; 13.Y.154.238; 13.Y.154.239; 13.Y.154.154; 13.Y.154.157; 13.Y.154.166; 13.Y.154.169; 13.Y.154.172; 13.Y.154.175; 13.Y.154.240; 13.Y.154.244; 13.Y.157.228; 13.Y.157.229; 13.Y.157.230; 13.Y.157.231; 13.Y.157.236; 13.Y.157.237; 13.Y.157.238; 13.Y.157.239; 13.Y.157.154; 13.Y.157.157; 13.Y.157.166; 13.Y.157.169; 13.Y.157.172; 13.Y.157.175; 13.Y.157.240; 13.Y.157.244; 13.Y.166.228; 13.Y.166.229; 13.Y.166.230; 13.Y.166.231; 13.Y.166.236; 13.Y.166.237; 13.Y.166.238; 13.Y.166.239; 13.Y.166.154; 13.Y.166.157; 13.Y.166.166; 13.Y.166.169; 13.Y.166.172; 13.Y.166.175; 13.Y.166.240; 13.Y.166.244; 13.Y.169.228; 13.Y.169.229; 13.Y.169.230; 13.Y.169.231; 13.Y.169.236; 13.Y.169.237; 13.Y.169.238; 13.Y.169.239; 13.Y.169.154; 13.Y.169.157; 13.Y.169.166; 13.Y.169.169; 13.Y.169.172; 13.Y.169.175; 13.Y.169.240; 13.Y.169.244; 13.Y.172.228; 13.Y.172.229; 13.Y.172.230; 13.Y.172.231; 13.Y.172.236; 13.Y.172.237; 13.Y.172.238; 13.Y.172.239; 13.Y.172.154; 13.Y.172.157; 13.Y.172.166; 13.Y.172.169; 13.Y.172.172; 13.Y.172.175; 13.Y.172.240; 13.Y.172.244; 13.Y.175.228; 13.Y.175.229; 13.Y.175.230; 13.Y.175.231; 13.Y.175.236; 13.Y.175.237; 13.Y.175.238; 13.Y.175.239; 13.Y.175.154; 13.Y.175.157; 13.Y.175.166; 13.Y.175.169; 13.Y.175.172; 13.Y.175.175; 13.Y.175.240; 13.Y.175.244; 13.Y.240.228; 13.Y.240.229; 13.Y.240.230; 13.Y.240.231; 13.Y.240.236; 13.Y.240.237; 13.Y.240.238; 13.Y.240.239; 13.Y.240.154; 13.Y.240.157; 13.Y.240.166; 13.Y.240.169; 13.Y.240.172; 13.Y.240.175; 13.Y.240.240; 13.Y.240.244; 13.Y.244.228; 13.Y.244.229; 13.Y.244.230; 13.Y.244.231; 13.Y.244.236; 13.Y.244.237; 13.Y.244.238; 13.Y.244.239; 13.Y.244.154; 13.Y.244.157; 13.Y.244.166; 13.Y.244.169; 13.Y.244.172; 13.Y.244.175; 13.Y.244.240; 13.Y.244.244;

Prodrugs of 14.AH

14.AH.4.157; 14.AH.4.158; 14.AH.4.196; 14.AH.4.223; 14.AH.4.240; 14.AH.4.244; 14.AH.4.243; 14.AH.4.247; 14.AH.5.157; 14.AH.5.158; 14.AH.5.196; 14.AH.5.223; 14.AH.5.240; 14.AH.5.244; 14.AH.5.243; 14.AH.5.247; 14.AH.7.157; 14.AH.7.158; 14.AH.7.196; 14.AH.7.223; 14.AH.7.240; 14.AH.7.244; 14.AH.7.243; 14.AH.7.247; 14.AH.15.157; 14.AH.15.158; 14.AH.15.196; 14.AH.15.223; 14.AH.15.240; 14.AH.15.244; 14.AH.15.243; 14.AH.15.247; 14.AH.16.157; 14.AH.16.158; 14.AH.16.196; 14.AH.16.223; 14.AH.16.240; 14.AH.16.244; 14.AH.16.243; 14.AH.16.247; 14.AH.18.157; 14.AH.18.158; 14.AH.18.196; 14.AH.18.223; 14.AH.18.240; 14.AH.18.244; 14.AH.18.243; 14.AH.18.247; 14.AH.26.157; 14.AH.26.158; 14.AH.26.196; 14.AH.26.223; 14.AH.26.240; 14.AH.26.244; 14.AH.26.243; 14.AH.26.247; 14.AH.27.157; 14.AH.27.158; 14.AH.27.196; 14.AH.27.223; 14.AH.27.240; 14.AH.27.244; 14.AH.27.243; 14.AH.27.247; 14.AH.29.157; 14.AH.29.158; 14.AH.29.196; 14.AH.29.223; 14.AH.29.240; 14.AH.29.244; 14.AH.29.243; 14.AH.29.247; 14.AH.54.157; 14.AH.54.158; 14.AH.54.196; 14.AH.54.223; 14.AH.54.240; 14.AH.54.244; 14.AH.54.243; 14.AH.54.247; 14.AH.55.157; 14.AH.55.158; 14.AH.55.196; 14.AH.55.223; 14.AH.55.240; 14.AH.55.244; 14.AH.55.243; 14.AH.55.247; 14.AH.56.157; 14.AH.56.158; 14.AH.56.196; 14.AH.56.223; 14.AH.56.240; 14.AH.56.244; 14.AH.56.243; 14.AH.56.247; 14.AH.157.157; 14.AH.157.158; 14.AH.157.196; 14.AH.157.223; 14.AH.157.240; 14.AH.157.244; 14.AH.157.243; 14.AH.157.247; 14.AH.196.157; 14.AH.196.158; 14.AH.196.196; 14.AH.196.223; 14.AH.196.240; 14.AH.196.244; 14.AH.196.243; 14.AH.196.247; 14.AH.223.157; 14.AH.223.158; 14.AH.223.196; 14.AH.223.223; 14.AH.223.240; 14.AH.223.244; 14.AH.223.243; 14.AH.223.247; 14.AH.240.157; 14.AH.240.158; 14.AH.240.196; 14.AH.240.223; 14.AH.240.240; 14.AH.240.244; 14.AH.240.243; 14.AH.240.247; 14.AH.244.157; 14.AH.244.158; 14.AH.244.196; 14.AH.244.223; 14.AH.244.240; 14.AH.244.244; 14.AH.244.243; 14.AH.244.247; 14.AH.247.157; 14.AH.247.158; 14.AH.247.196; 14.AH.247.223; 14.AH.247.240; 14.AH.247.244; 14.AH.247.243; 14.AH.247.247;

Prodrugs of 14.AJ

14.AJ.4.157; 14.AJ.4.158; 14.AJ.4.196; 14.AJ.4.223; 14.AJ.4.240; 14.AJ.4.244; 14.AJ.4.243; 14.AJ.4.247; 14.AJ.5.157; 14.AJ.5.158; 14.AJ.5.196; 14.AJ.5.223; 14.AJ.5.240; 14.AJ.5.244; 14.AJ.5.243; 14.AJ.5.247; 14.AJ.7.157; 14.AJ.7.158; 14.AJ.7.196; 14.AJ.7.223; 14.AJ.7.240; 14.AJ.7.244; 14.AJ.7.243; 14.AJ.7.247; 14.AJ.15.157; 14.AJ.15.158; 14.AJ.15.196; 14.AJ.15.223; 14.AJ.15.240; 14.AJ.15.244; 14.AJ.15.243; 14.AJ.15.247; 14.AJ.16.157; 14.AJ.16.158; 14.AJ.16.196; 14.AJ.16.223; 14.AJ.16.240; 14.AJ.16.244; 14.AJ.16.243; 14.AJ.16.247; 14.AJ.18.157; 14.AJ.18.158; 14.AJ.18.196; 14.AJ.18.223; 14.AJ.18.240; 14.AJ.18.244; 14.AJ.18.243; 14.AJ.18.247; 14.AJ.26.157; 14.AJ.26.158; 14.AJ.26.196; 14.AJ.26.223; 14.AJ.26.240; 14.AJ.26.244; 14.AJ.26.243; 14.AJ.26.247; 14.AJ.27.157; 14.AJ.27.158; 14.AJ.27.196; 14.AJ.27.223; 14.AJ.27.240; 14.AJ.27.244; 14.AJ.27.243; 14.AJ.27.247; 14.AJ.29.157; 14.AJ.29.158; 14.AJ.29.196; 14.AJ.29.223; 14.AJ.29.240; 14.AJ.29.244; 14.AJ.29.243; 14.AJ.29.247; 14.AJ.54.157; 14.AJ.54.158; 14.AJ.54.196; 14.AJ.54.223; 14.AJ.54.240; 14.AJ.54.244; 14.AJ.54.243; 14.AJ.54.247; 14.AJ.55.157; 14.AJ.55.158; 14.AJ.55.196; 14.AJ.55.223; 14.AJ.55.240; 14.AJ.55.244; 14.AJ.55.243; 14.AJ.55.247; 14.AJ.56.157; 14.AJ.56.158; 14.AJ.56.196; 14.AJ.56.223; 14.AJ.56.240; 14.AJ.56.244; 14.AJ.56.243; 14.AJ.56.247; 14.AJ.157.157; 14.AJ.157.158; 14.AJ.157.196; 14.AJ.157.223; 14.AJ.157.240; 14.AJ.157.244; 14.AJ.157.243; 14.AJ.157.247; 14.AJ.196.157; 14.AJ.196.158; 14.AJ.196.196; 14.AJ.196.223;

14.AJ.196.240; 14.AJ.196.244; 14.AJ.196.243; 14.AJ.196.247; 14.AJ.223.157; 14.AJ.223.158; 14.AJ.223.196; 14.AJ.223.223; 14.AJ.223.240; 14.AJ.223.244; 14.AJ.223.243; 14.AJ.223.247; 14.AJ.240.157; 14.AJ.240.158; 14.AJ.240.196; 14.AJ.240.223; 14.AJ.240.240; 14.AJ.240.244; 14.AJ.240.243; 14.AJ.240.247; 14.AJ.244.157; 14.AJ.244.158; 14.AJ.244.196; 14.AJ.244.223; 14.AJ.244.240; 14.AJ.244.244; 14.AJ.244.243; 14.AJ.244.247; 14.AJ.247.157; 14.AJ.247.158; 14.AJ.247.196; 14.AJ.247.223; 14.AJ.247.240; 14.AJ.247.244; 14.AJ.247.243; 14.AJ.247.247;

Prodrugs of 14.AN

14.AN.4.157; 14.AN.4.158; 14.AN.4.196; 14.AN.4.223; 14.AN.4.240; 14.AN.4.244; 14.AN.4.243; 14.AN.4.247; 14.AN.5.157; 14.AN.5.158; 14.AN.5.196; 14.AN.5.223; 14.AN.5.240; 14.AN.5.244; 14.AN.5.243; 14.AN.5.247; 14.AN.7.157; 14.AN.7.158; 14.AN.7.196; 14.AN.7.223; 14.AN.7.240; 14.AN.7.244; 14.AN.7.243; 14.AN.7.247; 14.AN.15.157; 14.AN.15.158; 14.AN.15.196; 14.AN.15.223; 14.AN.15.240; 14.AN.15.244; 14.AN.15.243; 14.AN.15.247; 14.AN.16.157; 14.AN.16.158; 14.AN.16.196; 14.AN.16.223; 14.AN.16.240; 14.AN.16.244; 14.AN.16.243; 14.AN.16.247; 14.AN.18.157; 14.AN.18.158; 14.AN.18.196; 14.AN.18.223; 14.AN.18.240; 14.AN.18.244; 14.AN.18.243; 14.AN.18.247; 14.AN.26.157; 14.AN.26.158; 14.AN.26.196; 14.AN.26.223; 14.AN.26.240; 14.AN.26.244; 14.AN.26.243; 14.AN.26.247; 14.AN.27.157; 14.AN.27.158; 14.AN.27.196; 14.AN.27.223; 14.AN.27.240; 14.AN.27.244; 14.AN.27.243; 14.AN.27.247; 14.AN.29.157; 14.AN.29.158; 14.AN.29.196; 14.AN.29.223; 14.AN.29.240; 14.AN.29.244; 14.AN.29.243; 14.AN.29.247; 14.AN.54.157; 14.AN.54.158; 14.AN.54.196; 14.AN.54.223; 14.AN.54.240; 14.AN.54.244; 14.AN.54.243; 14.AN.54.247; 14.AN.55.157; 14.AN.55.158; 14.AN.55.196; 14.AN.55.223; 14.AN.55.240; 14.AN.55.244; 14.AN.55.243; 14.AN.55.247; 14.AN.56.157; 14.AN.56.158; 14.AN.56.196; 14.AN.56.223; 14.AN.56.240; 14.AN.56.244; 14.AN.56.243; 14.AN.56.247; 14.AN.157.157; 14.AN.157.158; 14.AN.157.196; 14.AN.157.223; 14.AN.157.240; 14.AN.157.244; 14.AN.157.243; 14.AN.157.247; 14.AN.196.157; 14.AN.196.158; 14.AN.196.196; 14.AN.196.223; 14.AN.196.240; 14.AN.196.244; 14.AN.196.243; 14.AN.196.247; 14.AN.223.157; 14.AN.223.158; 14.AN.223.196; 14.AN.223.223; 14.AN.223.240; 14.AN.223.244; 14.AN.223.243; 14.AN.223.247; 14.AN.240.157; 14.AN.240.158; 14.AN.240.196; 14.AN.240.223; 14.AN.240.240; 14.AN.240.244; 14.AN.240.243; 14.AN.240.247; 14.AN.244.157; 14.AN.244.158; 14.AN.244.196; 14.AN.244.223; 14.AN.244.240; 14.AN.244.244; 14.AN.244.243; 14.AN.244.247; 14.AN.247.157; 14.AN.247.158; 14.AN.247.196; 14.AN.247.223; 14.AN.247.240; 14.AN.247.244; 14.AN.247.243; 14.AN.247.247;

Prodrugs of 14.AP

14.AP.4.157; 14.AP.4.158; 14.AP.4.196; 14.AP.4.223; 14.AP.4.240; 14.AP.4.244; 14.AP.4.243; 14.AP.4.247; 14.AP.5.157; 14.AP.5.158; 14.AP.5.196; 14.AP.5.223; 14.AP.5.240; 14.AP.5.244; 14.AP.5.243; 14.AP.5.247; 14.AP.7.157; 14.AP.7.158; 14.AP.7.196; 14.AP.7.223; 14.AP.7.240; 14.AP.7.244; 14.AP.7.243; 14.AP.7.247; 14.AP.15.157; 14.AP.15.158; 14.AP.15.196; 14.AP.15.223; 14.AP.15.240; 14.AP.15.244; 14.AP.15.243; 14.AP.15.247; 14.AP.16.157; 14.AP.16.158; 14.AP.16.196; 14.AP.16.223; 14.AP.16.240; 14.AP.16.244; 14.AP.16.243; 14.AP.16.247; 14.AP.18.157; 14.AP.18.158; 14.AP.18.196; 14.AP.18.223; 14.AP.18.240; 14.AP.18.244; 14.AP.18.243; 14.AP.18.247; 14.AP.26.157; 14.AP.26.158; 14.AP.26.196; 14.AP.26.223; 14.AP.26.240; 14.AP.26.244; 14.AP.26.243; 14.AP.26.247; 14.AP.27.157; 14.AP.27.158; 14.AP.27.196; 14.AP.27.223;

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Prodrugs of 14.AZ

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Prodrugs of 14.BF

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Prodrugs of 14.CI

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Prodrugs of 14.CO

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Recursive Substituents

Selected substituents within the compounds of the invention are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number of compounds may be present in any given embodiment. For example, R^x contains a R^y substituent. R^y can be R^2, which in turn can be R^3. If R^3 is selected to be R^{3c}, then a second instance of R^x can be selected. One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

By way of example and not limitation, W^3, R^y and R^3 are all recursive substituents in certain embodiments. Typically, each of these may independently occur 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given embodiment. More typically, each of these may independently occur 12 or fewer times in a given embodiment. More typically yet, W^3 will occur 0 to 8 times, R^y will occur 0 to 6 times and R^3 will occur 0 to 10 times in a given embodiment. Even more typically, W^3 will occur 0 to 6 times, R^y will occur 0 to 4 times and R^3 will occur 0 to 8 times in a given embodiment.

Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an embodiment of the invention, the total number will be determined as set forth above.

Protecting Groups

In the context of the present invention, embodiments of protecting groups include prodrug moieties and chemical protecting groups.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, i.e. routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group "PRT" will be dependent upon the chemistry of the reaction to be protected against (e.g.,

acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PRT groups do not need to be, and generally are not, the same if the compound is substituted with multiple PRT. In general, PRT will be used to protect functional groups such as carboxyl, hydroxyl or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free, deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

Various functional groups of the compounds of the invention may be protection. For example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) are embodiments of "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

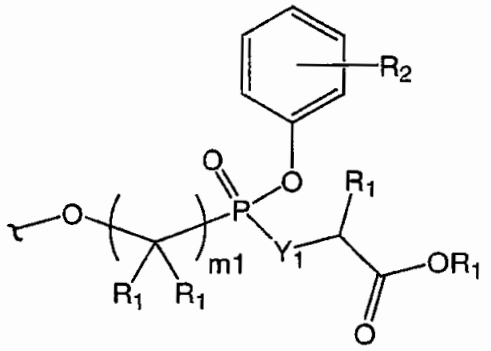
A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; "Protecting Groups" (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

Ether- and Ester-forming protecting groups

Ester-forming groups include: (1) phosphonate ester-forming groups, such as phosphonamidate esters, phosphorothioate esters, phosphonate esters, and phosphon-bis-amidates; (2) carboxyl ester-forming groups, and (3) sulphur ester-forming groups, such as sulphonate, sulfate, and sulfinate.

The phosphonate moieties of the compounds of the invention may or may not be prodrug moieties, i.e. they may or may not be susceptible to hydrolytic or enzymatic cleavage or modification. Certain phosphonate moieties are stable under most or nearly all metabolic conditions. For example, a dialkylphosphonate, where the alkyl groups are two or more carbons, may have appreciable stability *in vivo* due to a slow rate of hydrolysis.

Within the context of phosphonate prodrug moieties, a large number of structurally-diverse prodrugs have been described for phosphonic acids (Freeman and Ross in Progress in Medicinal Chemistry 34: 112-147 (1997) and are included within the scope of the present invention. An exemplary embodiment of a phosphonate ester-forming group is the phenyl carbocycle in substructure A_3 having the formula:



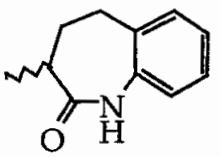
wherein m1 is 1, 2, 3, 4, 5, 6, 7 or 8, and the phenyl carbocycle is substituted with 0 to 3 R_2 groups. Also, in this embodiment, where Y_1 is O, a lactate ester is formed. Alternatively, where Y_1 is $N(R_2)$, $N(OR_2)$ or $N(N(R_2)_2$, then phosphonamidate esters result. R_1 may be H or C_1–C_{12} alkyl. The corollary exemplary substructure A^3 is included in the invention with Y^1, R^1 and R^2 substituents.

In its ester-forming role, a protecting group typically is bound to any acidic group such as, by way of example and not limitation, a $-CO_2H$ or $-C(S)OH$ group, thereby resulting in $-CO_2R^x$ where R^x is defined herein. Also, R^x for example includes the enumerated ester groups of WO 95/07920.

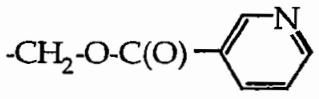
Examples of protecting groups include:

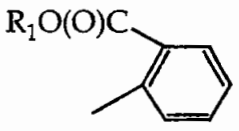
C_3–C_{12} heterocycle (described above) or aryl. These aromatic groups optionally are polycyclic or monocyclic. Examples include phenyl, spiryl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 1-, 2-, 3- and 4-pyridinyl, and 1-, 2-, 4- and 5-pyrimidinyl,

C_3-C_{12} heterocycle or aryl substituted with halo, R^1, R^1-O-C_1-C_{12} alkylene, C_1-C_{12} alkoxy, CN, NO_2, OH, carboxy, carboxyester, thiol, thioester, C_1-C_{12} haloalkyl (1-6 halogen atoms), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl. Such groups include 2-, 3- and 4-alkoxyphenyl (C_1-C_{12} alkyl), 2-, 3- and 4-methoxyphenyl, 2-, 3- and 4-ethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-diethoxyphenyl, 2- and 3-carboethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-5-hydroxyphenyl, 2- and 3-ethoxy-6-hydroxyphenyl, 2-, 3- and 4-O-acetylphenyl, 2-, 3- and 4-dimethylaminophenyl, 2-, 3- and 4-methylmercaptophenyl, 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl and 2-, 3- and 4-chlorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-biscarboxyethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 3,5-difluorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylphenyl), 2-, 3- and 4-cyanophenyl, 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylbenzyl and 2-, 3- and 4-trichloromethylphenyl and 2-, 3- and 4-trichloromethylphenyl), 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 1-ethylpiperazinyl, benzyl, alkylsalicylphenyl (C_1-C_4 alkyl, including 2-, 3- and 4-ethylsalicylphenyl), 2-,3- and 4-acetylphenyl, 1,8-dihydroxynaphthyl (-$C_{10}H_6$-OH) and aryloxy ethyl [C_6-C_9 aryl (including phenoxy ethyl)], 2,2'-dihydroxybiphenyl, 2-, 3- and 4-N,N-dialkylaminophenol, -$C_6H_4CH_2$-N(CH_3)$_2$,



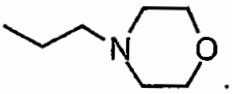
trimethoxybenzyl, triethoxybenzyl, 2-alkyl pyridinyl (C_{1-4} alkyl); ;



; 

; C4 - C8 esters of 2-carboxyphenyl; and C_1-C_4 alkylene-C_3-C_6 aryl (including benzyl, -CH_2-pyrrolyl, -CH_2-thienyl, -CH_2-imidazolyl, -CH_2-oxazolyl, -CH_2-isoxazolyl, -CH_2-thiazolyl, -CH_2-isothiazolyl, -CH_2-pyrazolyl, -CH_2-pyridinyl and -CH_2-pyrimidinyl) substituted in the aryl moiety by 3 to 5 halogen atoms or 1 to 2 atoms or groups selected from halogen, C_1-C_{12} alkoxy (including methoxy and ethoxy), cyano, nitro, OH, C_1-C_{12} haloalkyl (1 to 6 halogen atoms; including -CH_2CCl_3), C_1-C_{12} alkyl (including methyl and ethyl), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl; alkoxy ethyl [C_1-C_6

alkyl including -CH_2-CH_2-O-CH_3 (methoxy ethyl)]; alkyl substituted by any of the groups set forth above for aryl, in particular OH or by 1 to 3 halo atoms (including -CH_3, -$CH(CH_3)_2$, -$C(CH_3)_3$, -CH_2CH_3, -$(CH_2)_2CH_3$, -$(CH_2)_3CH_3$, -$(CH_2)_4CH_3$, -$(CH_2)_5CH_3$,CH_2CH_2F, -CH_2CH_2Cl, -CH_2CF_3, and -CH_2CCl_3);



; -N-2-propylmorpholino, 2,3-dihydro-6-hydroxyindene, sesamol, catechol monoester, -CH_2-C(O)-$N(R^1)_2$, -CH_2-S(O)(R^1), -CH_2-$S(O)_2$(R^1), -CH_2-CH(OC(O)CH_2R^1)-CH_2(OC(O)CH_2R^1), cholesteryl, enolpyruvate (HOOC-C(=CH_2)-), glycerol;

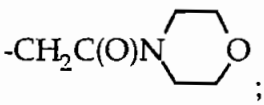
a 5 or 6 carbon monosaccharide, disaccharide or oligosaccharide (3 to 9 monosaccharide residues);

triglycerides such as α-D-β-diglycerides (wherein the fatty acids composing glyceride lipids generally are naturally occurring saturated or unsaturated C_{6-26}, C_{6-18} or C_{6-10} fatty acids such as linoleic, lauric, myristic, palmitic, stearic, oleic, palmitoleic, linolenic and the like fatty acids) linked to acyl of the parental compounds herein through a glyceryl oxygen of the triglyceride;

phospholipids linked to the carboxyl group through the phosphate of the phospholipid;

phthalidyl (shown in Fig. 1 of Clayton et al., *Antimicrob. Agents Chemo.* (1974) 5(6):670-671;

cyclic carbonates such as (5-R_d-2-oxo-1,3-dioxolen-4-yl) methyl esters (Sakamoto et al., *Chem. Pharm. Bull.* (1984) 32(6)2241-2248) where R_d is R_1, R_4 or aryl; and



;

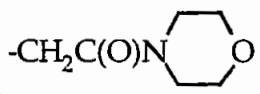
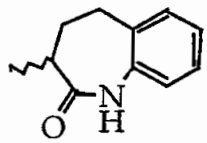
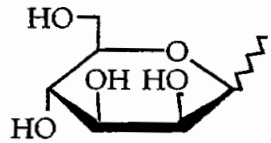
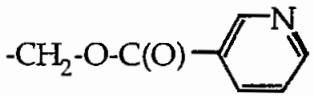
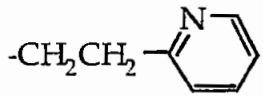
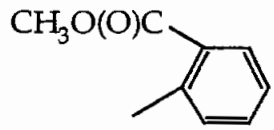
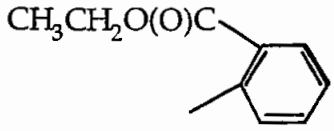
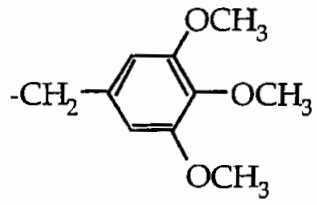
The hydroxyl groups of the compounds of this invention optionally are substituted with one of groups III, IV or V disclosed in WO 94/21604, or with isopropyl.

As further embodiments, Table A lists examples of protecting group ester moieties that for example can be bonded via oxygen to -C(O)O- and -P(O)(O-)$_2$ groups. Several amidates also are shown, which are bound directly to -C(O)- or -$P(O)_2$. Esters of structures 1-5, 8-10 and 16, 17, 19-22 are synthesized by reacting the compound herein having a free hydroxyl with the corresponding halide (chloride or acyl chloride and the like) and N ,N-dicyclohexyl-N-morpholine carboxamidine (or another base such as DBU, triethylamine, $CsCO_3$, N,N-

dimethylaniline and the like) in DMF (or other solvent such as acetonitrile or N-methylpyrrolidone). When the compound to be protected is a phosphonate, the esters of structures 5-7, 11, 12, 21, and 23-26 are synthesized by reaction of the alcohol or alkoxide salt (or the corresponding amines in the case of compounds such as 13, 14 and 15) with the monochlorophosphonate or dichlorophosphonate (or another activated phosphonate).

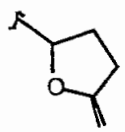
TABLE A

1. $-CH_2-C(O)-N(R_1)_2$ *
2. $-CH_2-S(O)(R_1)$
3. $-CH_2-S(O)_2(R_1)$
4. $-CH_2-O-C(O)-CH_2-C_6H_5$
5. 3-cholesteryl
6. 3-pyridyl
7. N-ethylmorpholino
8. $-CH_2-O-C(O)-C_6H_5$
9. $-CH_2-O-C(O)-CH_2CH_3$
10. $-CH_2-O-C(O)-C(CH_3)_3$
11. $-CH_2-CCl_3$
12. $-C_6H_5$
13. $-NH-CH_2-C(O)O-CH_2CH_3$
14. $-N(CH_3)-CH_2-C(O)O-CH_2CH_3$
15. $-NHR_1$
16. $-CH_2-O-C(O)-C_{10}H_{15}$
17. $-CH_2-O-C(O)-CH(CH_3)_2$
18. $-CH_2-C\#H(OC(O)CH_2R_1)-CH_2-(OC(O)CH_2R_1)$*

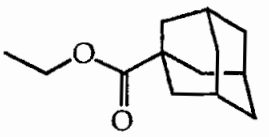
19. 
20. 
21. 
22. 
23. 
24. 
25. 
26. 

- chiral center is (R), (S) or racemate.

Other esters that are suitable for use herein are described in EP 632048.

Protecting groups also includes "double ester" forming profunctionalities such as  $-CH_2OC(O)OCH_3$, $-CH_2SCOCH_3$, $-CH_2OCON(CH_3)_2$, or alkyl- or aryl-acyloxyalkyl groups of the structure $-CH(R^1 \text{ or } W^5)O((CO)R^{37})$ or

-CH(R^1 or W^5)((CO)OR^{38}) (linked to oxygen of the acidic group) wherein R^{37} and R^{38} are alkyl, aryl, or alkylaryl groups (see U.S. Patent No. 4,968,788). Frequently R^{37} and R^{38} are bulky groups such as branched alkyl, ortho-substituted aryl, meta-substituted aryl, or combinations thereof, including normal, secondary, iso- and tertiary alkyls of 1-6 carbon atoms. An example is the pivaloyloxymethyl group. These are of particular use with prodrugs for oral administration. Examples of such useful protecting groups are alkylacyloxymethyl esters and their derivatives, including -

$CH(CH_2CH_2OCH_3)OC(O)C(CH_3)_3$,  ;

$-CH_2OC(O)C_{10}H_{15}$, $-CH_2OC(O)C(CH_3)_3$, $-CH(CH_2OCH_3)OC(O)C(CH_3)_3$, $-CH(CH(CH_3)_2)OC(O)C(CH_3)_3$, $-CH_2OC(O)CH_2CH(CH_3)_2$, $-CH_2OC(O)C_6H_{11}$, $-CH_2OC(O)C_6H_5$, $-CH_2OC(O)C_{10}H_{15}$, $-CH_2OC(O)CH_2CH_3$, $-CH_2OC(O)CH(CH_3)_2$, $-CH_2OC(O)C(CH_3)_3$ and $-CH_2OC(O)CH_2C_6H_5$.

For prodrug purposes, the ester typically chosen is one heretofore used for antibiotic drugs, in particular the cyclic carbonates, double esters, or the phthalidyl, aryl or alkyl esters.

In some embodiments the protected acidic group is an ester of the acidic group and is the residue of a hydroxyl-containing functionality. In other embodiments, an amino compound is used to protect the acid functionality. The residues of suitable hydroxyl or amino-containing functionalities are set forth above or are found in WO 95/07920. Of particular interest are the residues of amino acids, amino acid esters, polypeptides, or aryl alcohols. Typical amino acid, polypeptide and carboxyl-esterified amino acid residues are described on pages 11-18 and related text of WO 95/07920 as groups L1 or L2. WO 95/07920 expressly teaches the amidates of phosphonic acids, but it will be understood that such amidates are formed with any of the acid groups set forth herein and the amino acid residues set forth in WO 95/07920.

Typical esters for protecting acidic functionalities are also described in WO 95/07920, again understanding that the same esters can be formed with the acidic groups herein as with the phosphonate of the '920 publication. Typical ester groups are defined at least on WO 95/07920 pages 89-93 (under R^{31} or R^{35}), the table on page 105, and pages 21-23 (as R). Of particular interest are esters of unsubstituted aryl such as phenyl or arylalkyl such benzyl, or hydroxy-, halo-, alkoxy-, carboxy- and/or alkylestercarboxy-substituted aryl or alkylaryl,

especially phenyl, ortho-ethoxyphenyl, or C_1-C_4 alkylestercarboxyphenyl (salicylate C_1-C_{12} alkylesters).

The protected acidic groups, particularly when using the esters or amides of WO 95/07920, are useful as prodrugs for oral administration. However, it is not essential that the acidic group be protected in order for the compounds of this invention to be effectively administered by the oral route. When the compounds of the invention having protected groups, in particular amino acid amidates or substituted and unsubstituted aryl esters are administered systemically or orally they are capable of hydrolytic cleavage *in vivo* to yield the free acid.

One or more of the acidic hydroxyls are protected. If more than one acidic hydroxyl is protected then the same or a different protecting group is employed, e.g., the esters may be different or the same, or a mixed amidate and ester may be used.

Typical hydroxy protecting groups described in Greene (pages 14-118) include substituted methyl and alkyl ethers, substituted benzyl ethers, silyl ethers, esters including sulfonic acid esters, and carbonates. For example:

- Ethers (methyl, *t*-butyl, allyl);
- Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, *t*-Butylthiomethyl, (Phenyldimethylsilyl)methoxymethyl, Benzyloxymethyl, *p*-Methoxybenzyloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, *t*-Butoxymethyl, 4-Pentenyloxymethyl, Siloxymethyl, 2-Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyranyl, 3-Bromotetrahydropyranyl, Tetrahydropthiopyranyl, 1-Methoxycyclohexyl, 4-Methoxytetrahydropyranyl, 4-Methoxytetrahydrothiopyranyl, 4-Methoxytetrahydropthiopyranyl *S,S*-Dioxido, 1-[(2-Chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-Dioxan-2-yl, Tetrahydrofuranyl, Tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl));
- Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxyethyl, 1-Methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilylethyl, 2-(Phenylselenyl)ethyl,
- *p*-Chlorophenyl, *p*-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl);
- Substituted Benzyl Ethers (*p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *p*-Halobenzyl, 2,6-Dichlorobenzyl, *p*-Cyanobenzyl, *p*-Phenylbenzyl, 2- and

4-Picolyl, 3-Methyl-2-picolyl *N*-Oxido, Diphenylmethyl, *p,p'*-Dinitrobenzhydryl, 5-Dibenzosuberyl, Triphenylmethyl, α-Naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, Di(*p*-methoxyphenyl)phenylmethyl, Tri(*p*-methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenyldiphenylmethyl, 4,4',4"-Tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-Tris(levulinoyloxyphenyl)methyl, 4,4',4"-Tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4',4"-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzisothiazolyl *S,S*-Dioxido);

- Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, Dimethylisopropylsilyl, Diethylisopropylsilyl, Dimethylthexylsilyl, *t*-Butyldimethylsilyl, *t*-Butyldiphenylsilyl, Tribenzylsilyl, Tri-*p*-xylylsilyl, Triphenylsilyl, Diphenylmethylsilyl, *t*-Butylmethoxyphenylsilyl);
- Esters (Formate, Benzoylformate, Acetate, Choroacetate, Dichloroacetate, Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, *p*-Chlorophenoxyacetate, *p*-poly-Phenylacetate, 3-Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, *p*-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate));
- Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, *p*-Nitrophenyl, Benzyl, *p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *S*-Benzyl Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate);
- Groups With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Nitro-4-methylpentanoate, *o*-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl Carbonate, 4-(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate); Miscellaneous Esters (2,6-Dichloro-4-methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3 tetramethylbutyl)phenoxyacetate, 2,4-Bis(1,1-dimethylpropyl)phenoxyacetate, Chlorodiphenylacetate, Isobutyrate, Monosuccinate, (*E*)-2-Methyl-2-butenoate (Tigloate), *o*-(Methoxycarbonyl)benzoate, *p*-poly-Benzoate, α-Naphthoate, Nitrate, Alkyl *N,N,N',N'*-Tetramethylphosphorodiamidate,

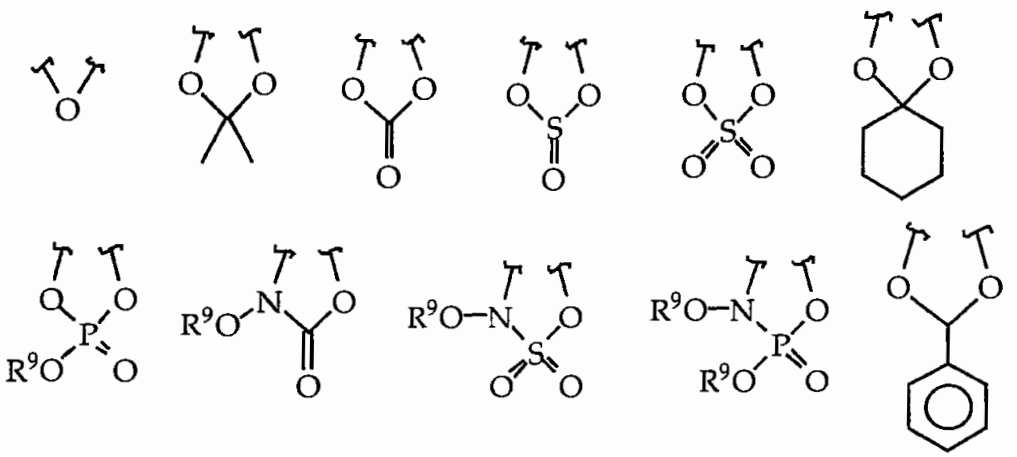
N-Phenylcarbamate, Borate, Dimethylphosphinothioyl, 2,4-Dinitrophenylsulfenate); and

- Sulfonates (Sulfate, Methanesulfonate (Mesylate), Benzylsulfonate, Tosylate).

Typical 1,2-diol protecting groups (thus, generally where two OH groups are taken together with the protecting functionality) are described in Greene at pages 118-142 and include Cyclic Acetals and Ketals (Methylene, Ethylidene, 1-*t*-Butylethylidene, 1-Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-Trichloroethylidene, Acetonide (Isopropylidene), Cyclopentylidene, Cyclohexylidene, Cycloheptylidene, Benzylidene, *p*-Methoxybenzylidene, 2,4-Dimethoxybenzylidene, 3,4-Dimethoxybenzylidene, 2-Nitrobenzylidene); Cyclic Ortho Esters (Methoxymethylene, Ethoxymethylene, Dimethoxymethylene, 1-Methoxyethylidene, 1-Ethoxyethylidine, 1,2-Dimethoxyethylidene, α-Methoxybenzylidene, 1-(*N,N*-Dimethylamino)ethylidene Derivative, α -(*N,N*-Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); Silyl Derivatives (Di-*t*-butylsilylene Group, 1,3-(1,1,3,3-Tetraisopropyldisiloxanylidene), and Tetra-*t*-butoxydisiloxane-1,3-diylidene), Cyclic Carbonates, Cyclic Boronates, Ethyl Boronate and Phenyl Boronate.

More typically, 1,2-diol protecting groups include those shown in Table B, still more typically, epoxides, acetonides, cyclic ketals and aryl acetals.

Table B



wherein R^9 is C_1-C_6 alkyl.

Amino protecting groups

Another set of protecting groups include any of the typical amino protecting groups described by Greene at pages 315-385. They include:

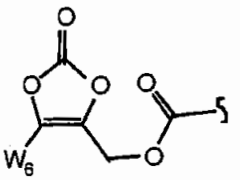
- Carbamates: (methyl and ethyl, 9-fluorenylmethyl, 9(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 4-methoxyphenacyl);
- Substituted Ethyl: (2,2,2-trichoroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'- and 4'-pyridyl)ethyl, 2-(*N,N*-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl);
- Groups With Assisted Cleavage: (2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-choro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl);
- Groups Capable of Photolytic Cleavage: (*m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl(*o*-nitrophenyl)methyl); Urea-Type Derivatives (phenothiazinyl-(10)-carbonyl, *N'*-*p*-toluenesulfonylaminocarbonyl, *N'*-phenylaminothiocarbonyl);
- Miscellaneous Carbamates: (*t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, *p*-(*p'*-Methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-trimethylbenzyl);
- Amides: (*N*-formyl, *N*-acetyl, *N*-choroacetyl, *N*-trichoroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridylcarboxamide, *N*-

benzoylphenylalanyl, *N*-benzoyl, *N*-*p*-phenylbenzoyl);

- Amides With Assisted Cleavage: (*N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N'*-dithiobenzyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxyphenyl)propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, 4,5-diphenyl-3-oxazolin-2-one);
- Cyclic Imide Derivatives: (*N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenylmaleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3-5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridonyl);
- *N*-Alkyl and *N*-Aryl Amines: (*N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, *N*-2-picolylamine *N'*-oxide);
- Imine Derivatives: (*N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*,(*N'*,*N'*-dimethylaminomethylene, *N*,*N'*-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, *N*-cyclohexylidene);
- Enamine Derivatives: (*N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl));
- *N*-Metal Derivatives (*N*-borane derivatives, *N*-diphenylborinic acid derivatives, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, *N*-copper or *N*-zinc chelate);
- N-N Derivatives: (*N*-nitro, *N*-nitroso, *N*-oxide);
- N-P Derivatives: (*N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, *N*-diphenyl phosphoryl);
- N-Si Derivatives, N-S Derivatives, and N-Sulfenyl Derivatives: (*N*-benzenesulfenyl, *N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl, *N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxybenzenesulfenyl, *N*-triphenylmethylsulfenyl, *N*-3-nitropyridinesulfenyl); and *N*-sulfonyl Derivatives (*N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-

4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxybenzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6,-tetramethyl-4-methoxybenzenesulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy-4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*-β-trimethylsilyethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, *N*-phenacylsulfonyl).

Protected amino groups include carbamates, amides and amidines, e.g. $-NHC(O)OR^1$, $-NHC(O)R^1$ or $-N=CR^1N(R^1)_2$. Another protecting group, also useful as a prodrug for amino or $-NH(R^5)$, is:



See for example Alexander, J. et al (1996) *J. Med. Chem.* 39:480-486.

Amino acid and polypeptide protecting group and conjugates

An amino acid or polypeptide protecting group of a compound of the invention has the structure $R^{15}NHCH(R^{16})C(O)-$, where R^{15} is H, an amino acid or polypeptide residue, or R^5, and R^{16} is defined below.

R^{16} is lower alkyl or lower alkyl (C_1-C_6) substituted with amino, carboxyl, amide, carboxyl ester, hydroxyl, C_6-C_7 aryl, guanidinyl, imidazolyl, indolyl, sulfhydryl, sulfoxide, and/or alkylphosphate. R^{16} also is taken together with the amino acid α-N to form a proline residue (R^{16} = $-CH_2)_3-$). However, R^{16} is generally the side group of a naturally-occurring amino acid such as H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2-CH(CH_3)_2$, $-CHCH_3-CH_2-CH_3$, $-CH_2-C_6H_5$, $-CH_2CH_2-S-CH_3$, $-CH_2OH$, $-CH(OH)-CH_3$, $-CH_2-SH$, $-CH_2-C_6H_4OH$, $-CH_2-CO-NH_2$, $-CH_2-CH_2-CO-NH_2$, $-CH_2-COOH$, $-CH_2-CH_2-COOH$, $-(CH_2)_4-NH_2$ and $-(CH_2)_3-NH-C(NH_2)-NH_2$. R^{16} also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl.

Another set of protecting groups include the residue of an amino-containing compound, in particular an amino acid, a polypeptide, a protecting group, $-NHSO_2R$,

NHC(O)R, -N(R)$_2$, NH_2 or -NH(R)(H), whereby for example a carboxylic acid is reacted, i.e. coupled, with the amine to form an amide, as in C(O)NR_2. A phosphonic acid may be reacted with the amine to form a phosphonamidate, as in -P(O)(OR)(NR_2).

Amino acids have the structure $R^{17}C(O)CH(R^{16})NH$-, where R^{17} is -OH, -OR, an amino acid or a polypeptide residue. Amino acids are low molecular weight compounds, on the order of less than about 1000 MW and which contain at least one amino or imino group and at least one carboxyl group. Generally the amino acids will be found in nature, i.e., can be detected in biological material such as bacteria or other microbes, plants, animals or man. Suitable amino acids typically are alpha amino acids, i.e. compounds characterized by one amino or imino nitrogen atom separated from the carbon atom of one carboxyl group by a single substituted or unsubstituted alpha carbon atom. Of particular interest are hydrophobic residues such as mono-or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues contribute to cell permeability by increasing the partition coefficient of the parental drug. Typically, the residue does not contain a sulfhydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof. Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline. Additionally, unnatural amino acids, for example, valanine, phenylglycine and homoarginine are also included. Commonly encountered amino acids that are not gene-encoded may also be used in the present invention. All of the amino acids used in the present invention may be either the D- or L- optical isomer. In addition, other peptidomimetics are also useful in the present invention. For a general review, see Spatola, A. F., in *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, B. Weinstein, eds., Marcel Dekker, New York, p. 267 (1983).

When protecting groups are single amino acid residues or polypeptides they optionally are substituted at R^3 of substituents A^1, A^2 or A^3 in Formula I, or substituted at R_3 of substituents A_1, A_2 or A_3 in Formula II. These conjugates are generally produced by forming an amide bond between a carboxyl group of the amino acid (or C-terminal amino acid of a polypeptide for example). Alternatively, conjugates are formed between R^3

(Formula I) or R_3 (Formula II) and an amino group of an amino acid or polypeptide. Generally, only one of any site in the scaffold drug-like compound is amidated with an amino acid as described herein, although it is within the scope of this invention to introduce amino acids at more than one permitted site. Usually, a carboxyl group of R^3 is amidated with an amino acid. In general, the α-amino or α-carboxyl group of the amino acid or the terminal amino or carboxyl group of a polypeptide are bonded to the scaffold, parental functionalities. Carboxyl or amino groups in the amino acid side chains generally may be used to form the amide bonds with the parental compound or these groups may need to be protected during synthesis of the conjugates as described further below.

With respect to the carboxyl-containing side chains of amino acids or polypeptides it will be understood that the carboxyl group optionally will be blocked, e.g. by R^1, esterified with R^5 or amidated. Similarly, the amino side chains R^{16} optionally will be blocked with R^1 or substituted with R^5.

Such ester or amide bonds with side chain amino or carboxyl groups, like the esters or amides with the parental molecule, optionally are hydrolyzable *in vivo* or *in vitro* under acidic (pH <3) or basic (pH >10) conditions. Alternatively, they are substantially stable in the gastrointestinal tract of humans but are hydrolyzed enzymatically in blood or in intracellular environments. The esters or amino acid or polypeptide amidates also are useful as intermediates for the preparation of the parental molecule containing free amino or carboxyl groups. The free acid or base of the parental compound, for example, is readily formed from the esters or amino acid or polypeptide conjugates of this invention by conventional hydrolysis procedures.

When an amino acid residue contains one or more chiral centers, any of the D, L, meso, threo or erythro (as appropriate) racemates, scalemates or mixtures thereof may be used. In general, if the intermediates are to be hydrolyzed non-enzymatically (as would be the case where the amides are used as chemical intermediates for the free acids or free amines), D isomers are useful. On the other hand, L isomers are more versatile since they can be susceptible to both non-enzymatic and enzymatic hydrolysis, and are more efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acids whose residues are represented by R^x or R^y include the following:

Glycine;

Aminopolycarboxylic acids, e.g., aspartic acid, β-hydroxyaspartic acid, glutamic acid, β -hydroxyglutamic acid, β-methylaspartic acid, β-methylglutamic acid, β, β-dimethylaspartic acid, γ-hydroxyglutamic acid, β, γ-dihydroxyglutamic acid, β -phenylglutamic acid, γ-methyleneglutamic acid, 3-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid;

Amino acid amides such as glutamine and asparagine;

Polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β -aminoalanine, γ -aminobutyrine, ornithine, citruline, homoarginine, homocitrulline, hydroxylysine, allohydroxylsine and diaminobutyric acid;

Other basic amino acid residues such as histidine;

Diaminodicarboxylic acids such as α, α'-diaminosuccinic acid, α, α'-diaminoglutaric acid, α, α'-diaminoadipic acid, α, α'-diaminopimelic acid, α, α'-diamino- β-hydroxypimelic acid, α, α'-diaminosuberic acid, α, α'-diaminoazelaic acid, and α, α'-diaminosebacic acid;

Imino acids such as proline, hydroxyproline, allohydroxyproline, γ-methylproline, pipecolic acid, 5-hydroxypipecolic acid, and azetidine-2-carboxylic acid;

A mono- or di-alkyl (typically C_1-C_8 branched or normal) amino acid such as alanine, valine, leucine, allylglycine, butyrine, norvaline, norleucine, heptyline, α-methylserine, α-amino-α-methyl-γ-hydroxyvaleric acid, α-amino- α-methyl-δ-hydroxyvaleric acid, α-amino-α-methyl-ε-hydroxycaproic acid, isovaline, α-methylglutamic acid, α-aminoisobutyric acid, α-aminodiethylacetic acid, α-aminodiisopropylacetic acid, α-aminodi-n-propylacetic acid, α-aminodiisobutylacetic acid, α-aminodi-n-butylacetic acid, α-aminoethylisopropylacetic acid, α-amino-n-propylacetic acid, α-aminodiisoamyacetic acid, α-methylaspartic acid, α-methylglutamic acid, 1-aminocyclopropane-1-carboxylic acid, isoleucine, alloisoleucine, *tert*-leucine, β-methyltryptophan and α-amino- β-ethyl-β-phenylpropionic acid;

β-phenylserinyl;

Aliphatic α-amino-β-hydroxy acids such as serine, β-hydroxyleucine, β-hydroxynorleucine, β -hydroxynorvaline, and α-amino-β-hydroxystearic acid;

α-Amino, α-, γ-, δ- or ε-hydroxy acids such as homoserine, δ -hydroxynorvaline, γ-hydroxynorvaline and ε-hydroxynorleucine residues; canavine and canaline; γ -hydroxyornithine;

2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid;

α-Amino-β-thiols such as penicillamine, β-thiolnorvaline or β-thiolbutyrine;

Other sulfur containing amino acid residues including cysteine; homocystine, β-phenylmethionine, methionine, S-allyl-L-cysteine sulfoxide, 2-thiolhistidine, cystathionine, and thiol ethers of cysteine or homocysteine;

Phenylalanine, tryptophan and ring-substituted α-amino acids such as the phenyl- or cyclohexylamino acids α-aminophenylacetic acid, α-aminocyclohexylacetic acid and α-amino-β-cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl, lower alkyl, hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (e.g., tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dichloro, *o*-, *m*- or *p*-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitro-phenylalanine); furyl-, thienyl-, pyridyl-, pyrimidinyl-, purinyl- or naphthyl-alanines; and tryptophan analogues and derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan;

α-Amino substituted amino acids including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-benzylvaline; and

α-Hydroxy and substituted α -hydroxy amino acids including serine, threonine, allothreonine, phosphoserine and phosphothreonine.

Polypeptides are polymers of amino acids in which a carboxyl group of one amino acid monomer is bonded to an amino or imino group of the next amino acid monomer by an amide bond. Polypeptides include dipeptides, low molecular weight polypeptides (about 1500-5000 MW) and proteins. Proteins optionally contain 3, 5, 10, 50, 75, 100 or more residues, and suitably are substantially sequence-homologous with human, animal, plant or microbial proteins. They include enzymes (e.g., hydrogen peroxidase) as well as immunogens such as KLH, or antibodies or proteins of any type against which one wishes to raise an immune response. The nature and identity of the polypeptide may vary widely.

The polypeptide amidates are useful as immunogens in raising antibodies against either the polypeptide (if it is not immunogenic in the animal to which it is administered) or against the epitopes on the remainder of the compound of this invention.

Antibodies capable of binding to the parental non-peptidyl compound are used to separate the parental compound from mixtures, for example in diagnosis or manufacturing of the parental compound. The conjugates of parental compound and polypeptide generally are more immunogenic than the polypeptides in closely homologous animals, and therefore make

the polypeptide more immunogenic for facilitating raising antibodies against it. Accordingly, the polypeptide or protein may be immunogenic in an animal typically used to raise antibodies, e.g., rabbit, mouse, horse, or rat. The polypeptide optionally contains a peptidolytic enzyme cleavage site at the peptide bond between the first and second residues adjacent to the acidic heteroatom. Such cleavage sites are flanked by enzymatic recognition structures, e.g. a particular sequence of residues recognized by a peptidolytic enzyme.

Peptidolytic enzymes for cleaving the polypeptide conjugates of this invention are well known, and in particular include carboxypeptidases, which digest polypeptides by removing C-terminal residues, and are specific in many instances for particular C-terminal sequences. Such enzymes and their substrate requirements in general are well known. For example, a dipeptide (having a given pair of residues and a free carboxyl terminus) is covalently bonded through its α-amino group to the phosphorus or carbon atoms of the compounds herein. In certain embodiments, a phosphonate group substituted with an amino acid or peptide will be cleaved by the appropriate peptidolytic enzyme, leaving the carboxyl of the proximal amino acid residue to autocatalytically cleave the phosphonoamidate bond.

Suitable dipeptidyl groups (designated by their single letter code) are AA, AR, AN, AD, AC, AE, AQ, AG, AH, AI, AL, AK, AM, AF, AP, AS, AT, AW, AY, AV, RA, RR, RN, RD, RC, RE, RQ, RG, RH, RI, RL, RK, RM, RF, RP, RS, RT, RW, RY, RV, NA, NR, NN, ND, NC, NE, NQ, NG, NH, NI, NL, NK, NM, NF, NP, NS, NT, NW, NY, NV, DA, DR, DN, DD, DC, DE, DQ, DG, DH, DI, DL, DK, DM, DF, DP, DS, DT, DW, DY, DV, CA, CR, CN, CD, CC, CE, CQ, CG, CH, CI, CL, CK, CM, CF, CP, CS, CT, CW, CY, CV, EA, ER, EN, ED, EC, EE, EQ, EG, EH, EI, EL, EK, EM, EF, EP, ES, ET, EW, EY, EV, QA, QR, QN, QD, QC, QE, QQ, QG, QH, QI, QL, QK, QM, QF, QP, QS, QT, QW, QY, QV, GA, GR, GN, GD, GC, GE, GQ, GG, GH, GI, GL, GK, GM, GF, GP, GS, GT, GW, GY, GV, HA, HR, HN, HD, HC, HE, HQ, HG, HH, HI, HL, HK, HM, HF, HP, HS, HT, HW, HY, HV, IA, IR, IN, ID, IC, IE, IQ, IG, IH, II, IL, IK, IM, IF, IP, IS, IT, IW, IY, IV, LA, LR, LN, LD, LC, LE, LQ, LG, LH, LI, LL, LK, LM, LF, LP, LS, LT, LW, LY, LV, KA, KR, KN, KD, KC, KE, KQ, KG, KH, KI, KL, KK, KM, KF, KP, KS, KT, KW, KY, KV, MA, MR, MN, MD, MC, ME, MQ, MG, MH, MI, ML, MK, MM, MF, MP, MS, MT, MW, MY, MV, FA, FR, FN, FD, FC, FE, FQ, FG, FH, FI, FL, FK, FM, FF, FP, FS, FT, FW, FY, FV, PA, PR, PN, PD, PC, PE, PQ, PG, PH, PI, PL, PK, PM, PF, PP, PS, PT, PW, PY, PV, SA, SR, SN, SD, SC, SE, SQ, SG, SH, SI, SL, SK, SM, SF, SP, SS, ST, SW, SY, SV, TA, TR, TN,

TD, TC, TE, TQ, TG, TH, TI, TL, TK, TM, TF, TP, TS, TT, TW, TY, TV, WA, WR, WN, WD, WC, WE, WQ, WG, WH, WI, WL, WK, WM, WF, WP, WS, WT, WW, WY, WV, YA, YR, YN, YD, YC, YE, YQ, YG, YH, YI, YL, YK, YM, YF, YP, YS, YT, YW, YY, YV, VA, VR, VN, VD, VC, VE, VQ, VG, VH, VI, VL, VK, VM, VF, VP, VS, VT, VW, VY and VV.

Tripeptide residues are also useful as protecting groups. When a phosphonate is to be protected, the sequence -X^4-pro-X^5- (where X^4 is any amino acid residue and X^5 is an amino acid residue, a carboxyl ester of proline, or hydrogen) will be cleaved by luminal carboxypeptidase to yield X^4 with a free carboxyl, which in turn is expected to autocatalytically cleave the phosphonoamidate bond. The carboxy group of X^5 optionally is esterified with benzyl.

Dipeptide or tripeptide species can be selected on the basis of known transport properties and/or susceptibility to peptidases that can affect transport to intestinal mucosal or other cell types. Dipeptides and tripeptides lacking an α-amino group are transport substrates for the peptide transporter found in brush border membrane of intestinal mucosal cells (Bai, J.P.F., (1992) *Pharm Res.* 9:969-978. Transport competent peptides can thus be used to enhance bioavailability of the amidate compounds. Di- or tripeptides having one or more amino acids in the D configuration may be compatible with peptide transport. Amino acids in the D configuration can be used to reduce the susceptibility of a di- or tripeptide to hydrolysis by proteases common to the brush border such as aminopeptidase N. In addition, di- or tripeptides alternatively are selected on the basis of their relative resistance to hydrolysis by proteases found in the lumen of the intestine. For example, tripeptides or polypeptides lacking asp and/or glu are poor substrates for aminopeptidase A, di- or tripeptides lacking amino acid residues on the N-terminal side of hydrophobic amino acids (leu, tyr, phe, val, trp) are poor substrates for endopeptidase, and peptides lacking a pro residue at the penultimate position at a free carboxyl terminus are poor substrates for carboxypeptidase P. Similar considerations can also be applied to the selection of peptides that are either relatively resistant or relatively susceptible to hydrolysis by cytosolic, renal, hepatic, serum or other peptidases. Such poorly cleaved polypeptide amidates are immunogens or are useful for bonding to proteins in order to prepare immunogens.

Phosphonate analogs of known experimental or approved Protease Inhibitor Drugs

The known experimental or approved protease inhibitor drugs which can be derivatized in accord with the present invention must contain at least one functional group capable of linking, i.e. bonding to the phosphorus atom in the phosphonate moiety. The phosphonate derivatives of Formulas I-VIII may cleave *in vivo* in stages after they have reached the desired site of action, i.e. inside a cell. One mechanism of action inside a cell may entail a first cleavage, e.g. by esterase, to provide a negatively-charged "locked-in" intermediate. Cleavage of a terminal ester grouping in Formulas I-VIII thus affords an unstable intermediate which releases a negatively charged "locked in" intermediate.

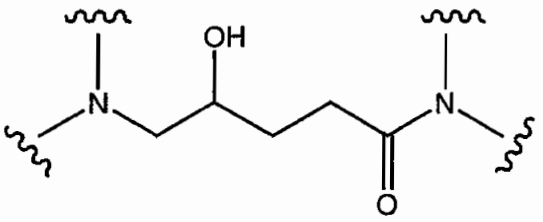
After passage inside a cell, intracellular enzymatic cleavage or modification of the phosphonate prodrug compound may result in an intracellular accumulation of the cleaved or modified compound by a "trapping" mechanism. The cleaved or modified compound may then be "locked-in" the cell, i.e. accumulate in the cell by a significant change in charge, polarity, or other physical property change which decreases the rate at which the cleaved or modified compound can exit the cell, relative to the rate at which it entered as the phosphonate prodrug. Other mechanisms by which a therapeutic effect is achieved may be operative as well. Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases.

In selected instances in which the drug is of the nucleoside type, such as is the case of zidovudine and numerous other antiretroviral agents, it is known that the drug is activated *in vivo* by phosphorylation. Such activation may occur in the present system by enzymatic conversion of the "locked-in" intermediate with phosphokinase to the active phosphonate diphosphate and/or by phosphorylation of the drug itself after its release from the "locked-in" intermediate as described above. In either case, the original nucleoside-type drug will be converted, via the derivatives of this invention, to the active phosphorylated species.

From the foregoing, it will be apparent that many structurally different known approved and experimental HIV protease inhibitor drugs can be derivatized in accord with the present invention. Numerous such drugs are specifically mentioned herein. However, it should be understood that the discussion of drug families and their specific members for derivatization according to this invention is not intended to be exhaustive, but merely illustrative.

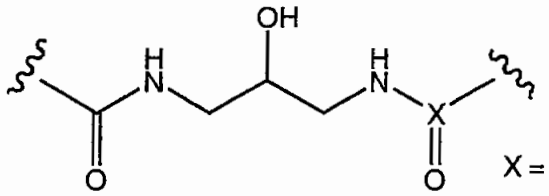
As another example, when the selected drug contains multiple reactive hydroxyl functions, a mixture of intermediates and final products may again be obtained. In the unusual case in which all hydroxy groups are approximately equally reactive, there is not expected to be a single, predominant product, as each mono-substituted product will be obtained in approximate by equal amounts, while a lesser amount of multiply-substituted product will also result. Generally speaking, however, one of the hydroxyl groups will be more susceptible to substitution than the other(s), e.g. a primary hydroxyl will be more reactive than a secondary hydroxyl, an unhindered hydroxyl will be more reactive than a hindered one. Consequently, the major product will be a mono-substituted one in which the most reactive hydroxyl has been derivatized while other mono-substituted and multiply-substituted products may be obtained as minor products.

Formula I compounds having a 3-hydroxy-5-amino-pentamide core include Indinavir-like phosphonate protease inhibitors (ILPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 3-hydroxy-5-amino-pentamide core which have been identified as CGP-49689, CGP-53437, CGP-57813 (Novartis); L-689502, L-693549, L-748496, L-754394, MK-944a, Iddb63, Iddb88 (Merck); Lasinavir (Bristol-Myers Squibb); U-81749 (PNU/Pfizer); SB-203386, SKF-108922 (SmithKline Beecham).



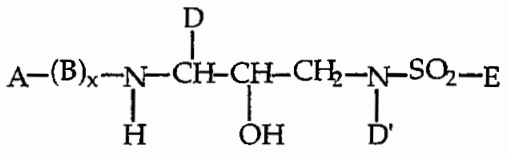
I

Formula II compounds having a 2-hydroxy-1, 3-amino-propylamide or 2-hydroxy-1,3-amino-propylaminosulfone core include Amprenavir-like phosphonate protease inhibitors (AMLPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 2-hydroxy-3-amido-propylamide or 2-hydroxy-3-amido-propylaminosulfone core which have been identified as Droxinavir, Telinavir, Iddb51 (Searle); Ph4556 (WO 95/29922; Ph5145 (WO 96/31527; DPC-681, DPC-684 (DuPont); VB-11328 (Vertex); TMC-114 (Tibotech/Johnson & Johnson). Formula II compounds also include phosphonate analogs of fosamprenavir where the 2-hydroxy is phosphorylated, i.e. having a or 2-phosphate-1,3-amino-propylaminosulfone core (US Patent No. 6,436,989).



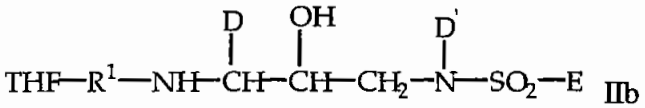
II

The embodiments of the invention also include the following phosphonate analogs of Formula II, represented as Formulas IIa-Ig:



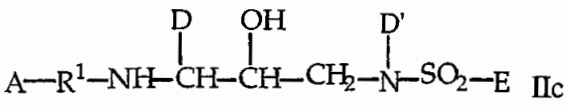
IIa

described as "(I)" in: WO 94/05639 (published 17 March 1994) at page 4, line 15, to page 6, line 27, page 15, line 21, to page 17, line 33, and Claim 1; US Patent No. 5,585,397 (issued 17 December 1996) at col. 2, line 45, to col. 3, line 53, and col. 8, line 1, to col. 9, line 12; US Patent No. 5,783, 701 (issued 21 July 1998) at col. 2, line 43, to col. 3, line 64, col. 8, line 13, to col. 9, line 33, and Claim 1; US Patent No. 5,856,353 (issued 5 January 1999) at col. 2, line 45, to col. 3, line 65, col. 8, line 14, to col. 9, line 37, and Claim 1; US Patent No. 5,977,137 (issued 2 November 1999) at col. 2, line 43, to col. 3, line 65, col. 8, line 15, to col. 9, line 38, and Claim 1; and US Patent No. 6,004,957 (issued 21 December 1999) at col. 2, line 47, to col. 4, line 3, col. 8, line 18, to col. 9, line 41, and Claim 1 therein.



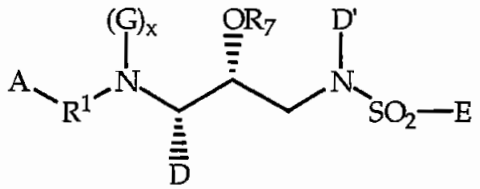
IIb

described as "(I)" in: WO 96/33184 (published 24 October 1996) at page 4, line 19, to page 6, line 5, page 17, line 11, to page 19, line 31, and Claim 1; and US Patent No. 5,723,490 (issued 3 March 1998) at col. 2, line 49, to col. 3, line 39, col. 8, line 66, to col. 10, line 36, and Claim 1.



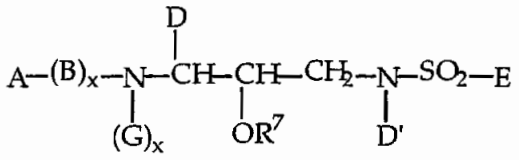
IIc

described as "(I)" in: WO 96/33187 (published 24 October 1996) at page 4, line 23, to page 6, line 18, page 18, line 8, to page 21, line 18, and Claims 1 and 6; US Patent No. 5,691,372 (issued 25 November 1997) at col. 2, line 43, to col. 3, line 47, col. 9, line 21, to col. 11, line 5, and Claims 1 and 5; and US Patent No. 5,990,155 (issued 23 November 1999) at col. 2, line 46, to col. 3, line 55, col. 9, line 25, to col. 11, line 13, and Claims 1 and 3.



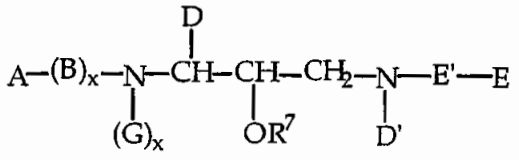
IId

described as "(I)" in: WO 99/33793 (published 8 July 1999) at page 4, line 1, to page 7, line 29, page 17, line 1, to page 20, line 33, and Claim 1.



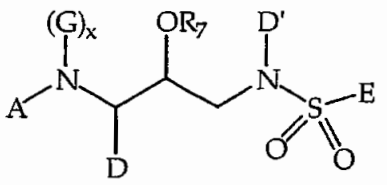
IIe

described as "(I)" in: WO 99/33815 (published 8 July 1999) at page 4, line 1, to page 7, line 19, page 12, line 18, to page 16, line 7, and Claim 1; and WO 99/65870 (published 23 December 1999) at page 4, line 7, to page 8, line 4, page 12, line 7, to page 16, line 4, and Claim 1.



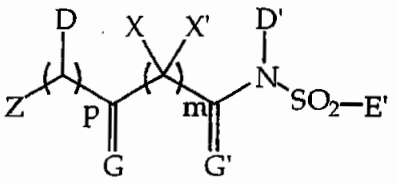
IIf

described as "(I)" in: WO 00/47551 (published 17 August 2000) at page 4, line 10, to page 8, line 29, page 13, line 14, to page 17, line 32, and Claim 1.



IIg

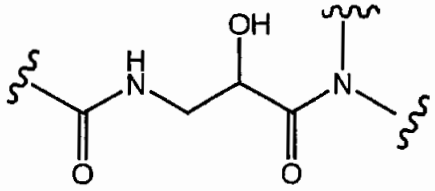
described as "(I)" in: WO 00/76961 (published 21 December 2000) at page 5, line 1, to page 10, line 24, page 14, line 28, to page 20, line 21, and Claim 1.



IIh

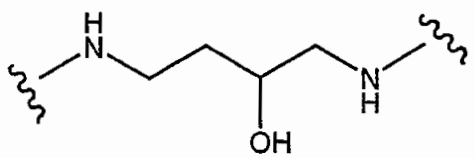
described as "(I)" in: WO 99/33792 (published 8 July 1999) at page 4, line 5, to page 7, line 35, page 17, line 10, to page 21, line 6, and Claim 1; WO 95/24385 (published 14 September 1995) at page 4, line 24, to page 7, line 14, page 16, line 20, to page 19, line 8, and Claims 1 and 29; and US Patent No. 6,127,372 (issued 3 October 2000) at col. 2, line 58, to col. 4, line 28, col. 8, line 66, to col. 10, line 37, and Claim 1.

Formula III compounds having a 2-hydroxy-3-amino-propylamide core include KNI-like phosphonate protease inhibitors (KNILPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 2-hydroxy-3-amido-propylamide or 2-hydroxy-3-amido-propylaminosulfone core which have been identified as KNI-764 (JE-2147, AG1776); KNI-102, KNI-227, KNI-241, KNI-272, KNI-413, KNI-549, KNI-577, KNI-727, JE-2178 (Japan Energy); Ph3939 (EP 587311); R-87366, Iddb134 (Sankyo); VLE-776 (Scripps Institute).



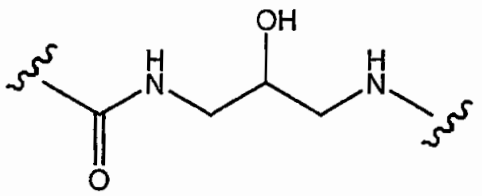
III

Formula IV compounds having a 2-hydroxy-4-amino-butylamine core include Ritonavir-like phosphonate protease inhibitors (RLPPI) and Lopinavir-like phosphonate protease inhibitors (LLPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 2-hydroxy-4-amino-butylamine core which have been identified as A-76928, A-80735, A-80987 (Abbott Laboratories).



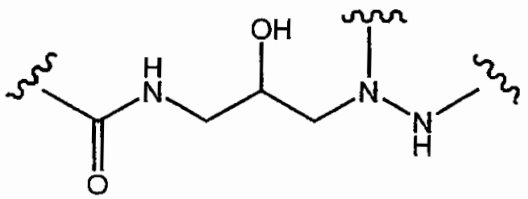
IV

Formula V compounds having an acylated 1,3-diaminopropane core include Saquinavir-like phosphonate protease inhibitors (SLPPI) and Nelfinavir-like phosphonate protease inhibitors (NLPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with an acylated 1,3-diaminopropane core which have been identified as Ro-33-2910, Ro-33-4649 (Hofman La Roche); BMS-182193, BMS-186318, BMS-187071 (Bristol-Myers Squibb); JG-365 (Univ. of Wisconsin); L-704325, L-738872, L-739594, L-743770 (Merck & Co.); LB-71206 (LG Chemical Ltd.); LY-296242, LY-314163, LY-316683, LY-326620 (Eli Lilly Co.), Palinavir (BioMega/BI); Ph5640, Ph6090 (WO 97/21100).



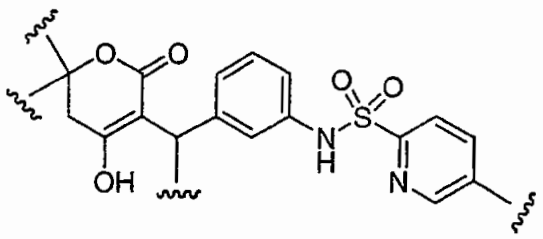
V

Formula VI compounds having a 2-hydroxy-3-diaza-propylamide core include Atazanavir-like phosphonate protease inhibitors (ATLPPI). Compounds of the invention include phosphonate analogs of other known PI compounds with a 2-hydroxy-3-diaza-propylamide core which have been identified as CGP-56603, CGP-53820, CGP-70726 (Novartis), ABT-538 (Abbott Laboratories), and DG-35 (National Cancer Institute).



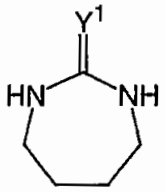
VI

Formula VII compounds having sulfonamide 5,6-dihydro-4-hydroxy-2-pyrone core include Tipranavir-like phosphonate protease inhibitors (TLPPI).

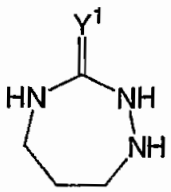


VII

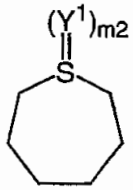
Formula VIII compounds have a six or seven-membered ring, cyclic carbonyl, sulfone, or sulfonyl core, where Y^1 is oxygen, sulfur, or substituted nitrogen and M2 is 1 or 2. The invention includes Cyclic carbonyl-like phosphonate protease inhibitor compounds (CCLPPI), e.g. Formula VIIIa-d.



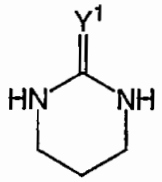
VIIIa



VIIIb

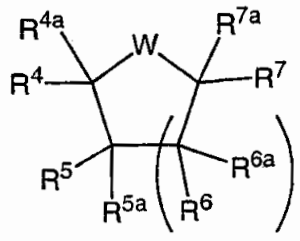


VIIIc and



VIIId;

Cyclic carbonyl protease inhibitors without a phosphonate group are described in US Patent Nos. RE37781; 6,503,898; 5,880,295; 5,811,422; 5,610,294; 5,559,252; and 5,506,355, as well as patent applications and granted patents which are equivalents of, or related by priority claims thereto. CCLPPI compounds also include phosphonate analogs of:



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described as "(I)" in WO 94/19329 (published 1 September 1994) at page 4, line 23, to page 21, line 16 and Claim 1. Also contemplated are patent applications and granted patents which are equivalents of or related by priority claims to WO 94/19329.

Stereoisomers

The compounds of the invention, exemplified by Formula I and II, may have chiral centers, e.g. chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

The compounds of the invention can also exist as tautomeric isomers in certain cases. All though only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the iinvention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

Salts and Hydrates

The compositions of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+, Li^+, K^+, Ca^{+2} and Mg^{+2}. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. Monovalent salts are preferred if a water soluble salt is desired.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt may be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic

acids, e.g., HCl, HBr, H_2SO_4, H_3PO_4 or organic sulfonic acids, to basic centers, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids. Any of the amino acids described above are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Methods of Inhibition of HIV Protease

Another aspect of the invention relates to methods of inhibiting the activity of HIV protease comprising the step of treating a sample suspected of containing HIV with a composition of the invention.

Compositions of the invention may act as inhibitors of HIV protease, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of HIV protease having a geometry unique to HIV protease. Compositions binding HIV protease may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of HIV protease. Accordingly, the invention relates to methods of detecting HIV protease in a sample suspected of containing HIV protease comprising the steps of: treating a sample suspected of containing HIV protease with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl, carboxyl, sulfhydryl or amino.

Within the context of the invention, samples suspected of containing HIV protease include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal

fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces HIV protease, frequently a pathogenic organism such as HIV. Samples can be contained in any medium including water and organic solvent\water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of HIV protease after application of the composition can be observed by any method including direct and indirect methods of detecting HIV protease activity. Quantitative, qualitative, and semiquantitative methods of determining HIV protease activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Organisms that contain HIV protease include the HIV virus. The compounds of this invention are useful in the treatment or prophylaxis of HIV infections in animals or in man.

However, in screening compounds capable of inhibiting human immunodeficiency viruses, it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay should be the primary screening tool.

Screens for HIV protease Inhibitors.

Compositions of the invention are screened for inhibitory activity against HIV protease by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of HIV protease *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Compositions having *in vitro* Ki (inhibitory constants) of less then about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for *in vivo* use.

Useful *in vitro* screens have been described in detail and will not be elaborated here. However, the examples describe suitable *in vitro* assays.

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextran, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For infections of the eye or other external tissues e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a

longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a

mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such

formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10%, and particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns, such as 0.5, 1, 30, 35 etc., which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of HIV infections as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the

condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy

Compositions of the invention are also used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating viral infections the compositions of the invention may be combined with other antivirals such as other protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors or HIV integrase inhibitors.

It is possible to combine any compound of the invention with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to an HIV infected patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. Second and third active ingredients in the combination may have anti-HIV activity. Exemplary active ingredients to be administered in combination with compounds of the invention are protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and HIV integrase inhibitors.

The combination therapy may provide "synergy" and "synergistic", i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g. in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect which is greater than the predicted purely additive effects of the individual compounds of the combination.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. ^{14}C or ^{3}H) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no HIV protease inhibitory activity of their own.

Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37°C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The phosphonate prodrugs of the invention typically will be stable in the digestive system but may be substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

Exemplary Methods of Making the Compounds of the Invention.

The invention provides many methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art, such as those elaborated in "Compendium of Organic Synthetic Methods" (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and

Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., "Advanced Organic Chemistry, Third Edition", (John Wiley & Sons, New York, 1985), "Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes", Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

Dialkyl phosphonates may be prepared according to the methods of: Quast et al (1974) *Synthesis* 490; Stowell et al (1990) *Tetrahedron Lett.* 3261; US Patent No. 5,663,159.

In general, synthesis of phosphonate esters is achieved by coupling a nucleophile amine or alcohol with the corresponding activated phosphonate electrophilic precursor. For example, chlorophosphonate addition on to 5'-hydroxy of nucleoside is a well known method for preparation of nucleoside phosphate monoesters. The activated precursor can be prepared by several well known methods. Chlorophosphonates useful for synthesis of the prodrugs are prepared from the substituted-1,3-propanediol (Wissner, et al, (1992) *J. Med Chem.* 35:1650). Chlorophosphonates are made by oxidation of the corresponding chlorophospholanes (Anderson, et al, (1984) *J. Org. Chem.* 49:1304) which are obtained by reaction of the substituted diol with phosphorus trichloride. Alternatively, the chlorophosphonate agent is made by treating substituted-1,3-diols with phosphorusoxychloride (Patois, et al, (1990) *J. Chem. Soc. Perkin Trans. I*, 1577). Chlorophosphonate species may also be generated in situ from corresponding cyclic phosphites (Silverburg, et al., (1996) *Tetrahedron Lett.*, 37:771-774), which in turn can be either made from chlorophospholane or phosphoramidate intermediate. Phosphoroflouridate intermediate prepared either from pyrophosphate or phosphoric acid may also act as precursor in preparation of cyclic prodrugs (Watanabe et al., (1988) *Tetrahedron Lett.*, 29:5763-66). Caution: fluorophosphonate compounds may be highly toxic!

Phosphonate prodrugs of the present invention may also be prepared from the precursor free acid by Mitsunobu reactions (Mitsunobu, (1981) *Synthesis*, 1; Campbell, (1992) *J. Org. Chem.*, 52:6331), and other acid coupling reagents including, but not limited to, carbodiimides (Alexander, et al, (1994) *Collect. Czech. Chem. Commun.* 59:1853; Casara, et al, (1992) *Bioorg. Med. Chem. Lett.*, 2:145; Ohashi, et al, (1988) *Tetrahedron Lett.*, 29:1189), and benzotriazolyloxytris-(dimethylamino)phosphonium salts (Campagne, et al, (1993) *Tetrahedron Lett.*, 34:6743).

Aryl halides undergo Ni^{+2} catalyzed reaction with phosphite derivatives to give aryl phosphonate containing compounds (Balthazar, et al (1980) *J. Org. Chem.* 45:5425). Phosphonates may also be prepared from the chlorophosphonate in the presence of a palladium catalyst using aromatic triflates (Petrakis, et al, (1987) *J. Am. Chem. Soc.* 109:2831; Lu, et al, (1987) *Synthesis*, 726). In another method, aryl phosphonate esters are prepared from aryl phosphates under anionic rearrangement conditions (Melvin (1981) *Tetrahedron Lett.* 22:3375; Casteel, et al, (1991) *Synthesis*, 691). N-Alkoxy aryl salts with alkali metal derivatives of cyclic alkyl phosphonate provide general synthesis for heteroaryl-2-phosphonate linkers (Redmore (1970) *J. Org. Chem.* 35:4114). These above mentioned methods can also be extended to compounds where the W^5 group is a heterocycle. Cyclic-1,3-propanyl prodrugs of phosphonates are also synthesized from phosphonic diacids and substituted propane-1,3-diols using a coupling reagent such as 1,3-dicyclohexylcarbodiimide (DCC) in presence of a base (e.g., pyridine). Other carbodiimide based coupling agents like 1,3-disopropylcarbodiimide or water soluble reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) can also be utilized for the synthesis of cyclic phosphonate prodrugs.

The carbamoyl group may be formed by reaction of a hydroxy group according to the methods known in the art, including the teachings of Ellis, US 2002/0103378 A1 and Hajima, US Patent No. 6,018,049.

Schemes and Examples

A number of exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods.

General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a

water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (e.g. inert gas environments) are common in the art and will be applied when applicable.

The terms "treated", "treating", "treatment", and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes above and in the examples (hereafter

"exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

A single stereoisomer, e.g. an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113:(3) 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2)

formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g. (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

All literature and patent citations above are hereby expressly incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described

in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following Embodiments. It is apparent that certain modifications of the methods and compositions of the following Embodiments can be made within the scope and spirit of the invention.

Examples General Section

The following Examples refer to the Schemes.

Some Examples have been performed multiple times. In repeated Examples, reaction conditions such as time, temperature, concentration and the like, and yields were within normal experimental ranges. In repeated Examples where significant modifications were made, these have been noted where the results varied significantly from those described. In Examples where different starting materials were used, these are noted. When the repeated Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl ester", this intends that an otherwise present group, in this case typically a methyl ester, is taken to be the same group modified as indicated.

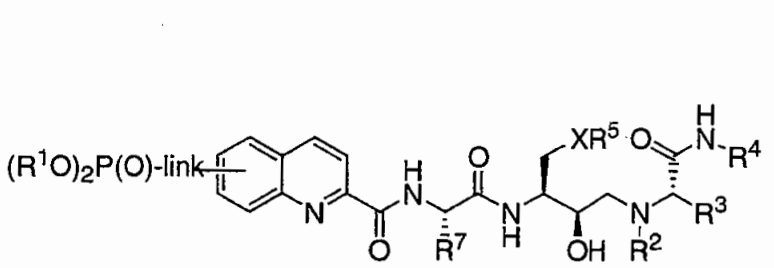
In a number of the following schemes, the term "etc" appears as a substituent on chemical structures and as a term within the schemes. When used in the charts, the term is defined for each chart. When the term "etc" appears in a scheme and is not a substituent on a chemical structure, it means "and the like".

Saquinavir-like phosphonate protease inhibitors (SLPPI)

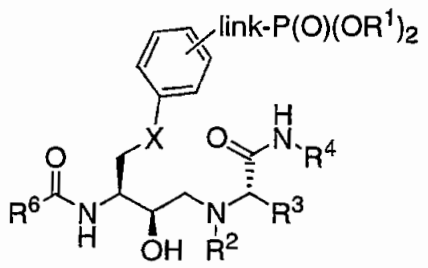
Preparation of the intermediate phosphonate esters.

The structures of the intermediate phosphonate esters **1** to **6**, and the structures for the component groups R^1, R^4 and R^7 of this invention are shown in Chart 1.
The structures of the $R^2NHCH(R^3)CONHR^4$ and R^5XCH_2 components are shown in Charts **2** and **2a**, and the structures of the R^6COOH components are shown in Charts **3a**, **3b** and **3c**.
Specific stereoisomers of some of the structures are shown in Charts **1**, **2** and **3**; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **6**. Subsequent chemical modifications to the compounds **1** to **6**, as described herein, permit the synthesis of the final compounds of this invention.
The intermediate compounds **1** to **6** incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **4** and **5** illustrate examples of the linking groups present in the structures **1** – **5**, and in which "etc" refers to the scaffold, e.g., saquinavir.

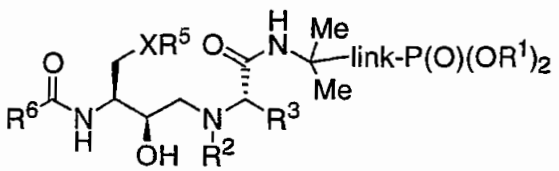
Chart 1



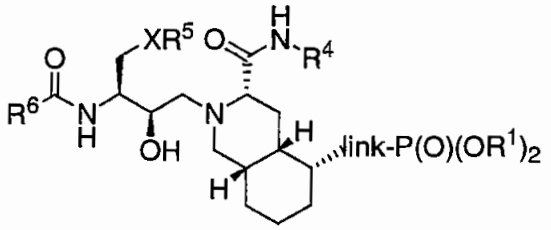
1



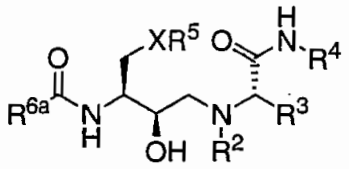
2



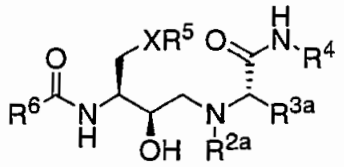
3



4



5



6

R^{6a} = phosphonate-containing R^6

R^{2a}, R^{3a} = phosphonate-containing R^2 or R^3

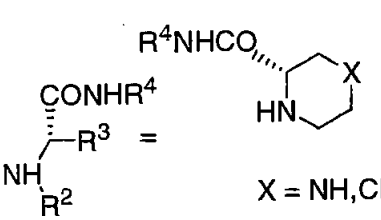
R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R^4 = $CH(CH_3)_3$; CH_2CF_3; $CH_2C_6H_4(CH_3)$-2

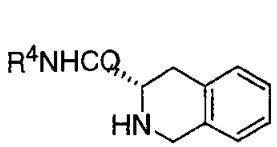
R^7 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

X = S, direct bond

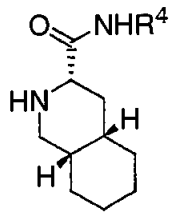
Chart 2



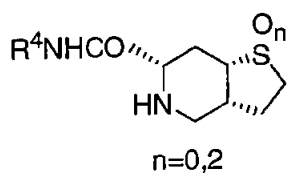
1.2 A1



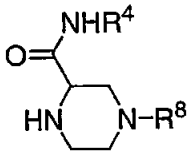
A2



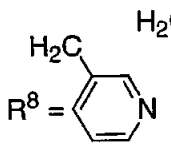
A3



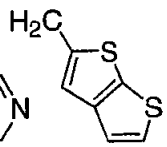
A4



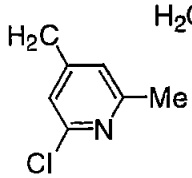
A5



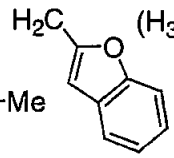
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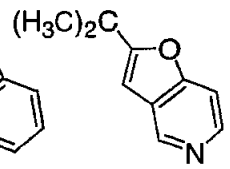
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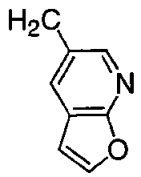
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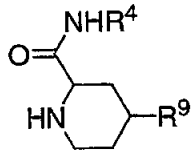
A9



A10

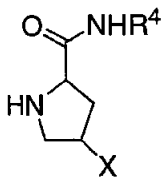


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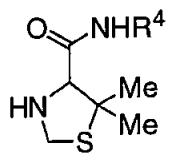


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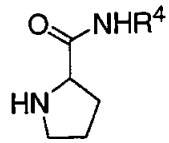
R^9 = OCH_2Ph
S-3-pyridyl
S-4-pyridyl
OCH_2-4-pyridyl



A13

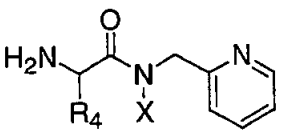


A14



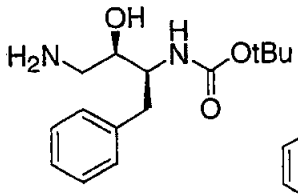
A15

X = Cl, OMe

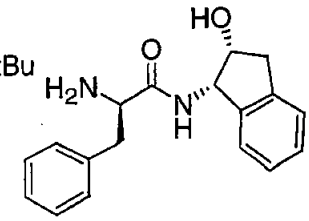


X=H or Me

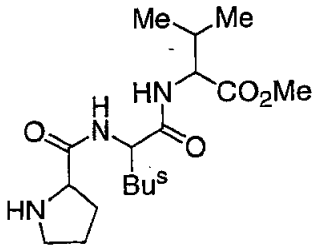
A16



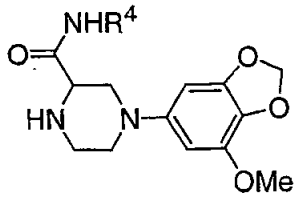
A17



A18

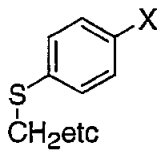


A19

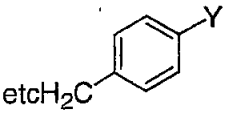


A20

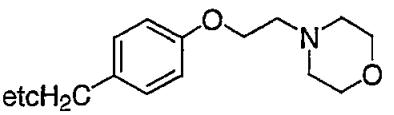
Chart 2a

R^5CH_2X = 

21



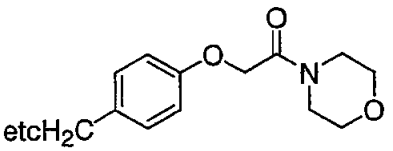
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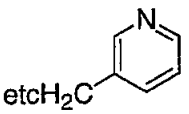
23

X = H, F

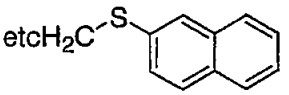
Y = H, OC_2H_5, $OCH_2C_6H_5$



24

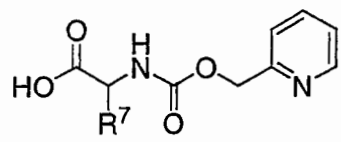


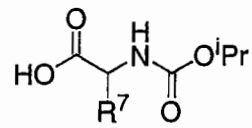
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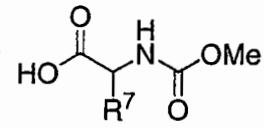


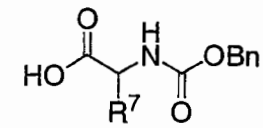
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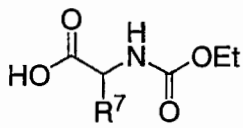
Chart 3a Structures of the R^6COOH components

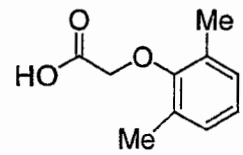

C1

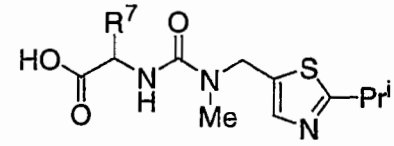

C2

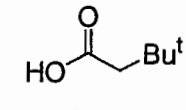

C3

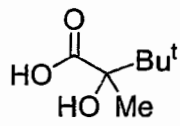

C4

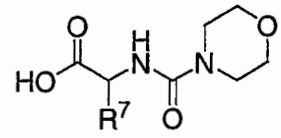

C5

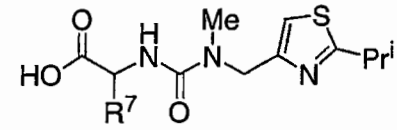

C6

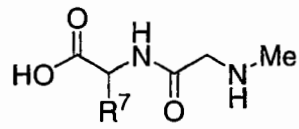

C7

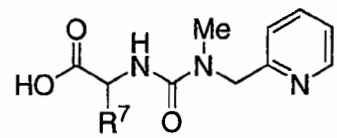

C8

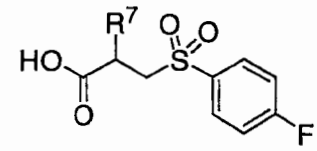

C9

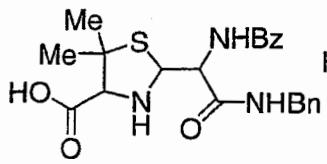

C10


C11

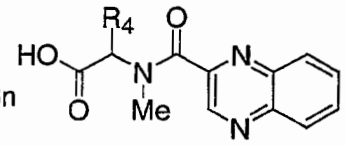

C12


C13

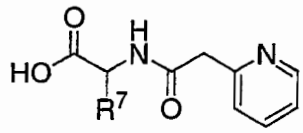

C14



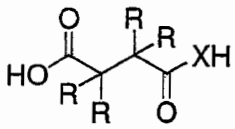
C15



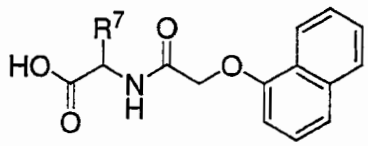
C16



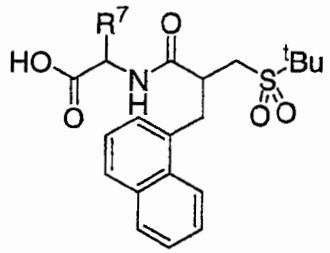
C17



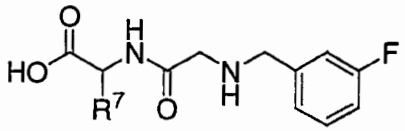
X = O, NH
R = H, alkyl
C18



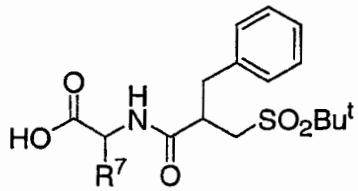
C19



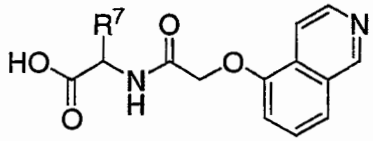
C20



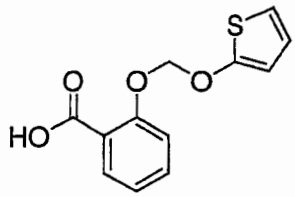
C21



C22



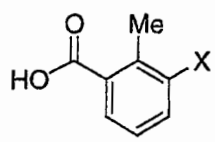
C23



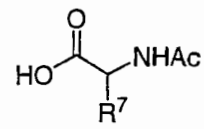
C24

R^7 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

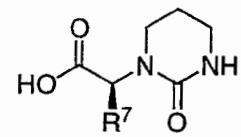
Chart 3b Structures of the R^6COOH components



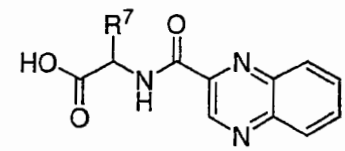
C25
X = OH, NH_2



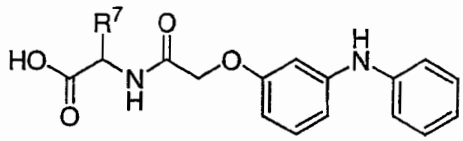
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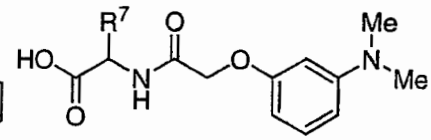
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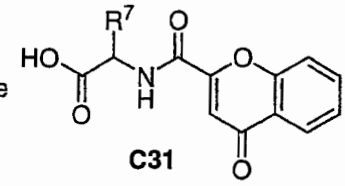
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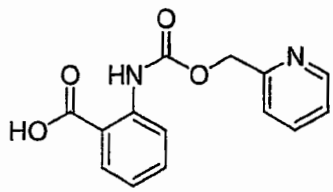
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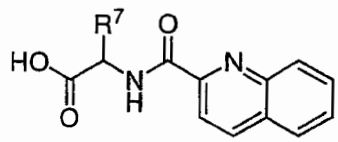
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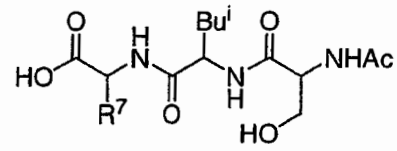
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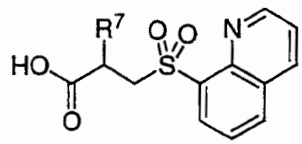
C32



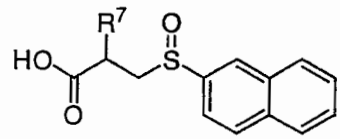
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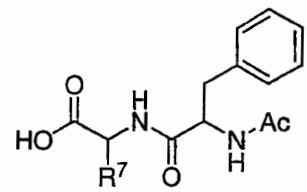
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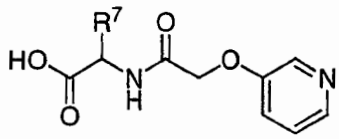
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C36



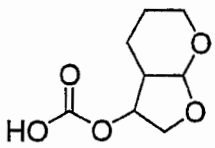
C37



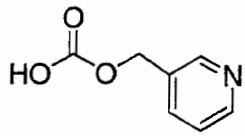
C38

R^7 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

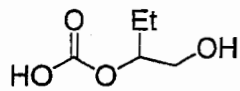
Chart 3c Structures of the R^6COOH components



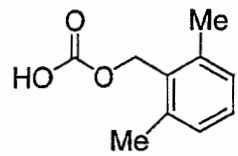
C38



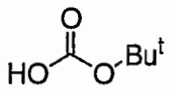
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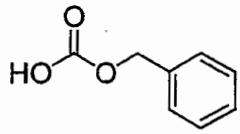
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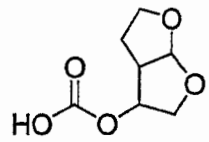
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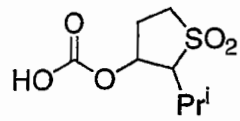
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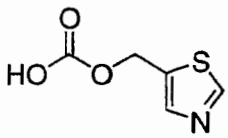
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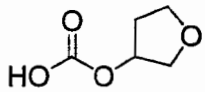
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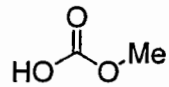
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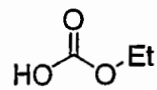
C46



C47

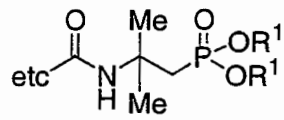
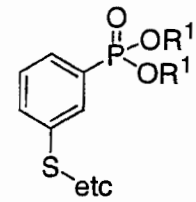
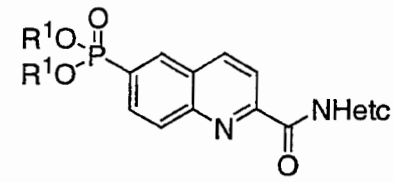
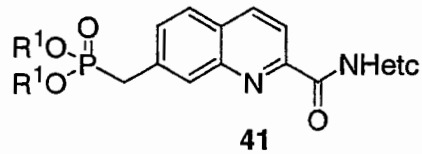
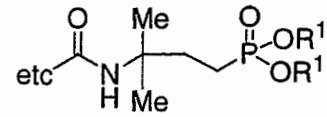
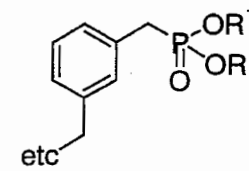
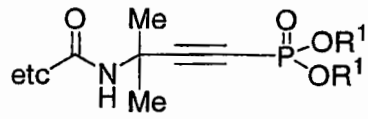
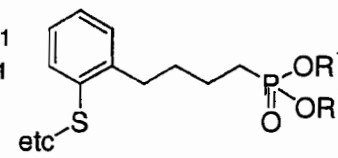
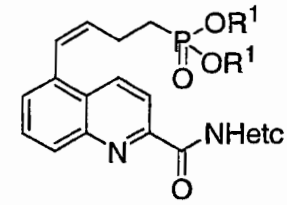
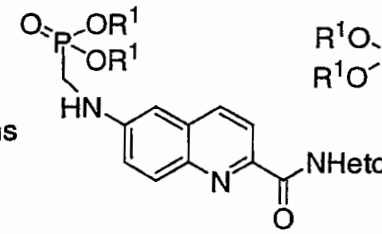
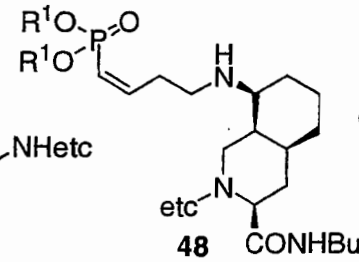
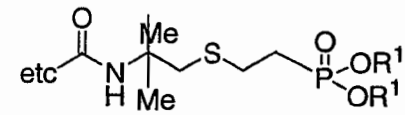
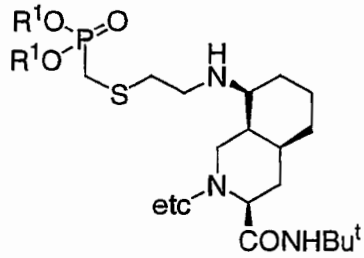
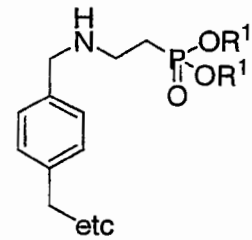
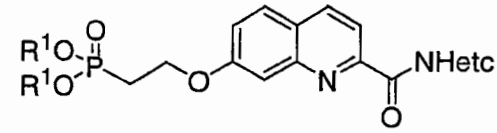


C48



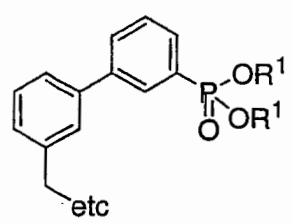
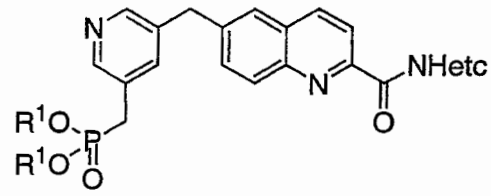
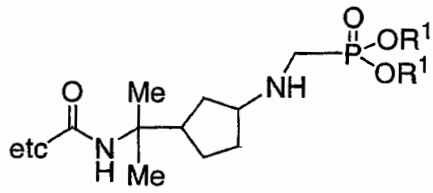
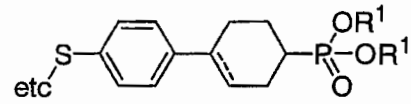
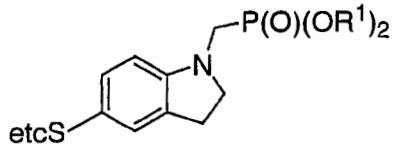
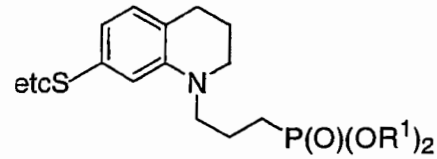
C49

Chart 4 Examples of the linking group between the scaffold and the phosphonate moiety.

link	examples
direct bond	 **38**  **39**  **40**
single carbon	 **41**  **42**  **43**
multiple carbon	 **44**  **45**  **46**
hetero atoms	 **47**  **48**  **49**
	 **50**  **51**  **52**

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Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.

link	examples
aryl, heteroaryl	 **53**
	 **55**
cycloalkyl	 **56**
	 **57**
cyclized	 **58**
	 **59**

Schemes **1** - **69** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1**- **4**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **5** and **6**, in which the phosphonate moiety is incorporated into the groups R^6COOH and $R^2NHCH(R^3)CONHR^4$, are also described below.

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the

art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate intermediates 1.

Scheme **1** illustrates one method for the preparation of the phosphonate esters **1.6** in which X is a direct bond. In this procedure, an amine $R^2NHCH(R^3)CONHR^4$ **1.2** is reacted with an epoxide **1.1** to afford the aminoalcohol **1.3**. The preparation of the epoxide **1.1** is described below, (Scheme **2**) The preparation of aminoalcohols by reaction between an amine and an epoxide is described, for example, in Advanced Organic Chemistry, by J. March, McGraw Hill, 1968, p 334. In a typical procedure, equimolar amounts of the reactants are combined in a polar solvent such as an alcohol or dimethylformamide and the like, at from ambient to about 100°, for from 1 to 24 hours, to afford the product **1.3**. The carbobenzyloxy protecting group is then removed. The removal of carbobenzyloxy protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 335. The reaction can be effected by means of catalytic hydrogenation in the presence of hydrogen or a hydrogen donor, by reaction with a Lewis acid such as aluminum chloride or boron tribromide, or by basic hydrolysis, for example employing barium hydroxide in an aqueous organic solvent mixture. Preferably, the protected amine **1.3** is converted into the free amine **1.4** by means of hydrogenation over 10% palladium on carbon catalyst in ethanol, as described in US Patent 5196438. The amine product **1.4** is then reacted with a carboxylic acid **1.5** to afford the amide **1.6**. The coupling reaction of amines **1.4** and a carboxylic acid **1.5** can be effected under a variety of conditions, for example as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid can be activated by conversion to an imidazolide, mixed anhydride or active ester such as, for example, the ester with hydroxybenztriazole or N-hydroxysuccinimide. Alternatively, the reactants can be combined in the presence of a carbodiimide, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, to afford the amide product **1.6**. Preferably, equimolar amounts of the amine and the carboxylic acid are reacted in tetrahydrofuran at ca. -10°, in the presence of dicyclohexylcarbodiimide, as described in

U.S. Patent 5,196,438, to afford the amide **1.6**. The carboxylic acid **1.5** employed in the above reaction is obtained by means of the reaction between the substituted quinoline-2-carboxylic acid **1.7**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor group thereto, such as [OH], [SH], Br, as described below, and an aminoacid **1.8**. The reaction is performed under similar conditions to those described above for the preparation of the amide **1.6**. Preferably, the quinoline carboxylic acid **1.7** is reacted with N-hydroxy succinimide and a carbodiimide to afford the hydroxysuccinimide ester, which is then reacted with the aminoacid **1.8** in dimethylformamide at ambient temperature for 2-4 days, as described in U.S. Patent 5,196,438, to afford the amide product **1.5**. The preparation of the substituted quinoline carboxylic acids **1.7** is described below, Schemes **24-27**.

Scheme **2** illustrates the preparation of the epoxides **1.1** used above in Scheme **1**. The preparation of the epoxide **1.1** in which R10 is H is described in J. Med. Chem., 1997, 40, 3979. Analogs in which R10 is one of the substituents defined in Chart **2** are prepared as shown in Scheme **2**. A substituted phenylalanine **2.1** is first converted into the benzyloxycarbonyl derivative **2.2**. The preparation of benzyloxycarbonyl amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The aminoacid **2.1** is reacted with benzyl chloroformate or dibenzyl carbonate in the presence of a suitable base such as sodium carbonate or triethylamine, to afford the protected amine product **2.2**. The conversion of the carboxylic acid **2.2** into the epoxide **1.1** for example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, is then effected. The carboxylic acid is first converted into an activated derivative such as the acid chloride **2.3**, in which X is Cl, for example by treatment with oxalyl chloride, or into a mixed carbonate, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone **2.4**. The reaction is performed by the addition of a solution of the activated carboxylic acid derivative to an ethereal solution of three or more molar equivalents of diazomethane at 0°C. The diazoketone is converted into the chloroketone **2.5** by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether, as described in J. Med. Chem., 1997, 40, 3979. The latter compound is then reduced, for example by the use of an equimolar amount of sodium borohydride in an ethereal solvent such as tetrahydrofuran at 0°C, to produce a mixture of chlorohydrins from which the desired 2S, 3S diastereomer **2.6** is

separated by chromatography. The chlorohydrin **2.6** is then converted into the epoxide **1.1** by treatment with a base such as an alkali metal hydroxide in an alcoholic solvent, for example as described in J. Med. Chem., 1997, 40, 3979. Preferably, the compound **2.6** is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide **1.1**.

Scheme **3** illustrates the preparation of the amine reactant $R^2NHCH(R^3)CONHR^4$ (**1.2**) employed above (Scheme **1**). In this procedure, the carboxylic acid $R^2NHCH(R^3)COOH$ **3.1** is first converted into the N-protected analog **3.2**, for example by reaction with benzyloxychloroformate and triethylamine in tetrahydrofuran. The carboxyl group is then activated, for example by conversion to the acid chloride or a mixed anhydride, or by reaction with isobutyl chloroformate, as described in Chimia, 50, 532, 1996 and in Synthesis, 1972, 453, and the activated derivative is then reacted with the amine R^4NH_2 to produce the amide **3.4**. Deprotection, for example as described above, then affords the free amine **1.2**.

Scheme **4** depicts an alternative method for the preparation of the compounds **1** in which X is a direct bond. In this procedure, a hydroxymethyl-substituted oxazolidinone **4.1** is converted into an activated derivative **4.2** which is then reacted with the amine $R^2NHCH(R^3)CONHR^4$ (**1.2**) to afford the amide **4.3**. The preparation of the hydroxymethyl-substituted oxazolidinone **4.1** is described below, (Scheme **5**) The hydroxyl group can be converted into a bromo derivative, for example by reaction with triphenylphosphine and carbon tetrabromide, as described in J. Am. Chem. Soc., 92, 2139, 1970, or a methanesulfonyloxy derivative, by reaction with methanesulfonyl chloride and a base, or, preferably, into the 4-nitrobenzenesulfonyloxy derivative **4.2**, by reaction in a solvent such as ethyl acetate or tetrahydrofuran, with 4-nitrobenzenesulfonyl chloride and a base such as triethylamine or N-methylmorpholine, as described in WO 9607642. The nosylate product **4.2** is then reacted with the amine component **1.2** to afford the displacement product **4.3**. Equimolar amounts of the reactants are combined in an inert solvent such as dimethylformamide, acetonitrile or acetone, optionally in the presence of an organic or inorganic base such as triethylamine or sodium carbonate, at from about 0°C to 100°C to afford the amine product **4.3**. Preferably, the reaction is performed in methyl isobutyl ketone at 80°C, in the presence of sodium carbonate, as described in WO 9607642. The oxazolidinone group present in the product **4.3** is then hydrolyzed to afford the hydroxyamine **4.4**. The hydrolysis reaction is effected in the presence

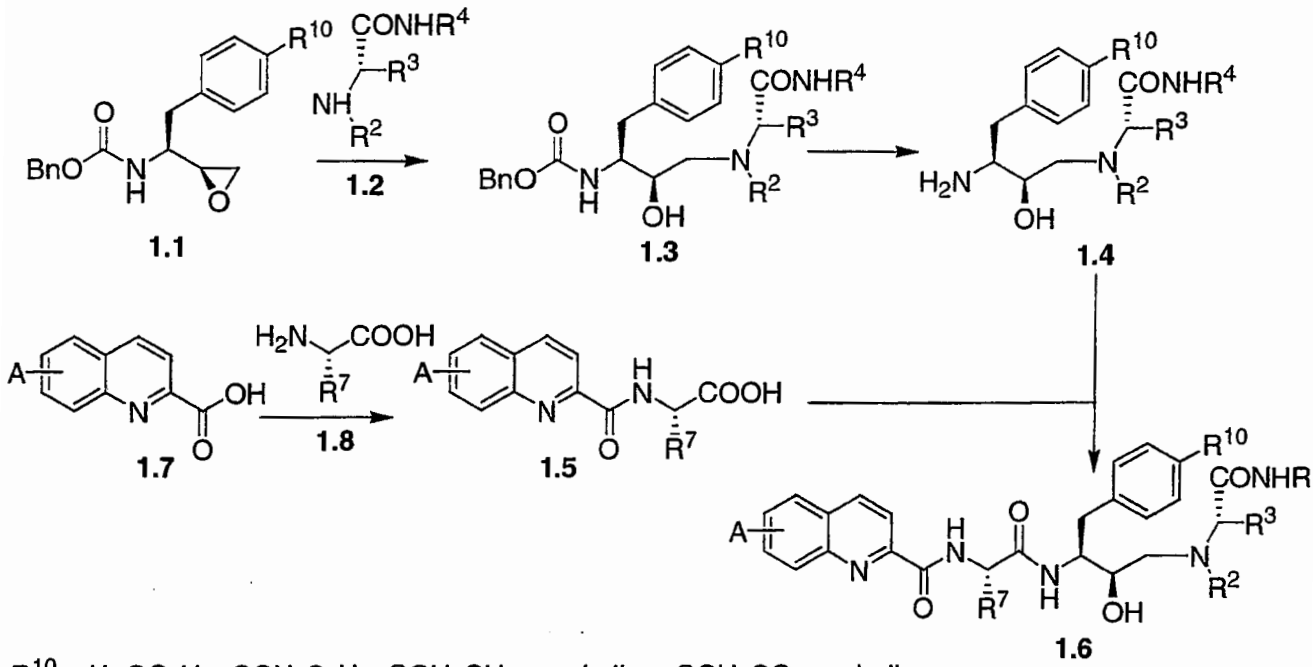
of aqueous solution of a base such as an alkali metal hydroxide, optionally in the presence of an organic co-solvent. Preferably, the oxazolidinone compound **4.3** is reacted with aqueous ethanolic sodium hydroxide at reflux temperature, as described in WO 9607642, to afford the amine **4.4**. This product is then reacted with the carboxylic acid or activated derivative thereof, **1.5**, the preparation of which is described above, to afford the product **1.6**. The amide-forming reaction is conducted under the same conditions as described above, (Scheme **1**)

Scheme **5** depicts the preparation of the hydroxymethyl oxazolidinones **4.1**, which are utilized in the preparation of the phosphonate esters **1**, as described above in Scheme **4**. In this procedure, phenylalanine, or a substituted derivative thereof, **2.1**, in which R^{10} is as defined in Chart **2**, is converted into the phthalimido derivative **5.1**. The conversion of amines into phthalimido derivatives is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 358. The amine is reacted with phthalic anhydride, 2-carboethoxybenzoyl chloride or N-carboethoxyphthalimide, optionally in the presence of a base such as triethylamine or sodium carbonate, to afford the protected amine **5.1**. Preferably, the aminoacid is reacted with phthalic anhydride in toluene at reflux, to yield the phthalimido product. The carboxylic acid is then transformed into an activated derivative such as the acid chloride **5.2**, in which X is Cl. The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of a tertiary amide such as dimethylformamide. Preferably, the carboxylic acid is transformed into the acid chloride by reaction with oxalyl chloride and a catalytic amount of dimethylformamide, in toluene solution at ambient temperature, as described in WO 9607642. The acid chloride **5.2**, X = Cl, is then converted into the aldehyde **5.3** by means of a reduction reaction. This procedure is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 620. The transformation can be effected by means of catalytic hydrogenation, a procedure which is referred to as the Rosenmund reaction, or by chemical reduction employing, for example, sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride or triethylsilane. Preferably, the acid chloride **5.2** X = Cl, is hydrogenated in toluene solution over a 5% palladium on carbon catalyst, in the presence of

butylene oxide, as described in WO 9607642, to afford the aldehyde **5.3**. The aldehyde **5.3** is then transformed into the cyanohydrin derivative **5.4**. The conversion of aldehydes into cyanohydrins is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 211. For example, the aldehyde **5.3** is converted into the cyanohydrin **5.4** by reaction with trimethylsilyl cyanide in an inert solvent such as dichloromethane, followed by treatment with an organic acid such as citric acid, as described in WO 9607642, or by alternative methods described therein. The cyanohydrin is then subjected to acidic hydrolysis, to effect conversion of the cyano group into the corresponding carboxy group, with concomitant hydrolysis of the phthalimido substituent to afford the aminoacid **5.5** The hydrolysis reactions are effected by the use of aqueous mineral acid. For example, the substrate **5.4** is reacted with aqueous hydrochloric acid at reflux, as described in WO 9607642, to afford the carboxylic acid product **5.5**. The aminoacid is then converted into a carbamate, for example the ethyl carbamate **5.6**. The conversion of amines into carbamates is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 317. The amine is reacted with a chloroformate, for example ethyl chloroformate, in the presence of a base such as potassium carbonate, to afford the carbamate **5.6**. For example, the aminoacid **5.5** is reacted, in aqueous solution, with ethyl chloroformate and sufficient aqueous sodium hydroxide to maintain a neutral pH, as described in WO 9607642, to afford the carbamate **5.6**. The latter compound is then transformed into the oxazolidinone **5.7**, for example by treatment with aqueous sodium hydroxide at ambient temperature, as described in WP 9607642. The resultant carboxylic acid is transformed into the methyl ester **5.8** by means of a conventional esterification reaction. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and an alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and an alkyl halide, for example an alkyl bromide. For example, the carboxylic acid **5.7** is converted into the methyl ester **5.8** by treatment with methanol at reflux temperature, in the presence of a catalytic amount of sulfuric acid, as described in WO 9607642. The carbomethoxyl group present in the compound **5.8** is then reduced to yield the corresponding carbinol **4.1**. The reduction of carboxylic esters to the carbinols is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 550. The transformation can be effected by the use of reducing agents such as

borane-dimethylsulfide, lithium borohydride, diisobutyl aluminum hydride, lithium aluminum hydride and the like. For example, the ester **5.8** is reduced to the carbinol **4.1** by reaction with sodium borohydride in ethanol at ambient temperature, as described in WO 9607642.

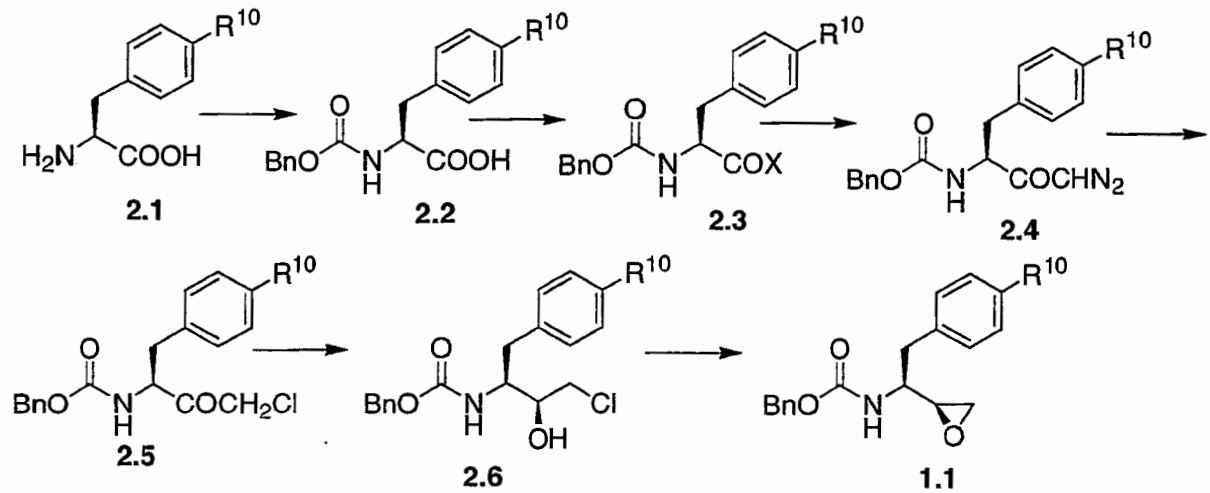
Scheme 1



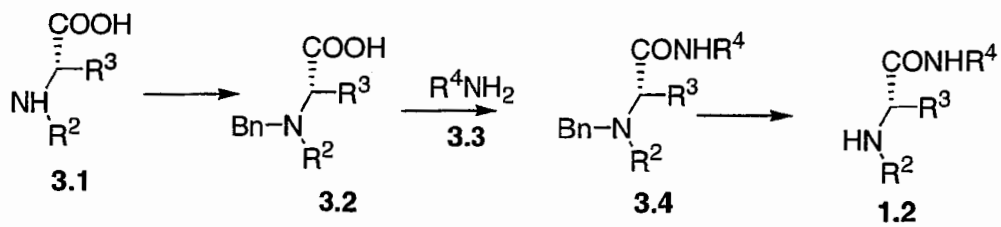
R^{10} = H, OC_2H_5, $OCH_2C_6H_5$, OCH_2CH_2morpholino, OCH_2COmorpholino

A = [OH], [SH], [NH_2], Br etc or link-P(O)(OR^1)$_2$

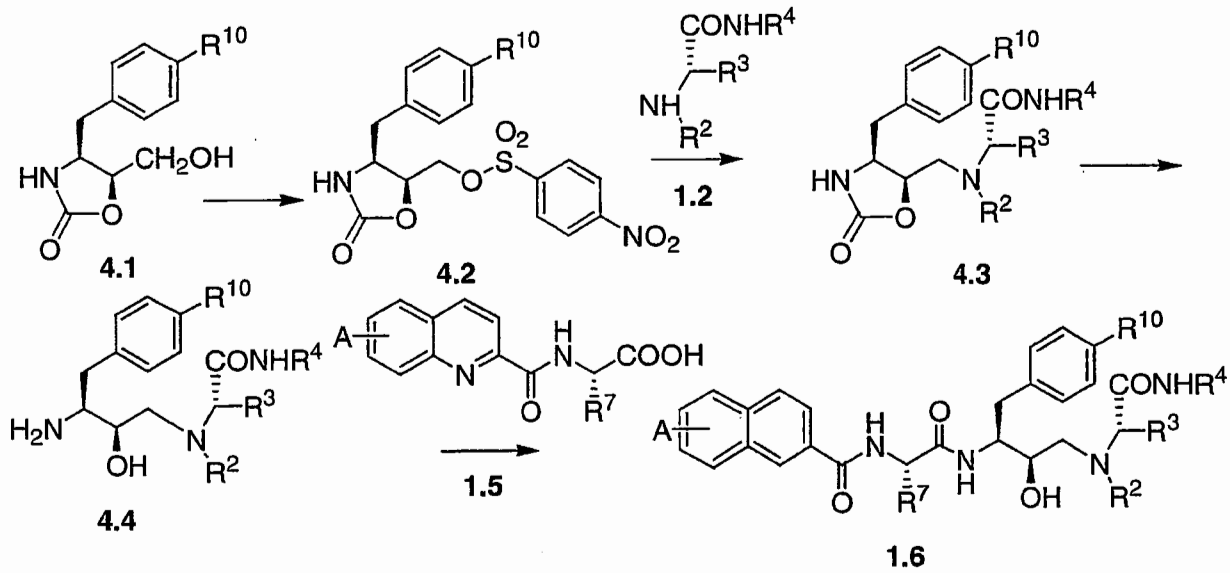
Scheme 2



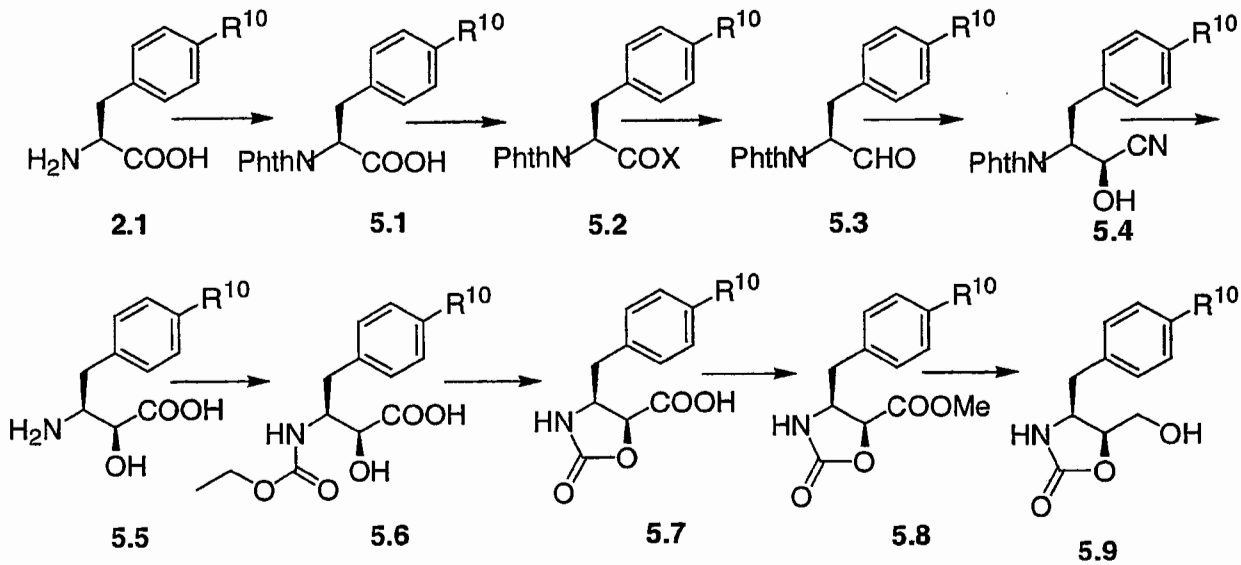
Scheme 3



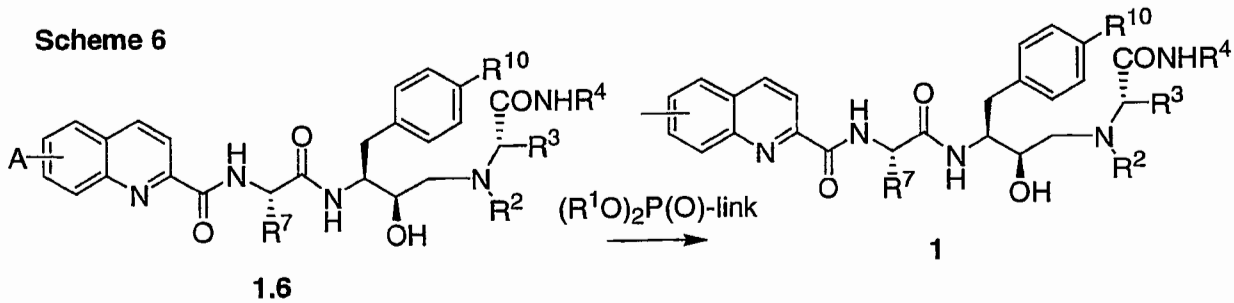
Scheme 4



Scheme 5

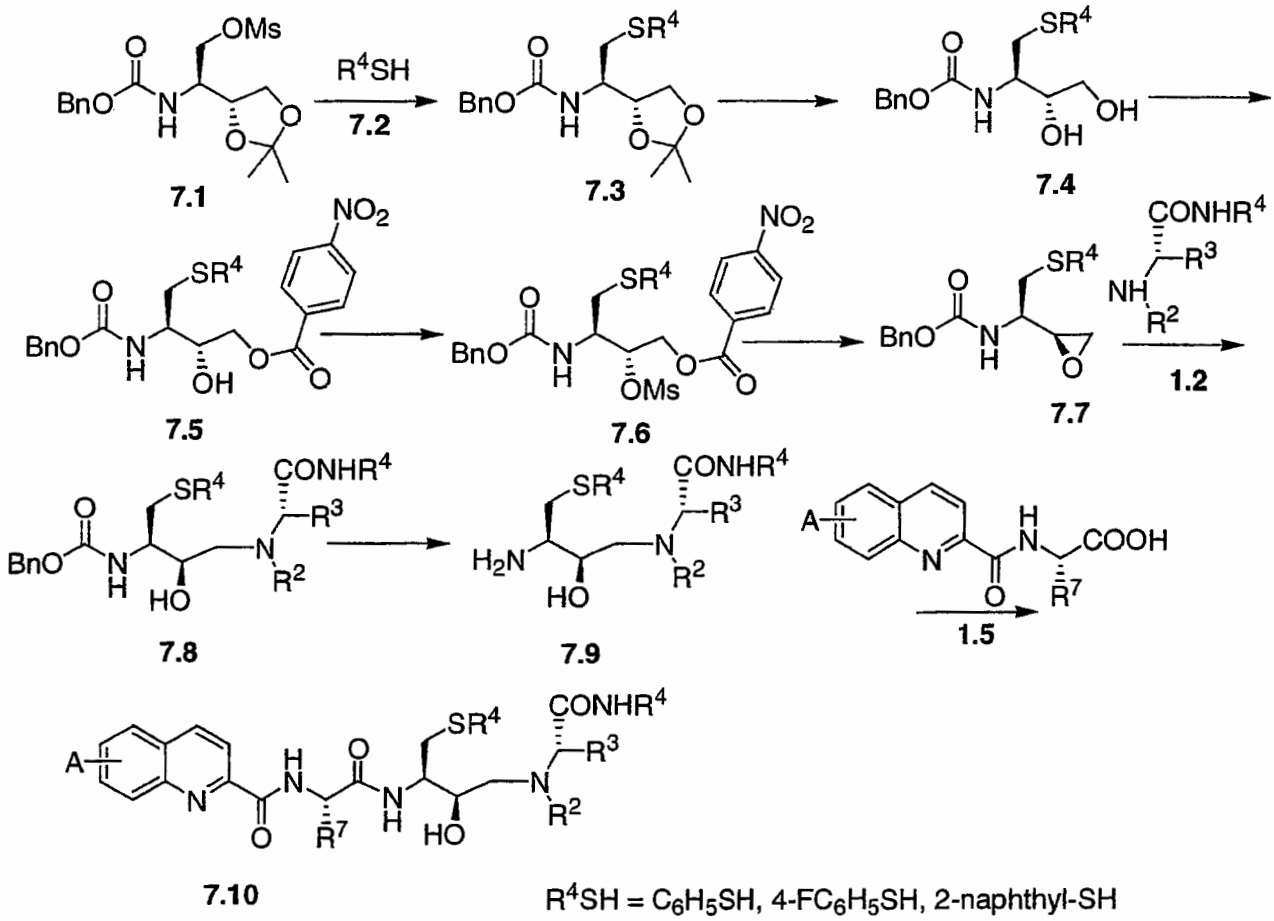


Scheme 6

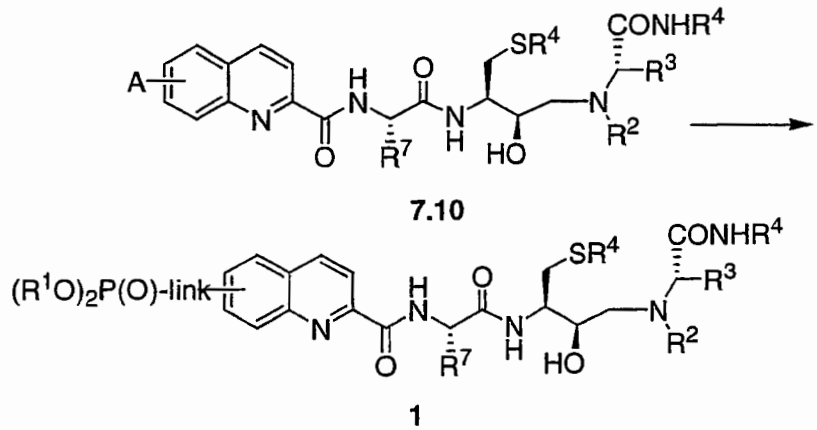


The procedures illustrated in Schemes **1** and **4** depict the preparation of the compounds **1.6** in which X is a direct bond, and in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **6** illustrates the conversion of compounds **1.6** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **1**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **24 - 69**). In the procedures illustrated above, Schemes **1**, **4** and in the procedures illustrated below (Schemes **24-69**) for the preparation of the phosphonate esters **2-6**, compounds in which the group A is a precursor to the group link-$P(O)(OR^1)_2$ may be converted into compounds in which A is link-$P(O)(OR^1)_2$ at any appropriate stage in the reaction sequence, or, as shown in Scheme **6**, at the end of the sequence. The selection of an appropriate stage to effect the conversion of the group A into the group link-$P(O)(OR^1)_2$ is made after consideration of the nature of the reactions involved in the conversion, and the stability of the various components of the substrate to those conditions.

Scheme 7



Scheme 8



Scheme **7** illustrates the preparation of the compounds **1** in which the substituent X is S, and in which the group A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below.

In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, **7.1**, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol R^4SH **7.2**, as defined above, to afford the thioether **7.3**.

The reaction is conducted in a suitable solvent such as, for example, pyridine, DMF and the like, in the presence of an inorganic or organic base, at from 0°C to 80°C, for from 1-12 hours, to afford the thioether **7.3**. Preferably the mesylate **7.1** is reacted with an equimolar amount of the thiol R^4SH, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°C, to give the product **7.3**. The 1,3-dioxolane protecting group present in the compound **7.3** is then removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol **7.4**. Methods for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p. 191. For example, the 1,3-dioxolane compound **7.3** is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture. Preferably, the 1,3-dioxolane **7.3** is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°C, to yield the product **7.4**.

The primary hydroxyl group of the diol **7.4** is then selectively acylated by reaction with an electron-withdrawing acyl halide such as, for example, pentafluorobenzoyl chloride or mono- or di-nitrobenzoyl chlorides. The reaction is conducted in an inert solvent such as dichloromethane and the like, in the presence of an inorganic or organic base. Preferably, equimolar amounts of the diol **7.4** and 4-nitrobenzoyl chloride are reacted in a solvent such as ethyl acetate, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, to afford the hydroxy ester **7.5**. The hydroxy ester is next reacted with a sulfonyl chloride such as methanesulfonyl chloride, 4-toluenesulfonyl chloride and the like, in the presence of a base, in an aprotic polar solvent at low temperature, to afford the corresponding sulfonyl ester **7.6**. Preferably, equimolar amounts of the carbinol **7.5** and methanesulfonyl chloride are reacted together in ethyl acetate containing triethylamine, at about 10°C, to yield the mesylate **7.6**. The compound **7.6** is then subjected to a hydrolysis-cyclization reaction to afford the oxirane **7.7**. The mesylate or analogous leaving group present in **7.6** is displaced by hydroxide ion, and the carbinol thus produced, without isolation, spontaneously transforms into the oxirane **7.7** with elimination of 4-nitrobenzoate. To effect

this transformation, the sulfonyl ester **7.6** is reacted with an alkali metal hydroxide or tetraalkylammonium hydroxide in an aqueous organic solvent. Preferably, the mesylate **7.6** is reacted with potassium hydroxide in aqueous dioxan at ambient temperature for about 1 hour, to afford the oxirane **7.7**.

The oxirane compound **7.7** is then subjected to regiospecific ring-opening reaction by treatment with a secondary amine **1.2**, to give the aminoalcohol **7.8**. The amine and the oxirane are reacted in a protic organic solvent, optionally in the additional presence of water, at 0°C to 100°C, and in the presence of an inorganic base, for 1 to 12 hours, to give the product **7.8**. Preferably, equimolar amounts of the reactants **7.7** and **1.2** are reacted in aqueous methanol at about 60°C in the presence of potassium carbonate, for about 6 hours, to afford the aminoalcohol **7.8**. The carbobenzyloxy (cbz) protecting group in the product **7.8** is removed to afford the free amine **7.9**. Methods for removal of cbz groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition, p. 335. The methods include catalytic hydrogenation and acidic or basic hydrolysis.

For example, the cbz-protected amine **7.8** is reacted with an alkali metal or alkaline earth hydroxide in an aqueous organic or alcoholic solvent, to yield the free amine **7.9**. Preferably, the cbz group is removed by the reaction of **7.8** with potassium hydroxide in an alcohol such as isopropanol at ca. 60°C to afford the amine **7.9**. The amine **7.9** so obtained is next acylated with a carboxylic acid or activated derivative **1.5**, using the conditions described above for the conversion of the amine **1.4** into the amide **1.6** (Scheme **1**), to yield the final amide product **7.10**.

The procedures illustrated in Scheme **7** depict the preparation of the compounds **1** in which X is S, and in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br , as described below. Scheme **8** illustrates the conversion of compounds **7.10** in which A is a precursor to the group link-P(O)$(OR^1)_2$ into the compounds **1**. Procedures for the conversion of the substituent A into the group link-P(O)$(OR^1)_2$ are illustrated below, (Schemes **24 - 69**).

The reactions illustrated in Schemes **1-7** illustrate the preparation of the compounds **1** in which A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as, for example, optionally protected OH, SH, NH , as described below. Scheme **8** depicts the conversion of the

compounds **1** in which A is OH, SH, NH , as described below, into the compounds **1** in which A is the group link-P(O)$(OR^1)_2$. Procedures for the conversion of the group A into the group link-P(O))$(OR^1)_2$ are described below, (Schemes **24-69**).

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below, (Scheme **54**)

Preparation of the phosphonate intermediates 2.

Scheme **9** depicts the one method for the preparation of the compounds **2** in which X is a direct bond, and in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. In this procedure, the hydroxymethyl oxazolidinone **9.1**, the preparation of which is described below, is converted into an activated derivative, for example the 4-nitrobenzenesulfonate **9.2**. The conditions for this transformation are the same as those described above (Scheme **4**) for the conversion of the carbinol **4.1** into the nosylate **4.2**. The activated ester **9.2** is then reacted with the amine **1.2**, under the same conditions as described above for the preparation of the amine **4.3** to afford the oxazolidinone amine **9.3**. The oxazolidinone group is then hydrolyzed by treatment with aqueous alcoholic base, to produce the primary amine **4.4**. For example, the oxazolidinone **9.3** is reacted with aqueous ethanolic sodium hydroxide at reflux temperature, as described in WO 9607642, to afford the amine product **9.4**. The latter compound is then coupled with the carboxylic acid **9.6**, to afford the amide **9.5**. The conditions for the coupling reaction are the same as those described above for the preparation of the amide **1.6**.

The phosphonate esters **2** - **6** which incorporate the group R^6 CO derived formally from the carboxylic acids depicted in Chart **2c** contain a carbamate group. Various methods for the preparation of carbamates are described below, (Scheme **55**)

Scheme **10** illustrates an alternative method for the preparation of the compounds **2** in which X is a direct bond, and in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. In this procedure, the oxirane **10.1**, the preparation of which is described below, is reacted with the amine **1.2** to afford the

aminoalcohol **10.2**. The reaction is conducted under the same conditions as are described above for the preparation of the aminoalcohol **1.3**. (Scheme **1**) The benzyloxycarbonyl protecting group is then removed from the product **10.2** to afford the free amine **10.3**. The conditions for the debenzylation reaction are the same as those described above for the debenzylation of the compound **1.3**. The amine **10.3** is then coupled with the carboxylic acid **9.6** to produce the amide **9.5**, employing the same conditions as are described above (Scheme **9**).

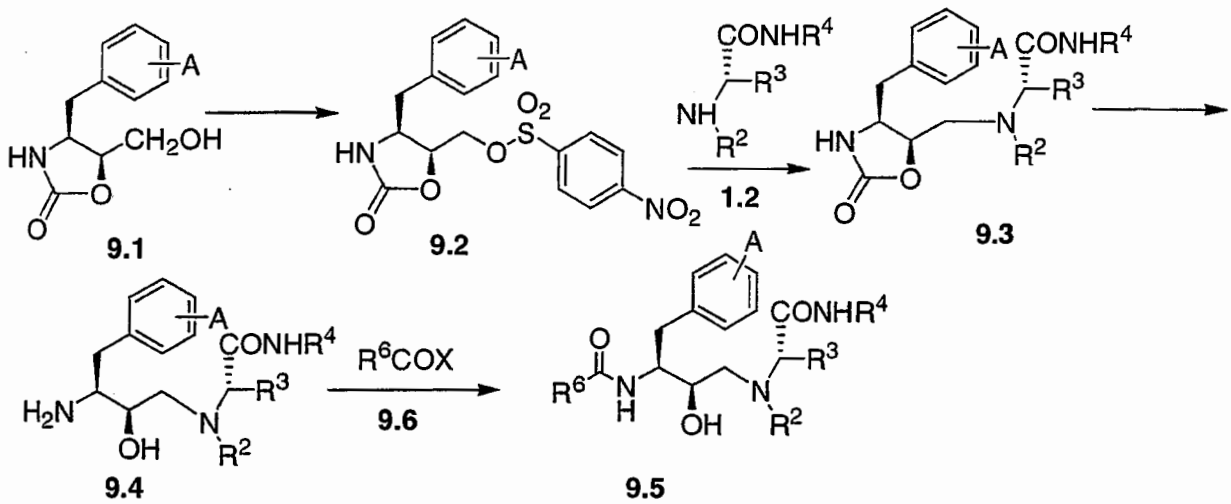
The procedures illustrated in Schemes **9** and **10** depict the preparation of the compounds **9.5** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **11** illustrates the conversion of compounds **9.5** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **2**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **24 -69**).

Schemes **12** and **13** depict the preparation of compounds **2** in which X is sulfur. As shown in Scheme **12**, a substituted thiophenol **12.2**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, is reacted with methanesulfonic acid 2-benzyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester **12.1**, the preparation of which is described in J. Org. Chem, 2000, 65, 1623, to afford the displacement product **12.3**. The conditions for the reaction are the same as described above for the preparation of the thioether **7.3**. Methods for the preparation of the substituted thiophenol **12.2** are described below, Schemes **35** - **44**. The thioether product **12.3** is then transformed, using the series of reactions described above, Scheme **7**, for the conversion of the thioether **7.3** into the amine **7.9**. The conditions employed for this series of reactions are the same as those described above, (Scheme **7**). The amine **12.4** is then reacted with the carboxylic acid or activated derivative thereof, **9.6** to afford the amide **12.5**. The conditions for the reaction are he same as those described above for the preparation of the amide **9.5**.

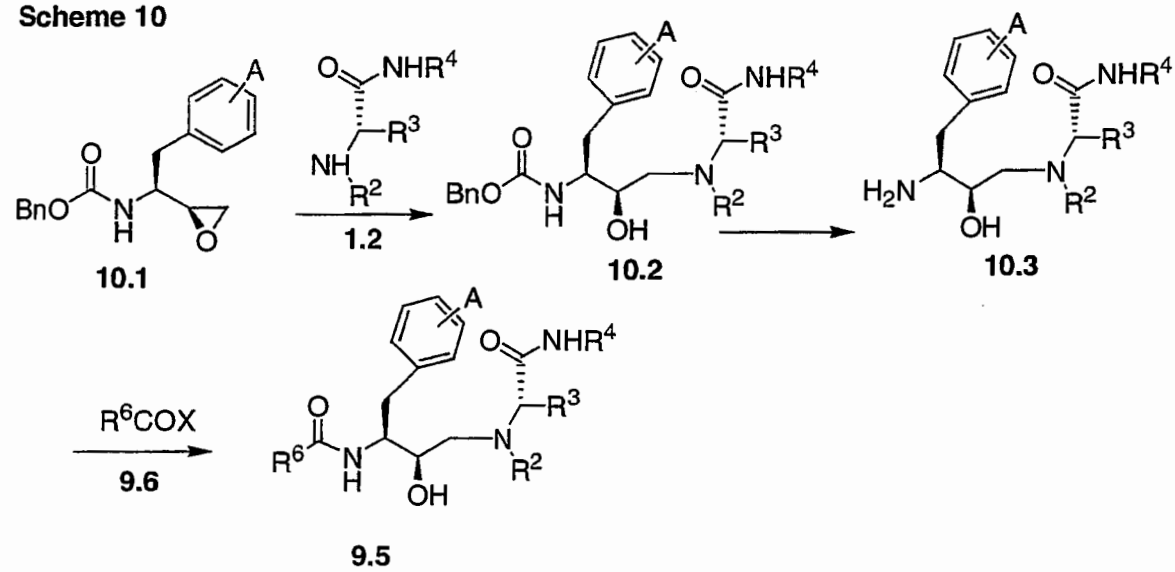
The procedures illustrated in Scheme **12** depict the preparation of the compounds **12.5** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **13** illustrates the conversion of compounds **12.5**

in which A is a precursor to the group link-P(O)$(OR^1)_2$ into the compounds **2**. Procedures for the conversion of the substituent A into the group link-P(O)$(OR^1)_2$ are illustrated below, (Schemes **24 - 69**).

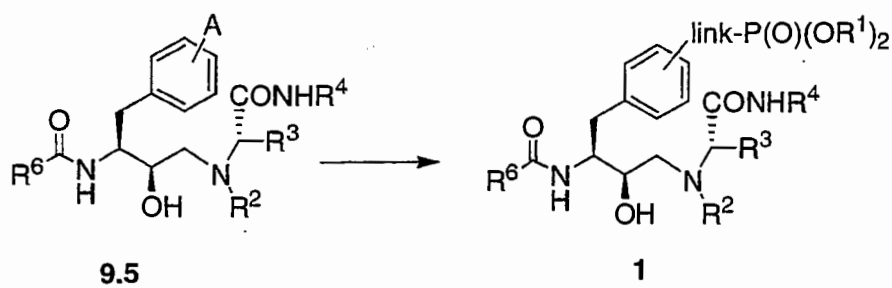
Scheme 9



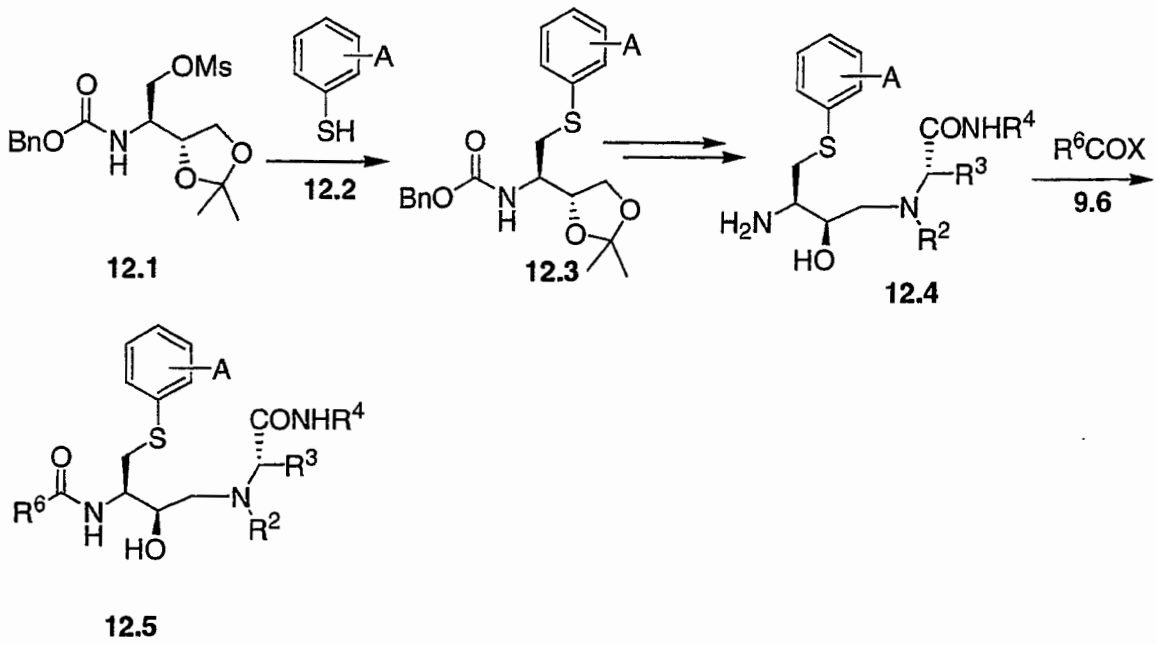
Scheme 10



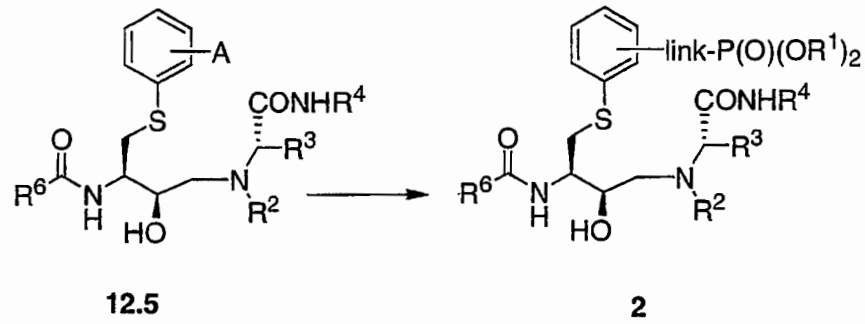
Scheme 11



Scheme 12



Scheme 13



Preparation of the phosphonate intermediates 3.

Schemes **14-16** depict the preparation of the phosphonate esters **3** in which X is a direct bond. As shown in Scheme **14**, the oxirane **1.1**, the preparation of which is described above, is reacted with the amine **14.1** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, to yield the hydroxyamine **14.2**. The conditions for the reaction are the same as described above for the preparation of the amine **1.3**. Methods for the preparation of the amine **14.1** are described below, Schemes **45** -

48. The hydroxyamine product **14.2** is then deprotected to afford the free amine **14.3**. The conditions for the debenzylation reaction are the same as those described above for the preparation of the amine **1.4**. (Scheme **1**). The amine **14.3** is then coupled with the carboxylic acid or activated derivative thereof, **9.6**, to afford the amide **14.4**, using the conditions described above for the preparation of the amide **12.5**.

Scheme **15** illustrates an alternative method for the preparation of the phosphonate esters **14.4**. In this reaction sequence, the 4-nitrobenzenesulfonate **4.2**, the preparation of which is described above, (Scheme **4**), is reacted with the amine **14.1**, in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, to yield the amine **15.1**. The reaction is conducted under the same conditions as described above for the preparation of the amide **4.3**. The oxazolidine moiety present in the product is then removed, using the procedure described above for the conversion of the oxazolidine **4.3** into the hydroxyamine **4.4**, to afford the hydroxyamine **15.2**. The latter compound is then coupled, as described above, with the carboxylic acid or activated derivative thereof, **9.6**, to afford the amide **14.4**.

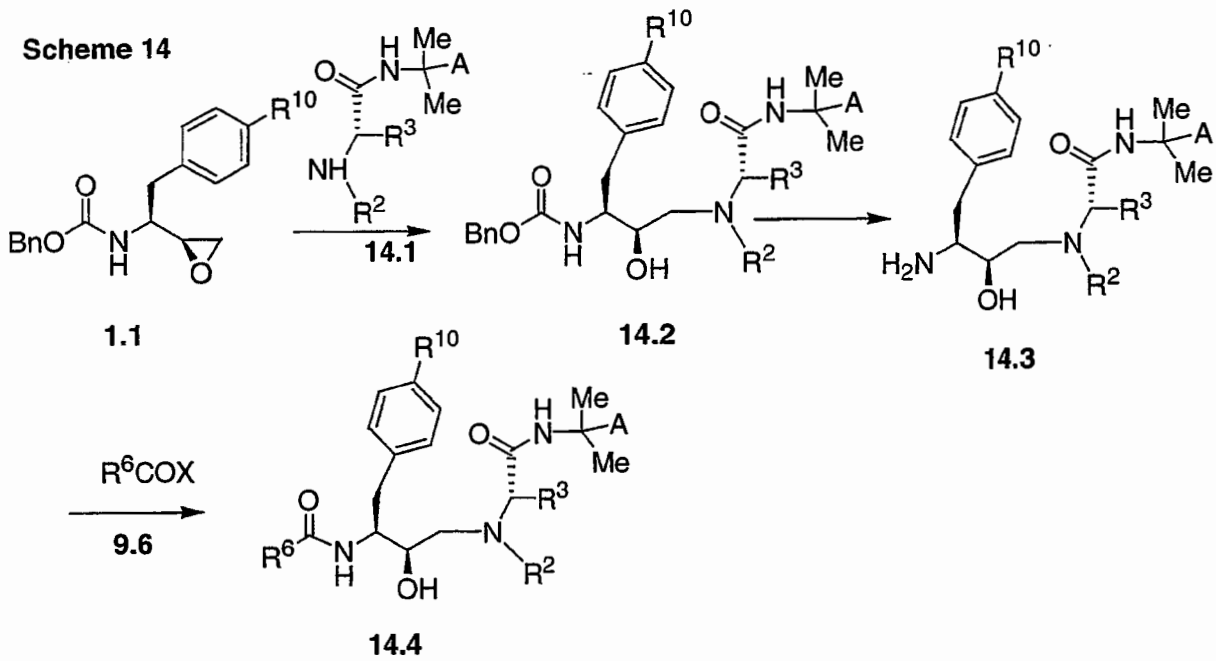
The procedures illustrated in Schemes **14** and **15** depict the preparation of the compounds **14.4** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **16** illustrates the conversion of compounds **14.4** in which A is a precursor to the group link-P(O)$(OR^1)_2$ into the compounds **3**. Procedures for the conversion of the substituent A into the group link-P(O)$(OR^1)_2$ are illustrated below, (Schemes **24 - 69**).

Schemes **17** and **18** illustrates the preparation of the phosphonate esters **3** in which X is sulfur. As shown in Scheme **17**, the oxirane **7.7**, the preparation of which is described above, (Scheme **7**) is reacted with the amine **14.1**. The conditions for the ring-opening reaction are the same as those described above for the preparation of the aminoalcohol **7.8**, (Scheme **7**). The benzyloxycarbonyl protecting group is then removed to produce the free amine **17.2**. The conditions for the deprotection reaction are the same as those described above for the conversion of the protected amine **7.8** to the amine **7.9** (Scheme **7**) The amine product **17.2** is

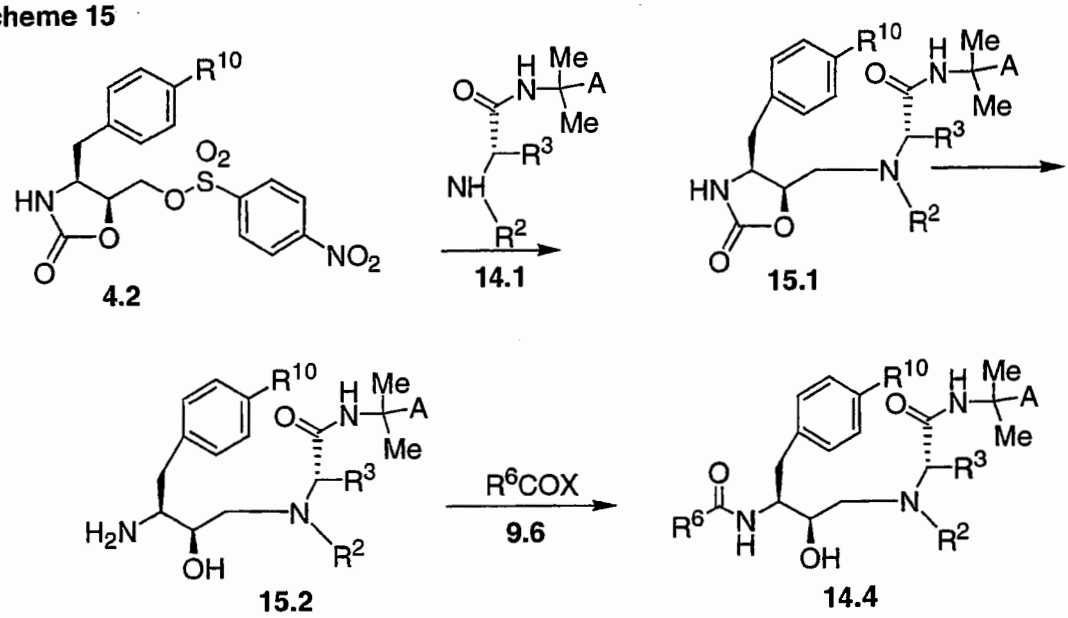
then coupled with the carboxylic acid or activated derivative thereof, **9.6**, using the same conditions as described above, to afford the amide **17.3**.

The procedures illustrated in Scheme **17** depict the preparation of the compound **17.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **18** illustrates the conversion of compounds **17.3** in which A is a precursor to the group link-P(O)$(OR^1)_2$ into the compounds **3**. Procedures for the conversion of the substituent A into the group link-P(O)$(OR^1)_2$ are illustrated below, (Schemes **24 - 69**).

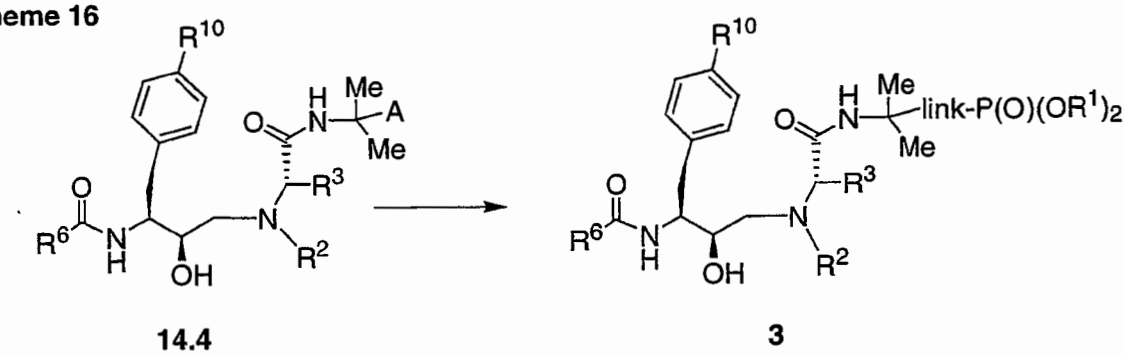
Scheme 14



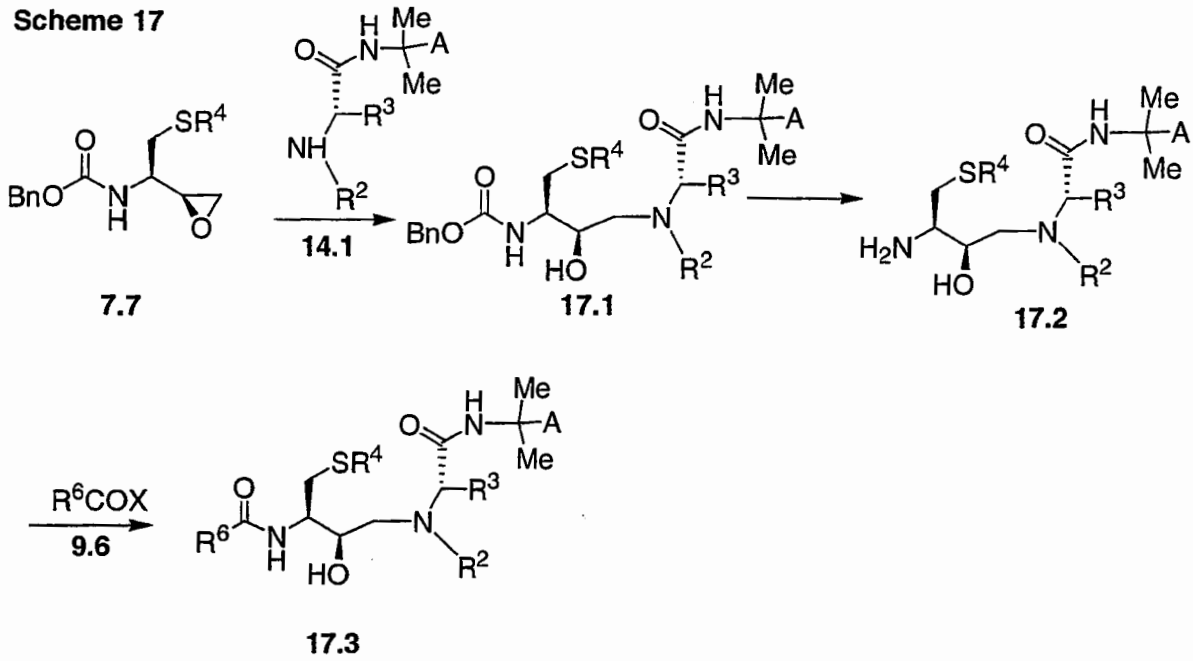
Scheme 15



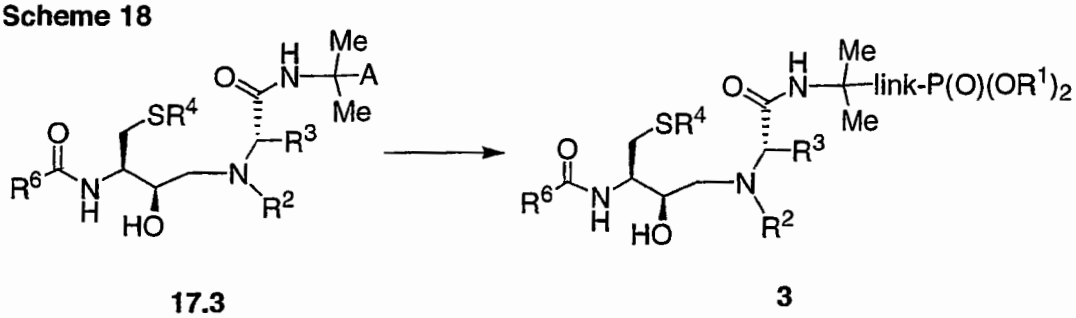
Scheme 16



Scheme 17



Scheme 18



Preparation of the phosphonate intermediates 4.

Scheme **19** illustrates one method for the preparation of the phosphonate esters **4** in which X is a direct bond. In this reaction sequence, the oxirane **1.1**, the preparation of which is described above (Scheme **2**) is reacted with the decahydroisoquinoline amine **19.1**, in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, to afford the aminoalcohol product **19.2**. The conditions for the ring-opening reaction are the same as those described above for the preparation of the aminoalcohol **1.3**. The preparation of the decahydroisoquinoline derivatives **19.1** is described below, (Schemes **48a - 52**). The cbz protecting group is then removed to yield the free amine **19.3**, using the same conditions as described above for the preparation of the amine **1.4**,

(Scheme **1**). The amine **19.3** is then coupled with the carboxylic acid or activated derivative thereof, **9.6**, using the same conditions as described above, to afford the amide **19.4**.

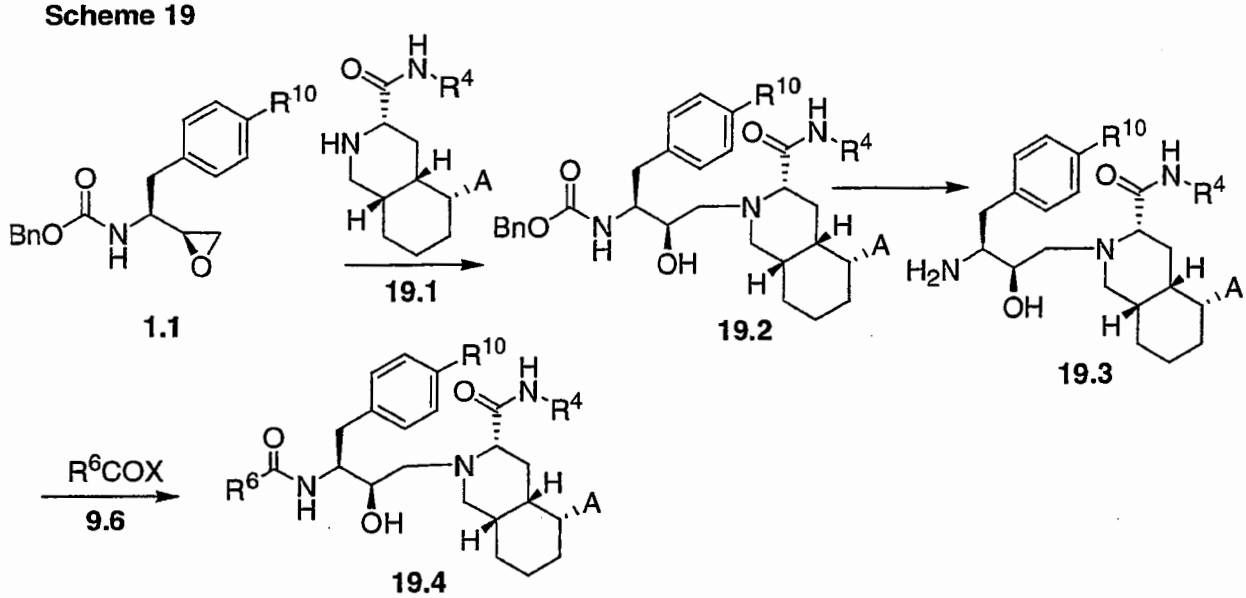
Scheme **20** illustrates an alternative method for the preparation of the phosphonate intermediates **19.4**. In this procedure, the 4-nitrobenzenesulfonyl ester **4.2**, the preparation of which is described above, (Scheme **4**) is reacted with the decahydroisoquinoline derivative **20.1**, in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. The reaction conditions for the displacement reaction are the same as those described above for the preparation of the amine **4.3**, (Scheme **4**). The oxazolidinone moiety present in the product **20.2** is then hydrolyzed, using the procedures described above (Scheme **4**) to afford the free amine **20.3**. This compound is then coupled with the carboxylic acid or activated derivative thereof, **9.6**, using the same conditions as are described above, to afford the amide product **19.4**.

The procedures illustrated in Schemes **19** and **20** depict the preparation of the compounds **19.4** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **21** illustrates the conversion of compounds **19.4** in which A is a precursor to the group link-P(O)$(OR^1)_2$ into the compounds **4**. Procedures for the conversion of the substituent A into the group link-P(O)$(OR^1)_2$ are illustrated below, (Schemes **24 - 69**).

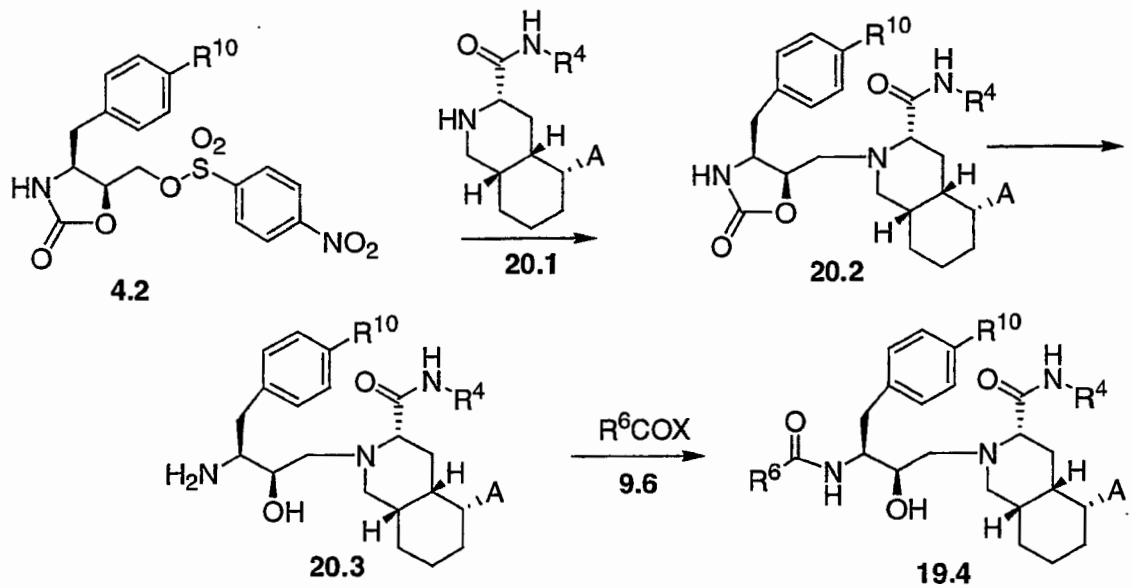
Schemes **22** and **23** depict the preparation of the phosphonate esters **4** in which X is sulfur. As shown in Scheme **22**, the oxirane **7.7**, prepared as described above (Scheme **7**) is reacted with the decahydroisoquinoline derivative **19.1**, in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. The reaction is conducted under the same conditions as described above for the preparation of the amine **7.8**, (Scheme **7**), to produce the hydroxyamine **22.1**. The cbz protecting group present in the product **22.1** is then removed, using the same procedures as described above (Scheme **7**) to afford the free amine **22.2**. This material is then coupled with the carboxylic acid or activated derivative thereof, **9.6** to yield the amide **22.3**. The coupling reaction is preformed under the same conditions as previously described.

The procedures illustrated in Scheme **22** depict the preparation of the compounds **22.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **23** illustrates the conversion of compounds **22.3** in which A is a precursor to the group link-P(O)$(OR^1)_2$ into the compounds **4**. Procedures for the conversion of the substituent A into the group link-P(O)$(OR^1)_2$ are illustrated below, (Schemes **24 - 69**).

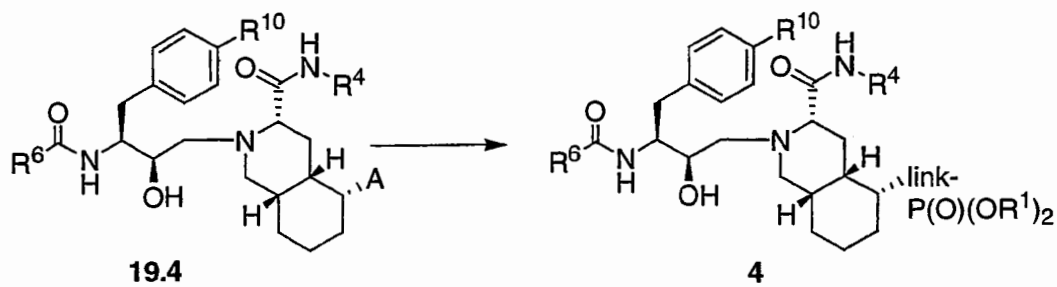
Scheme 19



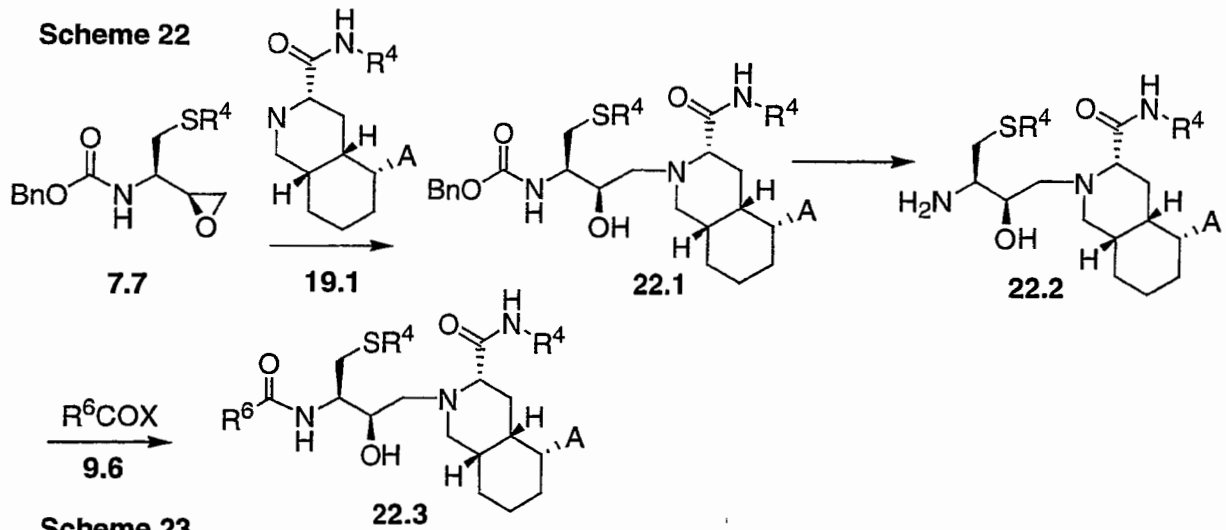
Scheme 20



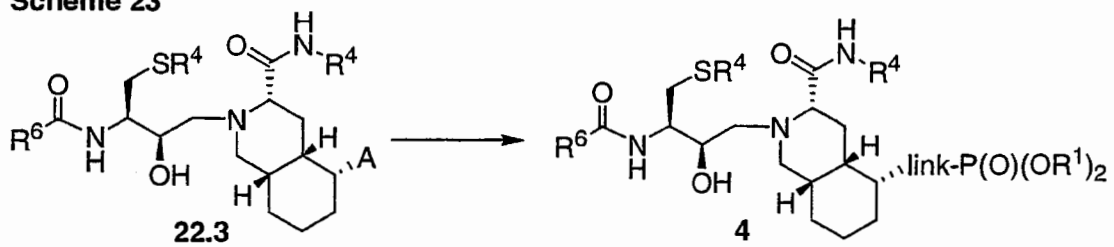
Scheme 21



Scheme 22

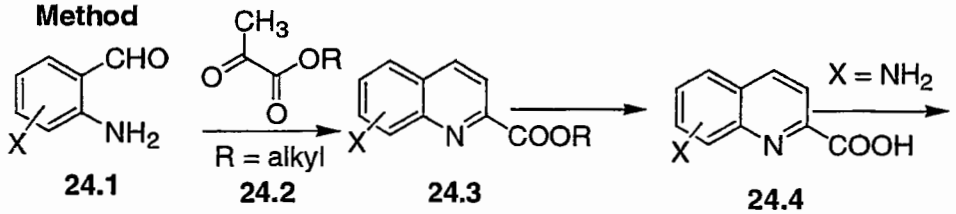


Scheme 23

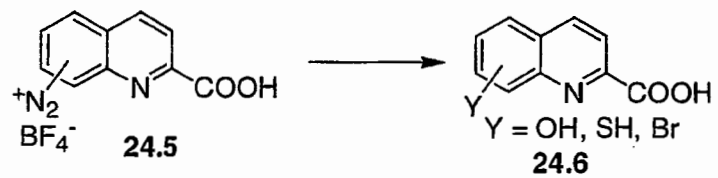


Scheme 24

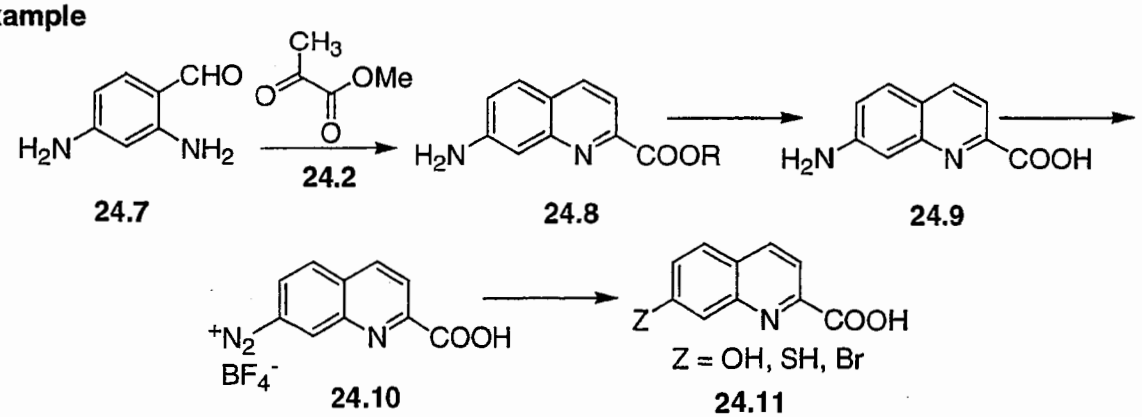
Method



X = OH, SH, NH_2, Br



Example



Preparation of quinoline 2-carboxylic acids 1.7 incorporating phosphonate moieties or precursors thereto.

The reaction sequence depicted in Scheme **1** requires the use of a quinoline-2-carboxylic acid reactant **1.7** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br.

A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het. Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines is described, for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p. 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.

Scheme **24** illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde **24.1** is reacted with an alkyl pyruvate ester **24.2**, in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester **24.3**. Hydrolysis of the ester, for example by the use of aqueous base, then afford the corresponding carboxylic acid **24.4**. The carboxylic acid product **24.4** in which X is NH_2 can be further transformed into the corresponding compounds **24.6** in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium

tetrafluoborate, is then heated in aqueous solution, for example as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol **24.6**, X = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, **24.6**, Y = Br. Alternatively, the diazonium tetrafluoborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 200, 24, 123, to afford the thiol **24.6**, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters **24.3** instead of the carboxylic acids **24.5**.

For example, 2,4-diaminobenzaldehyde **24.7** (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate **24.2** in methanol, in the presence if a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate **24.8**. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **24.9**. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoborate **24.10** by reaction with sodium nitrite and tetrafluoboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, **24.11**, Z = OH. Alternatively, the diazonium tetrafluoborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-bromoquinoline-2-carboxylic acid **24.11**, X = Br. Alternatively, the diazonium tetrafluoborate **24.10** is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid **24.11**, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde **24.7**, different aminobenzaldehydes **24.1**, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids **24.6** are obtained. The variously substituted quinoline carboxylic acids and esters can then be transformed, as described below, (Schemes **25** – **27**) into phosphonate-containing derivatives.

Scheme **25** depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester **25.1** is transformed, via a

diazotization procedure as described above (Scheme **24**) into the corresponding phenol or thiol **25.2**. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate **25.3**, under the conditions of the Mitsonobu reaction, to afford the phosphonate ester **25.4**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the thioether products **25.5**. Basic hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **25.6**.

For example, methyl 6-amino-2-quinoline carboxylate **25.7**, prepared as described in J. Het. Chem., 1989, 26, 929, is converted, by means of the diazotization procedure described above, into methyl 6-mercaptoquinoline-2-carboxylate **25.8**. This material is reacted with a dialkyl hydroxymethylphosphonate **25.9** (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether **25.10**. Basic hydrolysis then afford the carboxylic acid **25.11**.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline carboxylate **25.7**, different aminoquinoline carboxylic esters **25.1**, and/or different dialkyl hydroxymethylphosphonates **25.9** the corresponding phosphnoate ester products **25.3** are obtained.

Scheme **26** illustrates the preparation of quinoline-2-carboxylic acids incorporating phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester **26.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate **26.2**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate.

Thus, Heck coupling of the bromo compound **26.1** and the olefin **26.2** affords the olefinic ester **26.3**. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid **26.4**. Optionally, the unsaturated carboxylic acid **26.4** can be reduced to afford the saturated analog **26.5**. The reduction reaction can be effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5. For example, methyl 7-bromoquinoline-2-carboxylate, **26.6**, prepared as described in J. Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60°C with a dialkyl vinylphosphonate **26.7** (Aldrich) in the presence of 2 mol% of tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product **26.8**. The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid **26.9**. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product **26.10**.

Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate **26.6**, different bromoquinoline carboxylic esters **26.1**, and/or different dialkyl alkenylphosphonates **26.2**, the corresponding phosphonate ester products **26.4** and **26.5** are obtained.

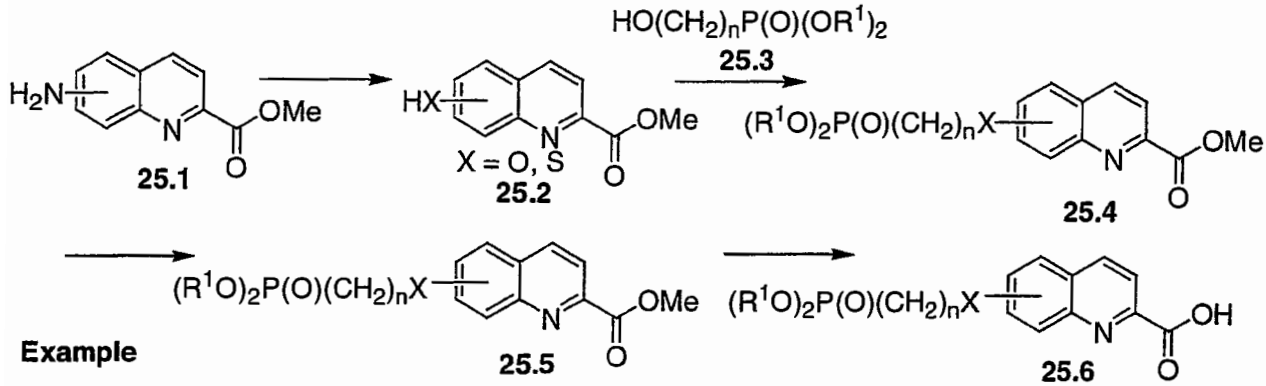
Scheme **27** depicts the preparation of quinoline-2-carboxylic acids **27.5** in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate **27.1** is reacted with a phosphonate aldehyde **27.2** under reductive amination conditions, to afford the aminoalkyl product **27.3**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product **27.4** is then hydrolyzed to yield the free carboxylic acid **27.5**.

For example, methyl 7-aminoquinoline-2-carboxylate **27.6**, prepared as described in J. Amer. Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **27.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **27.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **27.9**.

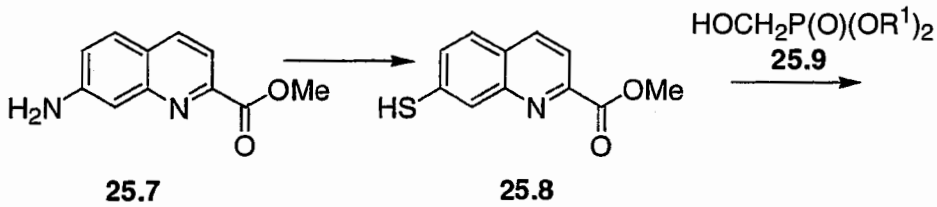
Using the above procedures, but employing, in place of the formylmethyl phosphonate **27.2**, different formylalkyl phosphonates, and/or different aminoquinolines **27.1**, the corresponding products **27.5** are obtained.

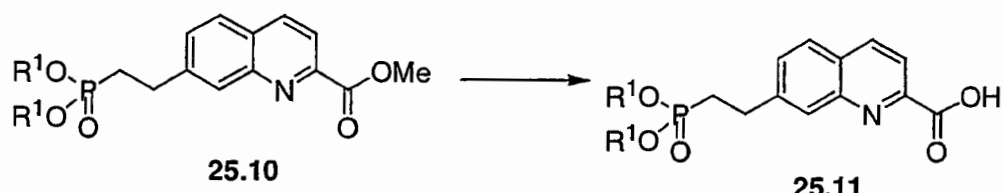
Scheme 25

Method



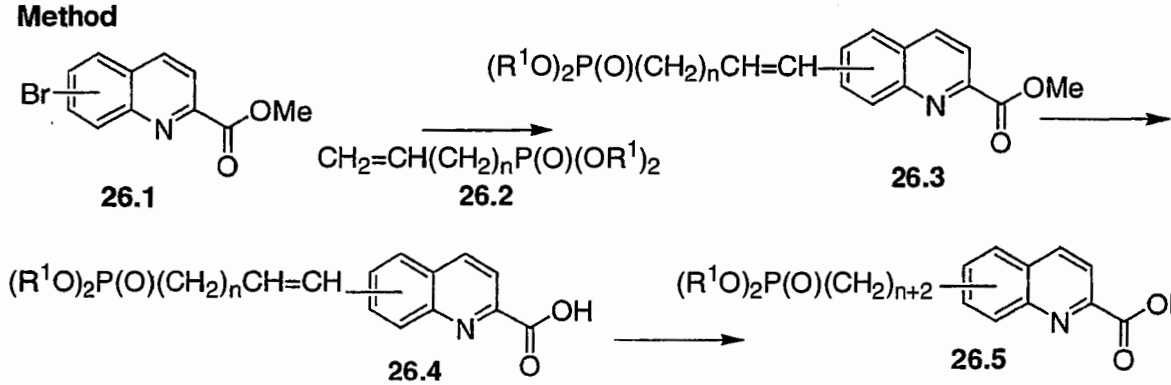
Example



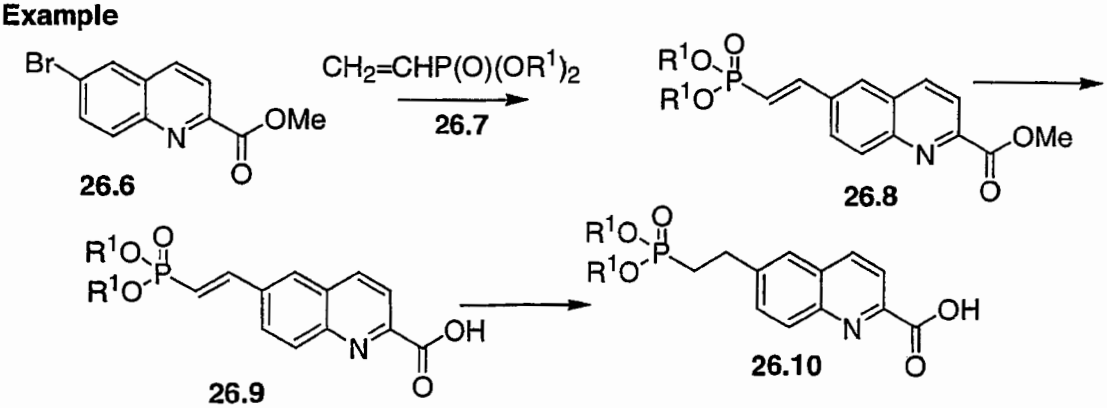


Scheme 26

Method

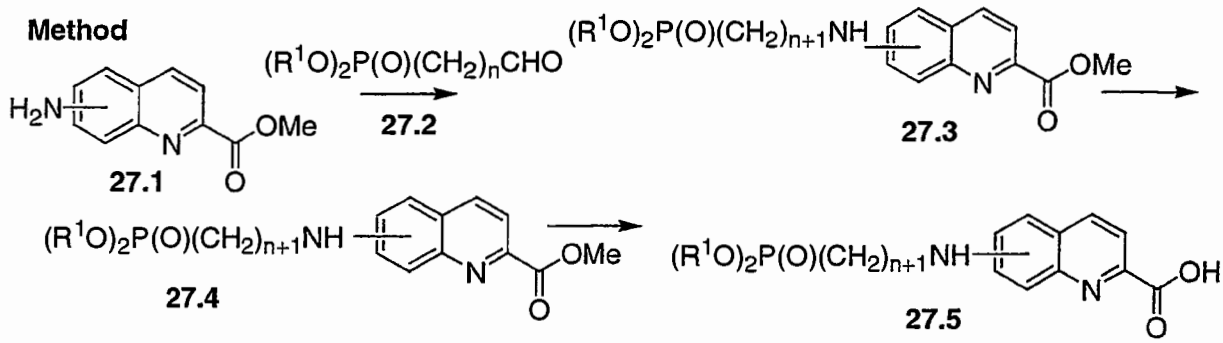


Example

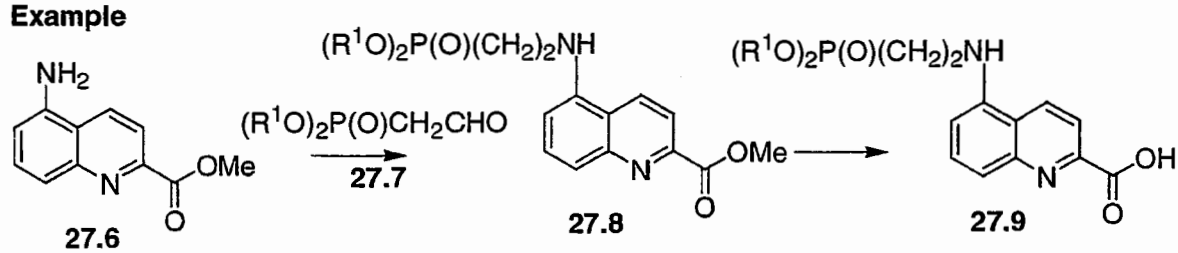


Scheme 27

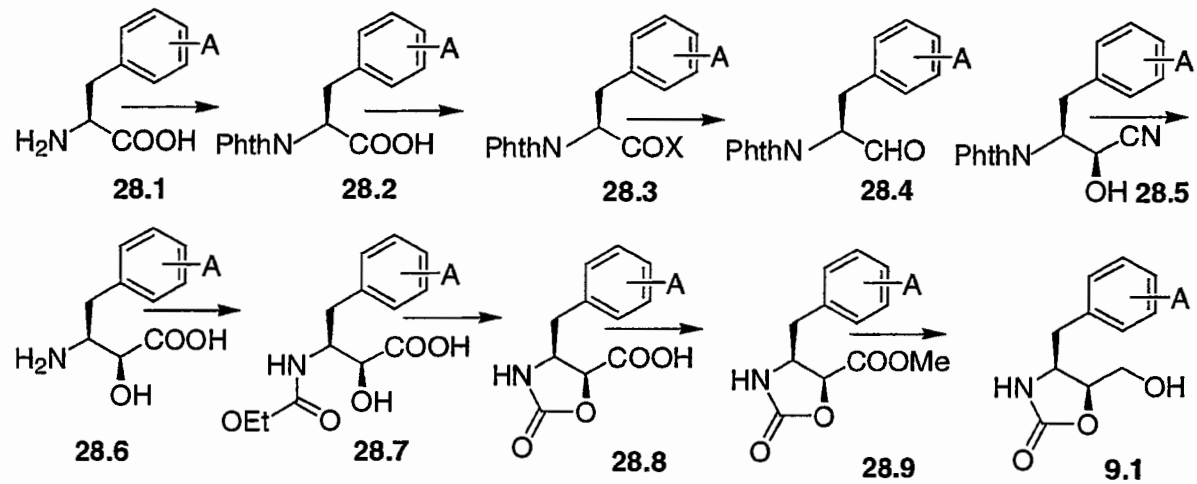
Method



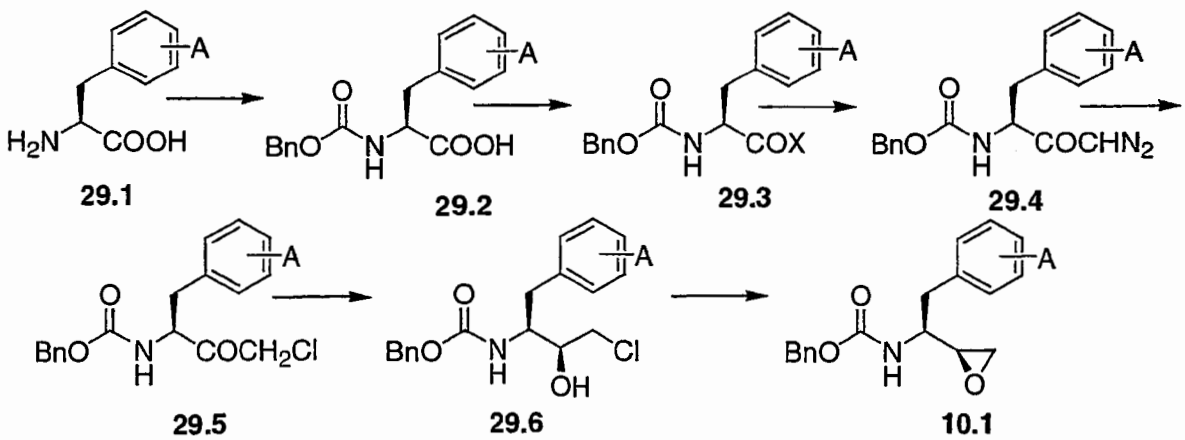
Example



Scheme 28



Scheme 29



Preparation of phenylalanine derivatives 9.1 and 10.1 incorporating phosphonate moieties or precursors thereto.

Scheme **28** illustrates the preparation of the hydroxymethyl oxazolidine derivative **9.1**, in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br. In this reaction sequence, the substituted phenylalanine **28.1**, in which A is as defined above, is transformed, via the intermediates **28.2-28.9**, into the hydroxymethyl product **9.1**. The reaction conditions for each step in the sequence are the same as those described above for the corresponding step shown in Scheme **5**. The conversion of the substituent A into the group link-P(O)$(OR^1)_2$ may be effected at any convenient step in the reaction sequence, or after the reactant **9.1** has been incorporated into the intermediates **9.5** (Scheme **9**). Specific examples of the preparation of the hydroxymethyl oxazolidinone reactant **9.1** are shown below, (Schemes **30-31**).

Scheme **29** illustrates the preparation of the oxirane intermediate **10.1**, in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br. In this reaction sequence, the substituted phenylalanine **29.1**, in which A is as defined above, is transformed, via the intermediates **29.2-29.6**, into the oxirane **10.1**. The reaction conditions for each step in the sequence are the same as those described above for the corresponding step shown in Scheme **2**. The conversion of the substituent A into the group link-P(O)$(OR^1)_2$ may be effected at any convenient step in the reaction sequence, or after the reactant **10.1** has been incorporated into the intermediates **9.5** (Scheme **10**). Specific examples of the preparation of the oxiranes reactant **10.1** are shown below, (Schemes **32-34**).

Scheme **30** depicts the preparation of hydroxymethyloxazolidinones **30.9** in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **30.1** is converted, using the series of reactions illustrated in Scheme **28**, into the bromophenyloxazolidinone **30.2**. The bromophenyl compound is then coupled, in the presence of a palladium (0) catalyst, with a dialkyl phosphite **30.3**, to afford the phosphonate product **30.4**. The reaction between aryl bromide and dialkyl phosphites to yield aryl phosphonates is described in Synthesis, 56, 1981, and in J. Med. Chem., 1992, 35, 1371.

The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°C, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The carbomethoxy substituent in the resultant phosphonate ester **30.4** is then reduced with sodium borohydride to the corresponding hydroxymethyl derivative **30.5**, using the procedure described above (Scheme **28**)

For example, 3-bromophenylalanine **30.6**, prepared as described in Pept. Res., 1990, 3, 176, is converted, using the sequence of reactions shown in Scheme **28**, into 4-(3-bromo-benzyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester **30.7**. This compound is then coupled with a dialkyl phosphite **30.3**, in toluene solution at reflux, in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to afford the phosphonate ester **30.8**. The carbomethoxy substituent is then reduced with sodium borohydride, as described above, to afford the hydroxymethyl product **30.9**.

Using the above procedures, but employing, in place of 3-bromophenylalanine **30.6** different bromophenylalanines **30.1** and/or different dialkyl phosphites **30.3**, the corresponding products **30.5** are obtained.

Scheme **31** illustrates the preparation of phosphonate-containing hydroxymethyl oxazolidinones **31.9** and **31.12** in which the phosphonate group is attached by means of a heteroatom and a carbon chain. In this sequence of reactions, a hydroxy or thio-substituted phenylalanine **31.1** is converted into the benzyl ester **31.2** by means of a conventional acid catalyzed esterification reaction. The hydroxyl or mercapto group is then protected. The protection of phenyl hydroxyl and thiol groups are described, respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, and p. 277. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The protected ester **31.3** is then reacted with phthalic anhydride, as described above (Scheme **28**) to afford the phthalimide **31.4**. The

benzyl ester is then removed, for example by catalytic hydrogenation or by treatment with aqueous base, to afford the carboxylic acid **31.5**. This compound is transformed, by means of the series of reactions shown in Scheme **28**, into the carbomethoxy oxazolidinone **31.6**, using in each step the same conditions as are described above (Scheme **28**). The protected OH or SH group is then deprotected. Deprotection of phenols and thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978. The resultant phenol or thiol **31.7** is then reacted with a hydroxyalkyl phosphonate **31.20** under the conditions of the Mitsonobu reaction, as described above (Scheme **25**), to afford the ether or thioether **31.8**. The latter compound is then reduced with sodium borohydride, as described above (Scheme **28**) to afford the hydroxymethyl analog **31.9**.

Alternatively, the phenol or thiophenol **31.7** is reacted with a dialkyl bromoalkyl phosphonate **31.10** to afford the alkylation product **31.11**. The alkylation reaction is preformed in a polar organic solvent such as dimethylformamide, acetonitrile and the like, optionally in the presence of potassium iodide, and in the presence of an inorganic base such as potassium or cesium carbonate, or an organic base such as diazabicyclononene or dimethylaminopyridine. The ether or thioether product is then reduced with sodium borohydride to afford the hydroxymethyl compound **31.12**.

For example, 3-hydroxyphenylalanine **31.13** (Fluka) is converted in to the benzyl ester **31.14** by means of a conventional acid-catalyzed esterification reaction. The ester is then reacted with tert-butylchlorodimethylsilane and imidazole in dimethylformamide, to afford the silyl ether **31.15**. The protected ether is then reacted with phthalic anhydride, as described above (Scheme **28**) to yield the phthalimido-protected compound **31.16**. Basic hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, then affords the carboxylic acid **31.17**. This compound is then transformed, by means of the series of reactions shown in Scheme **28**, into the carbomethoxy-substituted oxazolidinone **31.18**. The silyl protecting group is then removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, to produce the phenol **31.19**. The latter compound is reacted with a

dialkyl hydroxymethyl phosphonate **31.20** diethylazodicarboxylate and triphenylphosphine, by means of the Mitsonobu reaction, as described above (Scheme **25**) to yield the phenolic ether **31.21**. The carbomethoxy group is then reduced by reaction with sodium borohydride, as described above, to afford the carbinol **31.22**.

Using the above procedures, but employing, in place of 3-hydroxyphenylalanine **31.13**, different hydroxy or mercapto-substituted phenylalanines **31.1**, and/or different dialkyl hydroxyalkyl phosphonates **31.20**, the corresponding products **31.9** are obtained.

As a further example of the methods illustrated in Scheme **31**, 4-mercaptophenylalanine **31.23**, prepared as described in J. Amer. Chem. Soc., 1997, 119, 7173, is converted into the benzyl ester **31.24** by means of a conventional acid-catalyzed esterification reaction. The mercapto group is then protected by conversion to the S-adamantyl group, by reaction with 1-adamantanol and trifluoroacetic acid at ambient temperature as described in Chem. Pharm. Bull., 26, 1576, 1978. The amino group is then converted into the phthalimido group as described above, and the ester moiety is hydrolyzed with aqueous base to afford the carboxylic acid **31.27**. The latter compound is then transformed, by means of the series of reactions shown in Scheme **28**, into the carbomethoxy oxazolidinone **31.28**. The adamantyl protecting group is then removed by treatment of the thioether **31.28** with mercuric acetate in trifluoroacetic acid at 0°C, as described in Chem. Pharm. Bull., 26, 1576, 1978, to produce the thiol **31.29**. The thiol is then reacted with one molar equivalent of a dialkyl bromoethylphosphonate **31.30**, (Aldrich) and cesium carbonate in dimethylformamide at 70°C, to afford the thioether product **31.31**. The carbomethoxy group is then reduced with sodium borohydride, as described above, to prepare the carbinol **31.32**.

Using the above procedures, but employing, in place of 4-mercaptophenylalanine **31.23**, different hydroxy or mercapto-substituted phenylalanines **31.10**, and/or different dialkyl bromoalkyl phosphonates **31.10**, the corresponding products **31.12** are obtained.

Scheme **32** illustrates the preparation of phenylalanine derivatives **32.3** in which the phosphonate group is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **32.1** is converted, by means of the series of reactions shown in Scheme **29** into the oxirane **32.2**. This compound is then coupled with a dialkyl phosphite **30.3**, in the presence of a palladium(0) catalyst and an organic base, to afford the phosphonate

oxirane **32.3**. The coupling reaction is performed under the same conditions previously described, (Scheme **30**).

For example, 3-bromophenylalanine **32.4**, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, into the oxirane **32.5**. This compound is reacted, in toluene solution at reflux temperature, with a dialkyl phosphonate **30.3**, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine to afford the phosphonate ester **32.6**.

Using the above procedures, but employing, in place of 4-bromophenylalanine **32.4**, different bromo-substituted phenylalanines **32.1**, and/or different dialkyl phosphites **30.3**, the corresponding products **32.3** are obtained.

Scheme **33** depicts the preparation of compounds **33.4** in which the phosphonate group is attached to the phenyl ring by means of a styrene moiety. In this reaction sequence, a vinyl-substituted phenylalanine **33.1** is converted, by means of the series of reactions shown in Scheme **29**, into the oxirane **33.2**. This compound is then coupled with a dialkyl bromophenylphosphonate **33.3**, employing the conditions of the Heck reaction, as described above (Scheme **26**) to afford the coupled product **33.4**.

For example, 4-vinylphenylalanine **33.5**, prepared as described in EP 206460, is converted, as described above, into the oxirane **33.6**. This compound is then coupled with a dialkyl 4-bromophenylphosphonate **33.7**, prepared as described in J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, to yield the phosphonate ester **33.8**.

Using the above procedures, but employing, in place of 4-vinylphenylalanine **33.5**, different vinyl-substituted phenylalanines **33.1**, and/or different dialkyl bromophenylphosphonates **33.3**, the corresponding products **33.4** are obtained.

Scheme **34** depicts the preparation of phosphonate-substituted phenylalanine derivatives in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom. In this procedure, a hydroxymethyl-substituted phenylalanine **34.1** is converted into the cbz protected methyl ester **34.2**, using the procedures described above (Scheme **29**). The product **34.2** is then converted into a halomethyl-substituted compound **34.3**. For example, the carbinol **34.2** is treated with triphenylphosphine and carbon tetrabromide, as

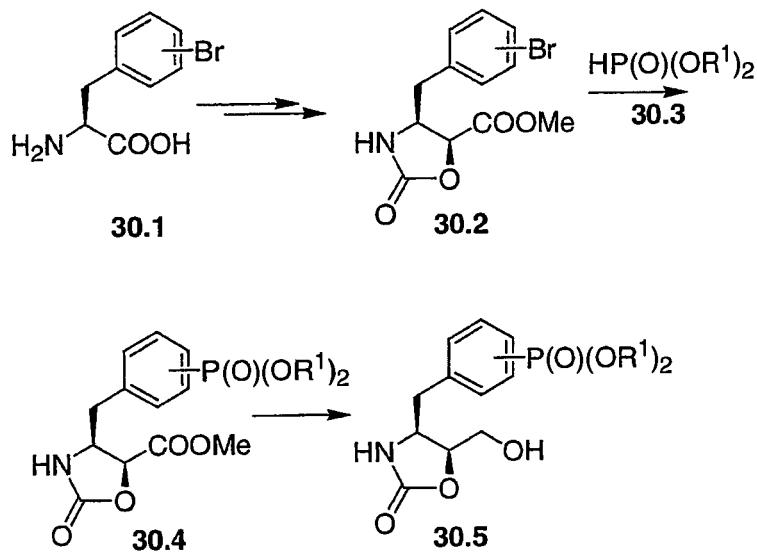
described in J. Amer. Chem. Soc., 108, 1035, 1986 to afford the product **34.3** in which Z is Br. The bromo compound is then reacted with a dialkyl terminally hetero-substituted alkylphosphonate **34.4**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is SH, NH_2 or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene or dimethylaminopyridine, can be employed. If X is OH, a strong base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **34.5,** which is hydrolyzed to afford the carboxylic acid **34.6**. The latter compound is then, by means of the sequence of reactions shown in Scheme **29**, is transformed into the epoxide **34.7**.

For example, the protected 4-hydroxymethyl-substituted phenylalanine derivative **34.9**, obtained from the 4-hydroxymethyl phenylalanine **34.8**, the preparation of which is described in Syn. Comm., 1998, 28, 4279, is converted into the bromo derivative **34.10**, as described above. The product is then reacted with a dialkyl 2-aminoethyl phosphonate **34.11**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the amine product **34.12**. The latter compound is then converted, using the sequence of reactions shown in Scheme **29**, into the epoxide **34.14**.

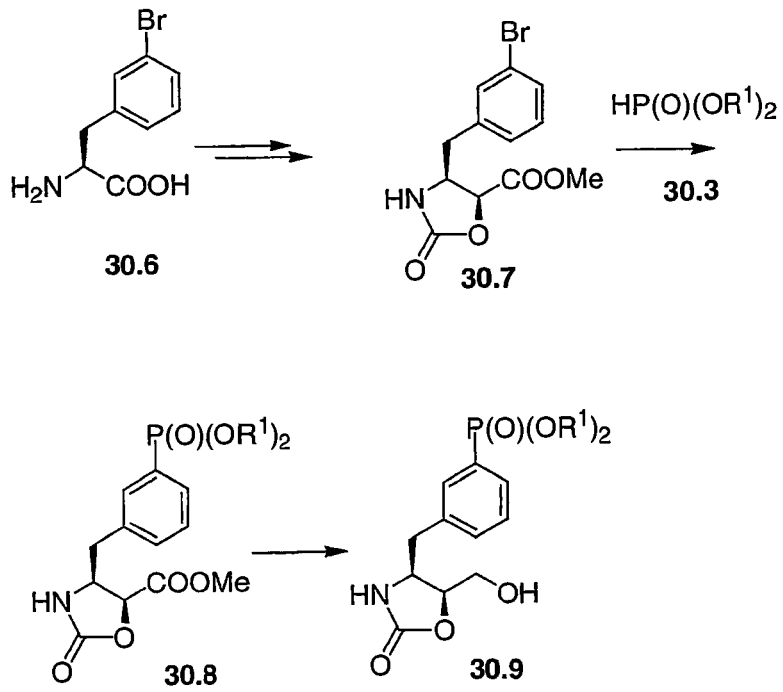
Using the above procedures, but employing different carbinols **34.1** in place of the carbinol **34.8**, and/or different phosphonates **34.4**, the corresponding products **34.7** are obtained.

Scheme 30

Method

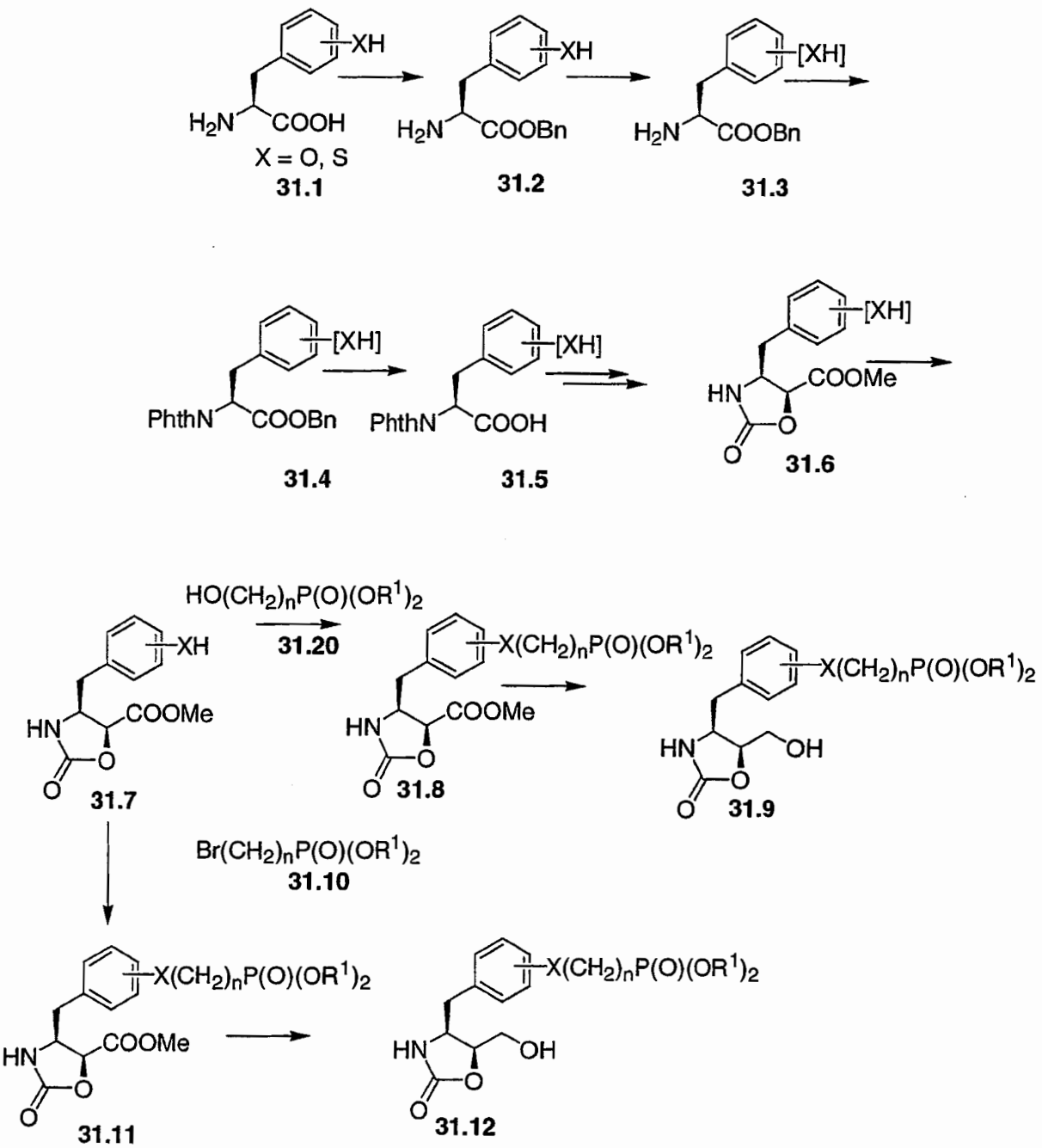


Example

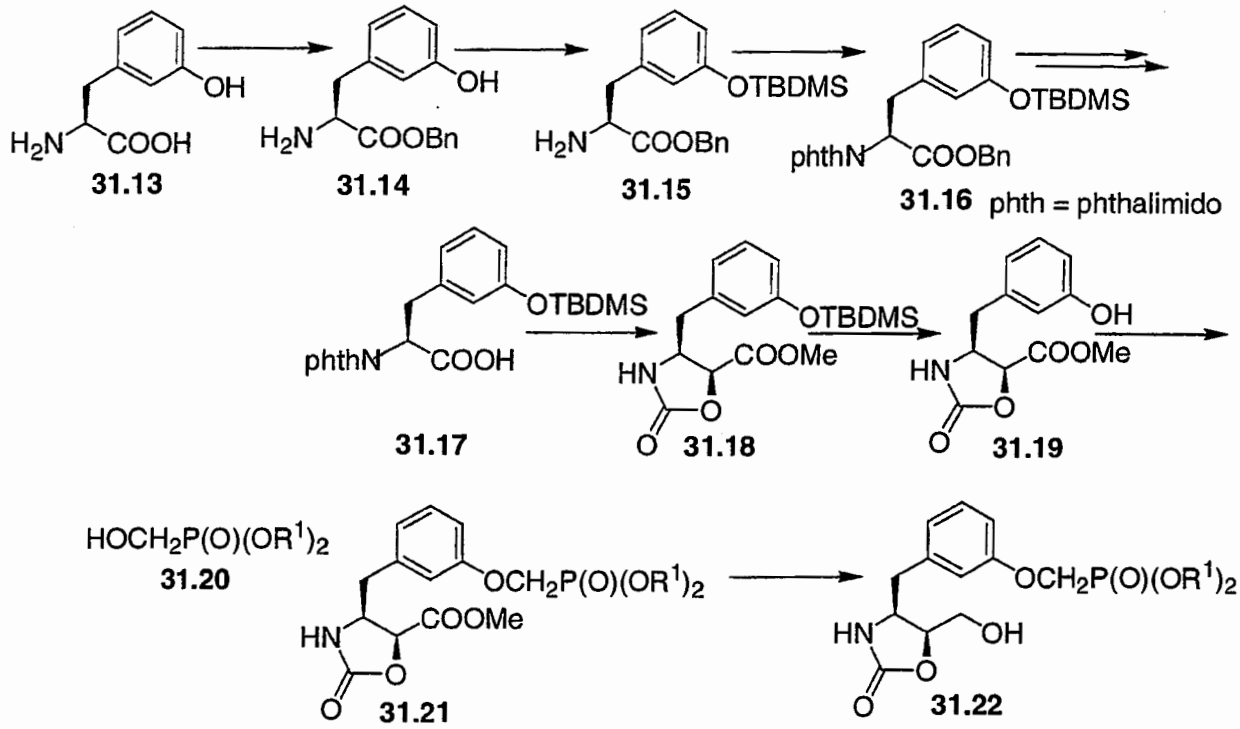


Scheme 31

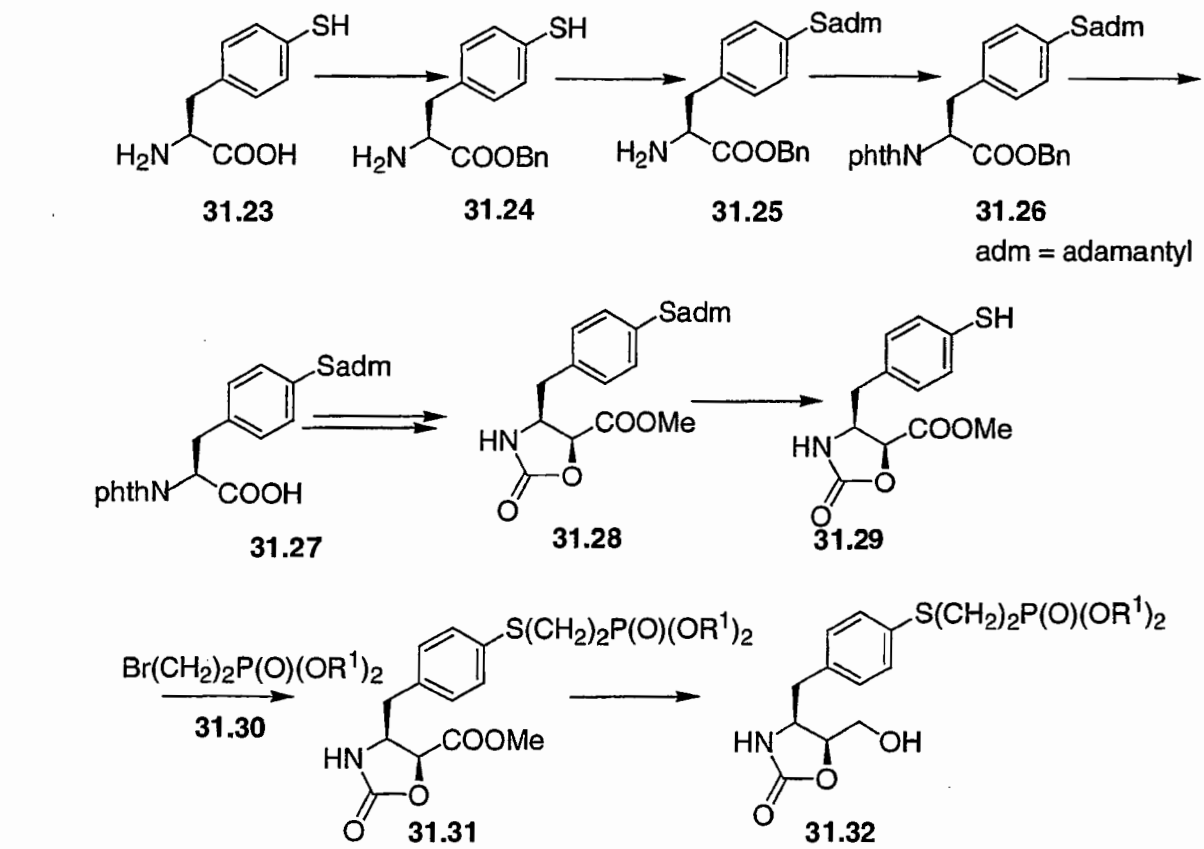
Method



Scheme 31 Example 1

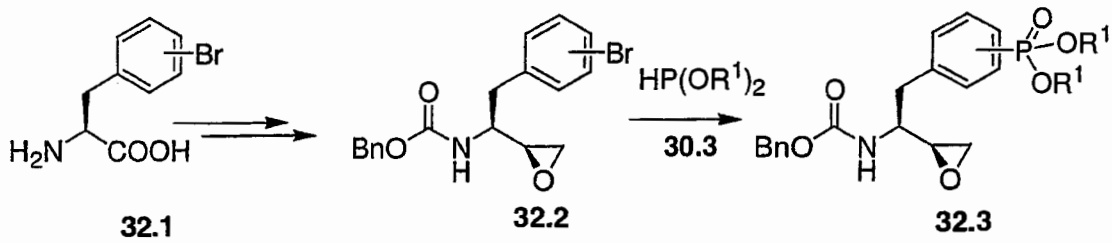


Scheme 31 Example 2

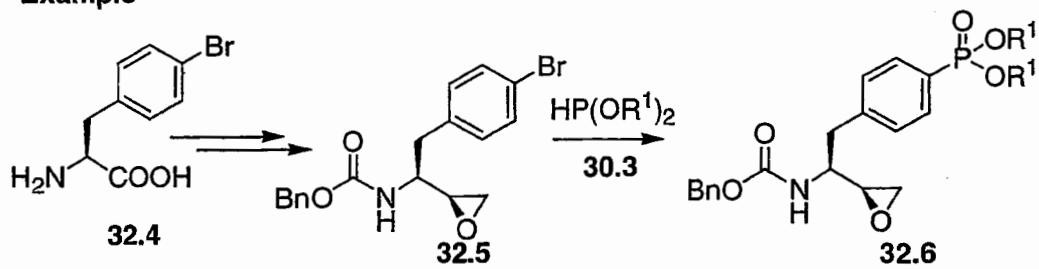


Scheme 32

Method

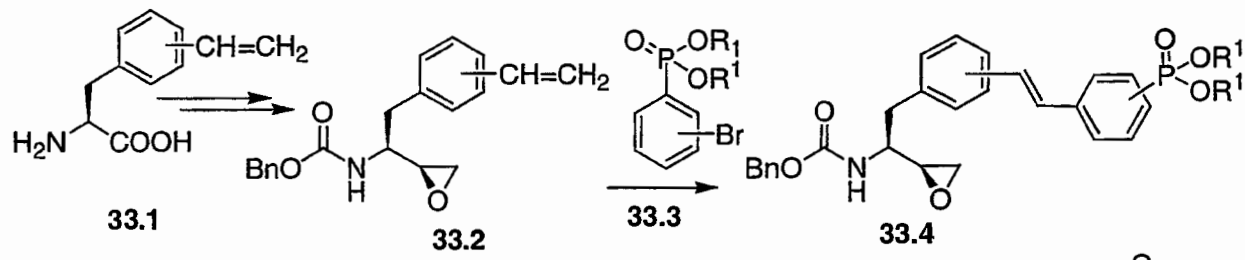


Example

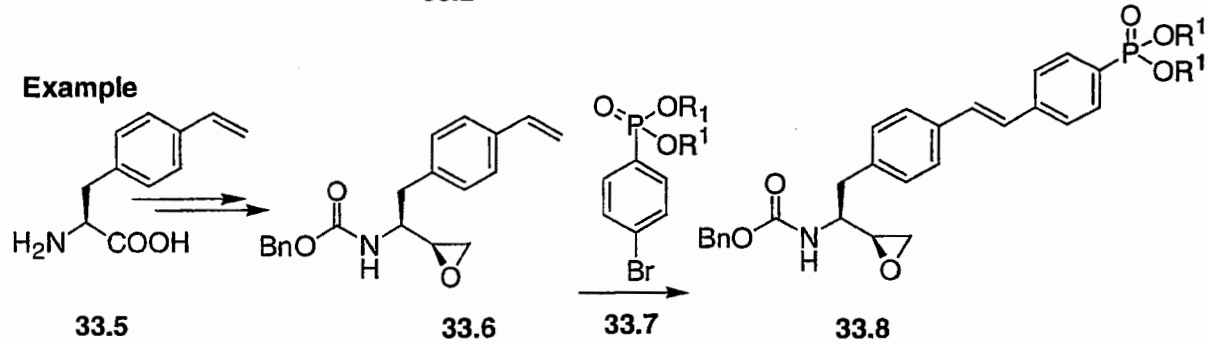


Scheme 33

Method

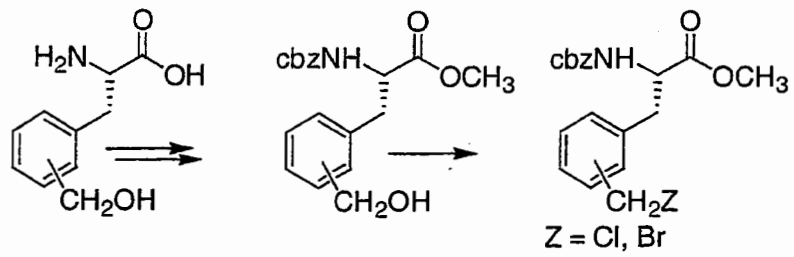


Example

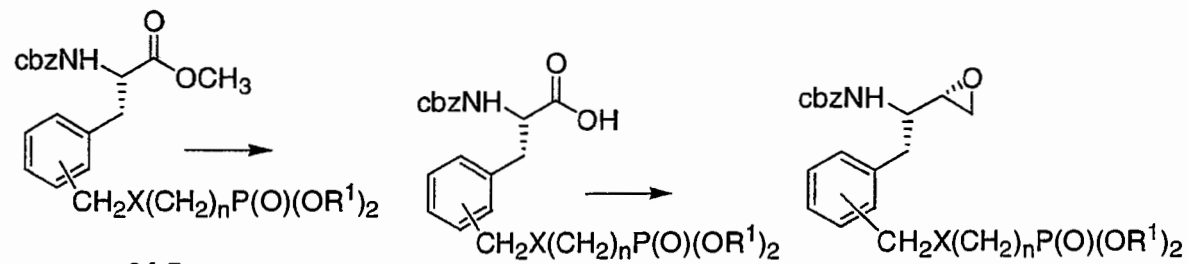


Scheme 34

Method

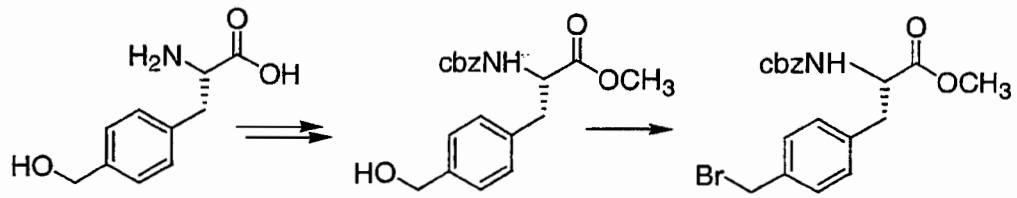


34.1 **34.2** **34.3** **34.4**

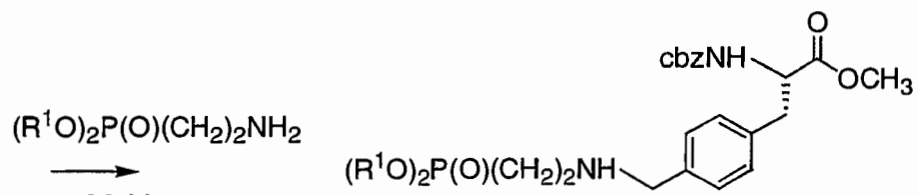


34.5 **34.6** **34.7**

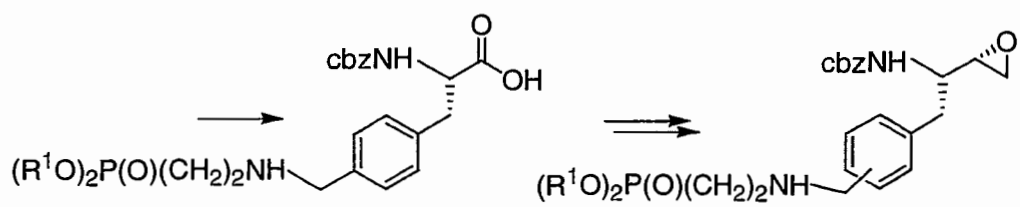
Example



34.8 **34.9** **34.10**



34.11 **34.12**



34.13 **34.14**

Preparation of thiophenols 12.2 incorporating phosphonate groups.

Scheme **35** illustrates the preparation of thiophenols in which a phosphonate moiety is attached directly to the aromatic ring. In this procedure, a halo-substituted thiophenol **35.1** is subjected to a suitable protection procedure. The protection of thiophenols is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 277ff. The protected compound **35.2** is then coupled, under the influence of a transition metal catalyst, with a dialkyl phosphite **30.3**, to afford the product **35.3**. The product is then deprotected to afford the free thiophenol **35.4**. Suitable protecting groups for this procedure include alkyl groups such as triphenylmethyl and the like. Palladium (0) catalysts are employed, and the reaction is conducted in an inert solvent such as benzene, toluene and the like, as described in J. Med. Chem., 35, 1371, 1992. Preferably, the 3-bromothiophenol **35.5** is protected by conversion to the 9-fluorenylmethyl derivative **35.6,** as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 284, and the product is reacted in toluene with a dialkyl phosphite in the presence of tetrakis(triphenylphosphine)palladium (0) and triethylamine, to yield the product **35.7**. Deprotection, for example by treatment with aqueous ammonia in the presence of an organic co-solvent, as described in J. Chem. Soc. Chem. Comm. 1501, 1986, then gives the thiol **35.8**.

Using the above procedures, but employing, in place of the bromo compound **35.5**, different bromo compounds **35.2**, and/or different phosphonates **30.3**, there are obtained the corresponding thiols **35.4**.

Scheme **36** illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol **36.2** is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative **36.3**. The latter compound is reacted with a halodialkyl phosphate **36.4,** followed by deprotection as described previously, to afford the product **36.5**.

For example, 4-bromothiophenol **36.7** is converted into the S-triphenylmethyl (trityl) derivative **36.8**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **36.9**

by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorodiethyl phosphite **36.10** to afford the phosphonate **36.11**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **36.12**.

Using the above procedures, but employing, in place of the bromo compound **36.7**, different halo compounds **36.2**, and/or different halo dialkyl phosphites **36.4**, there are obtained the corresponding thiols **36.6**.

Scheme **37** illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol **37.1** is subjected to free-radical bromination to afford a bromomethyl product **37.1a**. This compound is reacted with a sodium dialkyl phosphite **37.2** or a trialkyl phosphite, to give the displacement or rearrangement product **37.3**, which upon deprotection affords the thiophenols **37.4**.

For example, 2-methylthiophenol **37.5** is protected by conversion to the benzoyl derivative **37.6**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **37.7.** This material is reacted with a sodium dialkyl phosphite **37.2**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **37.8.**

Alternatively, the bromomethyl compound **37.7** can be converted into the phosphonate **37.8** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **37.7** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100^0C to produce the phosphonate **37.8**. Deprotection of **37.8**, for example by treatment with aqueous ammonia, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiol **37.9**.

Using the above procedures, but employing, in place of the bromomethyl compound **37.7**, different bromomethyl compounds **37.2**, there are obtained the corresponding thiols **37.4**.

Scheme **38** illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **38.1** is reacted with a dialkyl hydroxyalkylphosphonate **38.2** under the conditions of the Mitsonobu reaction, for example as described in Org. React., 1992, 42,

335, to afford the coupled product **38.3**. Deprotection then yields the O- or S-linked products **38.4**.

For example, the substrate 3-hydroxythiophenol, **38.5**, is converted into the monotrityl ether **38.6**, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **38.7** in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound **38.8**. Removal of the trityl protecting group, as described above, then affords the thiophenol **38.9**.

Using the above procedures, but employing, in place of the phenol **38.5**, different phenols or thiophenols **38.1**, and /or different phosphonates **38.2**, there are obtained the corresponding thiols **38.4**.

Scheme **39** illustrates the preparation of thiophenols **39.4** bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **39.1** is reacted with an activated ester, for example the trifluoromethanesulfonate **39.2**, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product **39.3**. Deprotection then affords the thiol **39.4**.

For example, 4-methylaminothiophenol **39.5**, is reacted with one equivalent of acetyl chloride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the product **39.6**. This material is then reacted with, for example, a dialkyl trifluoromethanesulfonylmethyl phosphonate **39.7**, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product **39.8**. Preferably, equimolar amounts of the phosphonate **39.7** and the amine **39.6** are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product **39.8**. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiophenol **39.9**.

Using the above procedures, but employing, in place of the thioamine **39.5**, different phenols, thiophenols or amines **39.1**, and/or different phosphonates **39.2**, there are obtained the corresponding products **39.4**.

Scheme **40** illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate **40.2**. In this procedure, a suitably protected

hydroxy, thio or amino substituted thiophenol **40.1** is reacted with a dialkyl bromoalkyl phosphonate **40.2** to afford the product **40.3**. Deprotection then affords the free thiophenol **40.4**.

For example, 3-hydroxythiophenol **40.5** is converted into the S-trityl compound **40.6**, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate **40.7**, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°C to yield the ether product **40.8**. Deprotection, as described above, then affords the thiol **40.9**.

Using the above procedures, but employing, in place of the phenol **40.5**, different phenols, thiophenols or amines **40.1**, and/or different phosphonates **40.2**, there are obtained the corresponding products **40.4**.

Scheme **41** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **41.2** is coupled with an aromatic bromo compound **41.1**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **41.4**, or the saturated analog **41.6**.

For example, 3-bromothiophenol is converted into the S-Fm derivative **41.7**, as described above, and this compound is reacted with diethyl 1-butenyl phosphonate **41.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **41.9**. Deprotection, as described above, then affords the thiol **41.10**.

Optionally, the initially formed unsaturated phosphonate **41.9** can be subjected to catalytic hydrogenation, using, for example, palladium on carbon as catalyst, to yield the saturated product **41.11**, which upon deprotection affords the thiol **41.12**.

Using the above procedures, but employing, in place of the bromo compound **41.7**, different bromo compounds **41.1**, and/or different phosphonates **41.2**, there are obtained the corresponding products **41.4** and **41.6**

Scheme **42** illustrates the preparation of an aryl-linked phosphonate ester **42.4** by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **42.1** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product **42.3** which is deprotected to yield the thiol **42.4**.
For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **42.5**. This material is reacted with diethyl 4-bromophenylphosphonate **42.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **42.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **42.8**.
Using the above procedures, but employing, in place of the boronate **42.5**, different boronates **42.1**, and/or different phosphonates **42.2**, there are obtained the corresponding products **42.4**.

Scheme **43** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **43.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **43.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **43.3** is then deprotected to afford the thiol **43.4**. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **43.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **43.5** is then reacted with, for example diethyl 4-(bromomethyl)phenylphosphonate, **43.6**,

the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C. The thioether product **43.7** thus obtained is deprotected, as described above, to afford the thiol **43.8**.

Using the above procedures, but employing, in place of the thiophenol **43.5**, different phenols, thiophenols or amines **43.1**, and/or different phosphonates **43.2**, there are obtained the corresponding products **43.4**.

Scheme **44** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

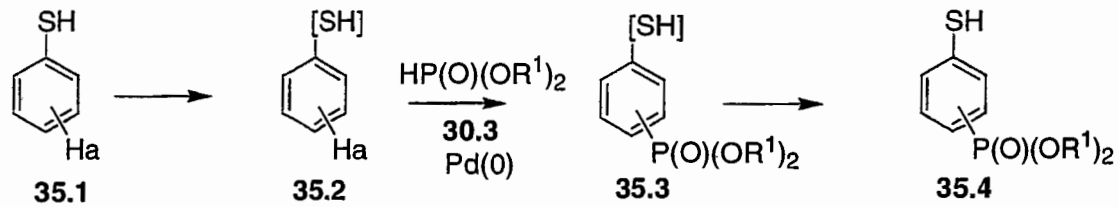
In this procedure, a suitably protected thiophenol **44.1**, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **44.2**, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **44.3**. Deprotection, as described above, then affords the thiol **44.4**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p 707.

For example, 2,3-dihydro-1H-indole-5-thiol, **44.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **44.6**, as described above, and the ester is then reacted with the triflate **44.7**, using the conditions described above for the preparation of **39.8**, (Scheme **39**, to yield the phosphonate **44.8**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **44.9**.

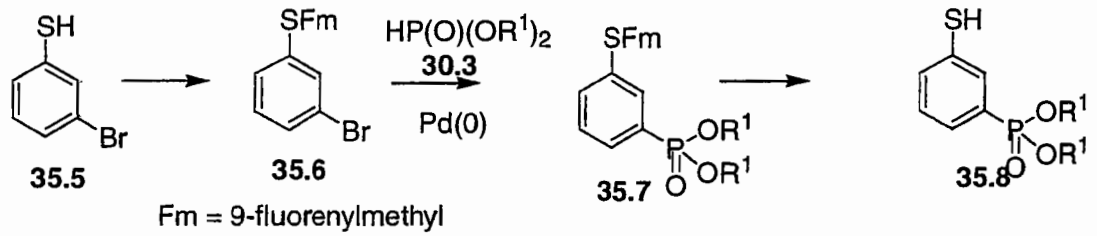
Using the above procedures, but employing, in place of the thiol **44.5**, different thiols **44.1**, and/or different triflates **44.2**, there are obtained the corresponding products **44.4**.

Scheme 35

Method



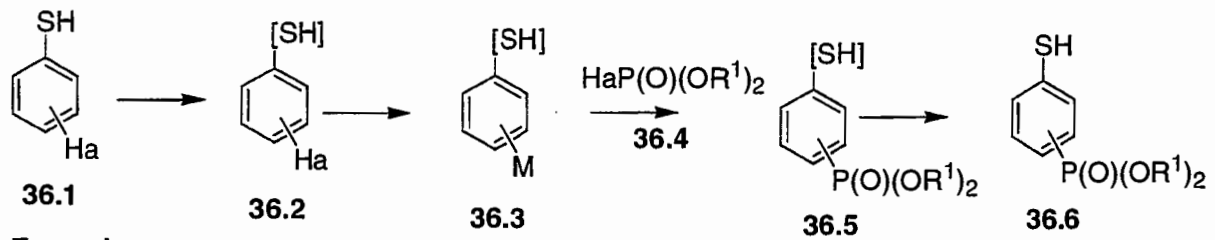
Example



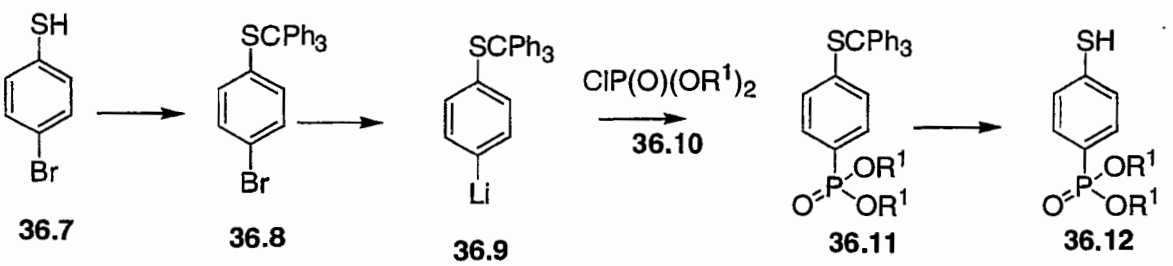
Fm = 9-fluorenylmethyl

Scheme 36

Method

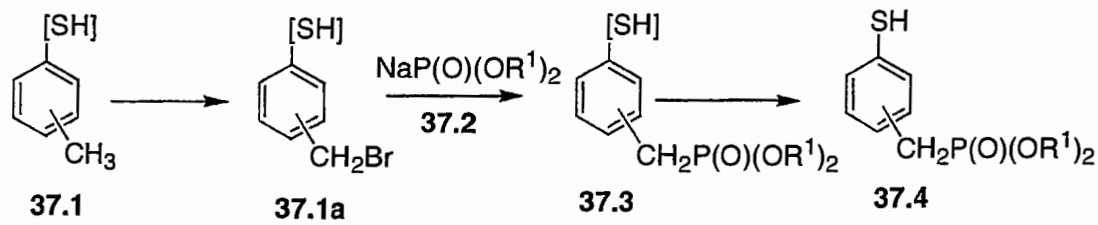


Example



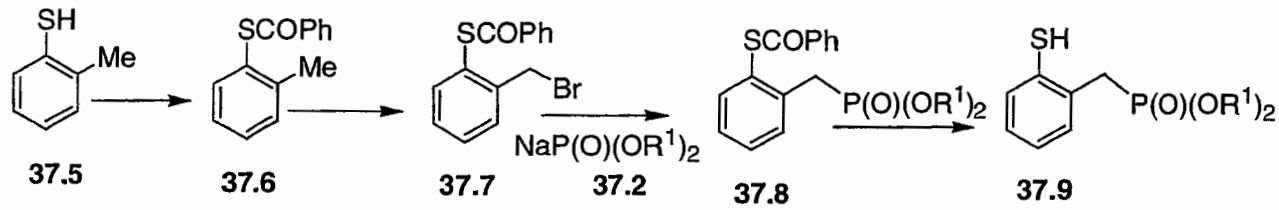
Scheme 37

Method



37.1 37.1a 37.3 37.4

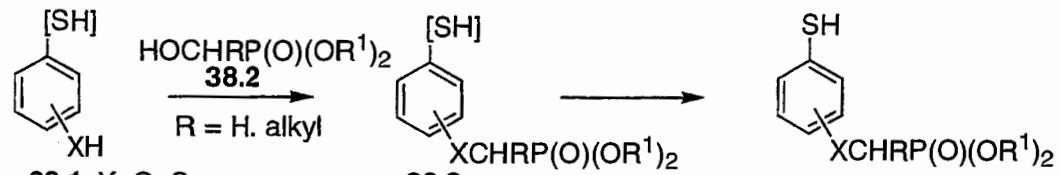
Example



37.5 37.6 37.7 37.2 37.8 37.9

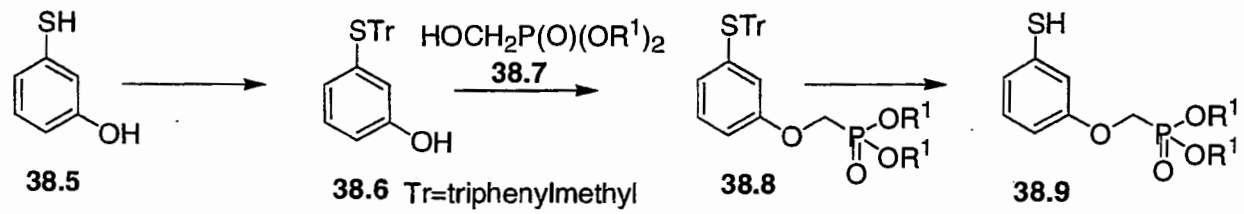
Scheme 38

Method



38.1 X=O, S 38.3 38.4 X=O, S

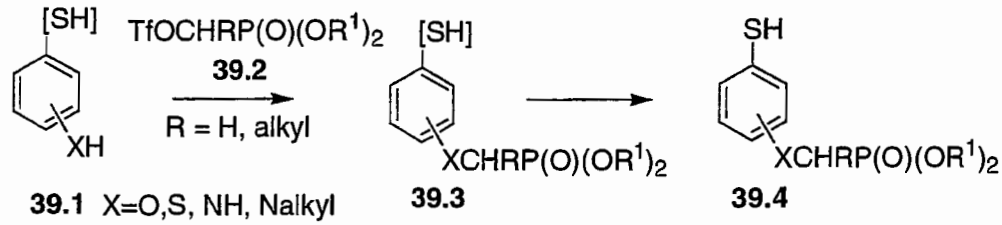
Example



38.5 38.6 Tr=triphenylmethyl 38.8 38.9

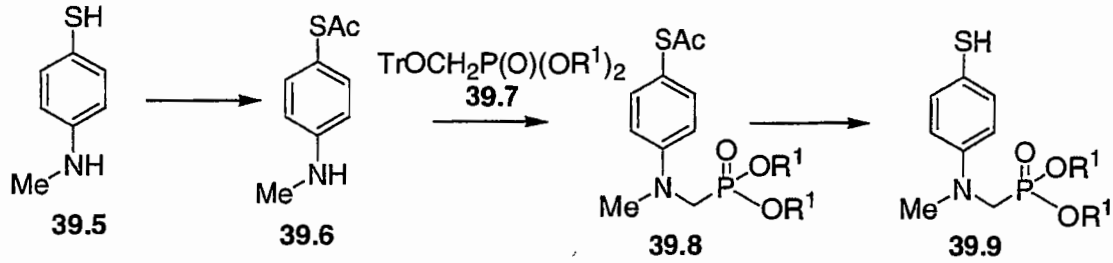
Scheme 39

Method



39.1 X=O,S, NH, Nalkyl **39.3** **39.4**

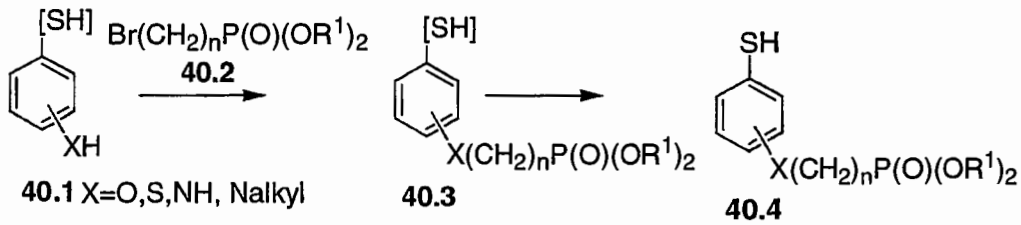
Example



39.5 **39.6** **39.8** **39.9**

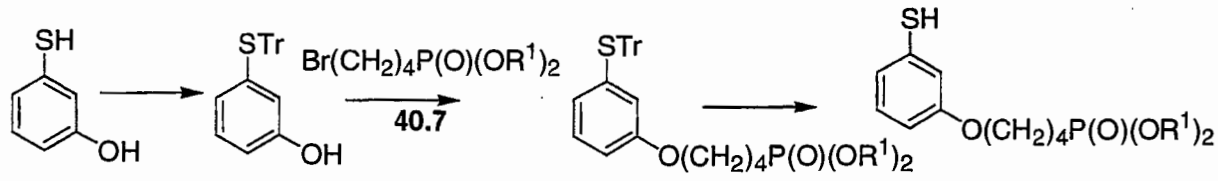
Scheme 40

Method



40.1 X=O,S,NH, Nalkyl **40.3** **40.4**

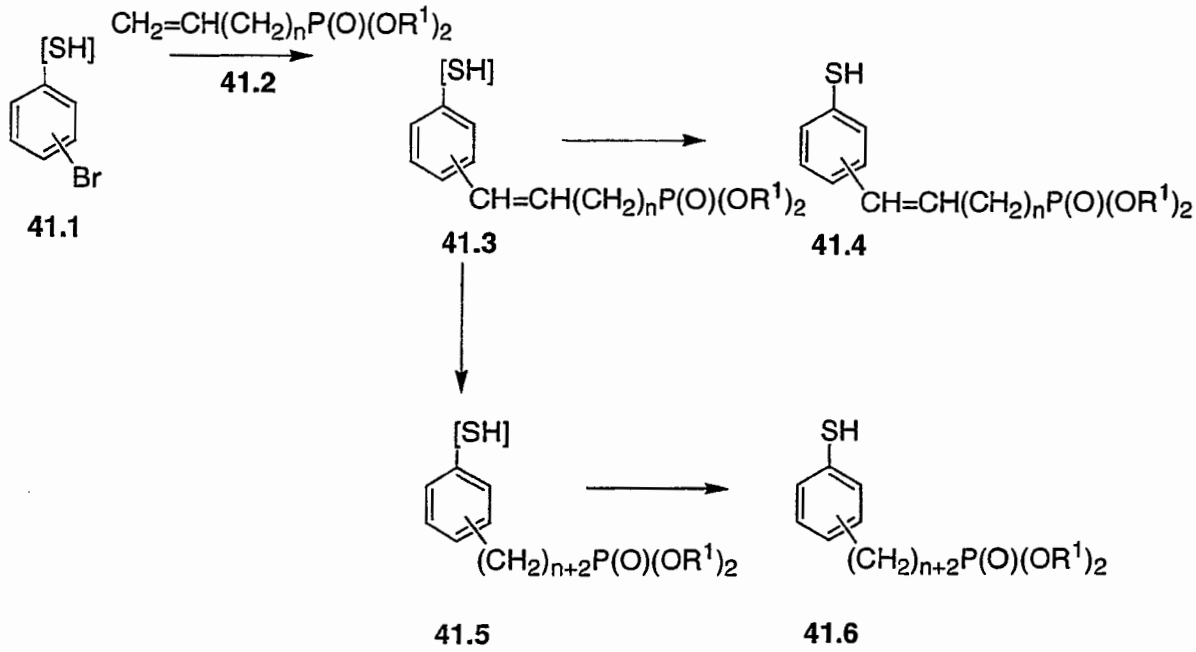
Example



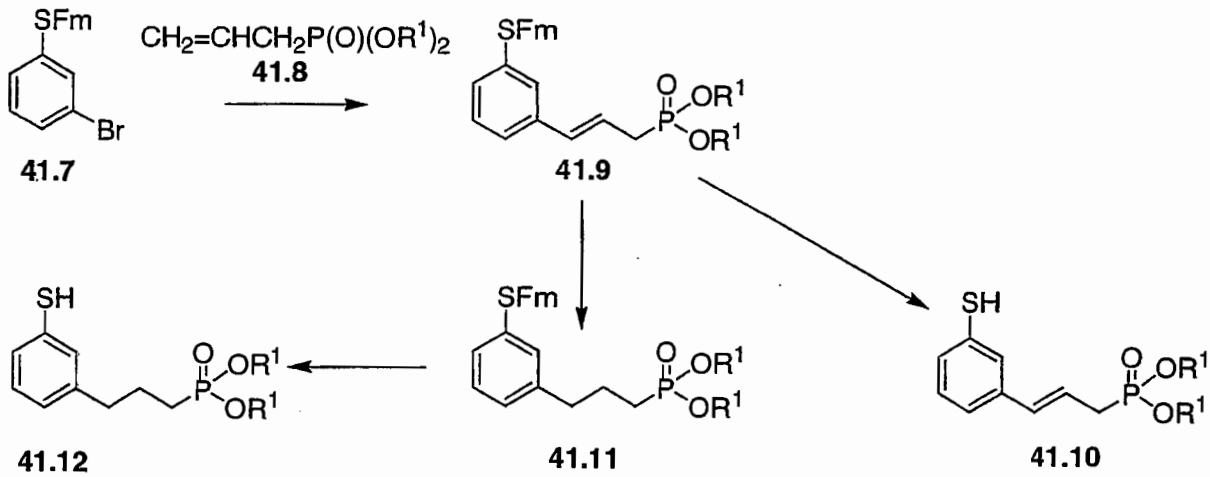
40.5 **40.6** Tr=triphenylmethyl **40.8** **40.9**

Scheme 41

Method

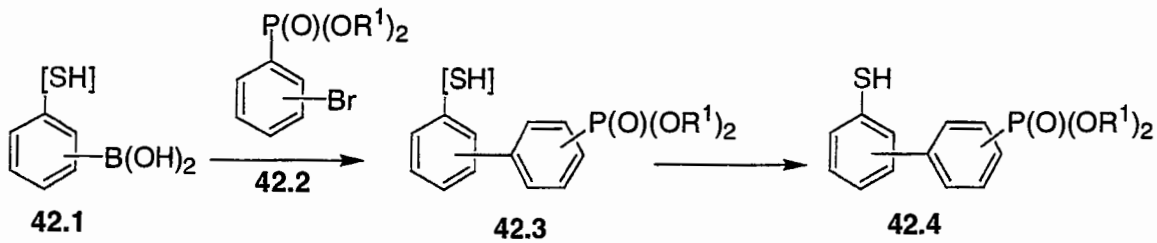


Example



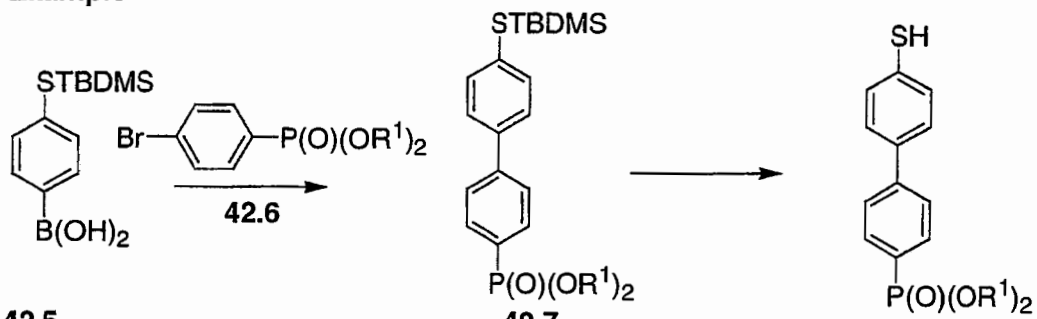
Scheme 42

Method



42.1 42.3 42.4

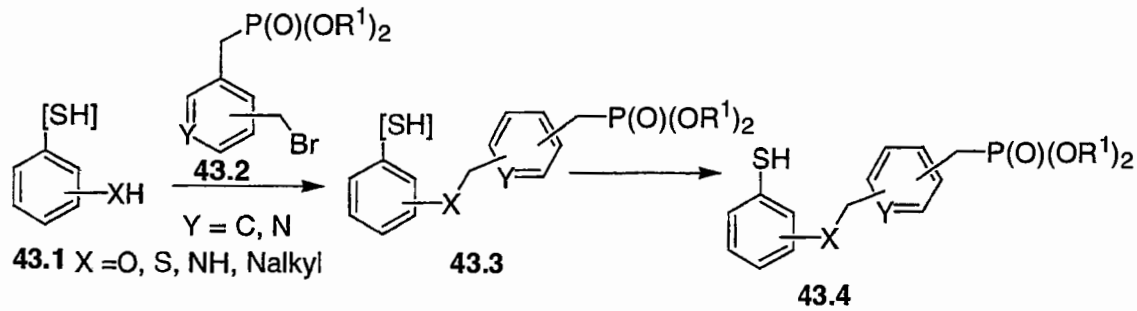
Example



42.5 42.7 42.8

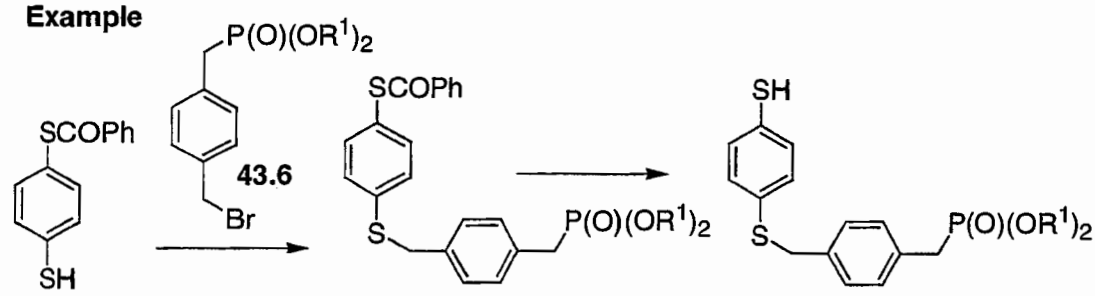
Scheme 43

Method



43.1 X =O, S, NH, Nalkyl 43.3 43.4

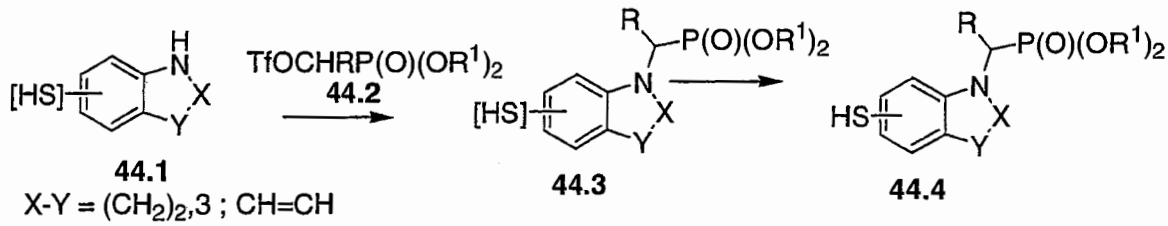
Example



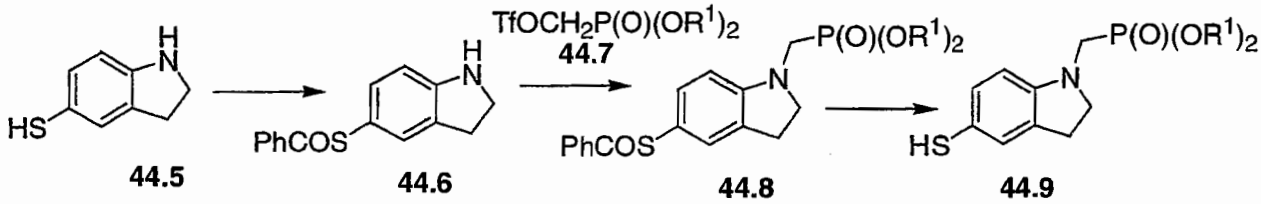
43.5 43.7 43.8

Scheme 44

Method



Example



Preparation of tert-butylamine derivatives incorporating phosphonate groups.

Scheme **45** describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2.2-dimethyl-2-aminoethyl bromide **45.1** is reacted with a trialkyl phosphite **45.2**, under the conditions of the Arbuzov reaction, as described above, to afford the phosphonate **45.3**, which is then deprotected as described previously to give **45.4**

For example, the cbz derivative of 2,2-dimethyl-2-aminoethyl bromide **45.6**, is heated with a trialkyl phosphite at ca 150°C to afford the product **45.7**. Deprotection, as previously described, then affords the free amine **45.8**.

Using the above procedures, but employing different trisubstituted phosphites, there are obtained the corresponding amines **45.4**.

Scheme **46** illustrates the preparation of phosphonate esters attached to the tert butylamine by means of a heteroatom and a carbon chain. An optionally protected alcohol or thiol **46.1** is reacted with a bromoalkylphosphonate **46.2,** to afford the displacement product **46.3**. Deprotection, if needed, then yields the amine **46.4**.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol **46.5** is reacted with a dialkyl 4-bromobutyl phosphonate **46.6**, prepared as described in Synthesis, 1994, 9, 909, in

dimethylformamide containing potassium carbonate and potassium iodide, at ca 60°C to afford the phosphonate **46.7** Deprotection then affords the free amine **46.8**.
Using the above procedures, but employing different alcohols or thiols **46.1**, and/or different bromoalkylphosphonates **46.2**, there are obtained the corresponding products **46.4**.

Scheme **47** describes the preparation of carbon-linked phosphonate tert butylamine derivatives, in which the carbon chain can be unsaturated or saturated.
In the procedure, a terminal acetylenic derivative of tert-butylamine **47.1** is reacted, under basic conditions, with a dialkyl chlorophosphite **47.2**, as described above in the preparation of **36.5**, (Scheme **36**). The coupled product **47.3** is deprotected to afford the amine **47.4.** Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products **47.5** and **47.6** respectively.
For example, 2-amino-2-methylprop-1-yne **47.7**, the preparation of which is described in WO 9320804, is converted into the N-phthalimido derivative **47.8**, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide in tetrahydrofuran at -78°C. The resultant anion is then reacted with a dialkyl chlorophosphite **47.2** to afford the phosphonate **47.9**. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine **47.10**. Partial catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p 566, produces the olefinic phosphonate **47.11**, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate **47.12**.
Using the above procedures, but employing different acetylenic amines **47.1**, and/or different dialkyl halophosphites, there are obtained the corresponding products **47.4**, **47.5** and **47.6**.

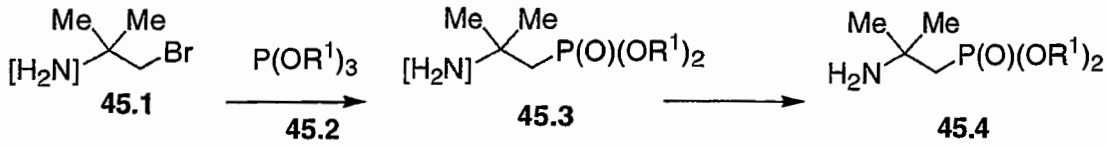
Scheme **48** illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.
In this method, an aminoethyl-substituted cyclic amine **48.1** is reacted with a limited amount of a bromoalkyl phosphonate **48.2**, using, for example, the conditions described above for the preparation of **40.3**, (Scheme **40**) to afford the displacement product **48.3**.

For example, 3-(1-amino-1-methyl)ethylpyrrolidine **48.4**, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with a dialkyl 4-bromobutyl phosphonate **48.5**, prepared as described in Synthesis, 1994, 9, 909, to afford the displacement product **48.6**.

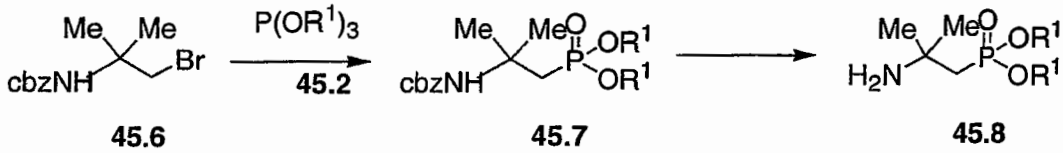
Using the above procedures, but employing different cyclic amines **48.1**, and/or different bromoalkylphosphonates **48.2**, there are obtained the corresponding products **48.3**.

Scheme 45

Method

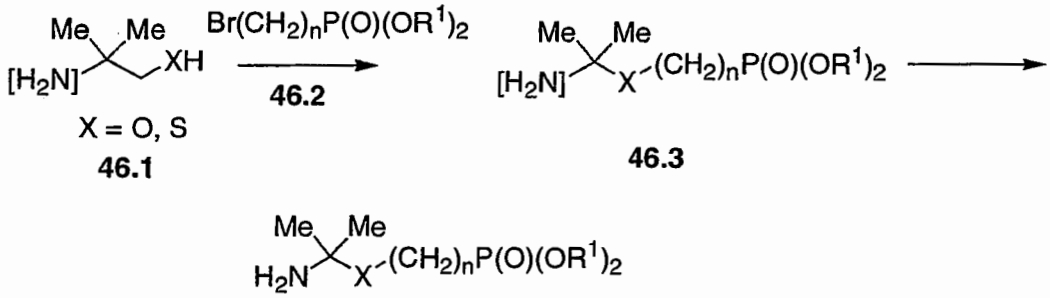


Example

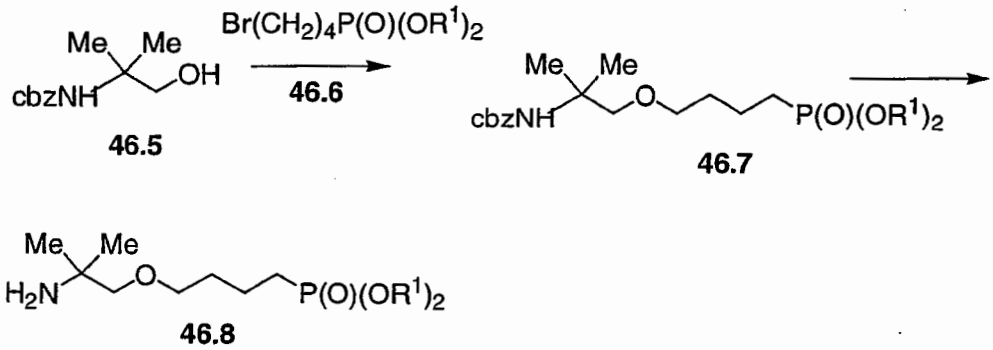


Scheme 46

Method

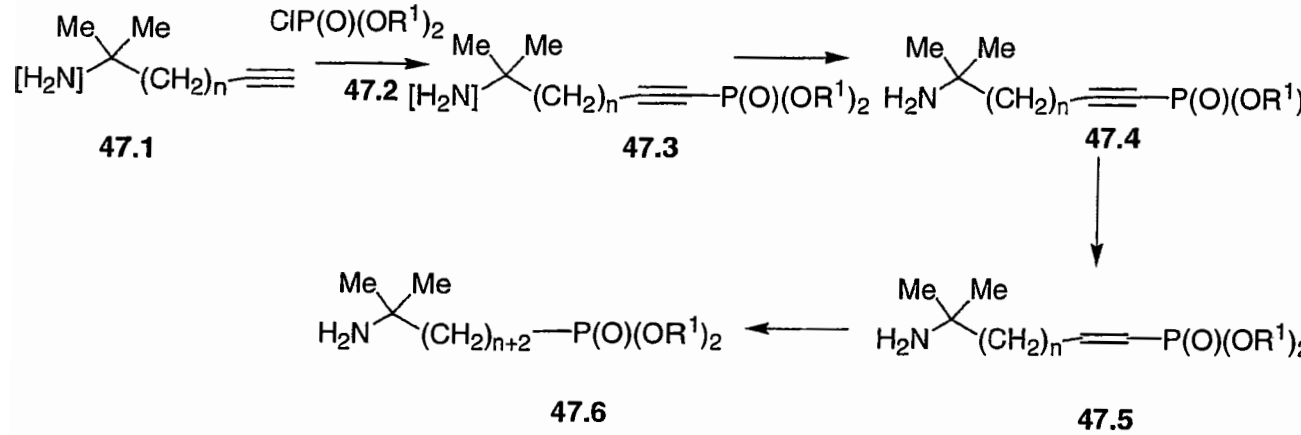


Example

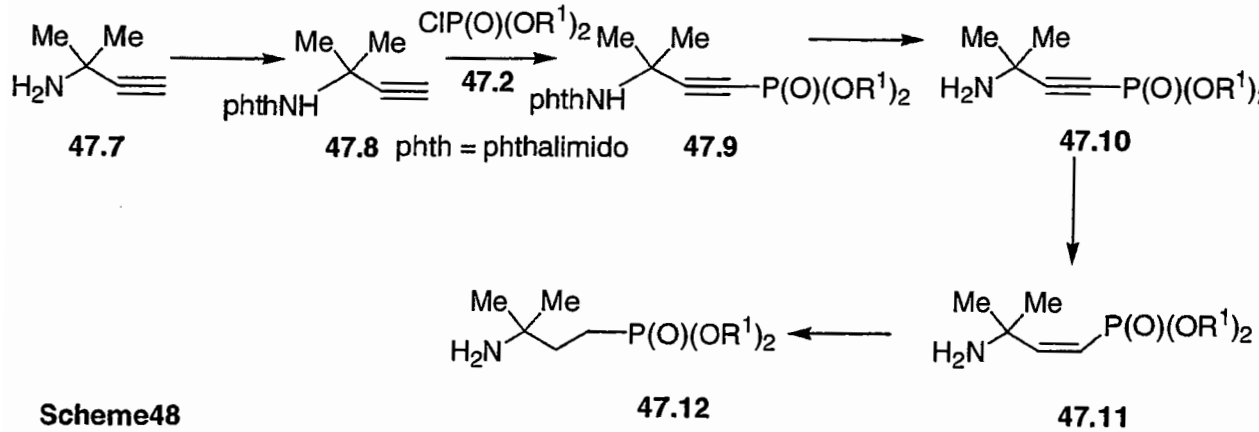


Scheme 47

Method

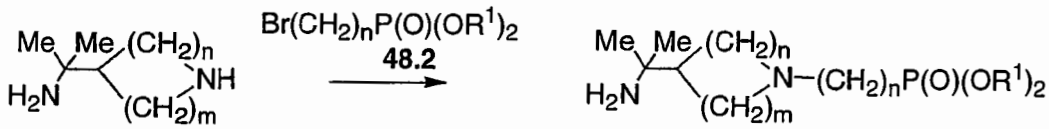


Example

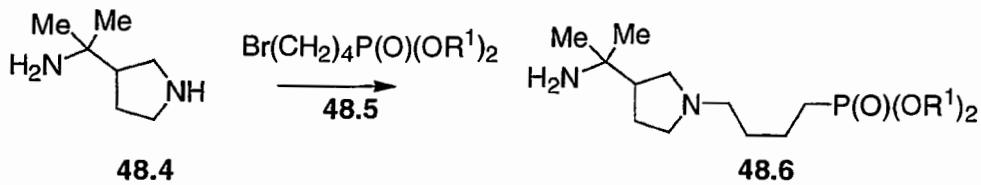


Scheme48

Method



Example



Preparation of decahydroquinolines with phosphonate moieties at the 6-position.

Scheme **48a** illustrates methods for the synthesis of intermediates for the preparation of decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the intermediate **48a.4** are shown.

In the first route, 2-hydroxy-6-methylphenylalanine **48a.1**, the preparation of which is described in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative **48a.2**. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product **48a.2**, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product **48a.3**. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound **48a.3** is then treated with acid, for example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline **48a.4**, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline **48a.4** can be obtained from 2-hydroxyphenylalanine **48a.5**, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem. Rev., 1995, 95, 1797.

Typically, the substrate **48a.5** is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product **48a.4**, in which R is H. Catalytic hydrogenation of the latter compound, using, for example, platinum as catalyst, as described in J. Amer. Chem. Soc., 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-substituted decahydroisoquinoline **48a.6**. The reduction can also be performed electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline **48a.4** is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at ca 50°C, to afford the decahydroisoquinoline **48a.6**.

Protection of the carboxyl and NH groups present in **48a.6** for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH into the N-cbz group, as described above, followed by oxidation, using, for example, pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone **48a.9**, in which R is trichloroethyl and R_1 is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in J. Amer. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butyl aluminum hydride, as described in J. Amer. Chem. Soc., 80, 5372, 1958, then affords the alcohol **48a.10**.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as isopropanol, at ambient temperature, to afford the alcohol **48a.10**.

The alcohol **48a.6** can be converted into the thiol **48a.13** and the amine **48a.14**, by means of displacement reactions with suitable nucleophiles, with inversion of stereochemistry. For example, the alcohol **48a.6** can be converted into an activated ester such as the trifluoromethanesulfonyl ester or the methanesulfonate ester **48a.7**, by treatment with methanesulfonyl chloride and a base. The mesylate **48a.7** is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol **48a.13**.

For example, the mesylate **48a.7** is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **48a.12**, in which R is $COCH_3$. The product then treated with, a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol **48a.13**.

The mesylate **48a.7** can be treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p. 399, followed by deprotection as described previously, to afford the amine **48a.14**.

For example, the mesylate **48a.7** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such

as, for example, dimethylformamide, at ambient temperature, to afford the displacement product **48a.8**, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the amine **48a.14**.

The application of the procedures described above for the conversion of the β-carbinol **48a.6** to the α-thiol **48a.13** and the α-amine **48a.14** can also be applied to the α-carbinol **48a.10**, so as to afford the β-thiol and β-amine, **48a.11**.

Scheme **49** illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain. In this procedure, an alcohol, thiol or amine **49.1** is reacted with a bromoalkyl phosphonate **49.2**, under the conditions described above for the preparation of the phosphonate **40.3** (Scheme **40**), to afford the displacement product **49.3**. Removal of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **49.8**.

For example, the compound **49.5**, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, **49.6**, the preparation of which is described in J. Amer. Chem. Soc., 2000, 122, 1554 to afford the displacement product **49.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **49.8**.

Using the above procedures, but employing, in place of the α-thiol **49.5**, the alcohols, thiols or amines **48a.6, 48a.10, 48a.11, 48a.13, 48a.14**, of either α- or β-orientation, there are obtained the corresponding products **49.4**, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme **50** illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive Organic Transformations, by R. C. Larock, p. 421.

In this procedure, the amines **48a.14** or **48a.11** are reacted with a phosphonate aldehyde **50.1**, in the presence of a reducing agent, to afford the alkylated amine **50.2**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **50.3**.

For example, the protected amino compound **48a.14** is reacted with a dialkyl formylphosphonate **50.4**, the preparation of which is described in U.S. Patent 3,784,590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate **50.5**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **50.6**.

Using the above procedures, but employing, instead of the α-amine **48a.14**, the β isomer, **48a.11** and/or different aldehydes **50.1**, there are obtained the corresponding products **50.3**, in which the orientation of the side chain is the same as that of the amine precursor.

Scheme **51** depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain.

In this procedure, a thiol phosphonate **51.2** is reacted with a mesylate **51.1**, to effect displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product **51.3**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **51.4**.

For example, the protected mesylate **51.5** is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate **51.6**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thio ether phosphonate **51.7**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **51.8**

Using the above procedures, but employing, instead of the phosphonate **51.6**, different phosphonates **51.2**, there are obtained the corresponding products **51.4**.

Scheme **52** illustrates the preparation of decahydroisoquinoline phosphonates **52.4** in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The

compounds are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates **52.1** and a bromomethyl substituted phosphonate **52.2**. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant **52.1**. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate can be employed. If X is O, a strong base such as sodium hydride or lithium hexamethyldisilylazide is required. The displacement reaction affords the ether, thioether or amine compounds **52.3**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **52.4**.

For example, the protected alcohol **52.5** is reacted at ambient temperature with a dialkyl 3-bromomethyl phenylmethylphosphonate **52.6**, the preparation of which is described above, (Scheme **43**). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a strong base, such as, for example, lithium hexamethyldisilylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate **52.6**, to afford the product **52.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **53**) then yields the amine **52.8**.

Using the above procedures, but employing, instead of the β-carbinol **52.5**, different carbinols, thiols or amines **52.1**, of either α- or β-orientation, and/or different phosphonates **52.2**, in place of the phosphonate **52.6**, there are obtained the corresponding products **52.4** in which the orientation of the side-chain is the same as that of the starting material **52.1**.

Schemes **49-52** illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

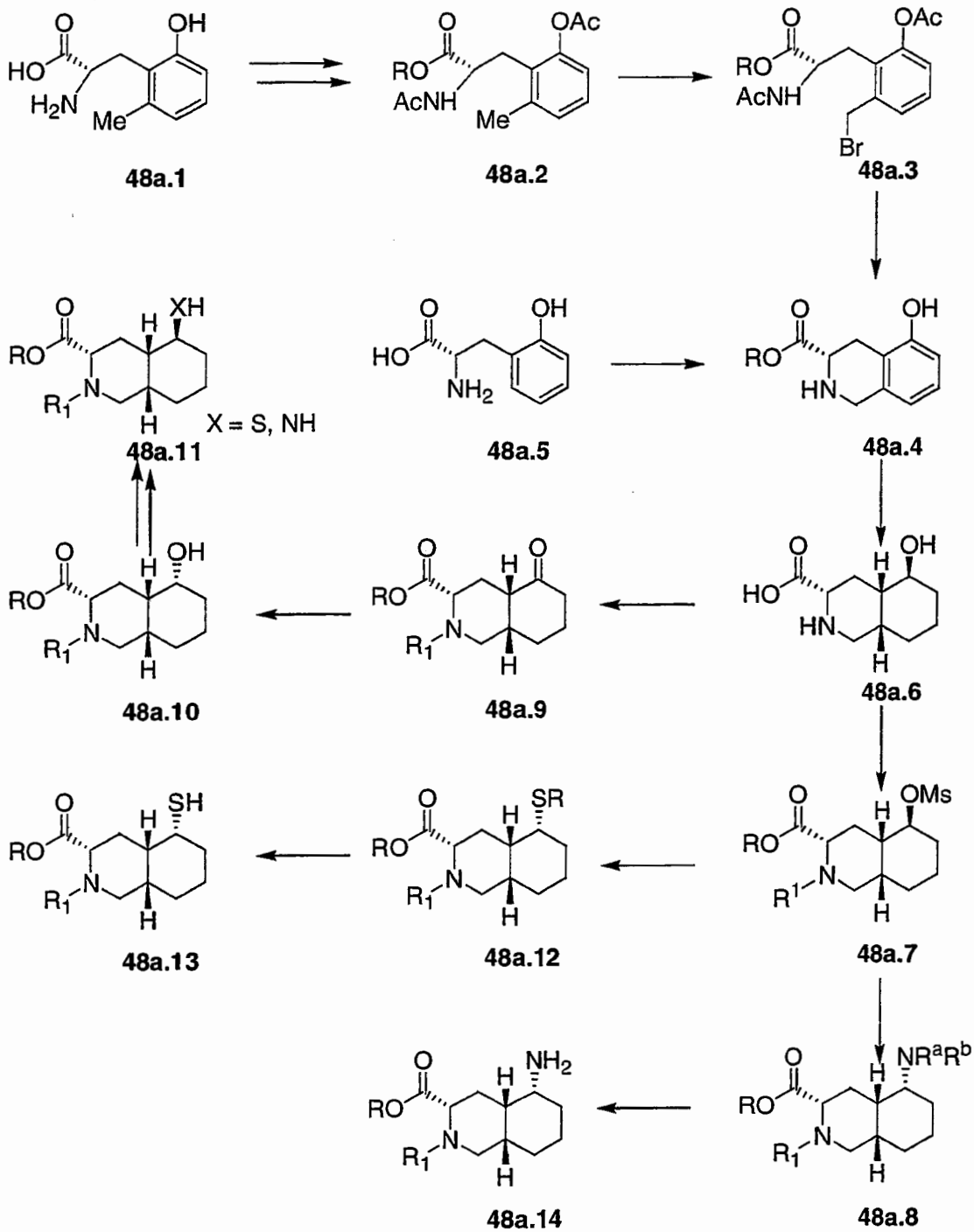
Scheme **53** illustrates the conversion of the latter group of compounds **53.1** (in which the group B is link-$P(O)(OR^1)_2$ or optionally protected precursor substituents thereto, such as, for example, OH, SH, NH_2) to the corresponding R^4NH amides **53.5**.

As shown in Scheme **53**, the ester compounds **53.1** are deprotected to form the corresponding carboxylic acids **53.2**. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R^2, and the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is removed by treatment with zinc in acetic acid, as described in J. Amer. Chem. Soc., 88, 852, 1966.

Conversion of the carboxylic acid **53.2** to the R^4NH amide **53.4** is then accomplished by reaction of the carboxylic acid, or an activated derivative thereof, with the amine R^4NH_2 **53.3** to afford the amide **53.4**, using the conditions described above for the preparation of the amide **1.6**. Deprotection of the NR^2 group, as described above, then affords the free amine **53.5**.

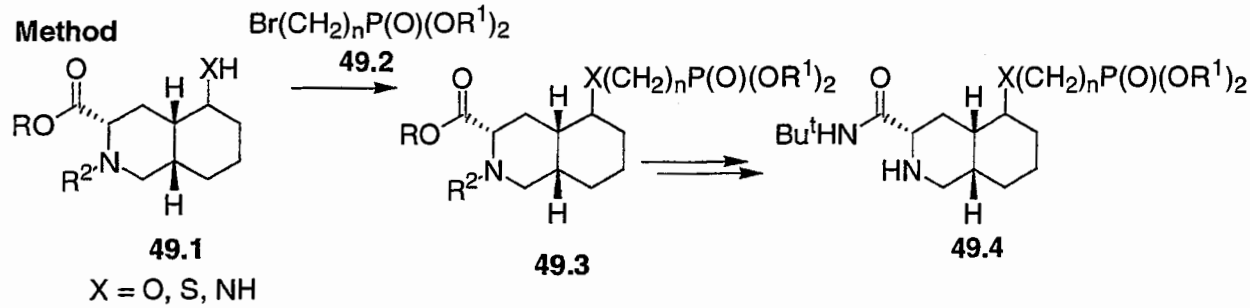
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Scheme 48a. Intermediates for the preparation of phosphonate-containing decahydroisoquinolines.

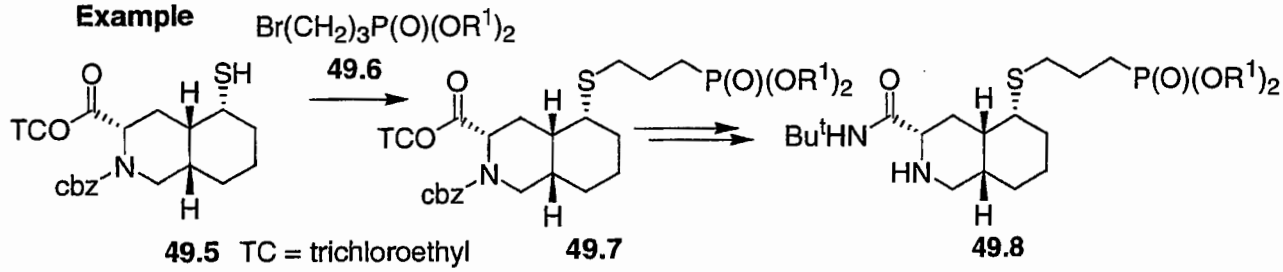


Scheme 49

Method

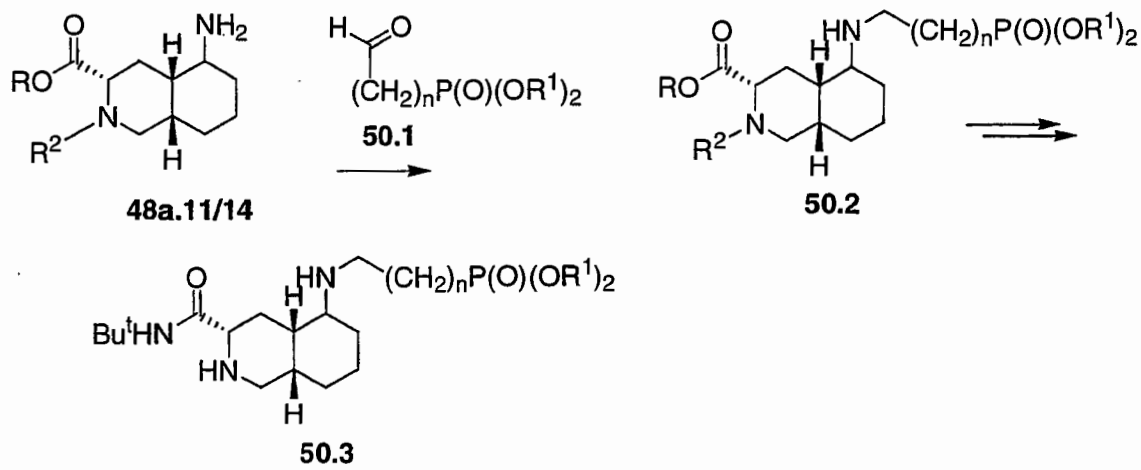


Example

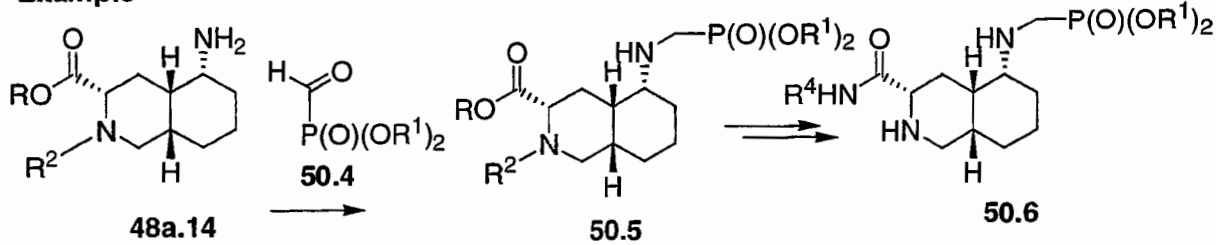


Scheme 50

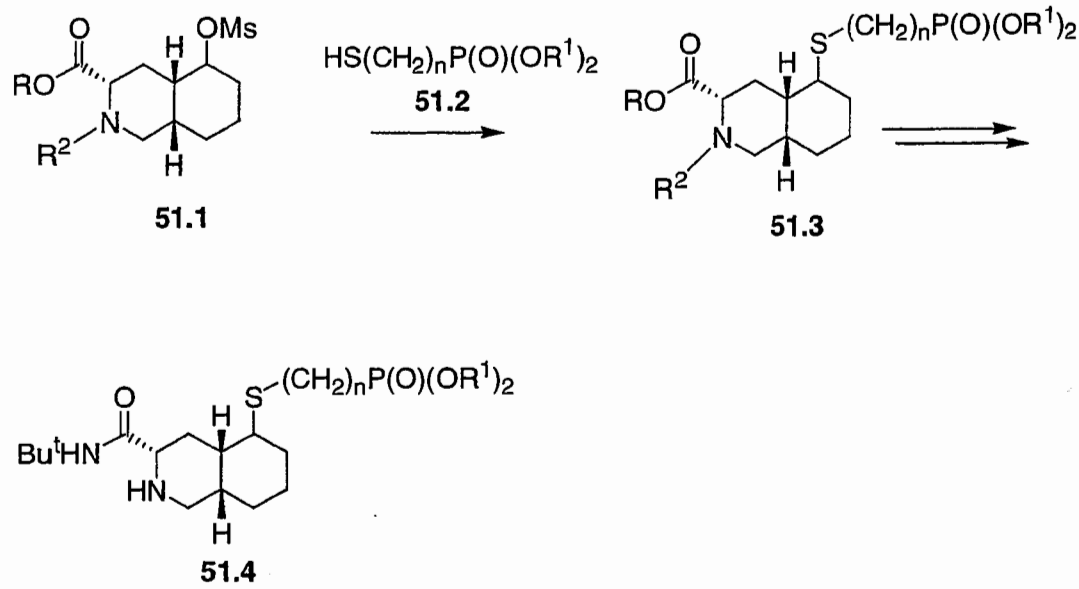
Method



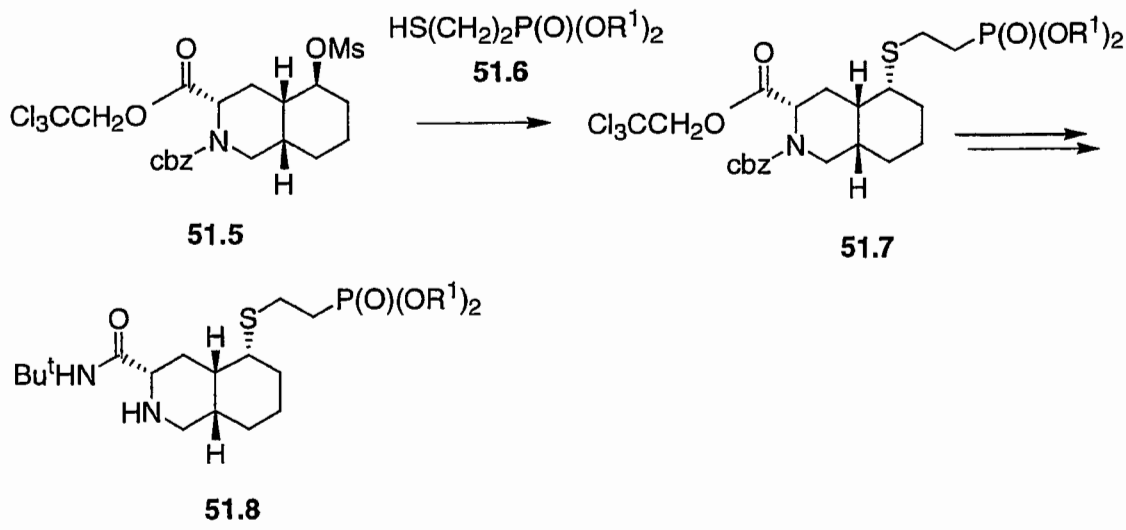
Example



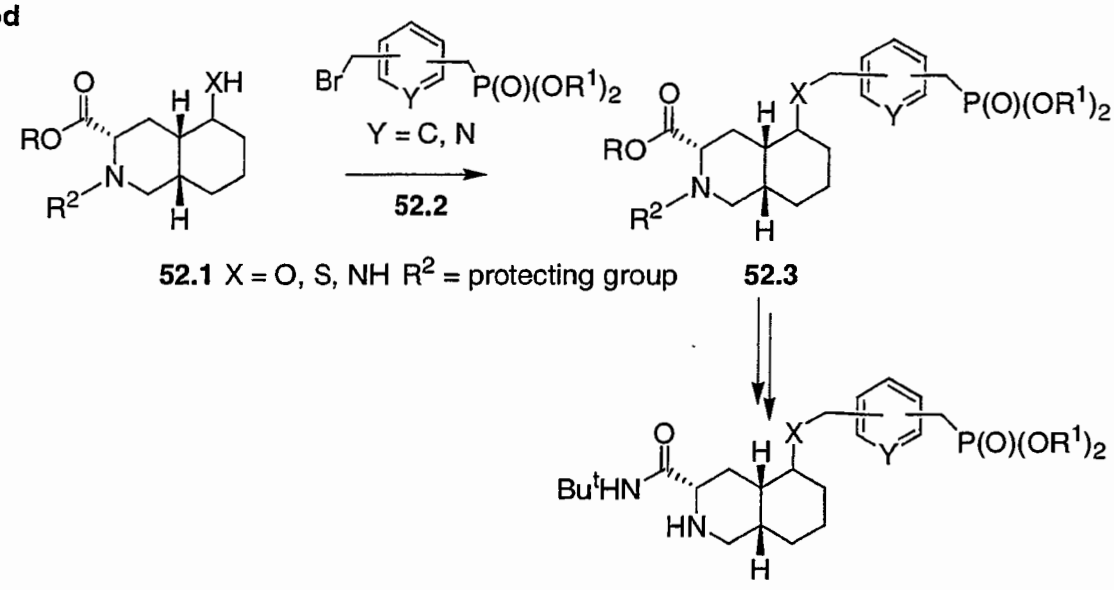
Scheme 51
Method



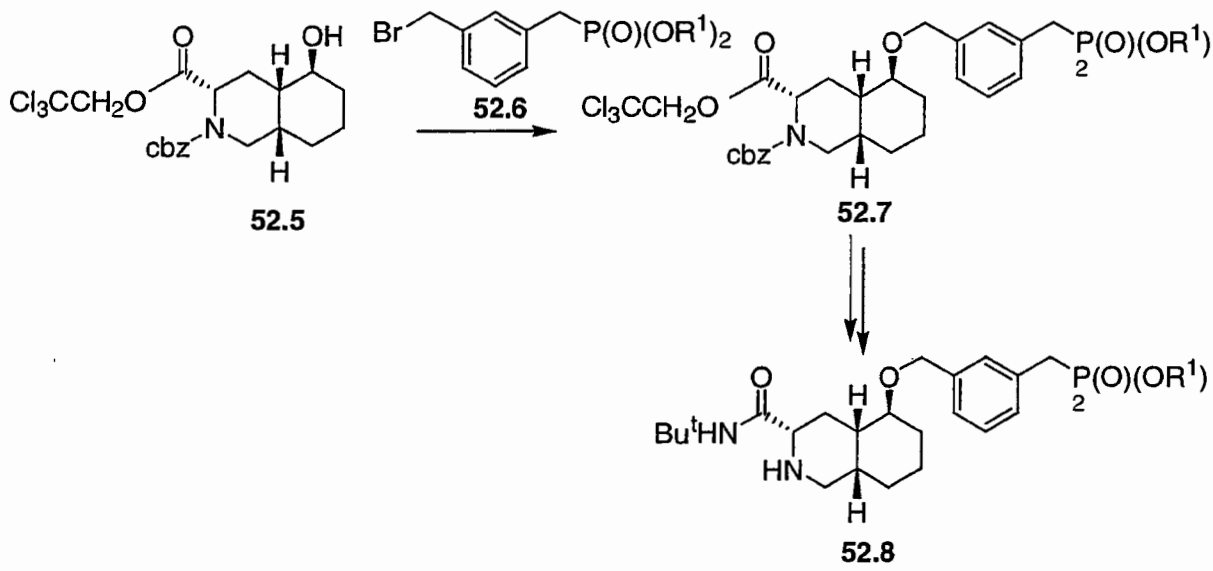
Example



Scheme 52
Method

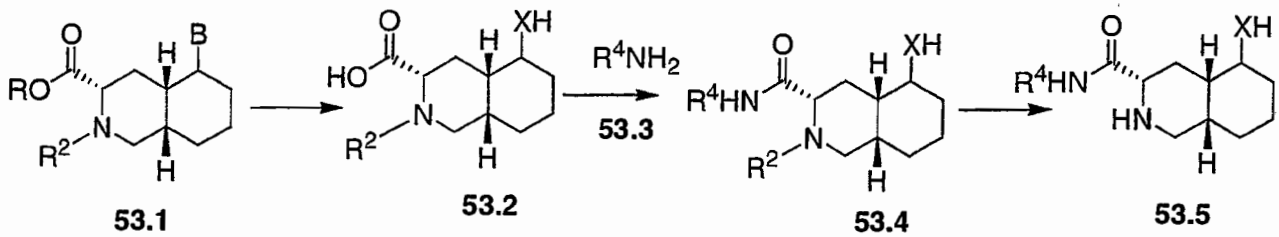


Example

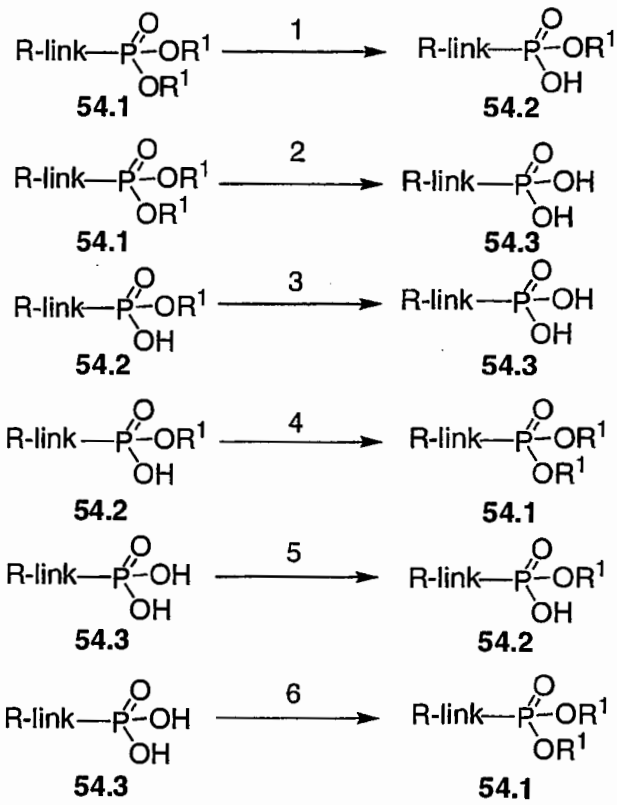


Scheme 53

Method



Scheme 54



Interconversions of the phosphonates R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH) and R-link-P(O)(OH)$_2$.

Schemes **1** - **69** described the preparations of phosphonate esters of the general structure R-link-P(O)(OR^1)$_2$, in which the groups R^1, the structures of which are defined in Chart **1**, may be the same or different. The R^1 groups attached to a phosphonate esters **1**-**6**, or to precursors thereto, may be changed using established chemical transformations. The

interconversions reactions of phosphonates are illustrated in Scheme **54**. The group R in Scheme **54** represents the substructure to which the substituent link-P(O)(OR^1)$_2$ is attached, either in the compounds **1-6** or in precursors thereto. The R^1 group may be changed, using the procedures described below, either in the precursor compounds, or in the esters **1-6**. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **54.1** into the corresponding phosphonate monoester **54.2** (Scheme **54**, Reaction 1) can be accomplished by a number of methods. For example, the ester **54.1** in which $R^1$is an aralkyl group such as benzyl, can be converted into the monoester compound **54.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester **54.1** in which $R^1$is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **54.2** can be effected by treatment of the ester **54.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **54.1** in which one of the groups $R^1$is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **54.2** in which $R^1$is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups $R^1$are alkenyl, such as allyl, can be converted into the monoester **54.2** in which $R^1$is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **54.1** or a phosphonate monoester **54.2** into the corresponding phosphonic acid **54.3** (Scheme **54**, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **54.2** in which $R^1$is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid

54.3 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **54.2** in which $R^1$is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **54.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **54.1** in which $R^1$is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **54.1** in which $R^1$is phenyl is described in J. Amer. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester **54.2** into a phosphonate diester **54.1** (Scheme **54**, Reaction 4) in which the newly introduced R^1group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **54.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **54.2** to the diester **54.1** can be effected by the use of the Mitsonobu reaction, as described above (Scheme **25**). The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **54.2** can be transformed into the phosphonate diester **54.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **54.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is

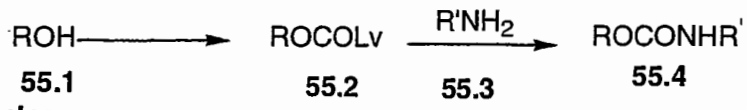
then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **54.1**.

A phosphonic acid R-link-$P(O)(OH)_2$ can be transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **54**, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ **54.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

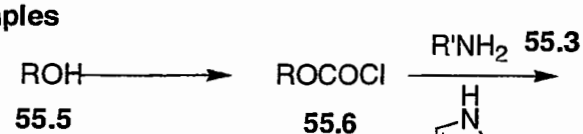
A phosphonic acid R-link-$P(O)(OH)_2$ **54.3** can be transformed into a phosphonate diester R-link-$P(O)(OR^1)_2$ **54.1** (Scheme **54**, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **54.3** can be transformed into phosphonic esters **54.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°C. Alternatively, phosphonic acids **54.3** can be transformed into phosphonic esters **54.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **54.1**.

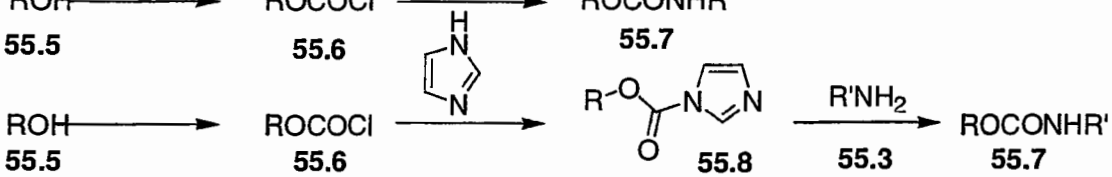
Scheme 55

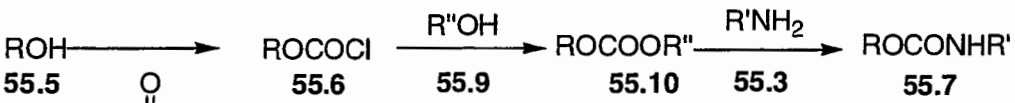
General reaction

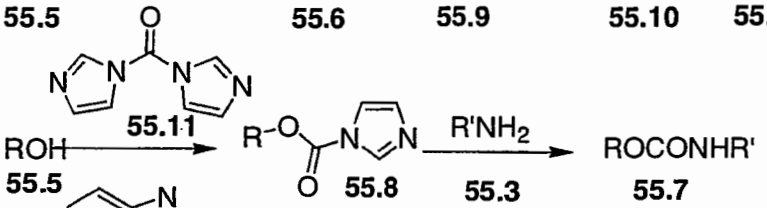


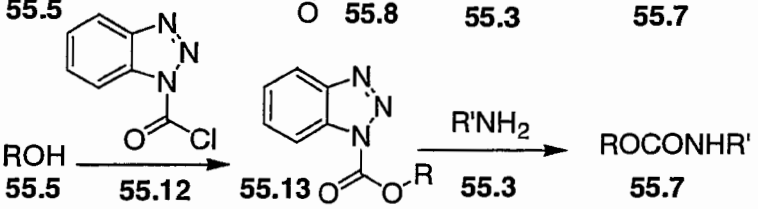
Examples

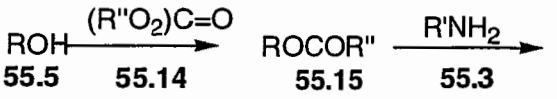
(1) 

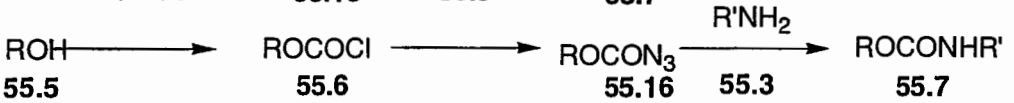
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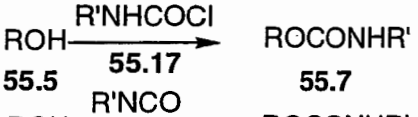
(3) 

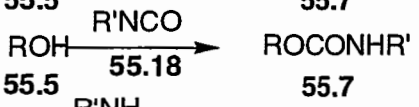
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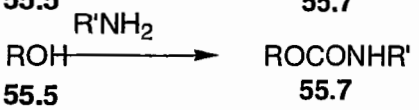
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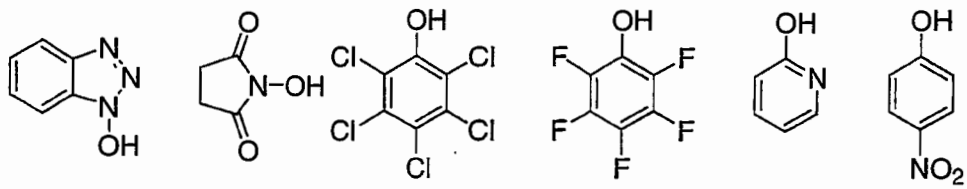
(6) 

(7) 

(8) 

(9) 

(10) 

R"OH = 

Preparation of the phosphonate esters 1-6 incorporating carbamate moieties.

The phosphonate esters **1-6** in which the R^6CO group is formally derived from the carboxylic acid synthons **C39 - C49** as shown in Chart **2c**, contain a carbamate moiety. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme **55** illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme **55**, in the general reaction generating carbamates, a carbinol **55.1** is converted into the activated derivative **55.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **55.2** is then reacted with an amine **55.3**, to afford the carbamate product **55.4**. Examples **1 – 7** in Scheme **55** depict methods by which the general reaction can be effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.

Scheme **55**, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **55.5**. In this procedure, the carbinol **55.5** is reacted with phosgene, in an inert solvent such as toluene, at about 0°C, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **55.6**. The latter compound is then reacted with the amine component **55.3**, in the presence of an organic or inorganic base, to afford the carbamate **55.7**. For example, the chloroformyl compound **55.6** is reacted with the amine **55.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **55.7**. Alternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme **55**, Example **2** depicts the reaction of the chloroformate compound **55.6** with imidazole, **55.7**, to produce the imidazolide **55.8**. The imidazolide product is then reacted with the amine **55.3** to yield the carbamate **55.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°C, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme **55** Example **3**, depicts the reaction of the chloroformate **55.6** with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester **55.10**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **55.19** - **55.24** shown in Scheme **55**, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **55.19**, N-hydroxysuccinimide **55.20**, or pentachlorophenol, **55.21**, the mixed carbonate **55.10** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **55.22** or 2-hydroxypyridine **55.23** can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme **55** Example **4** illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **55.8** is employed. In this procedure, a carbinol **55.5** is reacted with an equimolar amount of carbonyl diimidazole **55.11** to prepare the intermediate **55.8**. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **55.8** is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **55.7**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate **55.7**.

Scheme **55**, Example **5** illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **55.13**. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **55.12**, to afford the alkoxycarbonyl product **55.13**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine $R'NH_2$ to afford the carbamate **55.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80°C as described in Syn., 1977, 704.

Scheme **55**, Example **6** illustrates the preparation of carbamates in which a carbonate $(R"O)_2CO$, **55.14**, is reacted with a carbinol **55.5** to afford the intermediate alkyloxycarbonyl intermediate **55.15**. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate **55.7**. The procedure in which the reagent **55.15** is derived from

hydroxybenztriazole **55.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **55.15** is derived from N-hydroxysuccinimide **55.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **55.15** is derived from 2-hydroxypyridine **55.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **55.15** is derived from 4-nitrophenol **55.24** is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate **55.14** is conducted in an inert organic solvent at ambient temperature.

Scheme **55**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides **55.16**. in this procedure, an alkyl chloroformate **55.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **55.16**. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **55.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme **55**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **55.7**.

Scheme **55**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **55.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **55.7**.

Scheme **55**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **55.7**.

Preparation of phosphonate intermediates 5 and 6 with phosphonate moieties incorporated into the group R^6COOH and $R^2NHCH(R^3)CONHR^4$.

The chemical transformations described in Schemes **1 - 55** illustrate the preparation of compounds **1-4** in which the phosphonate ester moiety is attached to the quinoline-2-carboxylate substructure, (Schemes **1-8**), the phenylalanine or thiophenol moiety (Schemes **9-13**), the tert-butylamine moiety (Schemes **14-18**) and the decahydroisoquinoline moiety (Schemes **19 - 22**).

The various chemical methods employed herein (Schemes **25 - 69**)for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds R^6COOH, as defined in Charts **3a**, **3b** and **3c**, and into the compounds $R^2NHCH(R^3)CONHR^4$ as defined in Chart **2**. For example, Schemes **56 - 61** illustrate the preparation of phosphonate-containing analogs of the phenoxyacetic acid **C8** (Chart **3a**), Schemes **62 - 65** illustrate the preparation of phosphonate-containing analogs of the carboxylic acid **C4**, Schemes **66 - 69** illustrate the preparation of phosphonate-containing analogs of the amine **A12** (Chart **2**), and Schemes **70-75** illustrate the preparation of phosphonate-containing analogs of the carboxylic acid **C38.** The resultant phosphonate-containing analogs $R^{6a}COOH$ and $R^{2a}NHCH(R^{3a})CONHR^4$ can then, using the procedures described above, be employed in the preparation of the compounds **5** and **6**. The procedures required for the introduction of the phosphonate-containing analogs $R^{6a}COOH$ and $R^{2a}NHCH(R^{3a})CONHR^4$ are the same as those described above for the introduction of the R^6CO and $R^2NHCH(R^3)CONHR^4$ moieties.

Preparation of dimethylphenoxyacetic acids incorporating phosphonate moieties.

Scheme **56** illustrates two alternative methods by means of which 2,6-dimethylphenoxyacetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the 2,6-dimethylphenol moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed 2,6-dimethylphenoxyacetic acid intermediate. In the first sequence, a substituted 2,6-dimethylphenol **56.1**, in which the substituent B is a precursor to the group link-$P(O)(OR^1)_2$, and in which the phenolic hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound **56.2**. Methods for

the conversion of the substituent B into the group link-P(O)$(OR^1)_2$ are described in Schemes **25 - 69**.

The protected phenolic hydroxyl group present in the phosphonate-containing product **56.2** is then deprotected, using methods described below, to afford the phenol **56.3**.

The phenolic product **56.3** is then transformed into the corresponding phenoxyacetic acid **56.4**, in a two step procedure. In the first step, the phenol **56.3** is reacted with an ester of bromoacetic acid **56.5**, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of phenols to afford phenolic ethers is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the phenol and the alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol **56.3** and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described in U.S. Patent 5,914,332, to afford the ester **56.6**.

The thus-obtained ester **56.6** is then hydrolyzed to afford the carboxylic acid **56.4**. The methods used for this reaction depend on the nature of the group R. If R is an alkyl group such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group, methods for hydrolysis are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. Preferably, the ester product **56.6** which R is ethyl is hydrolyzed to the carboxylic acid **56.4** by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in U.S. Patent 5,914,332.

Alternatively, an appropriately substituted 2,6-dimethylphenol **56.7**, in which the substituent B is a precursor to the group link-P(O)$(OR^1)_2$, is transformed into the corresponding phenoxyacetic ester **56.8**. The conditions employed for the alkylation reaction are similar to those described above for the conversion of the phenol **56.3** into the ester **56.6**.

The phenolic ester **56.8** is then converted, by transformation of the group B into the group link-P(O)$(OR^1)_2$ followed by ester hydrolysis, into the carboxylic acid **56.4**. The group B

which is present in the ester **56.4** may be transformed into the group link-P(O)$(OR^1)_2$ either before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes **56** - **61** illustrate the preparation of 2,6-dimethylphenoxyacetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of phenoxyacetic esters acids **56.8**, with, if appropriate, modifications made according to the knowledge of one skilled in the art.

Scheme **57** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester which is attached to the phenolic group by means of a carbon chain incorporating a nitrogen atom. The compounds **57.4** are obtained by means of a reductive alkylation reaction between a 2,6-dimethylphenol aldehyde **57.1** and an aminoalkyl phosphonate ester **57.2**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component **57.2** and the aldehyde component **57.1** are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product **57.3**. The amination product **57.3** is then converted into the phenoxyacetic acid compound **57.4**, using the alkylation and ester hydrolysis procedures described above, (Scheme **56**) For example, equimolar amounts of 4-hydroxy-3,5-dimethylbenzaldehyde **57.5** (Aldrich) and a dialkyl aminoethyl phosphonate **57.6**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in J. Amer. Chem. Soc., 91, 3996, 1969, to afford the amine product **57.3**. The product is then converted into the acetic acid **57.8**, as described above. Using the above procedures, but employing, in place of the aldehyde **57.5**, different aldehydes **57.1**, and/or different aminoalkyl phosphonates **57.2**, the corresponding products **57.4** are obtained.

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described above (Scheme **54**)

Scheme **58** depicts the preparation of 2,6-dimethylphenols incorporating a phosphonate group linked to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, an optionally protected bromo-substituted 2,6-dimethylphenol **58.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **58.2**. The coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst. Following the coupling reaction, the product **58.3** is converted, using the procedures described above, (Scheme **56**) into the corresponding phenoxyacetic acid **58.4**. Alternatively, the olefinic product **58.3** is reduced to afford the saturated 2,6-dimethylphenol derivative **58.5**. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or diimide. Following the reduction reaction, the product **58.5** is converted, as described above, (Scheme **56**) into the corresponding phenoxyacetic acid **58.6**.

For example, 3-bromo-2,6-dimethylphenol **58.7**, prepared as described in Can. J. Chem., 1983, 61, 1045, is converted into the tert-butyldimethylsilyl ether **58.8**, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 p. 77. The product **58.8** is reacted with an equimolar amount of a dialkyl allyl phosphonate **58.9**, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°C, to produce the coupled product **58.10**. The silyl group is removed, for example by the treatment of the ether **58.10** with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Am. Chem., Soc., 94, 6190, 1972, to afford the phenol **58.11**. This compound is converted, employing the procedures described above, (Scheme **56**) into the corresponding phenoxyacetic acid **58.12**. Alternatively, the unsaturated compound **58.11** is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog **58.13**. This compound is

converted, employing the procedures described above, (Scheme **56**) into the corresponding phenoxyacetic acid **58.14**.

Using the above procedures, but employing, in place of 3-bromo-2,6-dimethylphenol **58.7**, different bromophenols **58.1**, and/or different dialkyl alkenyl phosphonates **58.2**, the corresponding products **58.4** and **58.6** are obtained.

Scheme **59** illustrates the preparation of phosphonate-containing 2,6-dimethylphenoxyacetic acids **59.1** in which the phosphonate group is attached to the 2,6-dimethylphenoxy moiety by means of a carbocyclic ring. In this procedure, a bromo-substituted 2,6-dimethylphenol **59.2** is converted, using the procedures illustrated in Scheme **56**, into the corresponding 2,6-dimethylphenoxyacetic ester **59.3**. The latter compound is then reacted, by means of a palladium-catalyzed Heck reaction, with a cycloalkenone **59.4**, in which n is 1 or 2. The coupling reaction is conducted under the same conditions as those described above for the preparation of **58.3** (Scheme **58**). The product **59.5** is then reduced catalytically, as described above for the reduction of **58.3**, (Scheme **58**), to afford the substituted cycloalkanone **59.6**. The ketone is then subjected to a reductive amination procedure, by reaction with a dialkyl 2-aminoethylphosphonate **59.7** and sodium triacetoxyborohydride, as described in J. Org. Chem., 61, 3849, 1996, to yield the amine phosphonate **59.8**. The reductive amination reaction is conducted under the same conditions as those described above for the preparation of the amine **57.3** (Scheme **57**). The resultant ester **59.8** is then hydrolyzed, as described above, to afford the phenoxyacetic acid **59.1**.

For example, 4-bromo-2,6-dimethylphenol **59.9** (Aldrich) is converted, as described above, into the phenoxy ester **59.10**. The latter compound is then coupled, in dimethylformamide solution at ca. 60°C, with cyclohexenone **59.11**, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to yield the cyclohexenone **59.12**. The enone is then reduced to the saturated ketone **59.13**, by means of catalytic hydrogenation employing 5% palladium on carbon as catalyst. The saturated ketone is then reacted with an equimolar amount of a dialkyl aminoethylphosphonate **59.14**, prepared as described in J. Org. Chem., 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the amine **59.15**. Hydrolysis, employing lithium hydroxide in aqueous methanol at ambient temperature, then yields the acetic acid **59.16**.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylphenol **59.9**, different bromo-substituted 2,6-dimethylphenols **59.2**, and/or different cycloalkenones **59.4**, and/or different dialkyl aminoalkylphosphonates **59.7**, the corresponding products **59.1** are obtained.

Scheme **60** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate group attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an optionally protected hydroxy, thio or amino-substituted 2,6-dimethylphenol **60.1** is reacted, in the presence of a base such as, for example, potassium carbonate, and optionally in the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl phosphonate **60.2**. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°C. The product of the alkylation reaction, **60.3** is then converted, as described above (Scheme **56**) into the phenoxyacetic acid **60.4**.

For example, 2,6-dimethyl-4-mercaptophenol **60.5**, prepared as described in EP 482342, is reacted in dimethylformamide at ca. 60°C with an equimolar amount of a dialkyl bromobutyl phosphonate **60.6**, the preparation of which is described in Synthesis, 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the thioether product **60.7**. This compound is converted, employing the procedures described above, (Scheme **56**) into the corresponding phenoxyacetic acid **60.8**.

Using the above procedures, but employing, in place of 2,6-dimethyl-4-mercaptophenol **60.5**, different hydroxy, thio or aminophenols **60.1**, and/or different dialkyl bromoalkyl phosphonates **60.2**, the corresponding products **60.4** are obtained.

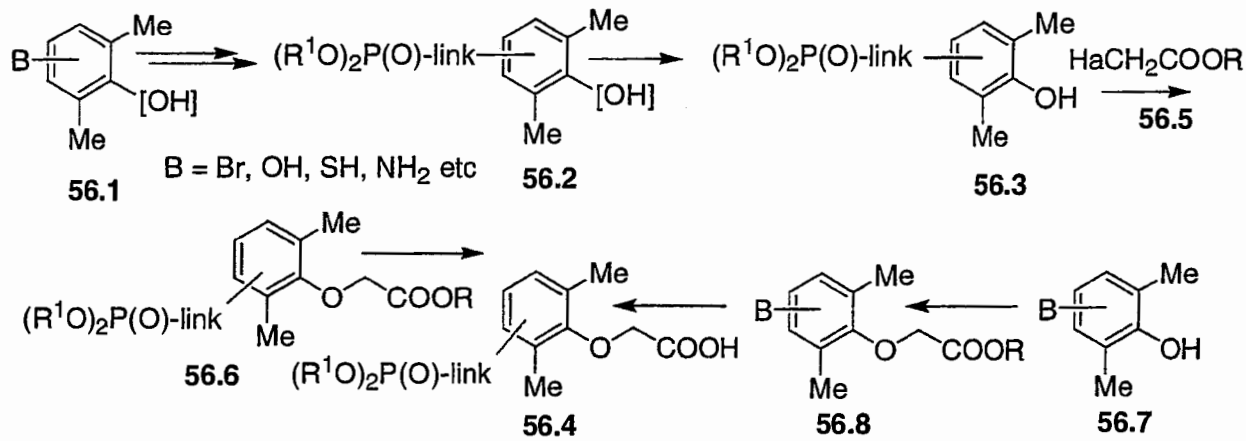
Scheme **61** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester group attached by means of an aromatic or heteroaromatic group. In this procedure, an optionally protected hydroxy, mercapto or amino-substituted 2.6-dimethylphenol **61.1** is reacted, under basic conditions, with a bis(halomethyl)aryl or heteroaryl compound **61.2**. Equimolar amounts of the phenol and the halomethyl compound are reacted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium or cesium carbonate, or dimethylaminopyridine, to afford

the ether, thioether or amino product **61.3**. The product **61.3** is then converted, using the procedures described above, (Scheme **56**) into the phenoxyacetic ester **61.4**. The latter compound is then subjected to an Arbuzov reaction by reaction with a trialkylphosphite **61.5** at ca. 100°C to afford the phosphonate ester **61.6**. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in Handb. Organophosphorus Chem., 1992, 115. The resultant product **61.6** is then converted into the acetic acid **61.7** by hydrolysis of the ester moiety, using the procedures described above, (Scheme **56**).

For example, 4-hydroxy-2,6-dimethylphenol **61.8** (Aldrich) is reacted with one molar equivalent of 3,5-bis(chloromethyl)pyridine, the preparation of which is described in Eur. J. Inorg. Chem., 1998, 2, 163, to afford the ether **61.10**. The reaction is conducted in acetonitrile at ambient temperature in the presence of five molar equivalents of potassium carbonate. The product **61.10** is then reacted with ethyl bromoacetate, using the procedures described above, (Scheme **56**) to afford the phenoxyacetic ester **61.11**. This product is heated at 100°C for 3 hours with three molar equivalents of triethyl phosphite **61.12**, to afford the phosphonate ester **61.13**. Hydrolysis of the acetic ester moiety, as described above, for example by reaction with lithium hydroxide in aqueous ethanol, then affords the phenoxyacetic acid **61.14**.

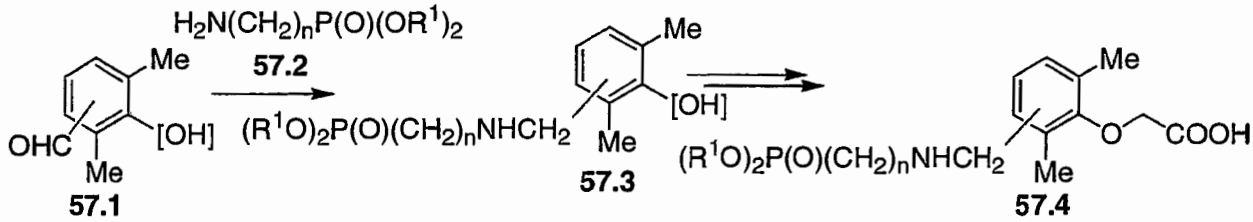
Using the above procedures, but employing, in place of the bis(chloromethyl) pyridine **61.9**, different bis(halomethyl) aromatic or heteroaromatic compounds **61.2**, and/or different hydroxy, mercapto or amino-substituted 2,6-dimethylphenols **61.1** and/or different trialkyl phosphites **61.5**, the corresponding products **61.7** are obtained.

Scheme 56

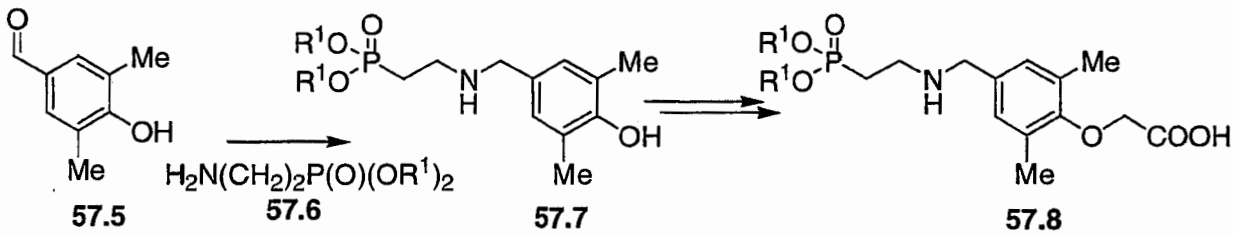


Scheme 57

Method

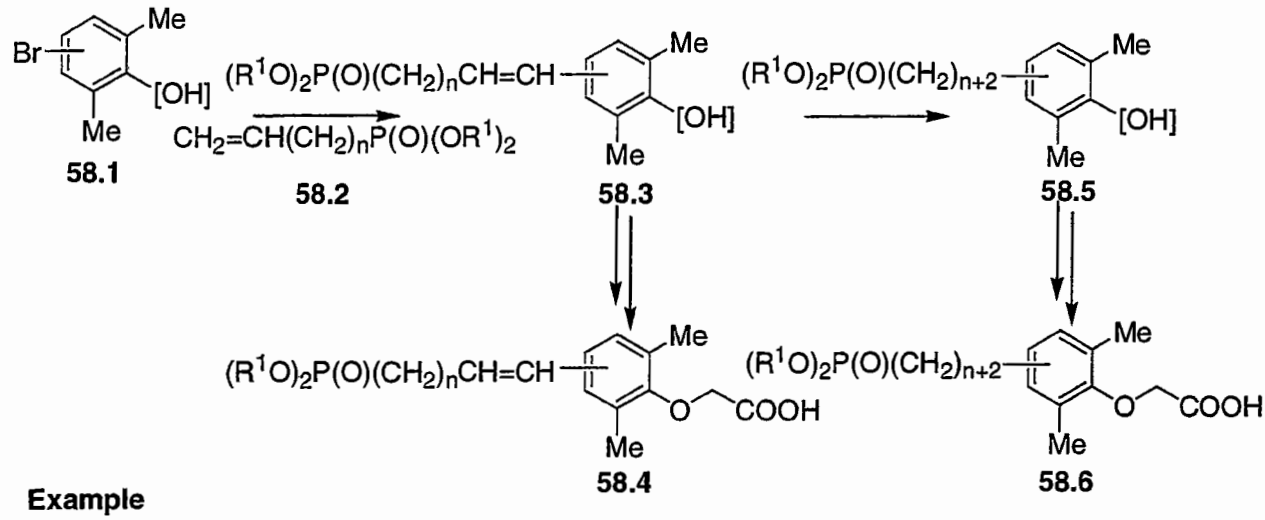


Example

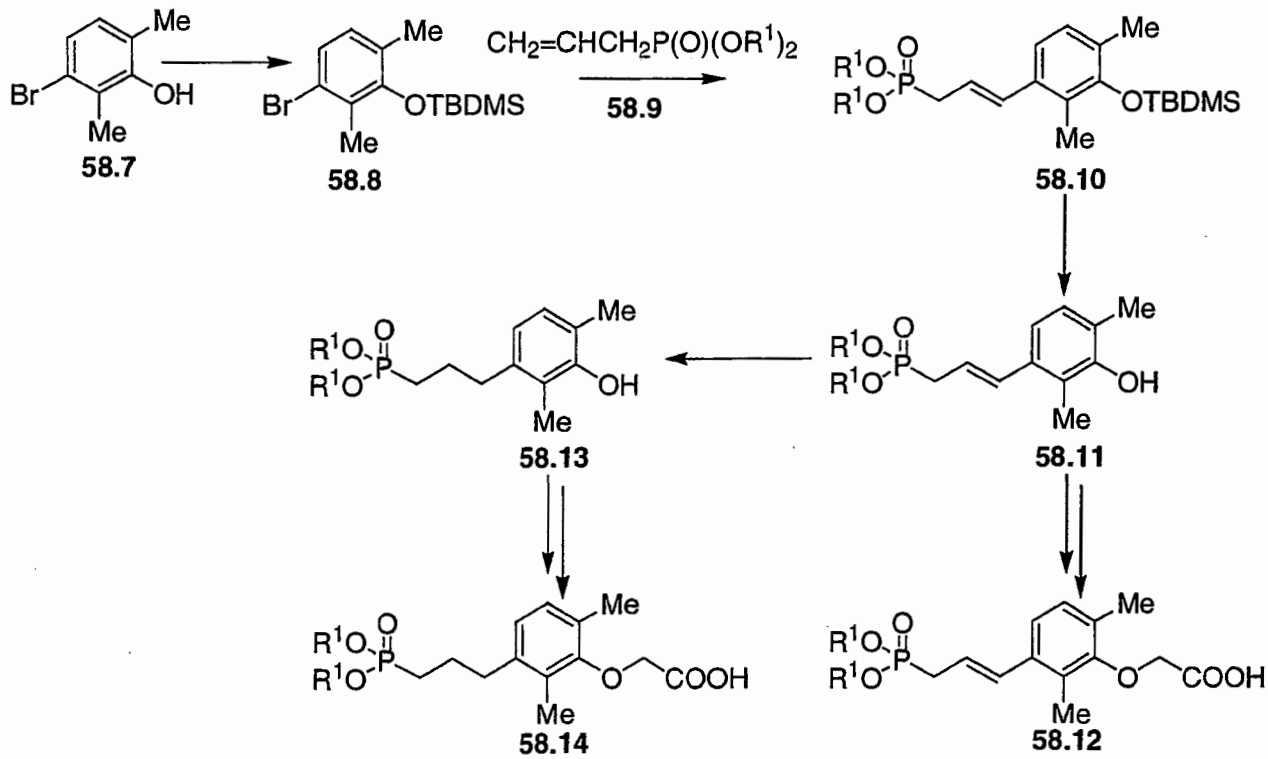


Scheme 58

Method

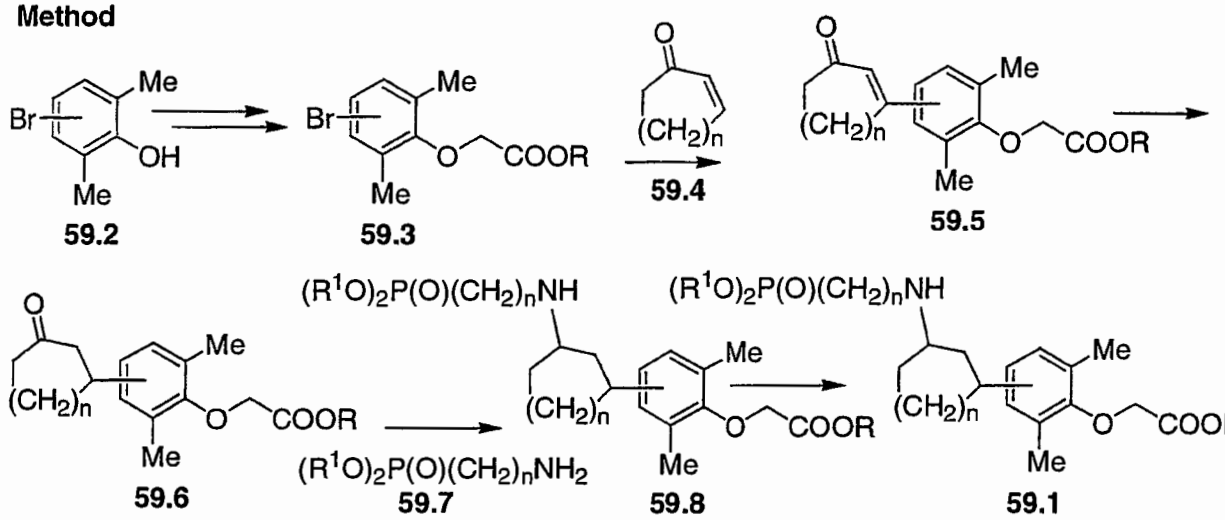


Example

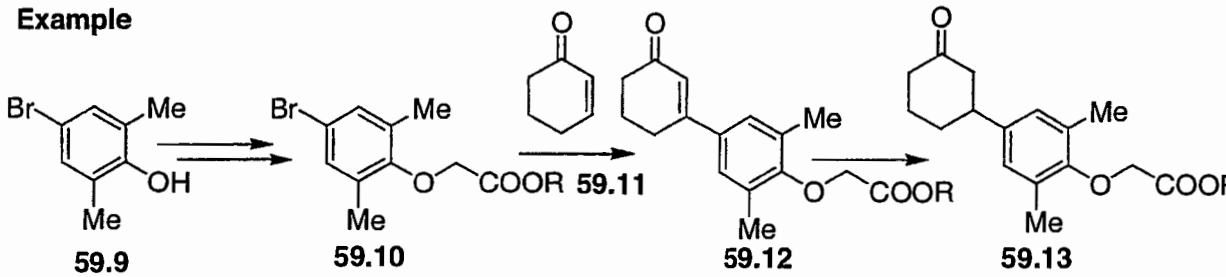


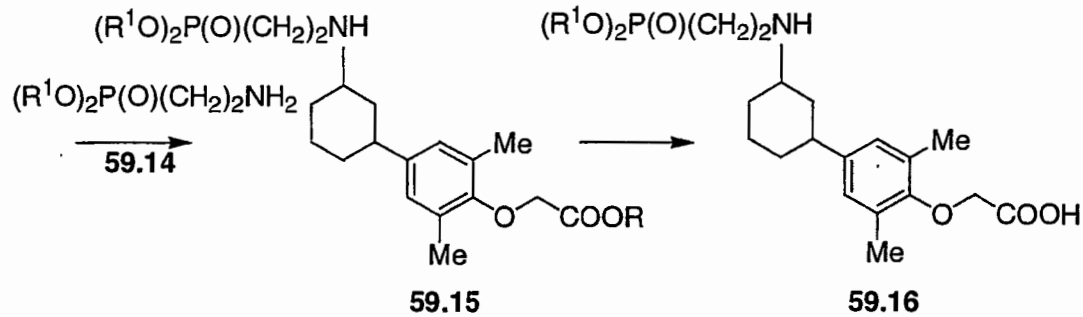
Scheme 59

Method



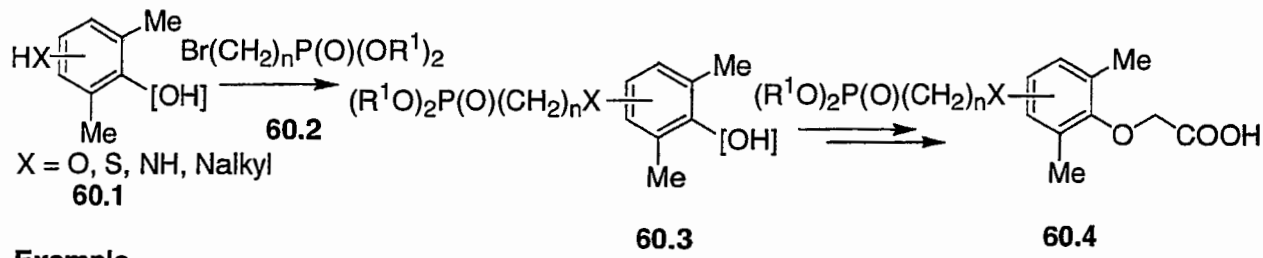
Example



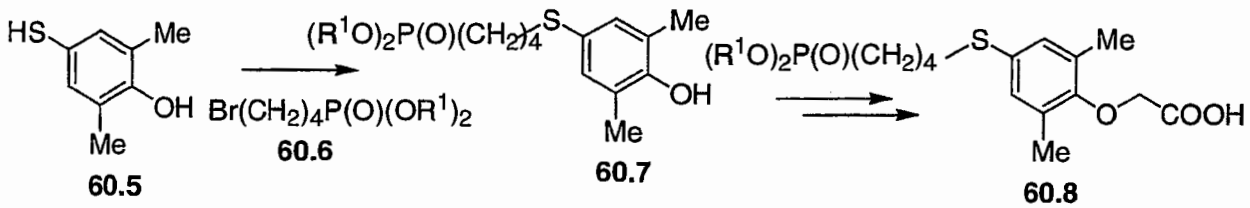


Scheme 60

Method

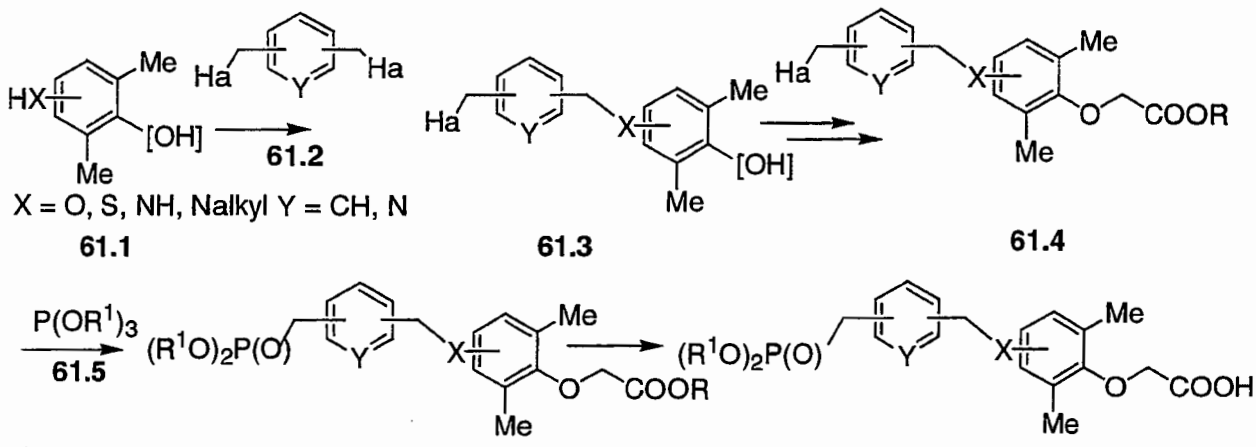


Example

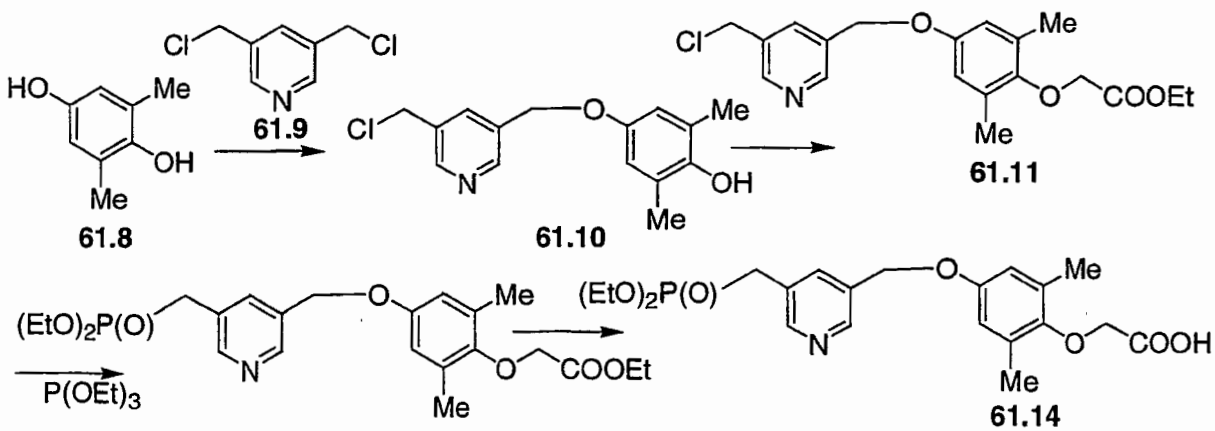


Scheme 61

Method



Example



Preparation of benzyl carbamate compounds incorporating phosphonate groups.

Scheme **62** depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative **C4** in which the phosphonate moiety is either directly attached to the phenyl ring or attached by means of an alkylene chain. In this procedure, a dialkyl hydroxymethylphenyl alkylphosphonate **62.1** is converted into an activated derivative **62.2**, in which Lv is a leaving group, as described above (Scheme **55**). The product is then reacted with a suitably protected aminoacid **62.3**, to afford the carbamate product **62.4**. The reaction is conducted under the conditions described above for the preparation of carbamates (Scheme **55**). The protecting group on the carboxylic acid group in the product **62.4** is then removed to afford the free carboxylic acid **62.5**. Methods for the protection and deprotection of carboxylic acids are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

For example, as shown in Scheme **62**, Example **1**, a dialkyl 4-hydroxymethylphenyl phosphonate **62.6**, prepared as described in US 5569664, is reacted with phosgene, or an equivalent thereof, as described above (Scheme **55**), to afford the chloroformyl product **62.7**. This compound is then reacted in an inert solvent such as dichloromethane or tetrahydrofuran, with the tert. butyl aminoacid ester **62.3**, in the presence of a base such as triethylamine, to yield the carbamate product **62.8**. The conversion of acids into tert. butyl esters is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 245ff. The ester can be prepared by the reaction of the carboxylic acid with isobutylene and an acid catalyst, or by conventional esterification procedures employing tert. butanol. The tert. butyl protecting group is then removed from the product **62.8**, for example by reaction with trifluoroacetic acid at ambient temperature for about one hour, to afford the carboxylic acid **62.9**.

As a further example, Scheme **62**, Example **2** shows the conversion of a dialkyl 4-hydroxymethyl benzyl phosphonate **62.10**, prepared as described in J. Am. Chem. Soc., 1996, 118, 5881, into the hydroxybenztriazole derivative **62.11**. The reaction is performed as described above (Scheme **55**). The activated derivative is then reacted with the aminoacid

derivative **62.3**, as described above, to afford the carbamate **62.12**. deprotection, as previously described, then affords the carboxylic acid **62.13**.

Using the above procedures, but employing, in place of the phosphonates **62.6** and **62.10**, different phosphonates **62.1**, and/or different aminoacid derivatives **62.3**, the corresponding products **62.5** are obtained.

Scheme **63** depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative **C4** in which the phosphonate moiety is attached to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted benzyl alcohol **63.1** is subjected to a palladium catalyzed Heck reaction, as described above, (Scheme **26**) with a dialkyl alkenyl phosphonate **63.2**, to afford the olefinic product **63.3**. The product is then converted into the activated derivative **63.4**, which is then reacted with aminoacid derivative **62.3**, as described above, to afford, after deprotection of the carboxyl group, the carbamate product **63.5**. Optionally, the olefinic coupling product can be reduced to the saturated analog **63.6**. The reduction reaction can be effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5. The product **63.6** is then converted, as described above, into the carbamate derivative **63.8**.

For example, 3-bromobenzyl alcohol **63.9** is coupled in acetonitrile solution, with a dialkyl allylphosphonate **63.10** (Aldrich), in the presence of palladium acetate, triethylamine and tri-o-tolylphosphine, as described in Synthesis, 1983, 556, to afford the product **63.11**. This material is then reacted with carbonyl diimidazole, as described above, (Scheme **55**) to afford the imidazolide **63.12**. The product is then coupled with the aminoacid derivative **62.3**, to afford after deprotection, the product **63.13**. Alternatively, the unsaturated phosphonate **63.11** is reduced, for example by reaction with diborane in tetrahydrofuran at ambient temperature, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5., to afford the saturated analog **63.14**. The latter compound is then transformed, as described above, into the carbamate aminoacid derivative **63.15**.

Using the above procedures, but employing, in place of the 3-bromobenzyl alcohol **63.9**, different bromobenzyl alcohols **63.1**, and/or different alkenyl phosphonates **63.2**, and/or different amino acid derivatives, the corresponding products **63.5** and **63.8** are obtained.

Scheme **64** depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative **C4** in which the phosphonate moiety is attached to the phenyl ring by means of an amino-containing alkylene chain. In this procedure, a formyl-substituted benzyl alcohol **64.1** is converted, using the procedures described above is Schemes **55** and **63**, into the aminoacid carbamate derivative **64.2**. The product is then subjected to a reductive amination reaction with a dialkyl aminoalkyl phosphonate **64.3**, to afford the phosphonate product **64.4**. Reductive amination of carbonyl compounds is described above (Scheme **27**). For example, 3-formyl benzyl alcohol **64.5** is converted into the carbamate derivative **64.6**. The product is then reacted in ethanol solution at ambient temperature with a dialkyl aminoethyl phosphonate **64.7**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the phosphonate product **64.8**. Using the above procedures, but employing, in place of the 3-formylbenzyl alcohol **64.5**, different formylbenzyl alcohols **64.1**, and/or different aminoalkyl phosphonates **64.3**, the corresponding products **64.4** are obtained.

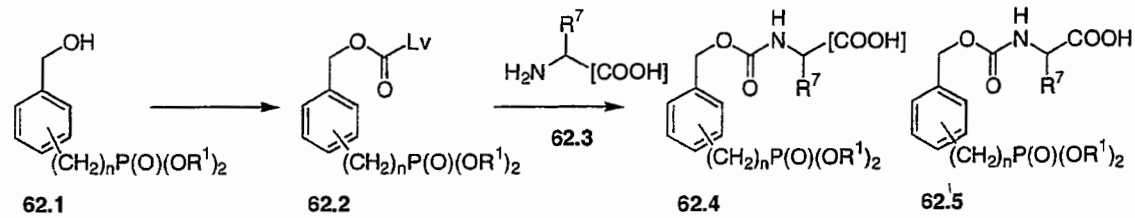
Scheme **65** depicts the preparation of phosphonate-containing analogs of the benzyl carbamate aminoacid derivative **C4** in which the phosphonate moiety is attached to the phenyl ring by means of an O, S or N-alkyl-containing alkylene chain. In this procedure, a chloromethyl-substituted benzyl alcohol **65.1** is reacted with a dialkyl hydroxy, mercapto or alkylaminoalkyl phosphonate **65.2**. The alkylation reaction is conducted between equimolar amounts of the reactants in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of an inorganic or organic base, such as diisopropylethylamine, dimethylaminopyridine, potassium carbonate and the like. The alkylated product **65.3** is then converted, as previously described, into the carbamate aminoacid derivative **65.4**.

For example, 4-chloromethylbenzyl alcohol **65.5**, (Aldrich) is reacted at ca. 60°C in acetonitrile solution with a dialkyl hydroxypropyl phosphonate **65.6**, the preparation of which is described in Zh. Obschei. Khim., 1974, 44, 1834, in the presence of dimethylaminopyridine, to afford the ether product **65.7**. The product is then converted, as previously described, into the carbamate derivative **65.8**.

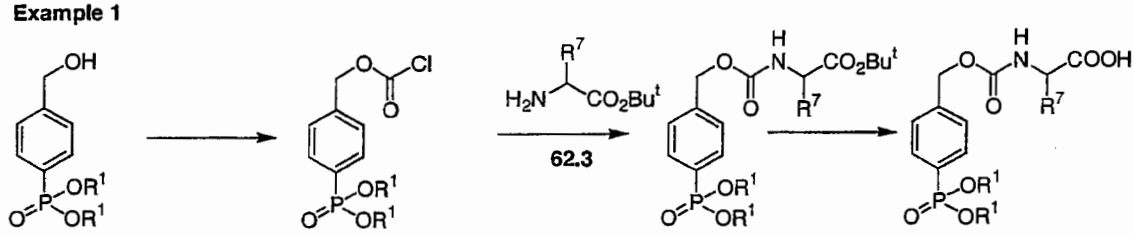
Using the above procedures, but employing, in place of 4-(chloromethyl)benzyl alcohol **65.5**, different chloromethyl benzyl alcohols **65.1**, and/or different hydroxy, mercapto or alkylamino phosphonates **65.2**, the corresponding products **65.4** are obtained.

Scheme 62

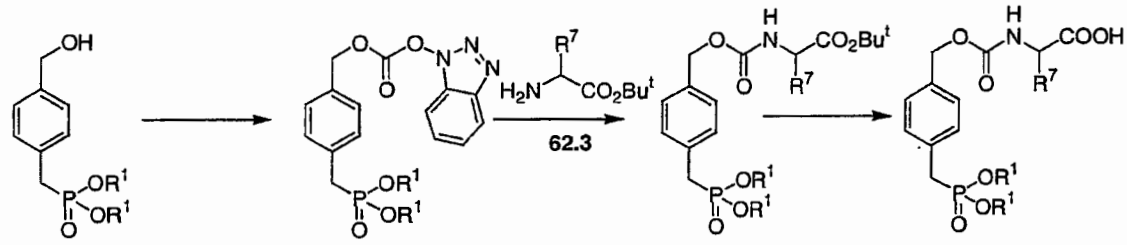
Method



Example 1

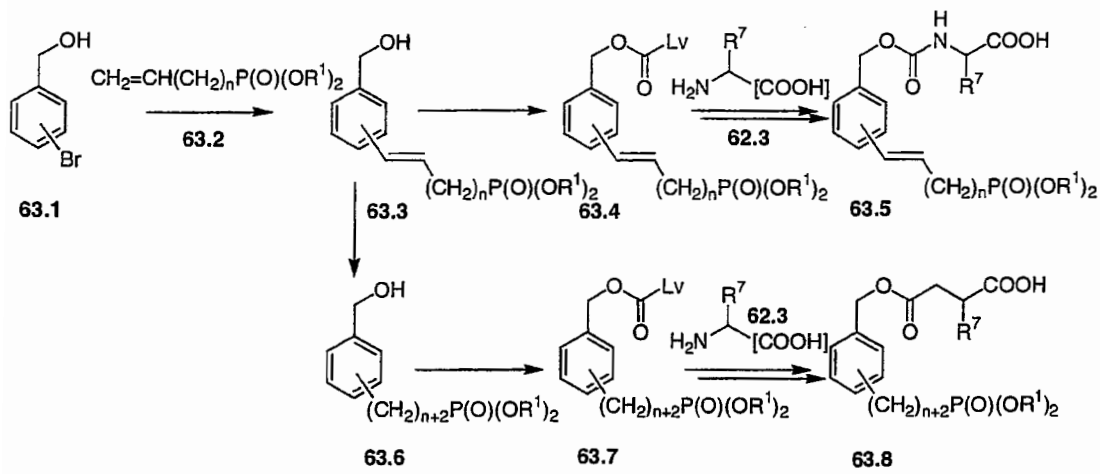


Example 2

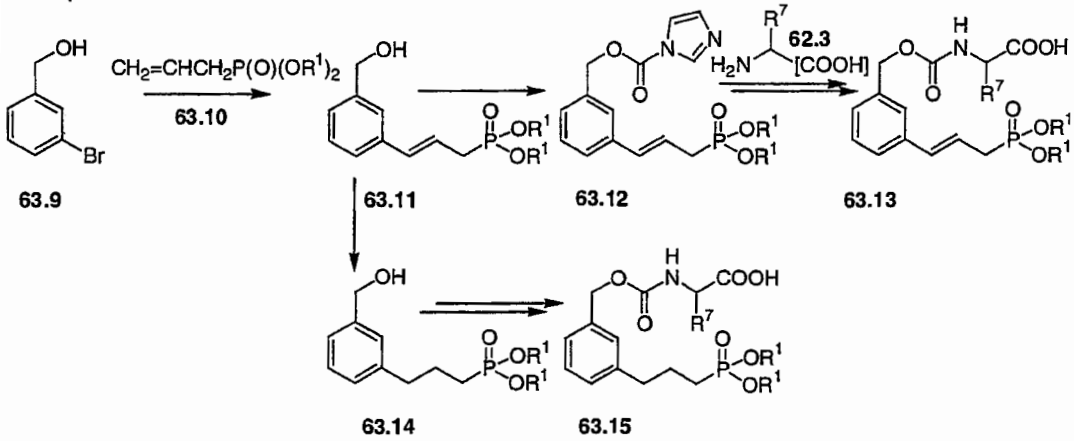


Scheme 63

Method

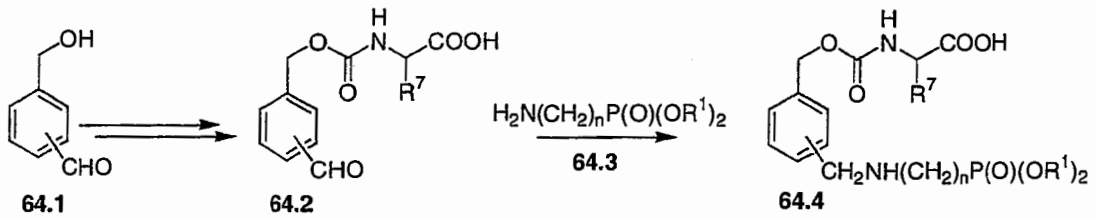


Example

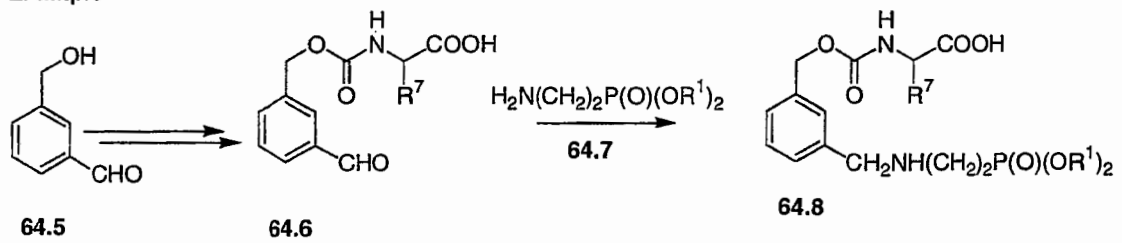


Scheme 64

Method

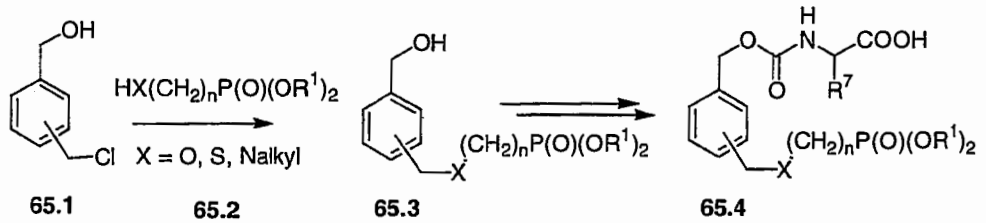


Example

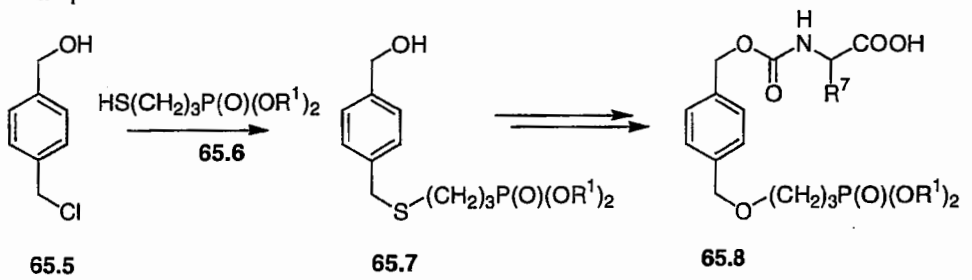


Scheme 65

Method



Example



Preparation of pyridinyloxymethyl piperidine derivatives incorporating phosphonate groups.

Scheme **66** illustrates the preparation of phosphonate-containing analogs of the amine **A12** in which the phosphonate moiety is attached to the pyridine ring by means of a heteroatom and an alkylene chain. In this procedure, 2-bromo-4-hydroxymethylpyridine, the preparation of which is described in Chem. Pharm. Bull., 1990, 38, 2446, is subjected to a nucleophilic

displacement reaction with a dialkyl hydroxy, thio or aminoalkyl-substituted alkyl phosphonate **66.2**. The preparation of pyridine ethers, thioethers and amines by means of displacement reactions of 2-bromopyridines by alcohols, thiols and amines is described, for example, in Heterocyclic Compounds, Volume 3, R. A. Abramovitch, ed., Wiley, 1975, p. 597, 191, and 41 respectively. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide at ca 100°C in the presence of a base such as potassium carbonate. The displacement product **66.3** is then converted into the activated derivative **66.4**, in which Lv is a leaving group such as halo, methanesulfonyloxy, p-toluenesulfonyloxy and the like. The conversion of alcohols into chlorides and bromides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. For example, benzyl alcohols can be transformed into the chloro compounds, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in J. Am. Chem. Soc., 106, 3286, 1984. Benzyl alcohols can be transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc., 92, 2139, 1970. Alcohols can be converted into sulfonate esters by treatment with the alkyl or aryl sulfonyl chloride and a base, in a solvent such as dichloromethane or pyridine. Preferably, the carbinol **66.3** is converted into the corresponding chloro compound, **66.4**, in which Lv is Cl, as described above. The product is then reacted with the piperidinol derivative **66.5**. The preparation of the compounds **66.5** is described in U.S. 5,614,533, and in J. Org. Chem., 1997, 62, 3440. The piperidinol derivative **66.5** is treated in dimethylformamide with a strong base such as sodium hydride, and the alkylating agent **66.4** is then added. The reaction proceeds to afford the ether product **66.6**, and the BOC protecting group is then removed to yield the free amine compound **66.7**. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC group is removed by treatment of the substrate **66.6** with hydrochloric acid, as described in J. Org. Chem., 1997, 62, 3440.

For example, 2-bromo-4-hydroxymethylpyridine **66.1** the preparation of which is described in Chem. Pharm. Bull., 1990, 38, 2446, is reacted in dimethylformamide solution at ca 80°C with an equimolar amount of a dialkyl mercaptoethyl phosphonate **66.8**, prepared as described in

Zh. Obschei. Khim., 1973, 43, 2364, and potassium carbonate, to yield the thioether product **66.9**. The product is then reacted with one molar equivalent of methanesulfonyl chloride in pyridine at 0°C, to produce the mesylate compound **66.10**. This material is reacted with the piperidinol reagent **66.5**, using the conditions described above, to afford the ether **66.11**. The BOC protecting group is then removed as previously described, to afford the amine product **66.12**.

Using the above procedures, but employing, in place of the mercaptoethyl phosphonate **66.8**, different hydroxy, mercapto or alkylamino phosphonates **66.2**, the corresponding products **66.7** are obtained.

Scheme **67** illustrates the preparation of phosphonate-containing analogs of the amine **A12** in which the phosphonate moiety is directly attached to the pyridine ring. In this procedure, a bromo-substituted 4-hydroxymethylpyridine **67.1** is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite **67.2**. The reaction between aryl bromides and dialkyl phosphites to yield aryl phosphonates is described in Synthesis, 56, 1981, and in J. Med. Chem., 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°C, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The thus-obtained pyridylphosphonate **67.3** is then converted, as described above (Scheme **66**) into an activated derivative **67.4**, and the latter compound is transformed as described above into the amine **67.5**.

For example, 3-bromo-4-hydroxymethylpyridine **67.5**, prepared as described in Bioorg. Med. Chem. Lett., 1992, 2, 1619, is reacted with a dialkyl phosphite **67.2**, as described above, to prepare the phosphonate **67.7**. The product is then transformed into the chloro derivative by reaction with triphenylphosphine and N-chlorosuccinimide, and the product is converted, as described above (Scheme **66**) into the amine **67.9**.

Using the above procedures, but employing, in place of the 3-bromopyridine derivative **67.6**, different bromopyridines **67.1**, and/or different phosphites, the corresponding products **67.5** are obtained.

Scheme **68** illustrates the preparation of phosphonate-containing analogs of the amine **A12** in which the phosphonate moiety is attached to the pyridine ring by means of an amine group and

an alkyl chain. In this procedure, an amino-substituted 4-hydroxymethylpyridine **68.1** is subjected to a reductive amination reaction with a dialkyl formylalkyl phosphonate **68.2**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The amine product **68.3** is then converted, as described above, into the piperidine derivative **68.5**.

For example, 2-amino-4-hydroymethylpyridine **68.6**, prepared as described in Aust. J. Chem., 1993, 46, 9897, is reacted in ethanol solution with a dialkyl formylmethylphosphonate **68.7**, prepared as described in Zh. Obschei. Khim., 1987, 57, 2793, in the presence of sodium cyanoborohydride, to yield the amine product **68.8**. This material is then transformed into the chloro derivative **68.9** by reaction with hydrogen chloride in ether. The chloro product is then transformed, as described above, into the piperidine derivative **68.10**.

Using the above procedures, but employing, in place of the 2-aminopyridine derivative **68.6**, different aminopyridines **68.1**, and/or different formylalkyl phosphonates **68.2** the corresponding products **68.5** are obtained.

Scheme **69** illustrates the preparation of phosphonate-containing analogs of the amine **A12** in which the phosphonate moiety is attached to the pyridine ring by means of a saturated or unsaturated alkyl chain. In this procedure, a bromo-substituted 4-hydroxymethylpyridine **69.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **69.2**. The coupling of aryl bromides and olefins is described above (Scheme **26**). The product is then converted, as described above, into the piperidine derivative **69.5**. Optionally, the latter compound can be reduced, for example as described above in Scheme **26**, to afford the saturated analog **69.6**.

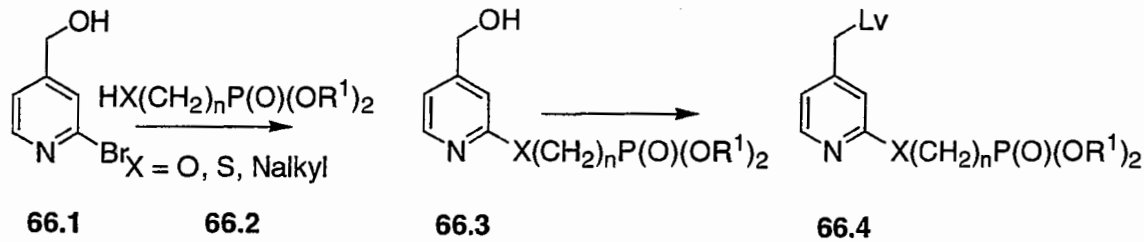
For example, 3-bromo-4-hydroxymethylpyridine **69.7**, prepared as described in Bioorg. Med. Chem. Lett., 1992, 2, 1619, is coupled with a dialkyl vinylphosphonate **69.8**, prepared as described in Synthesis, 1983, 556, to yield the olefinic product **69.9**. The product is reacted

with one molar equivalent of p-toluenesulfonyl chloride in pyridine at ambient temperature to afford the tosylate **69.10**. The latter compound is then transformed, as previously described, into the piperidine derivative **69.11**. Optionally, the latter compound is reduced, for example by reaction with diimide, to yield the saturated analog **69.12**.

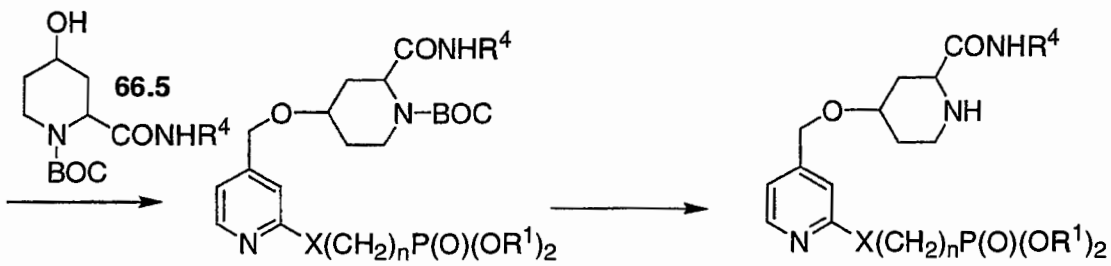
Using the above procedures, but employing, in place of the 3-bromopyridine derivative **69.7**, different bromopyridines **69.1**, and/or different alkenyl phosphonates **69.2** the corresponding products **69.5** and **69.6** are obtained.

Scheme 66

Method

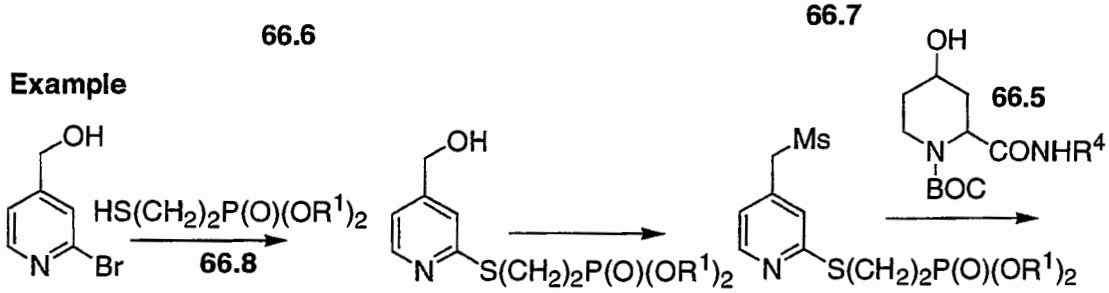


66.1 **66.2** **66.3** **66.4**

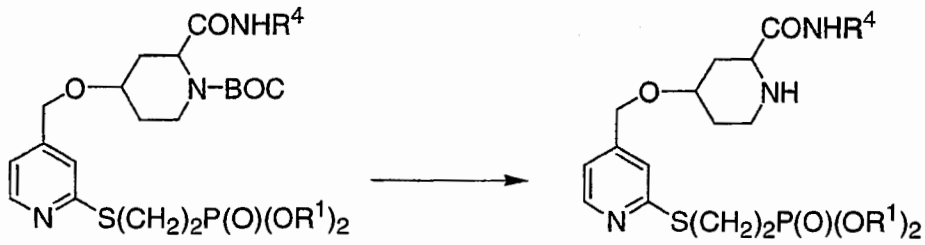


66.6 **66.7**

Example



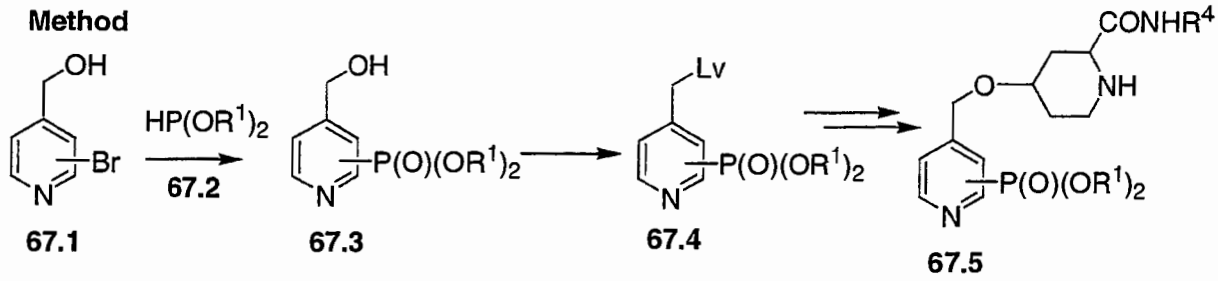
66.1 **66.9** **66.10**



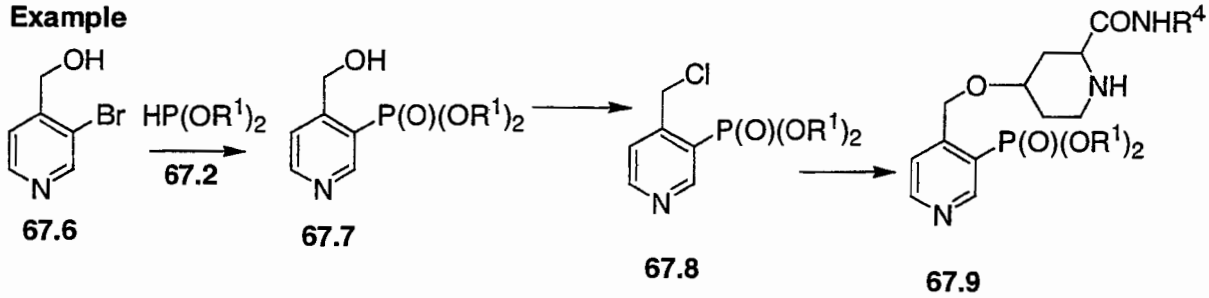
66.11 **66.12**

Scheme 67

Method

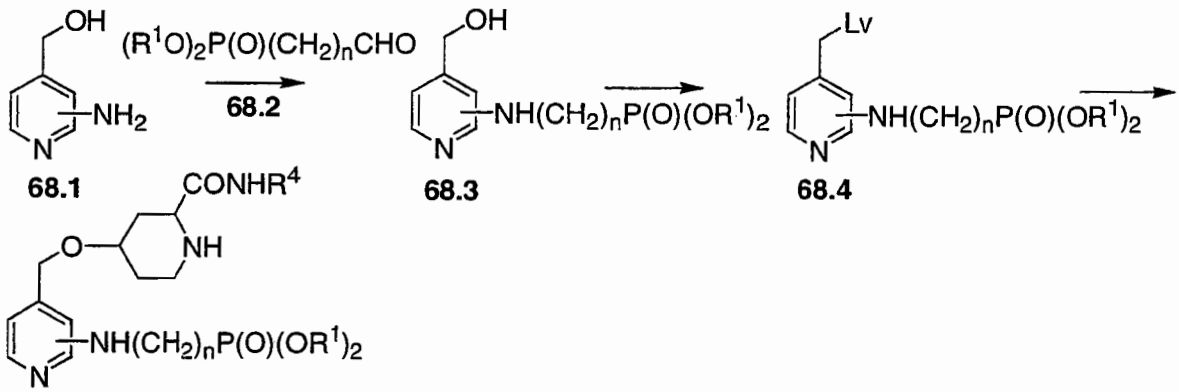


Example



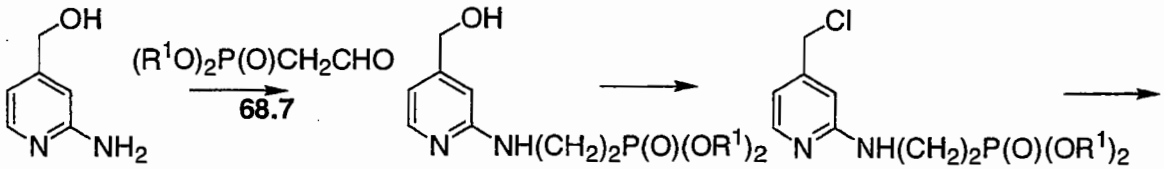
Scheme 68

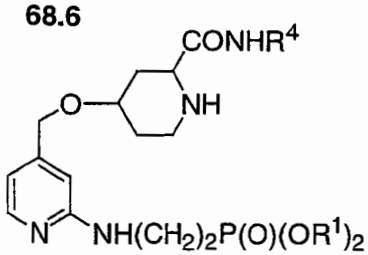
Method



68.5

Example

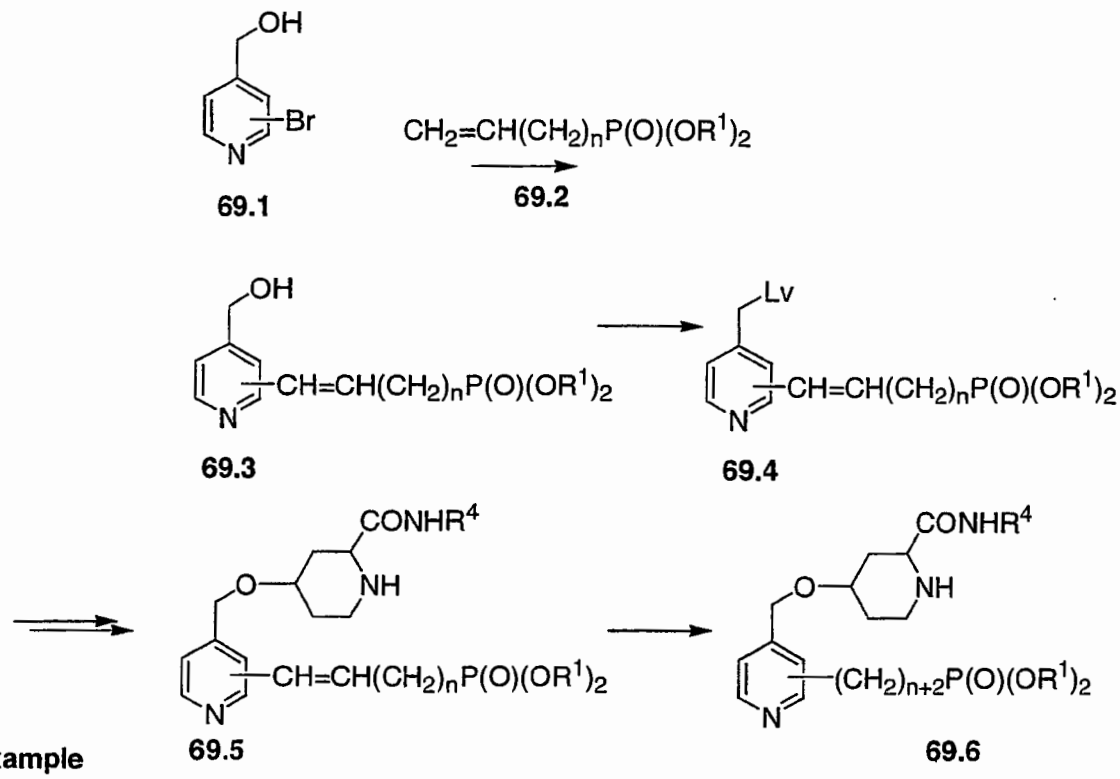




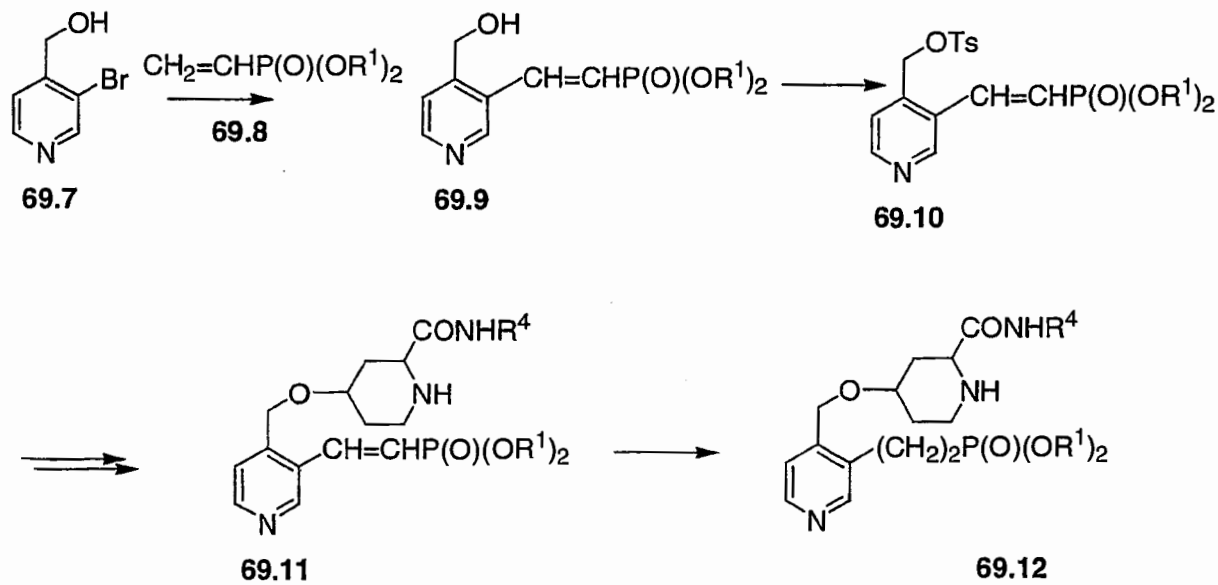
68.10

Scheme 69

Method



Example



General applicability of methods for introduction of phosphonate substituents.

The procedures described herein for the introduction of phosphonate moieties are, with appropriate modifications, transferable to different chemical substrates. For example, the methods described above for the introduction of phosphonate groups into the quinoline-2-carboxylic moiety (Schemes **24-27**), can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the phenylalanine, thiophenol, tert-butylamine and decahydroisoquinoline moieties. Similarly, the methods described above for the introduction of phosphonate groups into the phenylalanine moiety (Schemes **28-34**), the thiophenol moiety (Schemes **35-44**) the tert-butylamine moiety (Schemes **45-48**), decahydroisoquinoline moiety (Schemes **48a-52**), dimethylphenoxyacetic acids (Schemes **56 - 61**), benzyl carbamates (Schemes **62 - 65**) and pyridines (Schemes **66 - 69**) can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the quinoline-2-carboxylic acid component.

Preparation of (Pyridin-3-yloxy)-acetic acids incorporating phosphonate moieties.

Scheme **70** illustrates two alternative methods by means of which (pyridin-3-yloxy)-acetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the pyridyl moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed (Pyridin-3-yloxy)-acetic acid intermediate. In the first sequence, a substituted 3-hydroxypyridine **70.1**, in which the substituent B is a precursor to the group link-P(O)$(OR^1)_2$, and in which the aryl hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound **70.2**. Methods for the conversion of the substituent B into the group link-P(O)$(OR^1)_2$ are described in Schemes **25 - 75**.

The protected aryl hydroxyl group present in the phosphonate-containing product **70.2** is then deprotected, using methods described below, to afford the phenol **70.3.**

The product **70.3** is then transformed into the corresponding (pyridin-3-yloxy) acetic acid **70.4**, in a two step procedure. In the first step, the phenol **70.3** is reacted with an ester of bromoacetic acid **70.9**, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of aryl

hydroxyl groups to afford aryl ethers is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the aryl reagent and the alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol **70.3** and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described in U.S. Patent 5,914,332, to afford the ester **70.4**.

The thus-obtained ester **70.4** is then hydrolyzed to afford the carboxylic acid **70.5**. The methods used for this reaction depend on the nature of the group R. If R is an alkyl group such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group, methods for hydrolysis are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

Preferably, the ester product **70.4** which R is ethyl is hydrolyzed to the carboxylic acid **70.5** by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in U.S. Patent 5,914,332.

Alternatively, an appropriately substituted 3-hydroxypyridine **70.6**, in which the substituent B is a precursor to the group link-$P(O)(OR^1)_2$, is transformed into the corresponding acetic acid ester **70.7**. The conditions employed for the alkylation reaction are similar to those described above for the conversion of the phenol **70.3** into the ester **70.4**.

The acetic acid ester **70.7** is then converted into the carboxylic acid **70.5** using the 2 step procedure shown above, involving transformation of the group B into the group link-$P(O)(OR^1)_2$ followed by ester hydrolysis of the acetic acid ester. The group B which is present in the ester **70.7** may be transformed into the group link-$P(O)(OR^1)_2$ either before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes **70-75** illustrate the preparation of (Pyridin-3-yloxy)-acetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of acetic esters acids **70.7**, with, if appropriate, modifications made according to the knowledge of one skilled in the art.

Scheme **71** depicts the preparation of (pyridin-3-yloxy) acetic acids incorporating a phosphonate group linked to the pyridyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, an optionally protected halo-substituted 3-hydroxypyridine **71.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **71.2**. The coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl halide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst. Following the coupling reaction, the product **71.3** is converted, using the procedures described above, (Scheme **70**) into the corresponding (pyridin-3-yloxy) acetic acid **71.4**. Alternatively, the olefinic product **71.3** is reduced to afford the saturated derivative **71.5**. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or diimide. Following the reduction reaction, the product **71.5** is converted, as described above, (Scheme **70**) into the corresponding (pyridin-3-yloxy) acetic acid **71.6**.

For example, 2-iodo-5-hydroxy pyridine **71.7**, prepared as described in J. Org. Chem., 1990, 55, 18, p. 5287, is converted into the tert-butyldimethylsilyl ether **71.8**, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 p. 77. The product **71.8** is reacted with an equimolar amount of a dialkyl allyl phosphonate **71.9**, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°C, to produce the coupled product **71.10**. Alternatively see J. Med. Chem. 1999, 42, 4, p. 669 for alternative conditions for this reaction. The silyl group is removed, for example by the treatment of the ether **71.10** with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Am. Chem., Soc., 94, 6190, 1972, to afford the phenol **71.11**. This compound is converted, employing the procedures described above, (Scheme **70**) into the corresponding (pyridin-3-yloxy) acetic acid **71.12**. Alternatively, the unsaturated compound **71.11** is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog **71.13**. This

compound is converted, employing the procedures described above, (Scheme **70**) into the corresponding (pyridin-3-yloxy) acetic acid **71.14**.

Using the above procedures, but employing, in place of 2-iodo-5-hydroxy pyridine **71.7**, different iodo or bromohydroxypyridines **71.1**, and/or different dialkyl alkenyl phosphonates **71.2**, the corresponding products **71.4** and **71.6** are obtained.

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described above (Scheme **54**).

Scheme **72** illustrates the preparation of phosphonate-containing analogs of (pyridin-3-yloxy) acetic acids in which the phosphonate moiety is attached to the pyridine ring by means of a heteroatom and an alkyl chain. In this procedure, a suitably protected 2-halo-5-hydroxypyridine, (see Scheme **71**) is subjected to a nucleophilic displacement reaction with a dialkyl hydroxy, thio or aminoalkyl-substituted alkyl phosphonate **72.2**. The preparation of pyridine ethers, thioethers and amines by means of displacement reactions of 2-bromopyridines, by alcohols, thiols and amines is described, for example, in Heterocyclic Compounds, Volume 3, R. A. Abramovitch, ed., Wiley, 1975, p. 597, 191, and 41 respectively. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide at ca 100°C in the presence of a base such as potassium carbonate. The displacement product **72.3** is then converted into the hydroxyl derivative **72.4** and then into the (pyridin-3-yloxy) acetic acid phosphonate ester **72.5** using the procedures described above (Scheme **70**).

For example, 2-iodo-5-hydroxypyridine **71.7** (Scheme **71**) is treated with benzyl bromide in the presence of base such as potassium carbonate as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, p. 266 to give **72.6**. The benzyl ether **72.6** is reacted in dimethylformamide solution at ca 80°C with an equimolar amount of a dialkyl mercaptoethyl phosphonate **72.7**, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, and potassium carbonate, to yield the thioether product **72.8**. The benzyl group is then removed by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.

266ff., to afford the hydroxyl compound **72.9**. The product **72.9** is then converted into the (pyridin-3-yloxy) acetic acid phosphonate ester **72.10** using the procedures described above (Scheme **70**).

Using the above procedures, but employing, in place of the mercaptoethyl phosphonate **72.7**, different hydroxy, mercapto or alkylamino phosphonates **72.2**, and/or in place of the pyridine **71.7** different halo pyridines **71.1**, the corresponding products **72.5** are obtained.

Scheme **73** illustrates the preparation of phosphonate-containing analogs of (pyridin-3-yloxy) acetic acids in which the phosphonate moiety is directly attached to the pyridine ring. In this procedure, a suitably protected 2-bromo-5-hydroxypyridine **73.1** is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite **73.2**. The reaction between aryl bromides and dialkyl phosphites to yield aryl phosphonates is described in Synthesis, **70**, 1981, and in J. Med. Chem., 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°C, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The thus-obtained pyridylphosphonate **73.3** is then converted, as described above (Scheme **72**) into the (pyridin-3-yloxy) acetic acid phosphonate ester **73.5**.

For example, 3-bromo-5-hydroxypyridine **73.6** (Synchem-OHG) is treated with benzyl bromide in the presence of base such as potassium carbonate as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, p. 266 to give **73.7**. The product **73.7** is then treated with a dialkylphosphite **73.2** as described above to give the phosphonate **73.8**. Employing the conditions described above (Scheme **72**) **73.8** is converted in several steps to the (pyridin-3-yloxy) acetic acid phosphonate ester **73.10.**

Using the above procedures, but employing, in place of the 3-bromopyridine derivative **73.6**, different bromopyridines **73.1**, and/or different phosphites, the corresponding products **73.5** are obtained.

Scheme **74** illustrates the preparation of (pyridin-3-yloxy) acetic acids incorporating a phosphonate group attached to the pyridyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an hydroxy, thio or amino-substituted 3-hydroxy pyridine **74.1**, protected at the 3-hydroxyl position is reacted, in the presence of a base such as, for example, potassium carbonate, and optionally in

the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl phosphonate **74.6**. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°C. The product of the alkylation reaction, **74.2** is then converted, as described above for converting **72.3** to **72.5** (Scheme **72**) into the acid **74.5**.

Alternatively, the protected pyridine **74.7** is converted to the acetic acid ester derivative **74.8** using the procedures described above in Scheme **70**. The acetic acid ester **74.8**, is then deprotected following the procedures described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, ch 3,6, and 7, and the product treated with a dialkyl bromoalkyl phosphonate **74.6** to give **74.4.** The ester **74.4** is converted to the acid **74.5** using the procedures described above (Scheme **70**).

For example, 3-benzyloxy, 5-hydroxy pyridine **74.10**, prepared as described Bioorg and Med. Chem. Lett. 1998, p. 2797, is converted to the ester **74.11** by treatment with ethylbromoacetate as described above (Scheme **70**). The benzyl group is removed, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the hydroxy pyridine **74.12**. The product **74.12** is reacted in dimethylformamide at ca. 60°C with an equimolar amount of a dialkyl bromobutyl phosphonate **74.14**, the preparation of which is described in Synthesis, 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the phosphonate ether product **74.13**. This compound is converted, employing the procedures described above, (Scheme **70**) into the corresponding acid **74.15**.

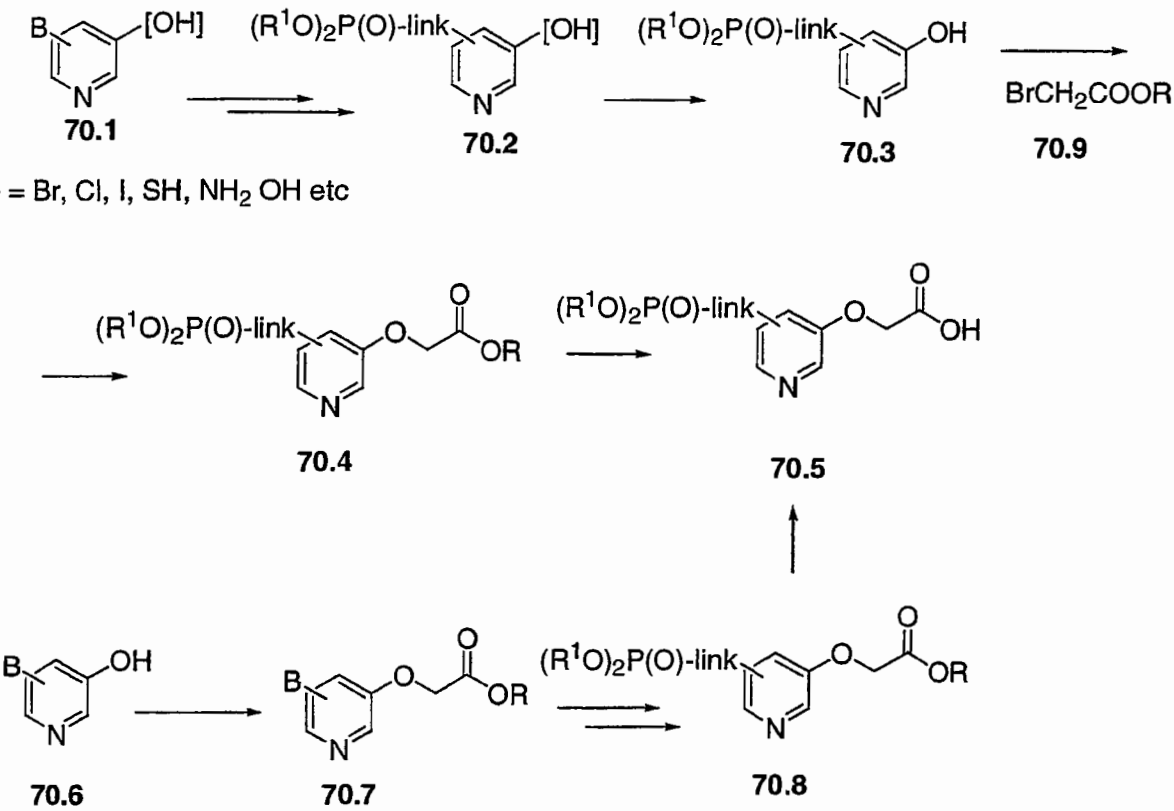
Using the above procedures, but employing, in place of the pyridine **74.10**, different hydroxy, thio or aminophenols **74.1**, and/or different dialkyl bromoalkyl phosphonates **74.6**, the corresponding products **74.5** are obtained.

Scheme **75** illustrates the preparation of (Pyridin-3-yloxy)-acetic acids incorporating a phosphonate ester which is attached to the pyridyl group by means of a carbon chain incorporating a nitrogen atom. The compounds **75.4** are obtained by means of a reductive alkylation reaction between hydroxyl protected 3-hydroxypyridyl aldehyde **75.1** and an aminoalkyl phosphonate ester **75.2**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations,

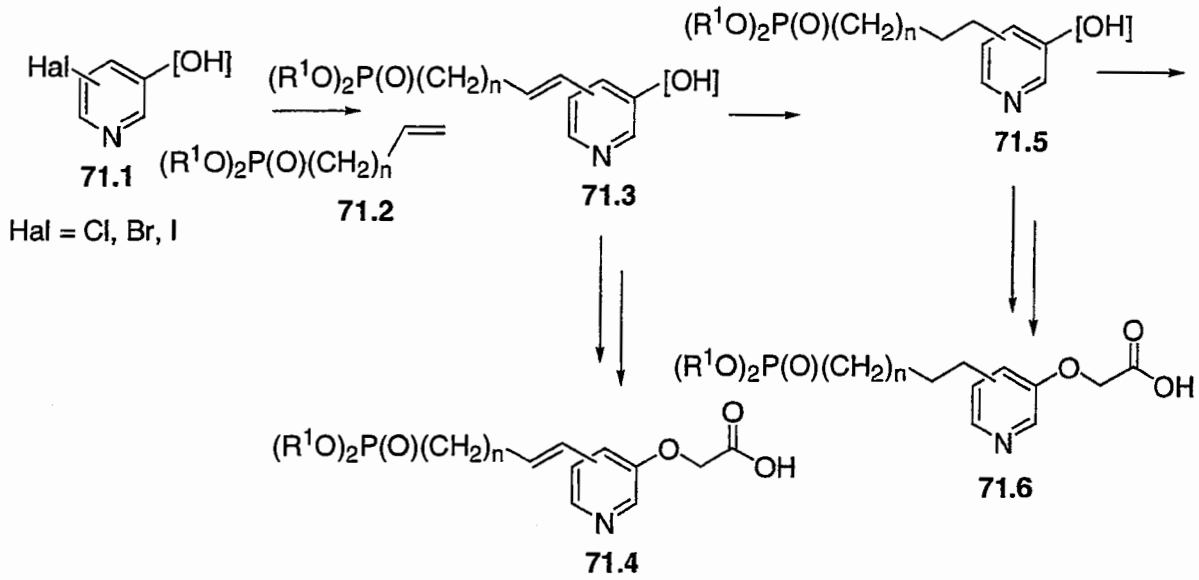
by R. C. Larock, VCH, p. 421. In this procedure, the amine component **75.2** and the aldehyde component **75.1** are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product **75.3**. The amination product **75.3** is then deprotected according to procedures described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, ch3, and subsequently converted into the (pyridin-3-yloxy) acetic acid compound **75.4**, using the alkylation and ester hydrolysis procedures described above (Scheme **70**).

For example, the ester **75.5** (TCI-US) is reacted with benzyl bromide in the presence of base such as potassium carbonate as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, p. 266 to give **75.6**. The benzyl ether **75.6** is then converted to the aldehyde **75.7** by reaction with DIBAL (see Comprehensive Organic Transformations, by R. C. Larock, 2nd Edition, 1999, p. 1267. for examples). Equimolar amounts of aldehyde **75.7,** and a dialkyl aminoethyl phosphonate **75.8**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in J. Amer. Chem. Soc., 91, 3996, 1969, to afford the amine product **75.9**. The benzyl group is then removed by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the hydroxyl compound **75.10**. The product **75.10** is then converted into the acetic acid **75.11**, as described above (Scheme **70**). Using the above procedures, but employing, in place of the aldehyde **75.7**, different aldehydes **75.1**, and/or different aminoalkyl phosphonates **75.2**, the corresponding products **75.4** are obtained.

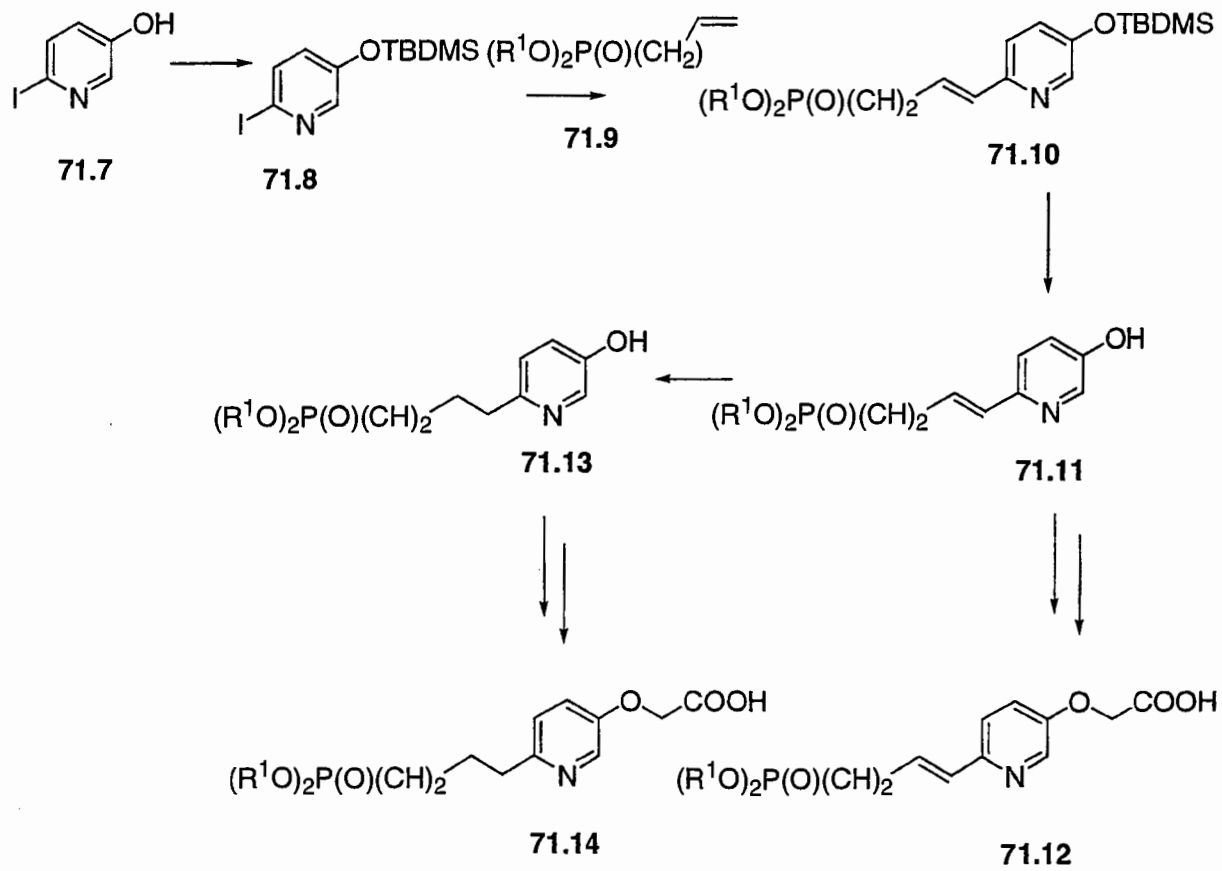
Scheme 70


B
[OH]
N
70.1
(R1O)2P(O)-link
[OH]
70.2
(R1O)2P(O)-link
OH
70.3
BrCH2COOR
70.9
B = Br, Cl, I, SH, NH2 OH etc
(R1O)2P(O)-link
O
OR
70.4
(R1O)2P(O)-link
O
OH
70.5
B
OH
70.6
B
O
OR
70.7
(R1O)2P(O)-link
O
OR
70.8
B = Br, Cl, I, [SH], [NH2], [OH] etc

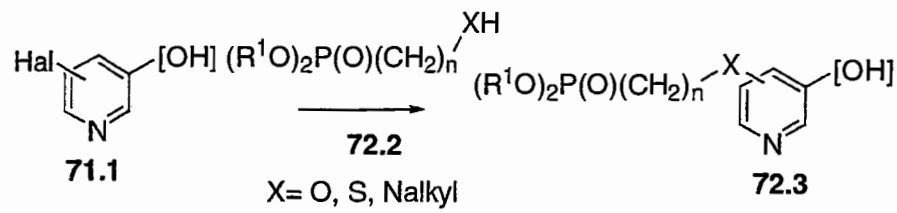
Scheme 71



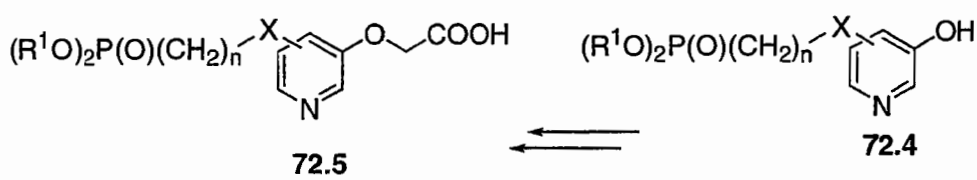
Example



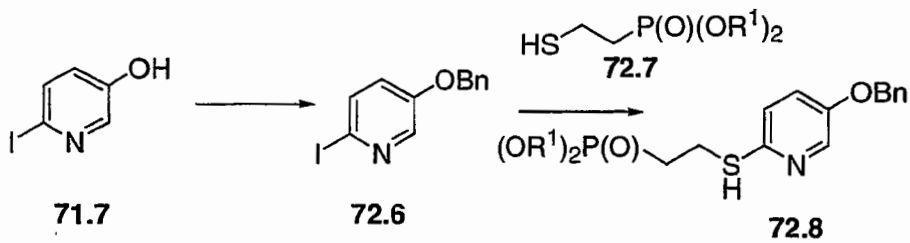
Scheme 72

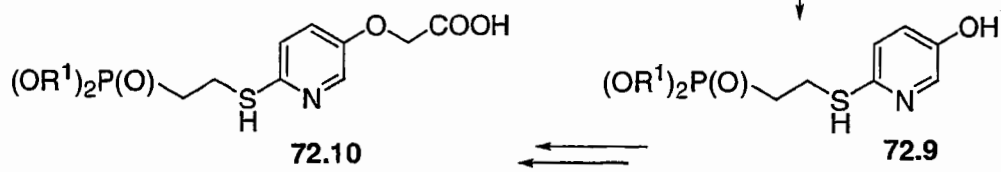


Hal = Cl, Br, I

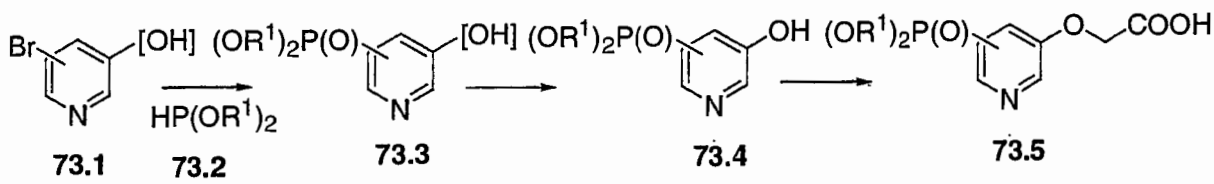


Example



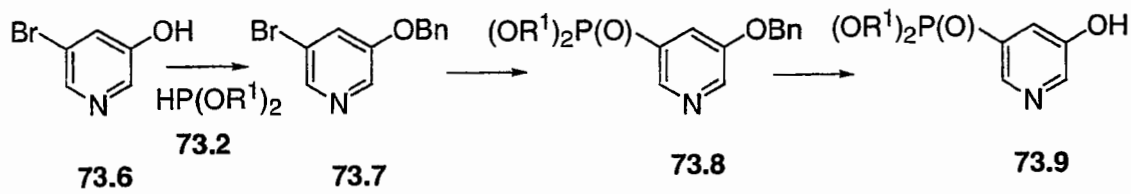


Scheme 73

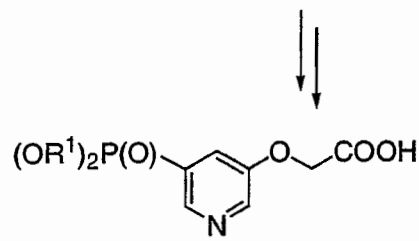


73.1 73.2 73.3 73.4 73.5

Example

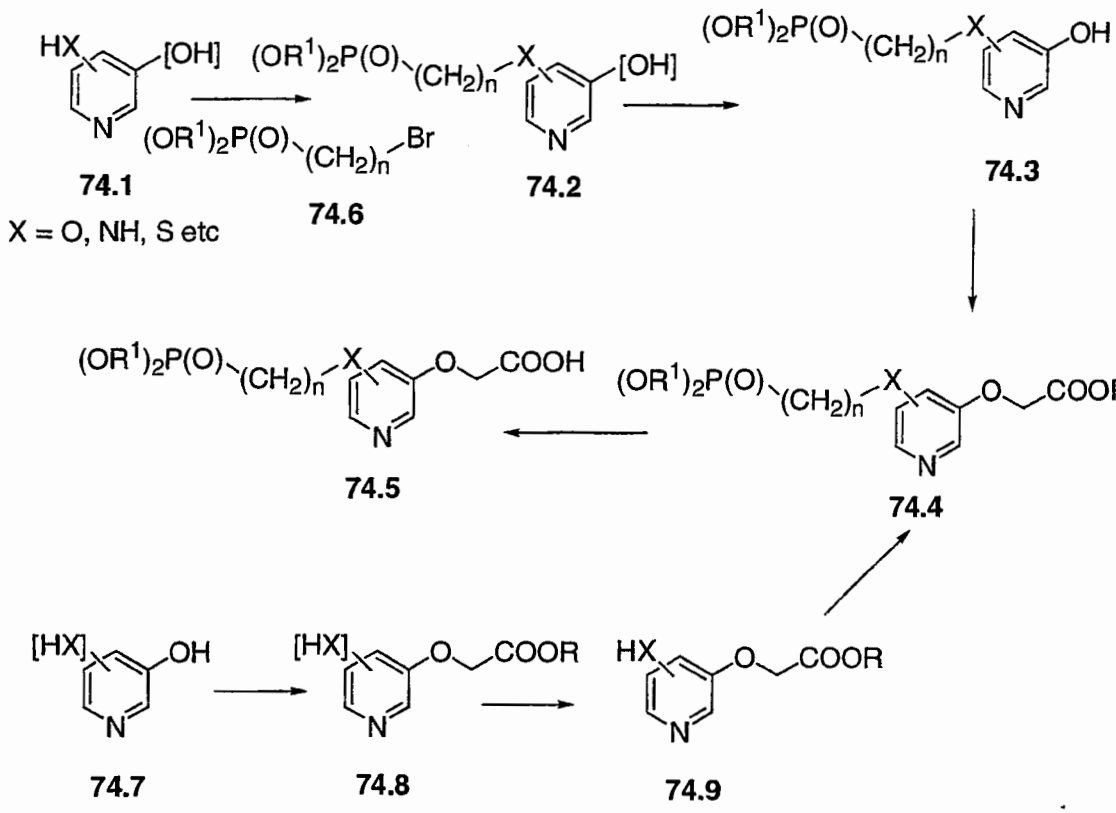


73.6 73.2 73.7 73.8 73.9

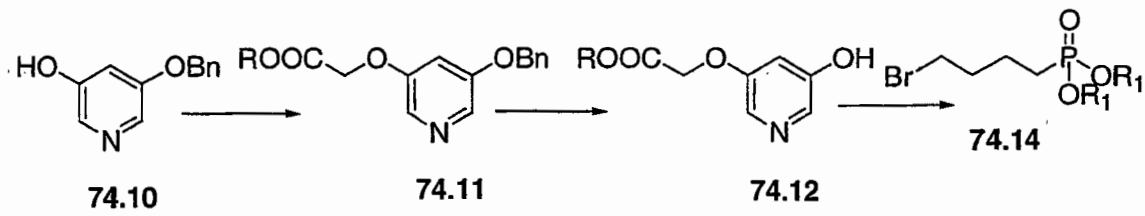


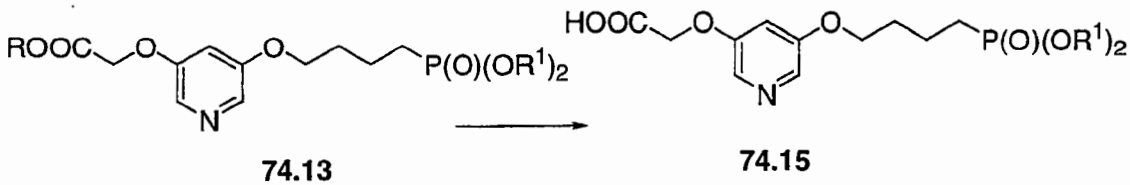
73.10

Scheme 74

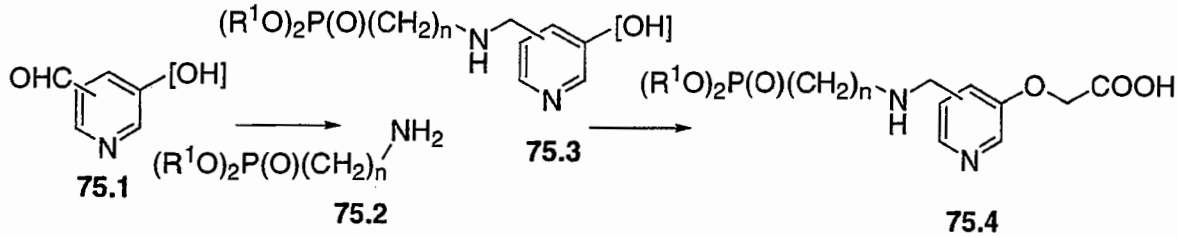


Example

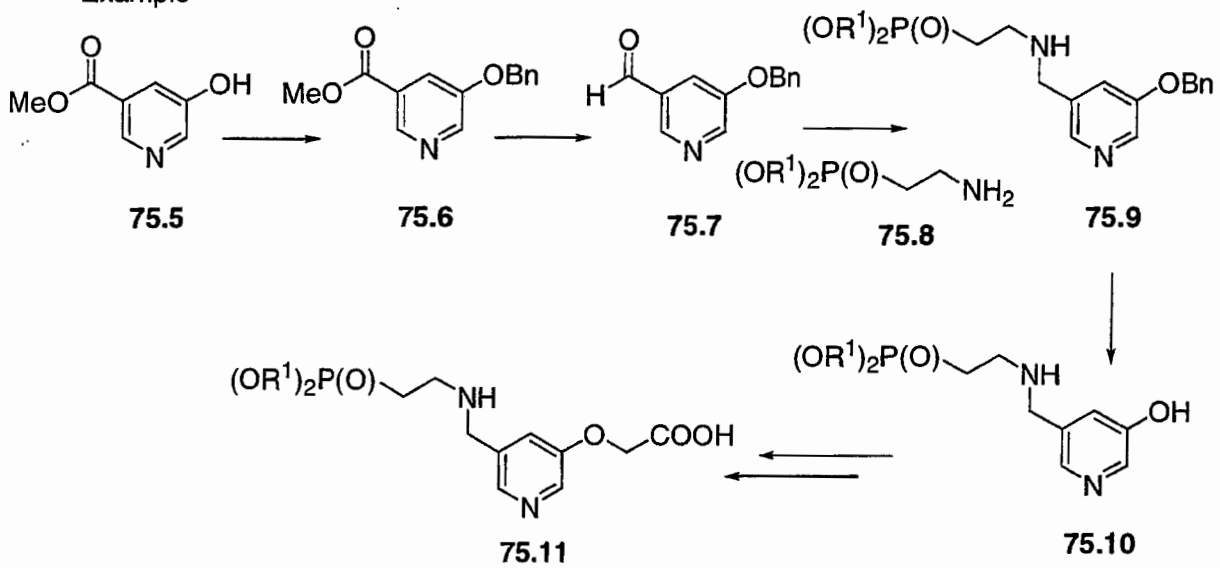




Scheme 75



Example



Ritonavir-like phosphonate protease inhibitors (RLPPI)

Chemistry for Ritonavir analogs.

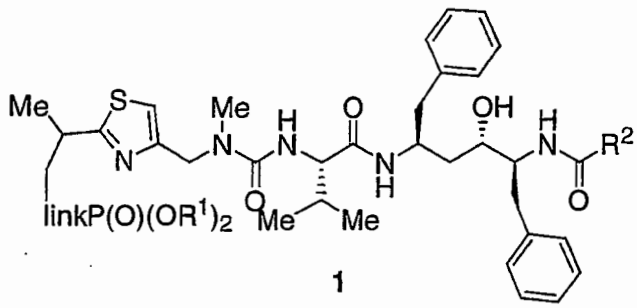
Preparation of the intermediate phosphonate esters.

The structures of the intermediate phosphonate esters **1** to **7**, and the structures for the component groups R^1 of this invention are shown in Chart 1. The structures of the components R^2COOH, R^3COOH and R^4 are shown in Charts **2a**, **2b** and **2c**. Specific stereoisomers of some of the structures are shown in Charts 1 and 2; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **7**. Subsequent chemical modifications to the compounds **1** to **7**, as described herein, permit the synthesis of the final compounds of this invention.

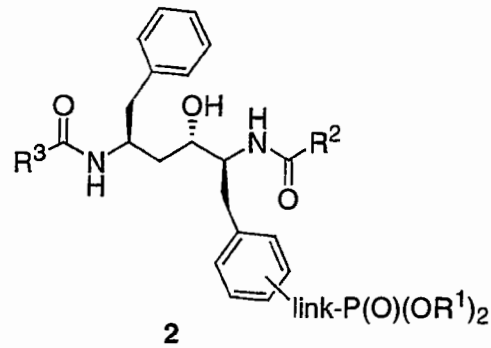
The intermediate compounds **1** to **7** incorporate a phosphonate moiety connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **3** and **4** illustrate examples of the linking groups present in the structures **1 – 7,** and in which "etc" refers to the scaffold, e.g., ritonavir.

Schemes **1 - 28** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1- 5**, and of the intermediate compounds necessary for their synthesis. The preparation of the compounds **6** and **7**, in which the phosphonate moiety is attached to the R^2COOH or R^3COOH group, is also described below.

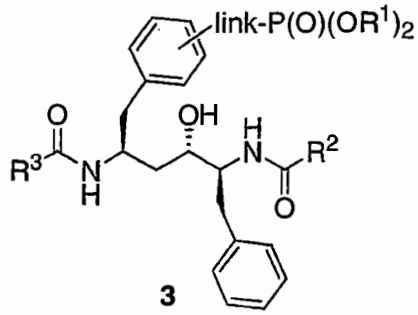
Chart 1 Structures of the intermediate phosphonate esters 1-7



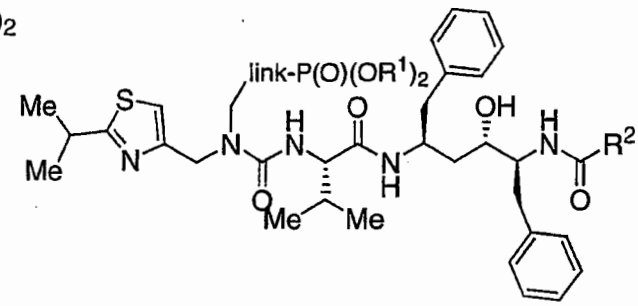
1



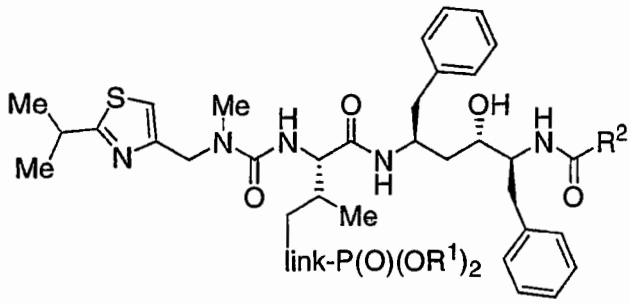
2



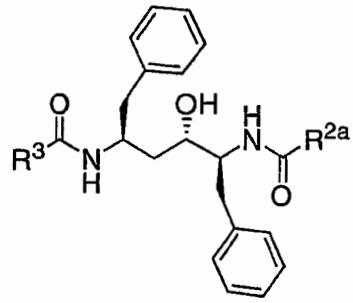
3



4

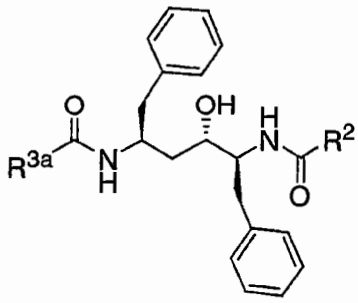


5



6

R^{2a} = phosphonate-containing R^2 group

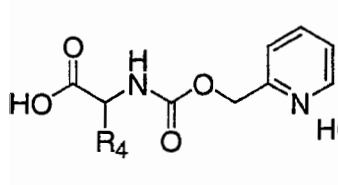


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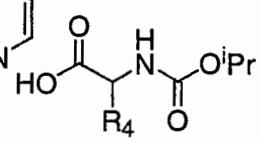
R^{3a} = phosphonate-containing R^3 group

R^1 = H, alkyl, alkenyl, aralkyl, aryl.

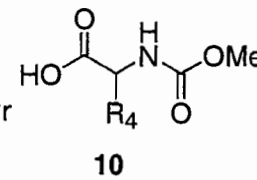
Chart 2a Structures of the R^2COOH and R^3COOH components



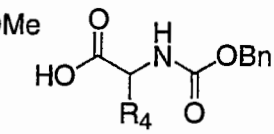
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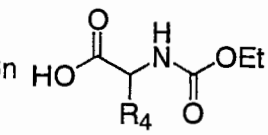
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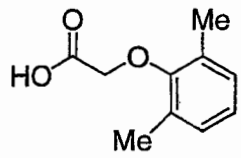
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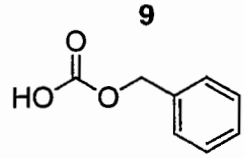
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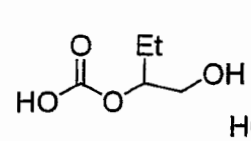
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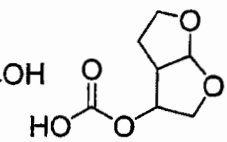
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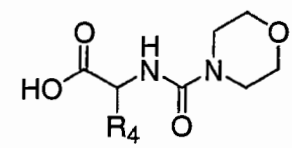
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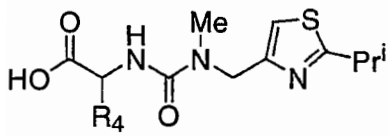
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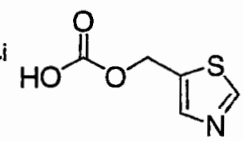
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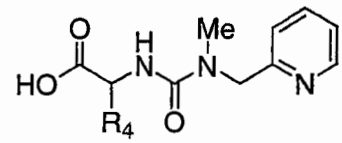
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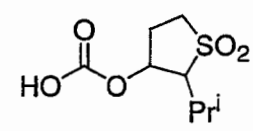
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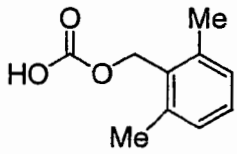
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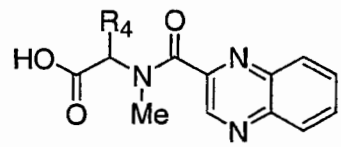
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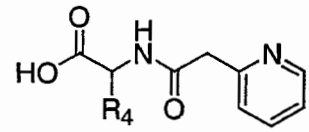
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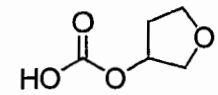
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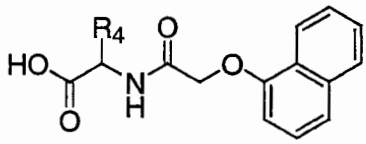
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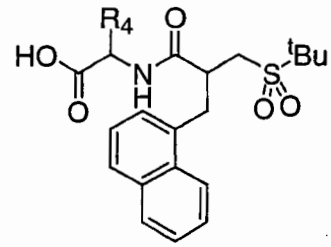
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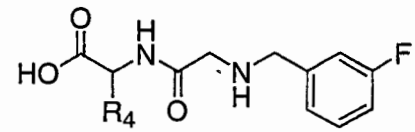
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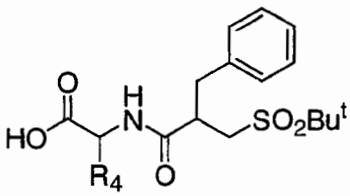
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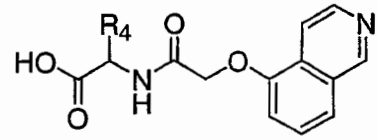
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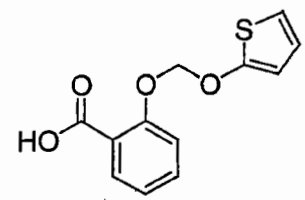
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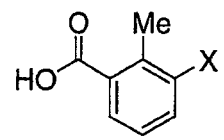
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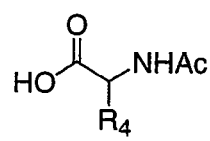
31

R^4 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

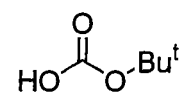
Chart 2b Structures of the R^2COOH and R^3COOH components



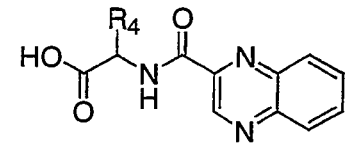
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X = OH, NH_2



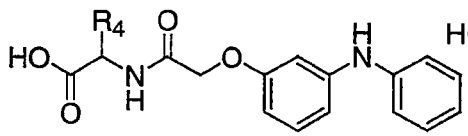
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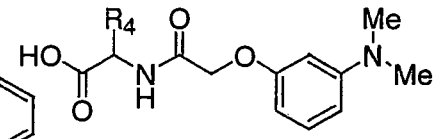
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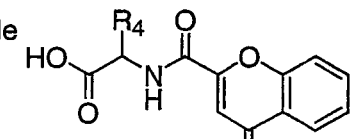
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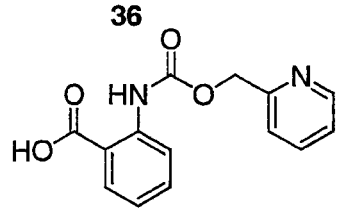
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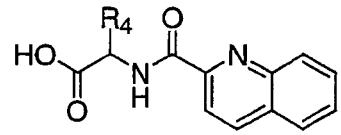
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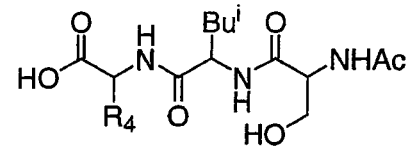
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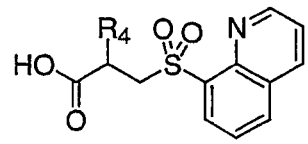
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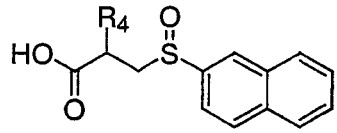
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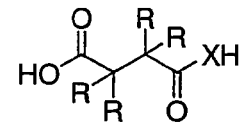
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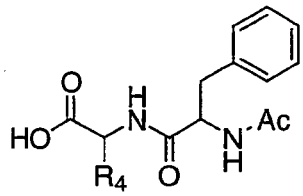
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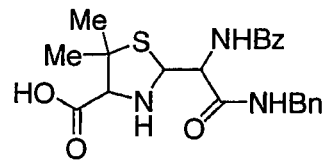
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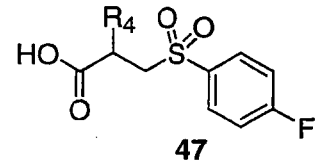
44
X = O, NH
R = H, alkyl



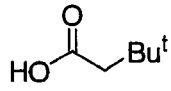
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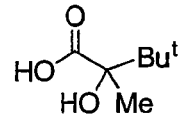
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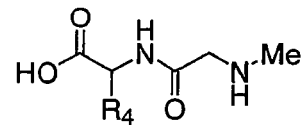
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48



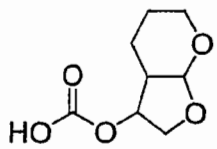
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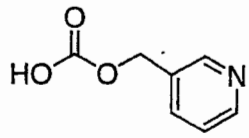
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R^4 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

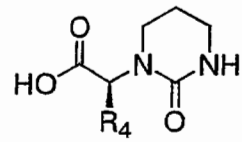
Chart 2c Structures of the R^2COOH and R^3COOH components



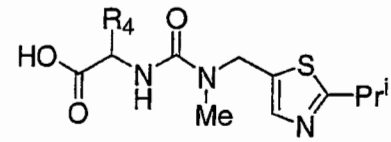
51



52



53



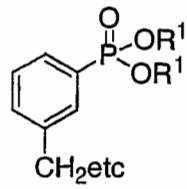
54

R^4 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

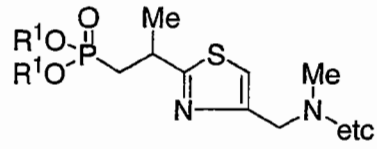
Chart 3 Examples of the linking group between the scaffold and the phosphonate moiety.

link **examples**

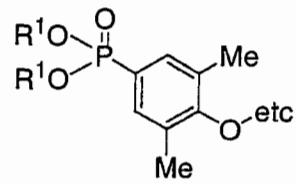
direct bond



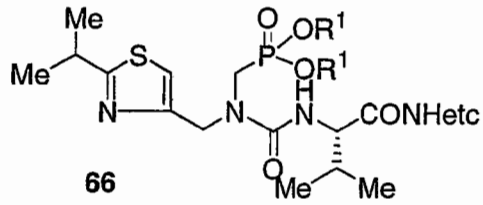
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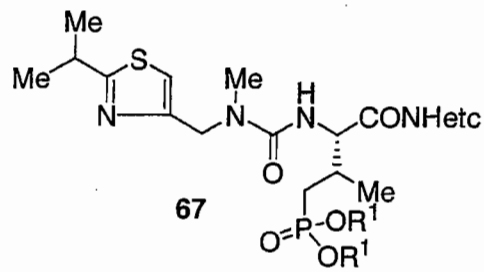
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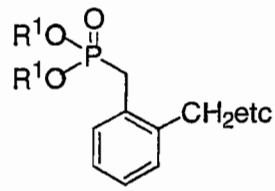


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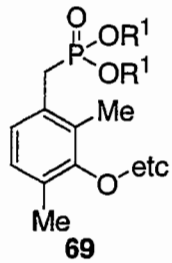


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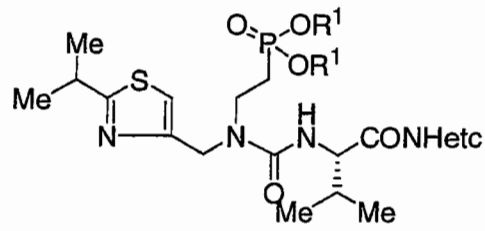
single carbon



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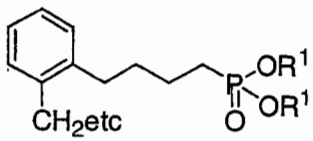


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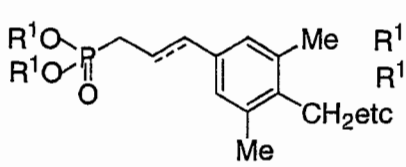


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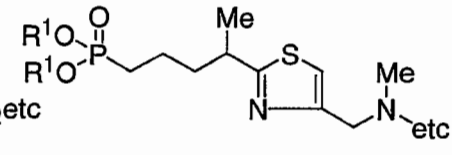
multiple carbon



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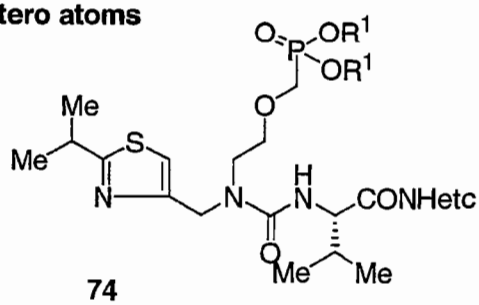


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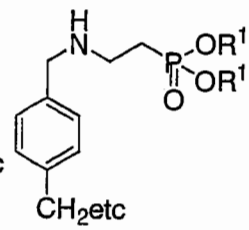


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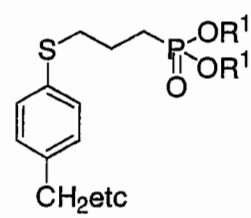
hetero atoms



74

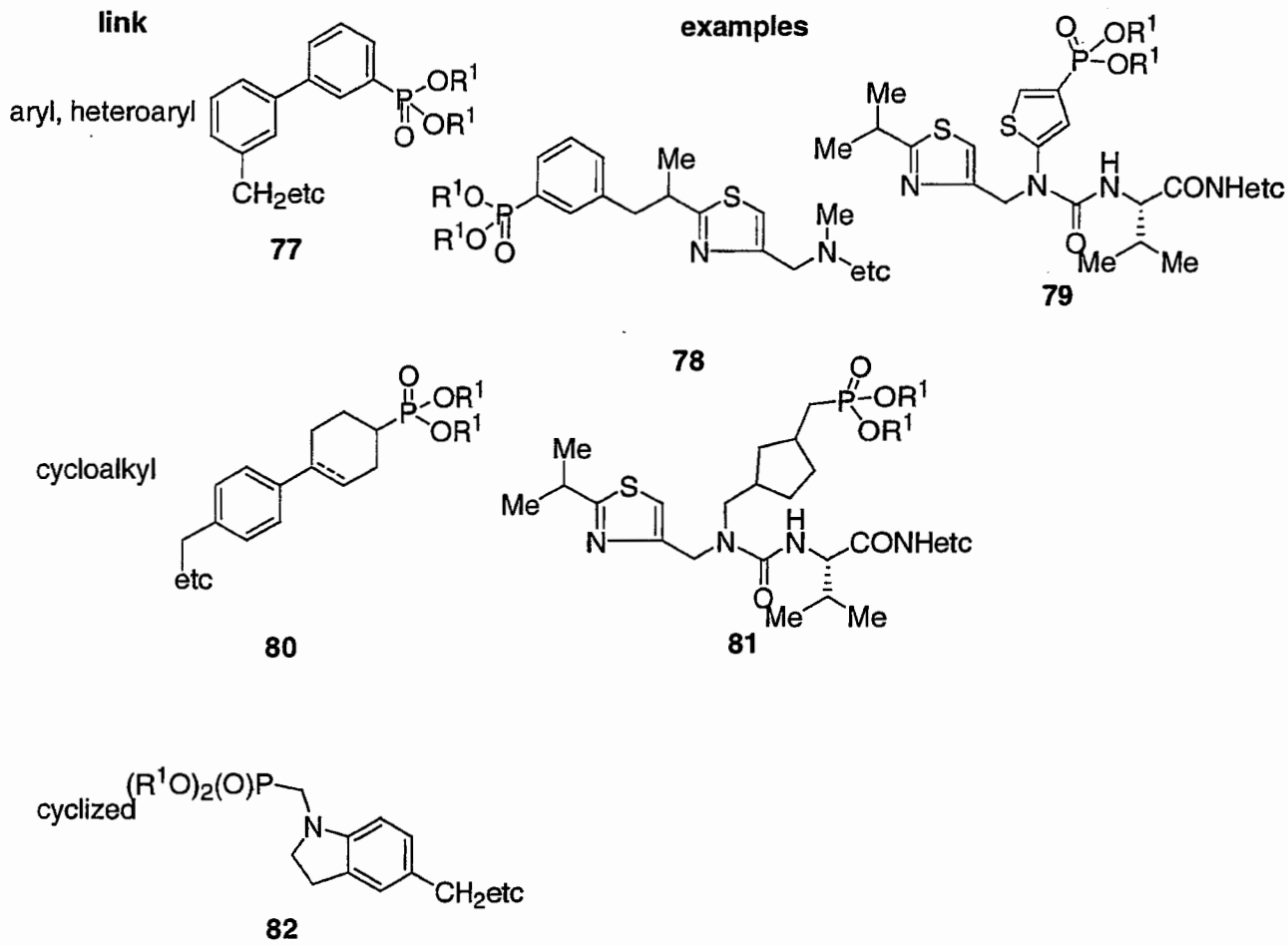


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Chart 4 Examples of the linking group between the scaffold and the phosphonate moiety.



Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate intermediates 1.

Two methods for the preparation of the phosphonate intermediate compounds **1**, in which the phosphonate moiety is attached to the isopropyl group of the carboxylic acid reactant **1.5**, are shown in Schemes **1** and **2**. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As shown in Scheme **1**, 5-amino-2-dibenzylamino-1,6-diphenyl-hexan-3-ol, **1.1**, the preparation of which is described in Org. Process Res. Dev., 1994, 3, 94, is reacted with a carboxylic acid R^2COOH **1.2**, or an activated derivative thereof, to produce the amide **1.3**. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, dimethylformamide or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid **1.2** is converted into the acid chloride, and the latter compound is reacted with an equimolar amount of the amine **1.1**, in an aprotic solvent such as, for example, tetrahydrofuran, at ambient temperature. The reaction is conducted in the presence of an organic base such as triethylamine, so as to afford the amide **1.3**.

The N, N-dibenzylamino amide product **1.3** is then transformed into the free amine compound **1.4** by means of a debenzylation procedure. The deprotection of N-benzyl amines is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 365. The transformation can be effected under

reductive conditions, for example by the use of hydrogen or a hydrogen donor, in the presence of a palladium catalyst, or by treatment of the N-benzyl amine with sodium in liquid ammonia, or under oxidative conditions, for example by treatment with 3-chloroperoxybenzoic acid and ferrous chloride.

Preferably, the N, N-dibenzyl compound **1.3** is converted into the amine **1.4** by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic ammonium formate and 5% palladium on carbon catalyst, at ca. 75°C for ca. 6 hours, for example as described in U.S. Patent 5,914,332.

The thus-obtained amine **1.4** is then transformed into the amide **1.6** by reaction with the carboxylic acid **1.5**, or an activated derivative thereof, in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto. Preparations of the carboxylic acids **1.5** are described below, Schemes **13** - **15**. The amide-forming reaction is conducted under similar conditions to those described above for the preparation of the amide **1.3**.

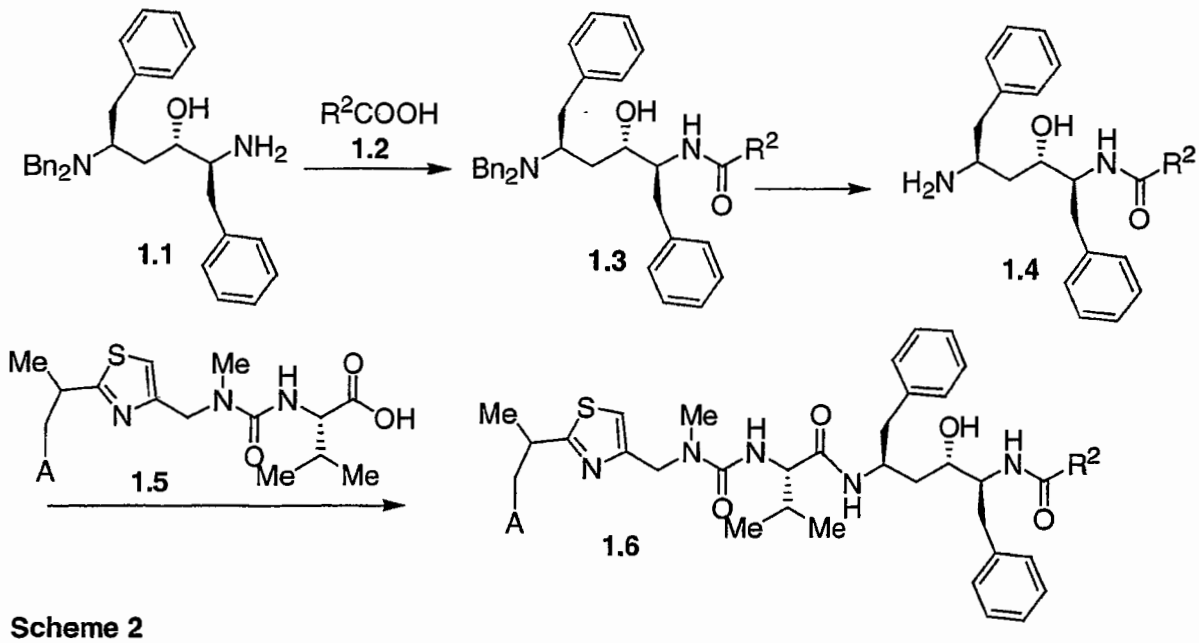
Preferably, the carboxylic acid is converted into the acid chloride, and the acid chloride is reacted with the amine **1.4** in a solvent mixture composed of an organic solvent such as ethyl acetate, and water, in the presence of a base such as sodium bicarbonate, for example as described in Org. Process Res. Dev., 2000, 4, 264, to afford the amide product **1.6**.

Scheme **2** illustrates an alternative method for the preparation of the phosphonate-containing diamides **1**. In this procedure, 2-phenyl-1-[4-phenyl-2-(1-vinyl-propenyl)-[1,3,2]oxazaborinan-6-yl]-ethylamine **2.1**, the preparation of which is described in WO 9414436, is reacted with the carboxylic acid R^2COOH **1.2**, or an activated derivative thereof, to afford the amide product **2.2**. The reaction is effected employing the same conditions as were described above for the preparation of the amide **1.3**. Preferably, equimolar amounts of the acid chloride derived from the carboxylic acid **1.2** is reacted with the amine **2.1** in a polar aprotic solvent such as tetrahydrofuran or dimethylformamide, at from ambient temperature to about -60°C, in the presence of an organic or inorganic base, to produce the amide **2.2**. The product is then reacted with the carboxylic acid **1.5**, or an activated derivative thereof, to afford the amide **1.6**. The amide-forming reaction is conducted under similar conditions to those described above for the preparation of the amide **1.3**. Preferably, the acid **1.5** and the amine **2.2** are reacted in the presence of hydroxybenztriazole, and N-ethyl-N'-dimethylaminopropyl carbodiimide, in tetrahydrofuran at ambient temperature, as described in U.S. Patent 5,484,801, to yield the amide **1.6**.

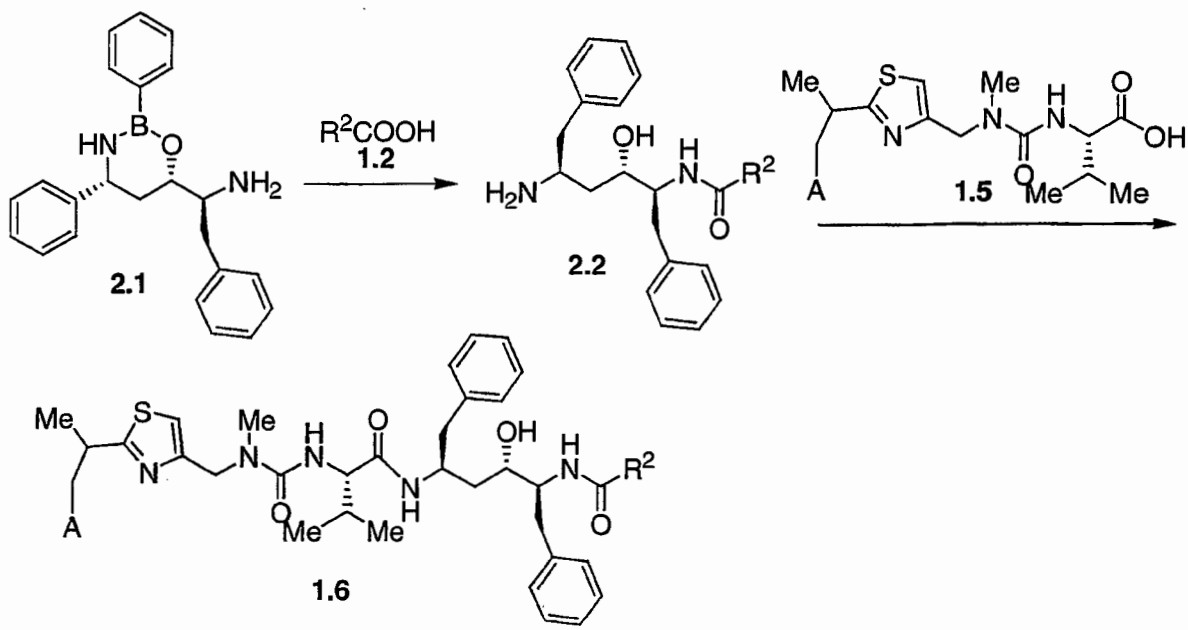
The reactions illustrated in Schemes **1** and **2** illustrate the preparation of the compounds **1.6** in which A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as, for example, optionally protected OH, SH, NH, as described below. Scheme **3** depicts the conversion of the compounds **1.6** in which A is OH, SH, NH, as described below, into the compounds **1** in which A is the group link-P(O)$(OR^1)_2$. Procedures for the conversion of the group A into the group link-P(O))$(OR^1)_2$ are described below, (Schemes **16-26**).

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below, (Scheme **27**)

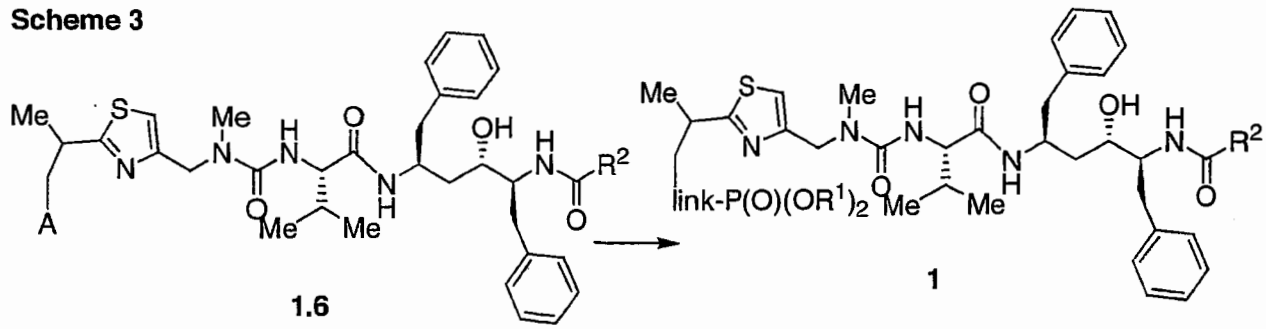
Scheme 1



Scheme 2



Scheme 3



Preparation of the phosphonate intermediates 2.

Two methods for the preparation of the phosphonate intermediate compounds **2** are shown in Schemes **4** and **5**. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As depicted in Scheme **4**, the tribenzylated phenylalanine derivative **4.1**, in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, as described below, is reacted with the anion **4.2** derived from acetonitrile, to afford the ketonitrile **4.3**. Preparations of the tribenzylated phenylalanine derivatives **4.1** are described below, Schemes **16-18**.

The anion of acetonitrile is prepared by the treatment of acetonitrile with a strong base, such as, for example, lithium hexamethyldisilylazide or sodium hydride, in an inert organic solvent such as tetrahydrofuran or dimethoxyethane, as described, for example, in U.S. Patent 5,491,253. The solution of the acetonitrile anion **4.2**, in an aprotic solvent such as tetrahydrofuran, dimethoxyethane and the like, is then added to a solution of the ester **4.1** at low temperature, to afford the coupled product **4.3**.

Preferably, a solution of ca. two molar equivalent of acetonitrile, prepared by the addition of ca. two molar equivalent of sodium amide to a solution of acetonitrile in tetrahydrofuran at -40°C, is added to a solution of one molar equivalent of the ester **4.1** in tetrahydrofuran at -40°C, as described in J. Org. Chem., 1994, 59, 4040, to produce the ketonitrile **4.3**.

The above-described ketonitrile compound **4.3** is then reacted with an organometallic benzyl reagent **4.4**, such as a benzyl Grignard reagent or benzyllithium, to afford the ketoenamine **4.5**. The reaction is conducted in an inert aprotic organic solvent such as diethyl ether, tetrahydrofuran or the like, at from -80°C to ambient temperature.

Preferably, the ketonitrile **4.3** is reacted with three molar equivalents of benzylmagnesium chloride in tetrahydrofuran at ambient temperature, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59, 4040, the ketoenamine **4.5**.

The ketoenamine **4.5** is then reduced, in two stages, via the ketoamine **4.6**, to produce the amino alcohol **4.7**. The transformation of the ketoenamine **4.5** to the aminoalcohol **4.7** can be

effected in one step, or in two steps, with or without isolation of the intermediate ketoamine **4.6**, as described in U.S. Patent 5,491,253.

For example, the ketoenamine **4.5** is reduced with a boron-containing reducing agent such as sodium borohydride, sodium cyanoborohydride and the like, in the presence of an acid such as methanesulfonic acid, as described in J. Org. Chem., 1994, 59, 4040, to afford the ketoamine **4.6**. The reaction is performed in an ethereal solvent such as, for example, tetrahydrofuran or methyl tert-butyl ether. The latter compound is then reduced with sodium borohydride-trifluoroacetic acid, as described in U.S. Patent 5,491,253, to afford the aminoalcohol **4.7**.

Alternatively, the ketoenamine **4.5** can be reduced to the aminoalcohol **4.7** without isolation of the intermediate ketoamine **4.6**. In this procedure, described in U.S. Patent 5,491,253, the ketoenamine **4.5** is reacted with sodium borohydride-methanesulfonic acid, in an ethereal solvent such as dimethoxyethane and the like. The reaction mixture is then treated with a quenching agent such as triethanolamine, and the procedure is continued by the addition of sodium borohydride and a solvent such as dimethyl formamide or dimethylacetamide or the like, to afford the aminoalcohol **4.7**.

The aminoalcohol **4.7** is converted into the amide **4.9** by reaction with the acid R^3COOH **4.8**, or an activated derivative thereof, to produce the amide **4.9**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**.

The dibenzylated amide product **4.9** is deprotected to afford the free amine **4.10**. The conditions for the debenzylation reaction are the same as those described above for the deprotection of the dibenzyl amine **1.3** to yield the amine **1.4**, (Scheme **1**).

The amine **4.10** is then reacted with the carboxylic acid R^2COOH **1.2**, or an activated derivative thereof, to produce the amide **4.11**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**.

Alternatively, the amide **4.11** can be prepared by means of the sequence of reactions illustrated in Scheme **5**.

In this sequence, the tribenzylated amino acid derivative **4.1** is converted, by means of the reaction sequence shown in Scheme **4** into the dibenzylated amine **4.7**. This compound is then converted into a protected derivative, for example the tert-butoxycarbonyl (BOC) derivative **5.1**. Methods for the conversion of amines into the BOC derivative are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990,

p. 327. For example, the amine can be reacted with di-tert-butoxycarbonylanhydride (BOC anhydride) and a base, or with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), and the like.

Preferably, the amine is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in U.S. Patent 5,914,3332, to yield the BOC-protected product **5.1**.

The N-benzyl protecting groups are then removed from the amide product **5.1** to afford the free amine **5.2**. The conditions for this transformation are similar to those described above for the preparation of the amine **1.4**, (Scheme 1).

Preferably, the N, N-dibenzyl compound **5.1** is converted into the amine **5.2** by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic ammonium formate and 5% palladium on carbon catalyst, at ca. 75°C for ca. 6 hours, for example as described in U.S. Patent 5,914,332.

The amine compound **5.2** is then reacted with the carboxylic acid R^2COOH **1.2**, or an activated derivative thereof, to produce the amide **5.3**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**, to afford the amide product **5.3**.

The latter compound is then converted into the amine **5.4** by removal of the BOC protecting group. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preferably, the BOC group is removed by treatment of the substrate **5.3** with trifluoroacetic acid in dichloromethane at ambient temperature, for example as described in U.S. Patent 5,914,232, to afford the free amine product **5.4**.

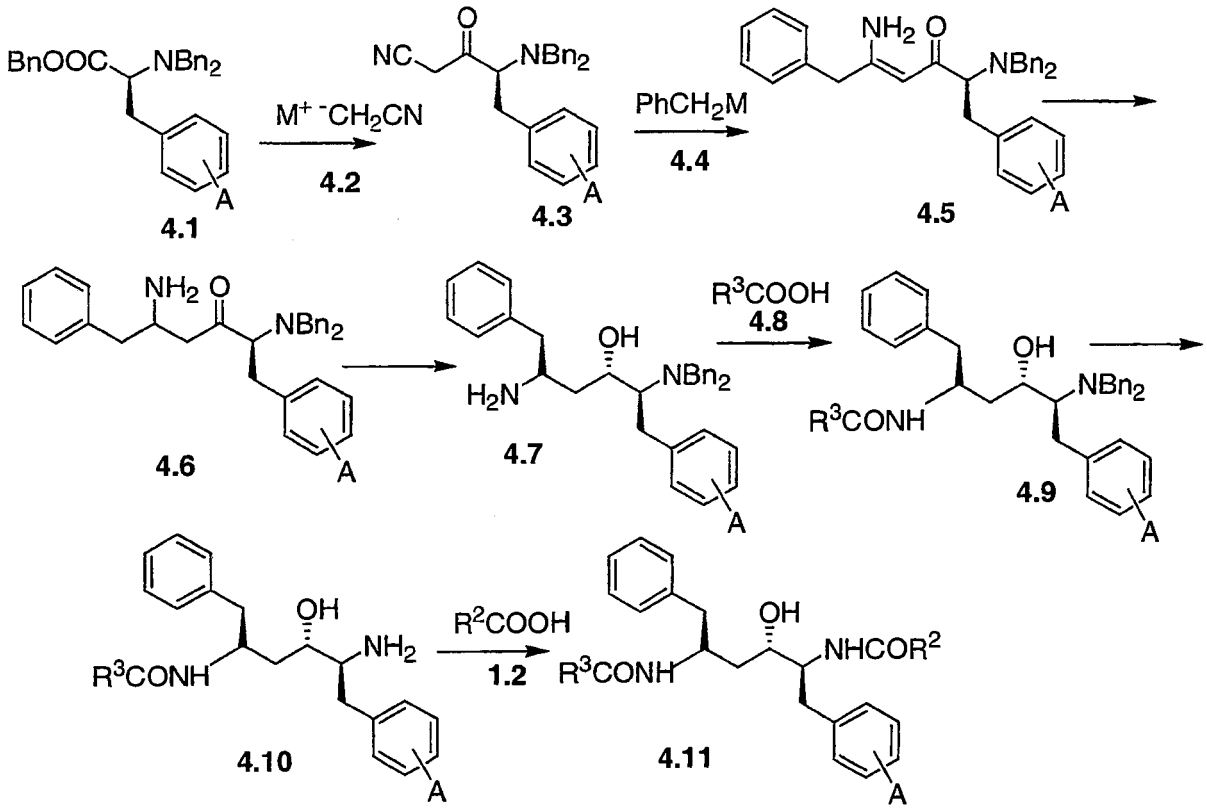
The free amine thus obtained is then reacted with the carboxylic acid R^3COOH **4.8**, or an activated derivative thereof, to produce the amide **4.11**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**.

The reactions shown in Schemes **4** and **5** illustrate the preparation of the compounds **4.11** in which A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as, for example,

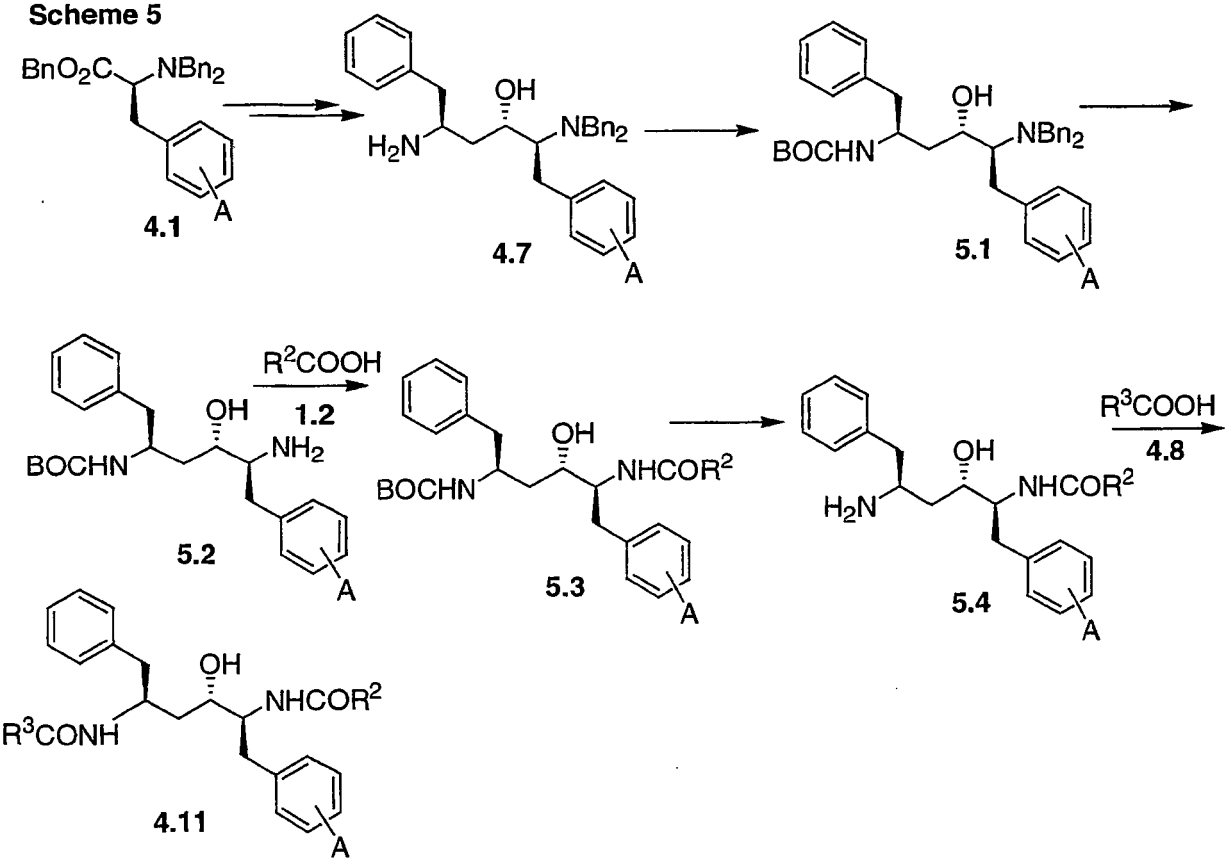
optionally protected OH, SH, NH, as described below. Scheme **6** depicts the conversion of the compounds **4.11** in which A is OH, SH, NH, as described below, into the compounds **2**. Procedures for the conversion of the group A into the group link-P(O))$(OR^1)_2$ are described below, (Schemes **16-26**).

5

Scheme 4



Scheme 5



Preparation of the phosphonate intermediates 3.

The phosphonate ester intermediate compounds **3** can be prepared by two alternative methods, illustrated in Schemes **7** and **8**. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As shown in Scheme **7**, 4-dibenzylamino-3-oxo-5-phenyl-pentanenitrile **7.1**, the preparation of which is described in J. Org. Chem., 1994, 59, 4040, is reacted with a substituted benzylmagnesium halide reagent **7.2**, in which the group B is a substituent, protected if appropriate, which can be converted, during or after the sequence of reactions shown in Scheme **7**, into the moiety link-$P(O)(OR^1)_2$. Examples of the substituent B are Br, [OH], [SH], [NH_2] and the like; procedures for the transformation of these groups into the phosphonate moiety are shown below in Schemes **16-26**. The conditions for the reaction between the benzylmagnesium halide and the ketonitrile are similar to those described above for the preparation of the ketoenamine **4.5** (Scheme **4**).

Preferably, the ketonitrile **7.1** is reacted with three molar equivalents of the substituted benzylmagnesium chloride **7.2** in tetrahydrofuran at ambient temperature, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59, 4040, the ketoenamine **7.3**.

The thus-obtained ketoenamine **7.3** is then transformed, via the intermediate compounds **7.4**, **7.5**, **7.6**, and **7.7** into the diacylated carbinol **7.8**. The conditions for each step in the conversion of the ketoenamine **7.3** to the diacylated carbinol **7.8** are the same as those described above (Scheme **4**) for the transformation of the ketoenamine **4.5** into the diacylated carbinol **4.11**.

The diacylated carbinol **7.8** is then converted into the phosphonate ester **3**, using procedures illustrated below in Schemes **16-26**.

Alternatively, the phosphonate esters **3** can be obtained by means of the reactions illustrated in Scheme **8**. In this procedure, the amine **7.5**, the preparation of which is described above, (Scheme **7**) is converted into the BOC derivative **8.1**. The conditions for the introduction of

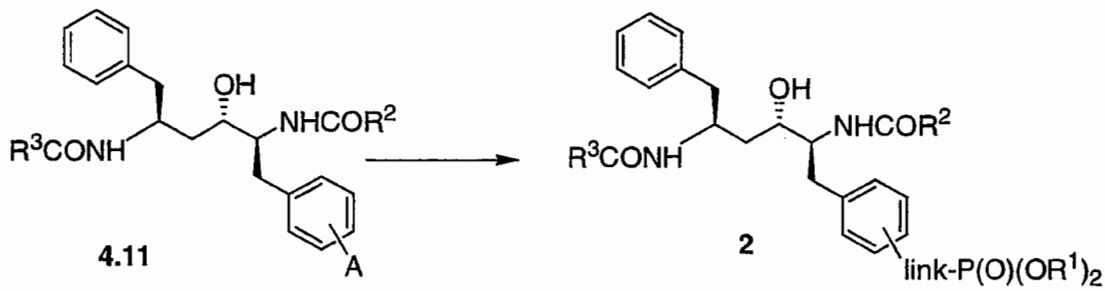
the BOC group are similar to those described above for the protection of the amine **5.1**, (Scheme **5**).

Preferably, the amine is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in U.S. Patent 5,914,332, to yield the BOC-protected product **8.1**.

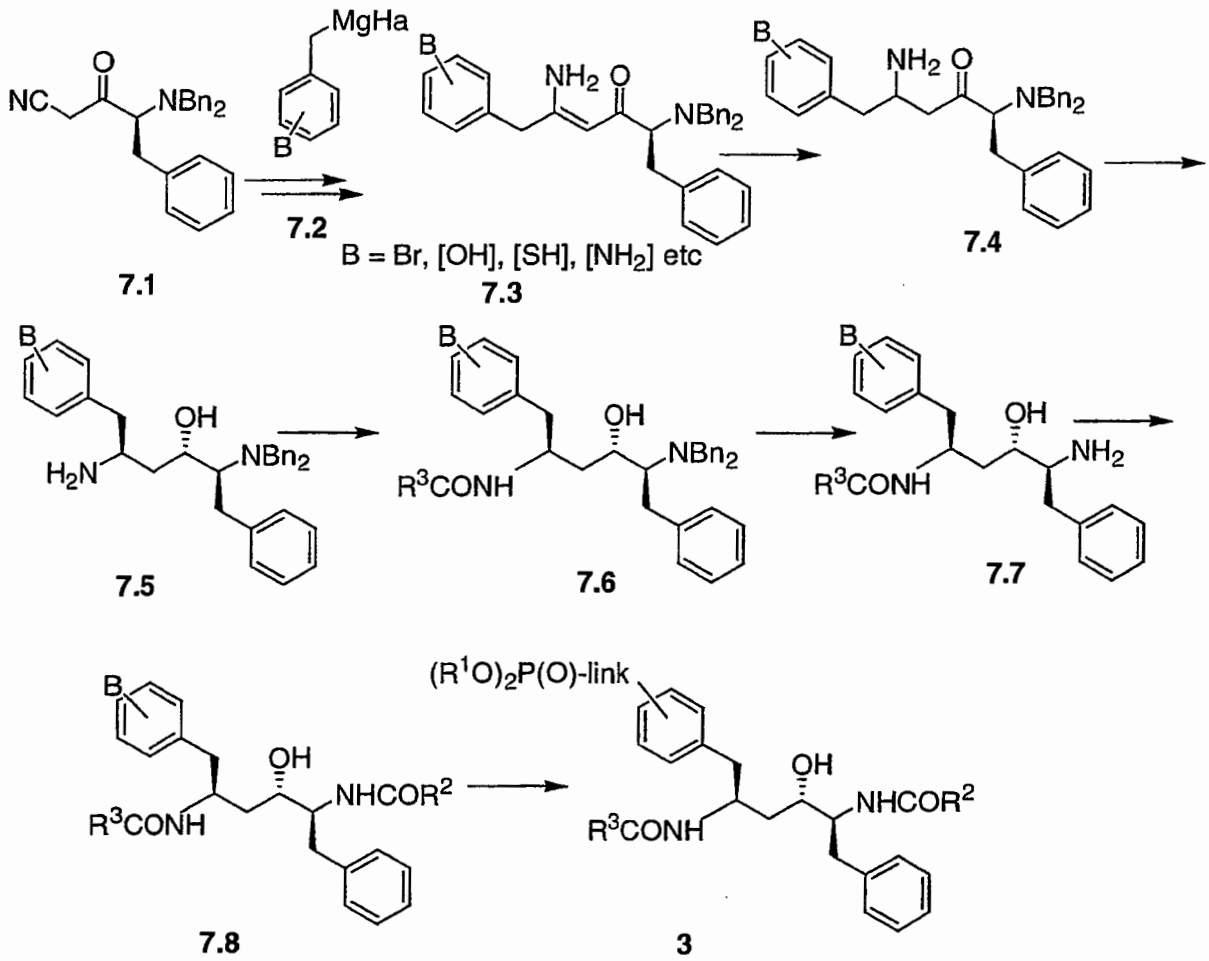
The BOC-protected amine **8.1** is then converted, via the intermediates **8.2**, **8.3** and **8.4** into the diacylated carbinol **8.5**. The reaction conditions for this sequence of reactions are similar to those described above for the transformation of the BOC-protected amine **5.1** into the diacylated carbinol **5.4** (Scheme **5**).

The diacylated carbinol **8.5** is then converted into the phosphonate ester **3**, using procedures illustrated below in Schemes **16**-**26**.

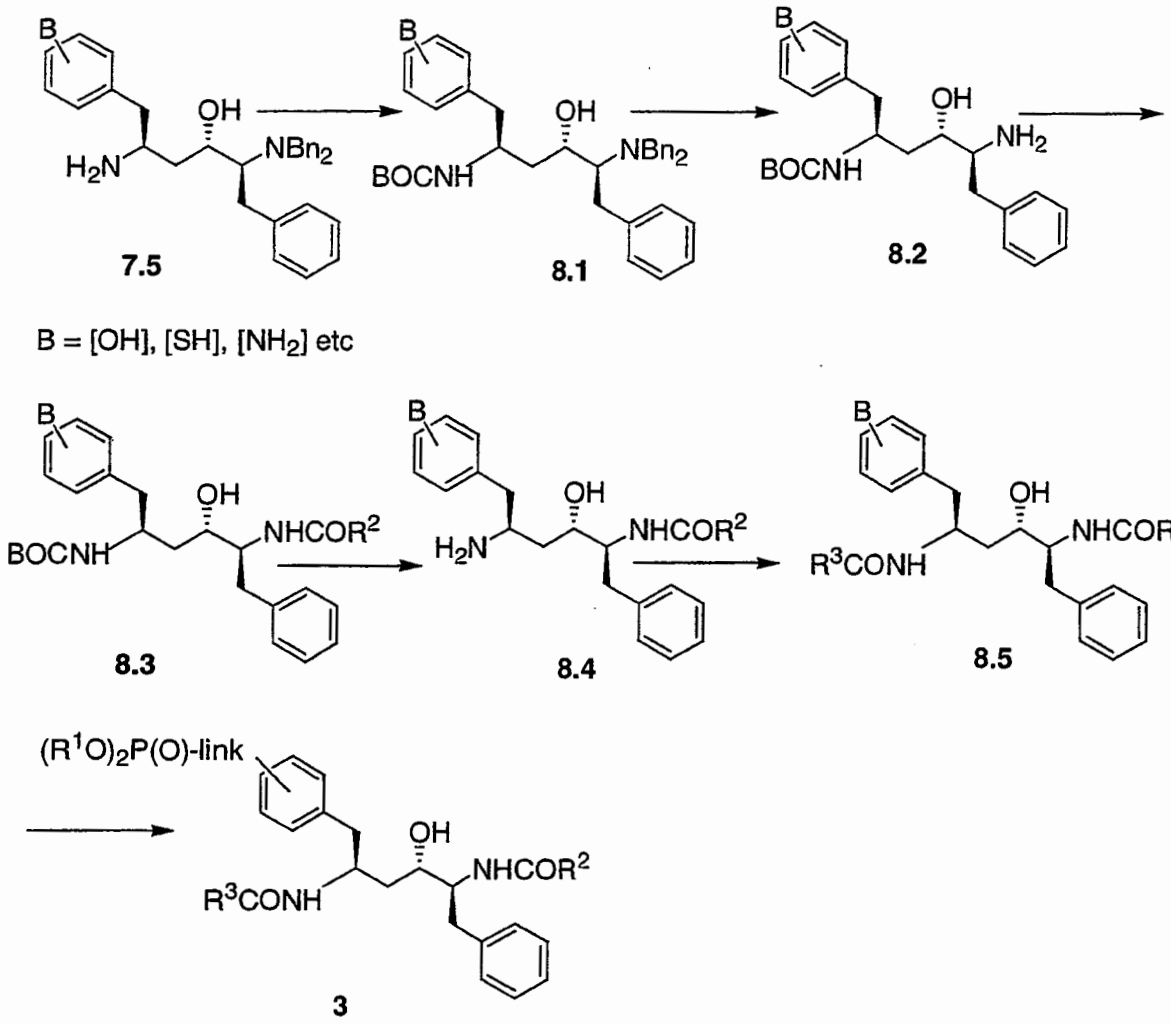
Scheme 6



Scheme 7


MgHa
B
NC
O
NBn2
7.1
7.2
B = Br, [OH], [SH], [NH2] etc
NH2
7.3
7.4
OH
H2N
7.5
R3CONH
7.6
7.7
(R1O)2P(O)-link
NHCOR2
7.8
3

Scheme 8



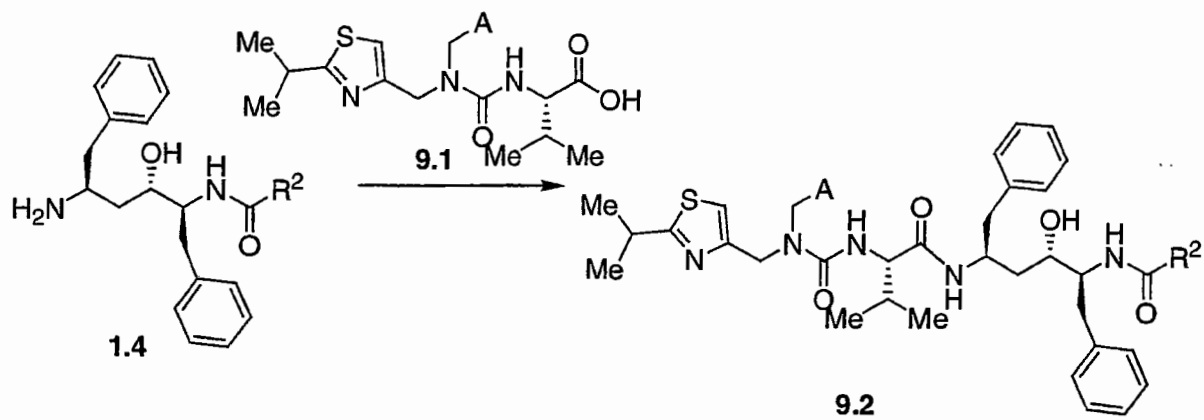
Preparation of the phosphonate intermediates 4.

Scheme **9** illustrates the preparation of the intermediate phosphonate esters **9.2** in which the substituent A, which is the phosphonate ester moiety or a precursor group thereto, is attached to one of the urea nitrogen atoms in the carboxylic acid reactant **9.1**. The preparation of the carboxylic acid reactant **9.1** is described below, Schemes **24-25**. In this procedure, the amine **1.4**, prepared as described in Scheme **1**, is reacted with the carboxylic acid **9.1**, to afford the amide **9.2**. The reaction between the amine **1.4** and the carboxylic acid **9.1**, or an activated derivative thereof, is conducted under the same general conditions as those described above for the preparation of the amide **1.6** (Scheme **1**). Preferably, the reactants are combined in the

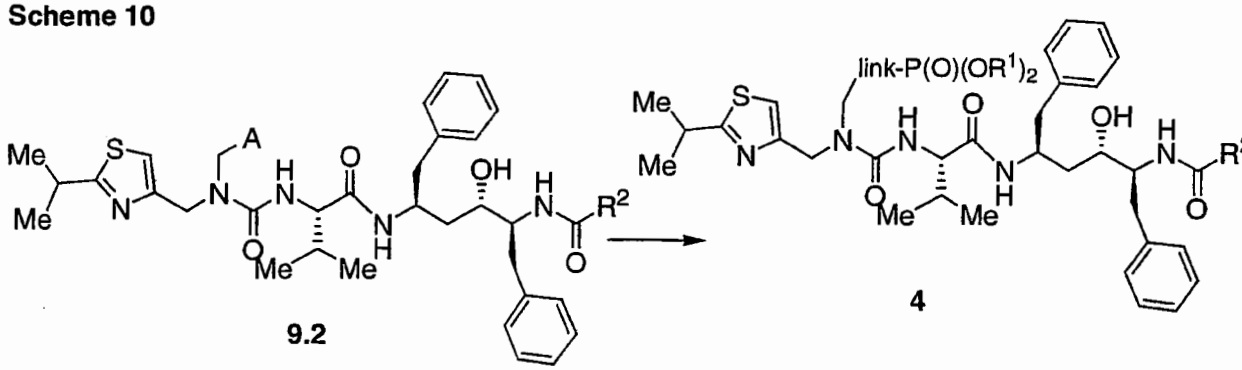
presence of hydroxybenztriazole and a carbodiimide, as described in U.S. Patent 5,484,801, to yield the amide product **9.2**.

The procedure shown in Scheme **9** describes the preparation of the compounds **9.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor group thereto, such as [OH], [SH, [NH], as described below. Scheme **10** depicts the conversion of compounds **9.2** in which A is [OH], [SH, [NH], into the compounds **4**, in which the group A has been transformed into the group link-P(O)(OR^1)$_2$. The methods for accomplishing this transformation are described below, Schemes **16-26**.

Scheme 9



Scheme 10



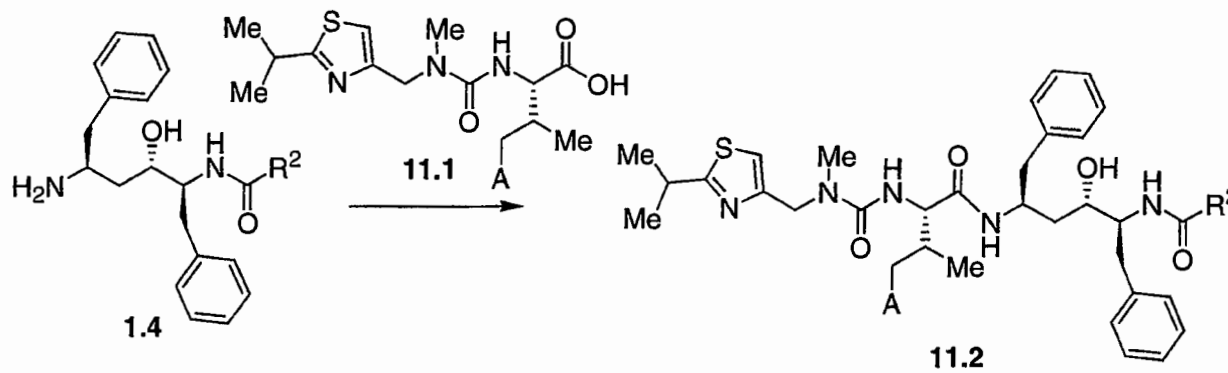
Preparation of the phosphonate intermediates 5.

Scheme **11** illustrates the preparation of the intermediate phosphonate esters **11.2** in which the substituent A, which is the phosphonate ester moiety or a precursor group thereto, is attached to the valine moiety in the carboxylic acid reactant **11.1**. The preparation of the carboxylic acid reactant **11.1** is described below, Scheme **26**. The reaction between the amine **1.4** and the

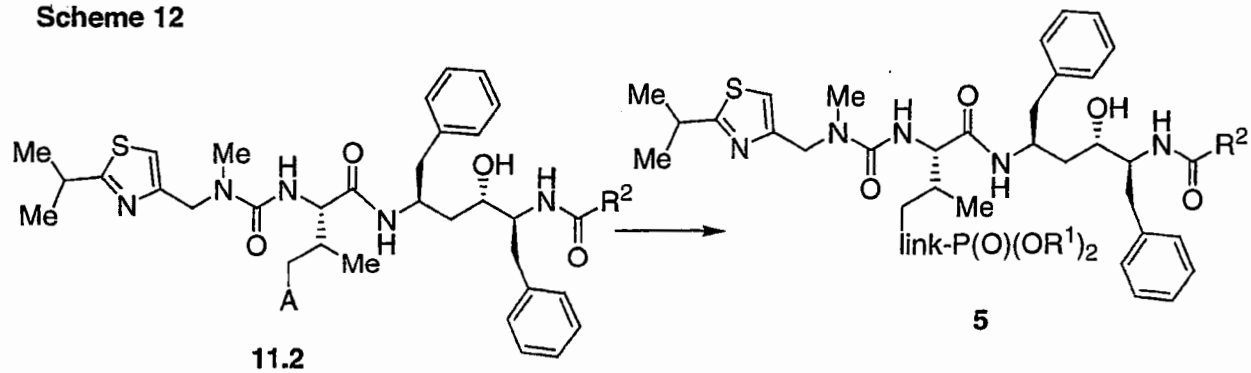
carboxylic acid **11.1**, or an activated derivative thereof, is conducted under the same general conditions as those described above for the preparation of the amide **1.3** (Scheme **1**). Preferably, the reactants are combined in the presence of hydroxybenztriazole and a carbodiimide, as described in U.S. Patent 5,484,801, to yield the amide product **11.2.**

The procedure shown in Scheme **11** describes the preparation of the compounds **11.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor group thereto, such as [OH], [SH, [NH] Ha, as described below. Scheme **12** depicts the conversion of compounds **11.2** in which A is [OH], [SH, [NH] Br, into the compounds **5**, in which the group A has been transformed into the group link-P(O)(OR^1)$_2$. The methods for accomplishing this transformation are described below, Schemes **16-26.**

Scheme 11



Scheme 12



Preparation of carboxylic acids 1.5, with a phosphonate moiety attached to the isopropyl group.

Scheme **13** illustrates the preparation of carboxylic acid reactants **1.5**, in which a substituent A, attached to the isopropyl group, is either the group link-$P(O)(OR^1)_2$ or a precursor group thereto, such as [OH], [SH, [NH] Br. During the series of reaction shown in Scheme **13**, the group A may, at an appropriate stage, be converted into the group link-$P(O)(OR^1)_2$, according to the knowledge of one skilled in the art. Alternatively, the carboxylic acid **1.5**, in which A is link-$P(O)(OR^1)_2$, may be incorporated into the diamide compounds **1.6**, as described above, (Schemes **1** and **2**) before effecting the transformation of the group A into the group link-$P(O)(OR^1)_2$.

As shown in Scheme **13**, a substituted derivative of isobutyramide **13.1** is converted into the corresponding thioamide **13.2**. The conversion of amides into thioamides is described in Synthetic Organic Chemistry, by R. B. Wagner and H. D. Zook, Wiley, 1953, p. 827. The amide is reacted with a sulfur-containing reagent such as phosphorus pentasulfide or Lawessson's reagent, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Wiley, Vol. 13, p. 38, to yield the thioamide **13.2**. Preferably, the amide **13.1** is reacted with phosphorus pentasulfide in ether solution, at ambient temperature, as described in U.S. Patent 5,484,801, to afford the amide **13.2**. The latter compound is then reacted with 1,3-dichloroacetone **13.3** to produce the substituted thiazole **13.4**. The preparation of thiazoles by the reaction between a thioamide and a chloroketone is described, for example, in Heterocyclic Chemistry, by T. A. Gilchrist, Longman, 1997, p. 321. Preferably, equimolar amounts of the reactants are combined in acetone solution at reflux temperature, in the presence of magnesium sulfate, as described in U.S. Patent 5,484,801, to produce the thiazole product **13.4**. The chloromethyl thiazole **13.4** is then reacted with methylamine to afford the substituted methylamine **13.6**. The preparation of amines by the reaction of amines with alkyl halides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397. Typically, the components are reacted together in a polar solvent such as an alkanol or dimethylformamide and the like. Preferably, the chloro compound **13.4** is reacted with excess aqueous methylamine at ambient temperature, as described in U.S. Patent 5,484,801, to afford the amine product **13.6**. The amine is then converted into the urea

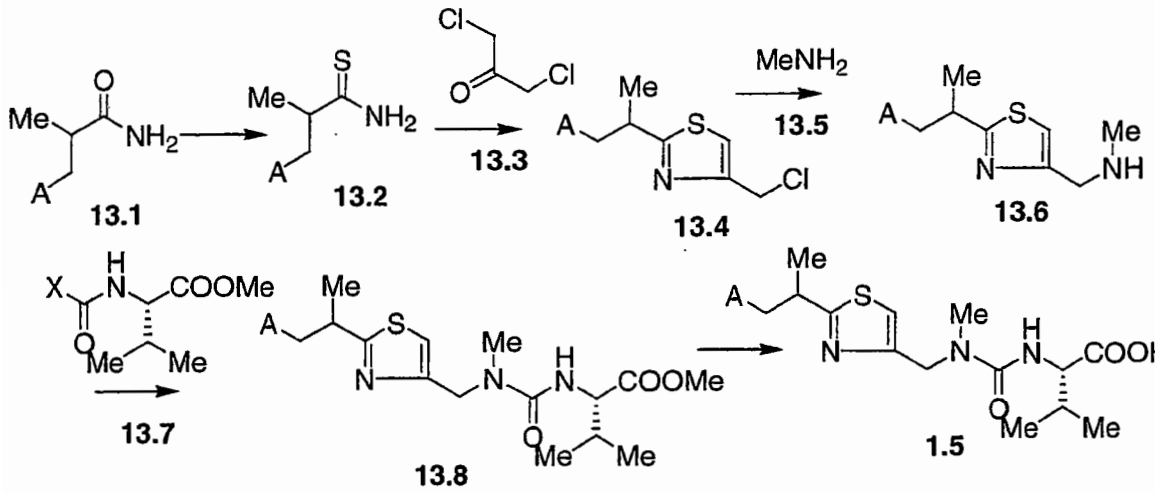
derivative **13.8** by reaction with an activated derivative of the valine carbamic acid **13.7**, in which X is a leaving group such as alkanoyloxy or 4-nitrophenoxy. The preparation of ureas by the reaction between carbamic acid derivatives and amines is described in Chem. Rev., 57, 47, 1957. Suitable carbamic acid derivatives are prepared by the reaction between an amine and an alkyl or aryl chloroformate, for example as described in WO 9312326. Preferably, the reaction is performed using carbamic acid derivative **13.7**, in which X is 4-nitrophenoxy, and the amine **13.8**; the reaction is conducted at about 0°C in an inert solvent such as dichloromethane, in the presence of an organic base such as dimethylaminopyridine or N-methylmorpholine, as described in U.S. Patent 5,484,801, to yield the urea product **13.8**. The ester group present in the urea product **13.8** is then hydrolyzed to afford the corresponding carboxylic acid **1.5**. Hydrolysis methods for converting esters into carboxylic acids are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 981. The methods include the use of enzymes such as pig liver esterase, and chemical methods such as the use of alkali metal hydroxides in aqueous organic solvent mixtures. Preferably, the methyl ester is hydrolyzed by treatment with lithium hydroxide in aqueous dioxan, as described in U.S. Patent 5,848,801, to yield the carboxylic acid **1.5**.

Scheme **14** illustrates the preparation of the carboxylic acids **9.1** in which the group A, attached to the amine moiety, is either the group link-P(O)$(OR^1)_2$ or a precursor group thereto, such as [OH], [SH, [NH] Br. During the series of reaction shown in Scheme **14**, the group A may, at an appropriate stage, be converted into the group link-P(O)$(OR^1)_2$, according to the knowledge of one skilled in the art. Alternatively, the carboxylic acid **9.1**, in which A is link-P(O)$(OR^1)_2$, may be incorporated into the diamide compounds **9.2**, as described above, (Scheme **9**) before effecting the transformation of the group A into the group link-P(O)$(OR^1)_2$. As shown in Scheme **14**, 4-chloromethyl-2-isopropyl-thiazole **14.1**, prepared as described in WO 9414436, is reacted with an amine **14.2**, in which A is as described above, to afford the amine **13.6**. The conditions for the alkylation reaction are the same as those described above for the preparation of the amine **13.6**. The product is then transformed, via the intermediate ester **14.4**, into the carboxylic acid **9.1**. The conditions for the reactions required to transform the amine **14.3** into the carboxylic acid **9.1** are the same as those described above (Scheme **13**) for the analogous chemical steps.

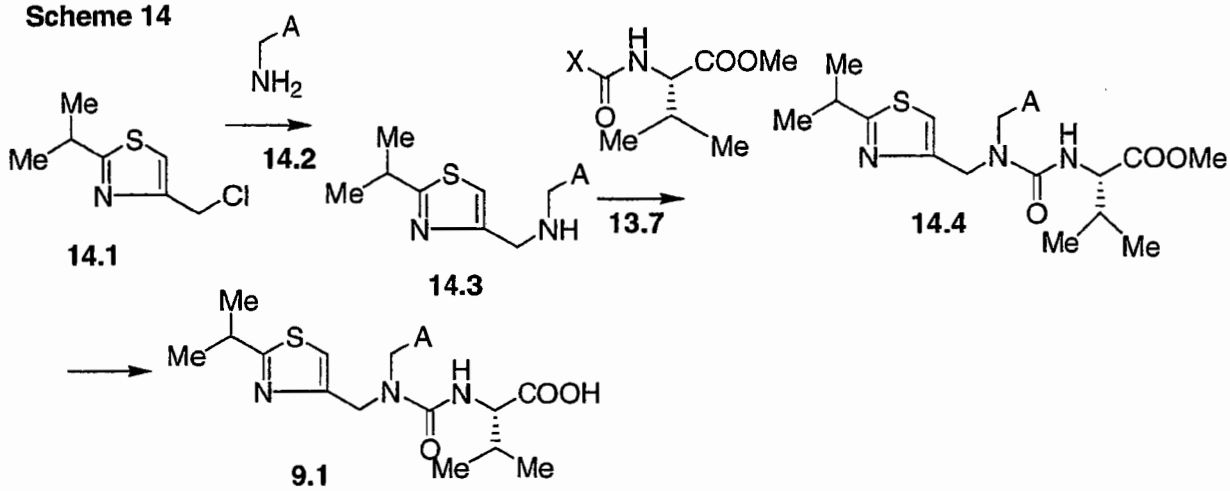
Scheme **15** illustrates the preparation of the carboxylic acids **11.1** in which the group A, attached to the valine moiety, is either the group link-$P(O)(OR^1)_2$ or a precursor group thereto, such as [OH], [SH, [NH] Br. During the series of reaction shown in Scheme **15**, the group A may, at an appropriate stage, be converted into the group link-$P(O)(OR^1)_2$, according to the knowledge of one skilled in the art. Alternatively, the carboxylic acid **11.1**, in which A is link-$P(O)(OR^1)_2$ may be incorporated into the diamide compounds **11.2**, as described above, (Scheme **11**) before effecting the transformation of the group A into the group link-$P(O)(OR^1)_2$.

As shown in Scheme **15**, (2-isopropyl-thiazol-4-ylmethyl)-methyl-amine, **15.1**, prepared as described in WO 9414436, is reacted with a substituted valine derivative **15.2**, in which the group A is as defined above. Methods for the preparation of the valine derivatives **15.2** are described below, Scheme **26**. The resultant ester **15.3** is then hydrolyzed, as described above, to afford the carboxylic acid **11.1**

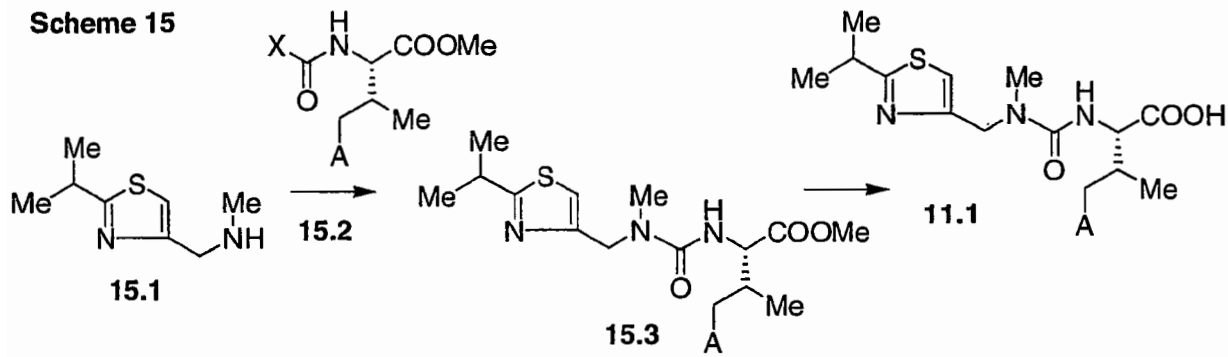
Scheme 13



Scheme 14



Scheme 15



Preparation of phenylalanine derivatives 4.1 incorporating phosphonate moieties.

Scheme **16** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives **16.1**.

In this procedure, a hydroxy or mercapto-substituted phenylalanine is converted into the benzyl ester **16.2**. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester **16.2** is then protected. Protection methods for phenols and thiols are described respectively, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p 277. For example, suitable protecting groups for phenols and thiophenols include tert-butyldimethylsilyl or tert-butyldiphenylsilyl. Thiophenols may also be protected as S-adamantyl groups, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. The protected hydroxy- or mercapto ester **16.3** is then reacted with a benzyl or substituted benzyl halide and a base, for example as described in U.S. Patent 5,491,253, to afford the N, N-dibenzyl product **16.4**. For example, the amine **16.3** is reacted at ca. 90°C with two molar equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, to afford the tribenzylated product **16.4**, as described in U.S. Patent 5,491,253. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride and the like, in a solvent such as tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972. S-Adamantyl groups can be removed by treatment with mercuric trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.

The resultant phenol or thiophenol **16.5** is then reacted under various conditions to provide protected phenylalanine derivatives **16.9**, **16.10** or **16.11**, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

In this step, the phenol or thiophenol **16.5** is reacted with a dialkyl bromoalkyl phosphonate **16.6** to afford the product **16.9**. The alkylation reaction between **16.5** and **16.6** is effected in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate, The reaction is performed at from ambient temperature to ca. 80°C, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product **16.9**.

For example, as illustrated in Scheme **16**, Example 1, a hydroxy-substituted phenylalanine derivative such as tyrosine, **16.12** is converted, as described above, into the benzyl ester **16.13**. The latter compound is then reacted with one molar equivalent of chloro tert-butyldimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether **16.14**. This compound is then converted, as described above, into the tribenzylated derivative **16.15**. The silyl protecting group is removed by treatment of **16.15** with a tetrahydrofuran solution of tetrabutyl ammonium fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol **16.16**. The latter compound is then reacted in dimethylformamide at ca. 60°C, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **16.17** (Aldrich), in the presence of cesium carbonate, to afford the alkylated product **16.18**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **16.12**, different hydroxy or thio-substituted phenylalanine derivatives **16.1**, and/or different bromoalkyl phosphonates **16.6**, the corresponding ether or thioether products **16.9** are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **16.5** is reacted with a dialkyl hydroxymethyl phosphonate **16.7** under the conditions of the Mitsonobu reaction, to afford the ether or thioether compounds **16.10**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an

aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **16.10**.

For example, as shown in Scheme **16**, Example 2, 3-mercaptophenylalanine **16.19**, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester **16.20**. The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether **16.21**. This compound is then converted, as described above for the preparation of the compound **16.4**, into the tribenzyl derivative **16.22**. The 4-methoxybenzyl group is then removed by the reaction of the thioether **16.22** with mercuric trifluoroacetate and anisole in trifluoroacetic acid, as described in J.Org. Chem., 52, 4420, 1987, to afford the thiol **16.23**. The latter compound is reacted, under the conditions of the Mitsonobu reaction, with diethyl hydroxymethyl phosphonate **16.7**, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product **16.24**.

Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative **16.19**, different hydroxy or mercapto-substituted phenylalanines **16.1**, and/or different dialkylhydroxymethyl phosphonates **16.7**, the corresponding products **16.10** are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **16.5** is reacted with an activated derivative of a dialkyl hydroxymethylphosphonate **16.8** in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base such as triethylamine or cesium carbonate, to afford the ether or thioether products **16.11**.

For example, as illustrated in Scheme **16**, Example 3, 3-hydroxyphenylalanine **16.25** (Fluka) is converted, using the procedures described above, into the tribenzylated compound **16.26**. The latter compound is reacted, in dimethylformamide at ca. 50°C, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate **16.27**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product **16.28**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **16.25**, different hydroxy or mercapto-substituted phenylalanines **16.1**, and/or different dialkyl trifluoromethanesulfonyloxymethylphosphonates **16.8**, the corresponding products **16.11** are obtained.

Scheme **17** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a formyl-substituted tribenzylated phenylalanine derivative **17.3** and a dialkyl aminoalkylphosphonate **17.4**.

In this procedure, a hydroxymethyl-substituted phenylalanine **17.1** is converted into the tribenzylated derivative **17.2** by reaction with three equivalents of a benzyl halide, for example, benzyl chloride, in the presence of an organic or inorganic base such as diazabicyclononene or potassium carbonate. The reaction is conducted in a polar solvent optionally in the additional presence of water. For example, the aminoacid **17.1** is reacted with three equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, as described in U.S. Patent 5,491,253, to afford the product **17.2**. The latter compound is then oxidized to afford the corresponding aldehyde **17.3**. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product **17.3**. For example, the carbinol **17.2** is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in J. Org. Chem., 43, 2480, 1978, to yield the aldehyde **17.3**. This compound is reacted with a dialkyl aminoalkylphosphonate **17.4** in the presence of a suitable reducing agent to afford the amine product **17.5**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990.

For example, 3-(hydroxymethyl)-phenylalanine **17.6**, prepared as described in Acta Chem. Scand. Ser. B, 1977, B31, 109, is converted, as described above, into the formylated derivative **17.7**. This compound is then reacted with a dialkyl aminoethylphosphonate **17.8**,

prepared as described in J. Org. Chem., 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated product **17.9**.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine **17.6**, different hydroxymethyl phenylalanines **17.1**, and/or different aminoalkyl phosphonates **17.4**, the corresponding products **17.5** are obtained.

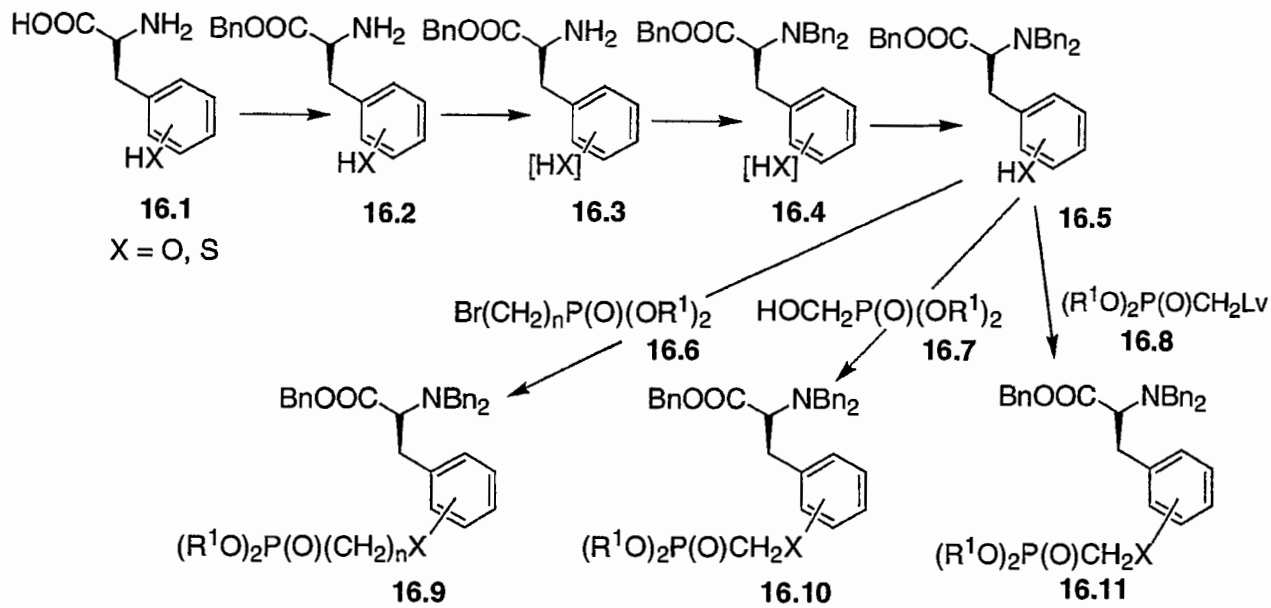
Scheme **18** depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **18.1** is converted, as described above, (Scheme **17**) into the tribenzylated derivative **18.2**. The product is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **18.3** to produce the phosphonate ester **18.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.

For example, 3-bromophenylalanine **18.5**, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme **17**) into the tribenzylated compound **18.6**. This compound is then reacted, in toluene solution at reflux, with diethyl phosphite **18.7**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product **18.8**.

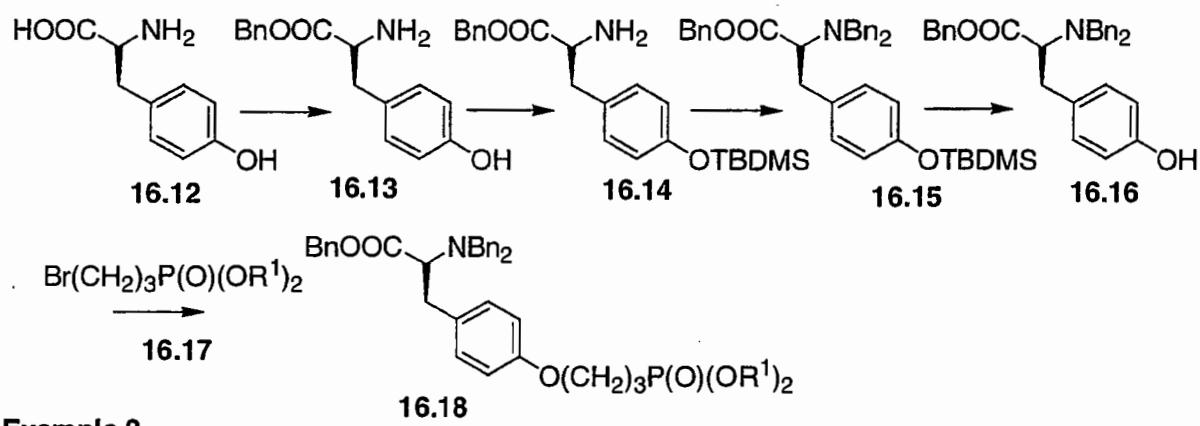
Using the above procedures, but employing, in place of 3-bromophenylalanine **18.5**, different bromophenylalanines b18.1, and/or different dialkylphosphites **18.3**, the corresponding products **18.4** are obtained.

Scheme 16

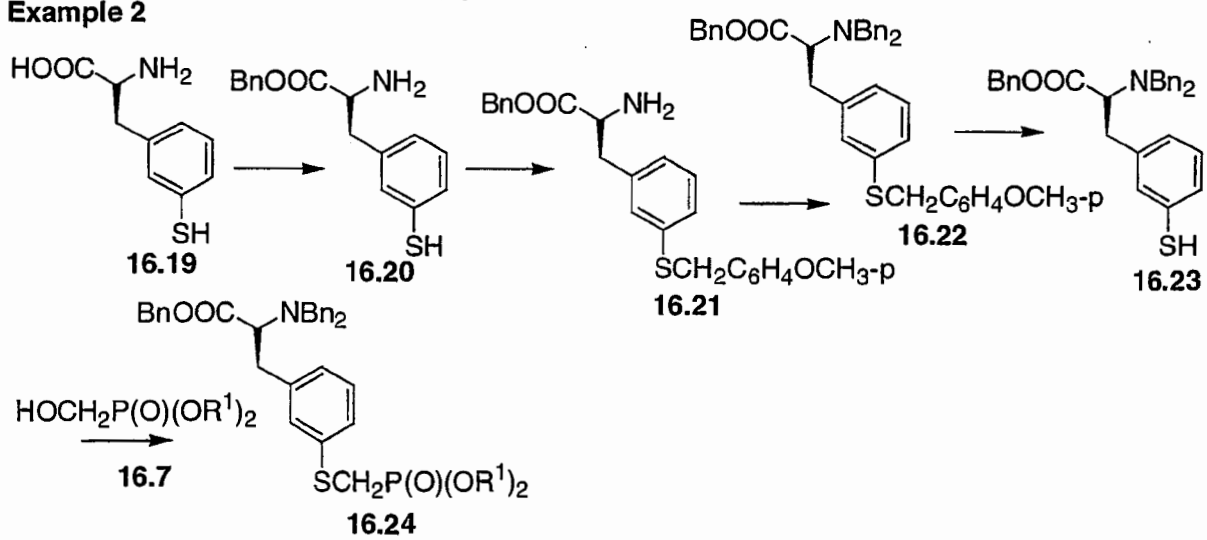
Method



Example1

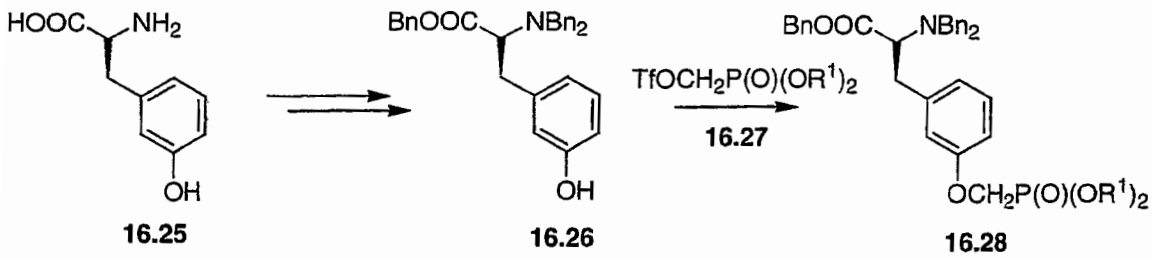


Example 2



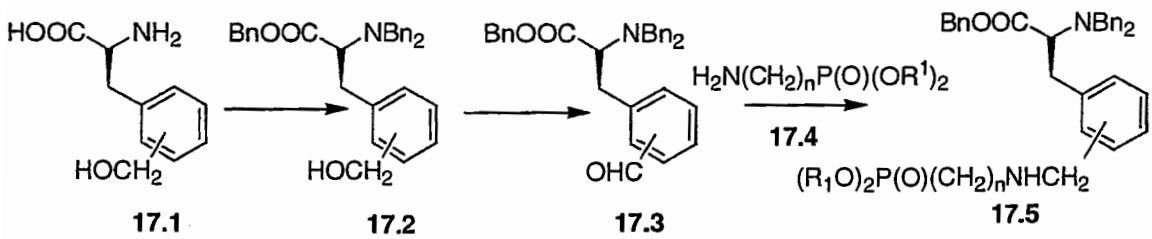
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Example 3

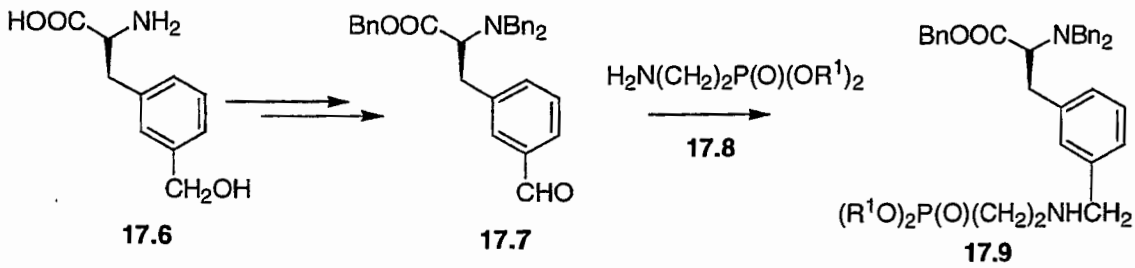


Scheme 17

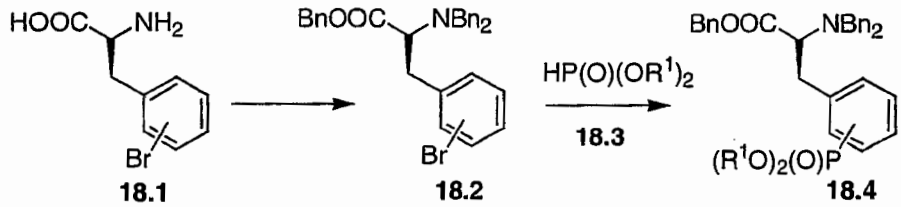
Method



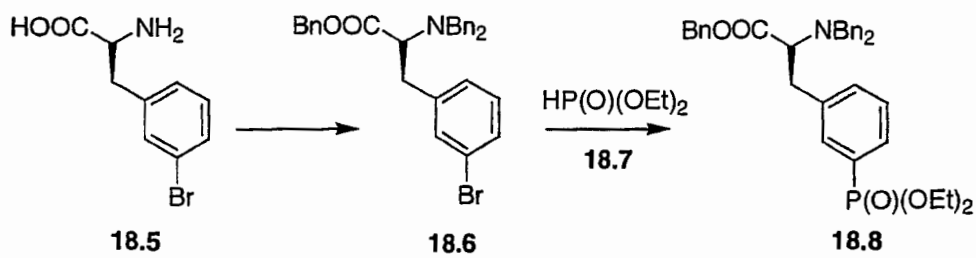
Example



Scheme 18



Example



Preparation of phosphonate esters with structure 3.

Scheme **19** illustrates the preparation of compounds **3** in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, the ketonitrile **7.1**, prepared as described in J. Org. Chem., 1994, 59, 4080, is reacted with a bromobenzylmagnesium halide reagent **19.1**. The resultant ketoenamine **19.2** is then converted into the diacylated bromophenyl carbinol **19.3**. The conditions required for the conversion of the ketoenamine **19.2** into the carbinol **19.3** are similar to those described above (Scheme **4**) for the conversion of the ketoenamine **4.5** into the carbinol **4.12**. The product **19.3** is then reacted with a dialkyl phosphite **18.3**, in the presence of a palladium (0) catalyst, to yield the phosphonate ester **19.4**. The conditions for the coupling reaction are the same as those described above (Scheme **18**) for the preparation of the phosphonate ester **18.4**.

For example, the ketonitrile **7.1** is reacted, in tetrahydrofuran solution at -40°C, with three molar equivalents of 4-bromobenzylmagnesium bromide **19.5**, the preparation of which is described in Tetrahedron, 2000, 56, 10067, to afford the ketoenamine **19.6**. The latter compound is then converted into the bromophenyl carbinol **19.7**, using the sequence of reactions described above (Scheme **4**) for the conversion of the ketoenamine **4.5** into the carbinol **4.12**. The resultant bromo compound **19.7** is then reacted with diethyl phosphite **18.3** and triethylamine, in toluene solution at reflux, in the presence of tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product **19.8**.

Using the above procedures, but employing, in place of 4-bromobenzylmagnesium bromide **19.5**, different bromobenzylmagnesium halides **19.1** and/or different dialkyl phosphites **18.3**, there are obtained the corresponding phosphonate esters **19.4**.

Scheme **20** illustrates the preparation of compounds **3** in which the phosphonate ester moiety is attached to the nucleus by means of a phenyl ring. In this procedure, a bromophenyl-substituted benzylmagnesium bromide **20.1**, prepared from the corresponding bromomethyl compound by reaction with magnesium, is reacted with the ketonitrile **7.1**. The conditions for this transformation are the same as those described above (Scheme **4**). The product of the Grignard addition reaction is then transformed, using the sequence of reactions described

above, (Scheme **4**) into the diacylated carbinol **20.2**. The latter compound is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **18.3**, to afford the phenylphosphonate **20.3**. The procedure for the coupling reaction is the same as those described above for the preparation of the phosphonate **19.8**.

For example, 4-(4-bromophenyl)benzyl bromide, prepared as described in DE 2262340, is reacted with magnesium to afford 4-(4-bromophenyl)benzylmagnesium bromine **20.4**. This product is then reacted with the ketonitrile **7.1**, as described above, to yield, after the sequence of reactions shown in Scheme **4**, the diacylated carbinol **20.5**. The latter compounds then reacted, as described above, (Scheme **18**) with a dialkyl phosphite **18.3**, to afford the phenylphosphonate **20.6**.

Using the above procedures, but employing, in place of 4-(4-bromophenyl)benzyl bromide **20.4**, different bromophenylbenzyl bromides **20.1**, and/or different dialkyl phosphites **18.3**, the corresponding products **20.3** are obtained.

Scheme **21** depicts the preparation of phosphonate esters **3** in which the phosphonate group is attached by means of a heteroatom and a methylene group. In this procedure, a hetero-substituted benzyl alcohol **21.1** is protected, affording the derivative **21.2**. The protection of phenyl hydroxyl, thiol and amino groups are described, respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277, 309. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. Amino groups can be protected, for example by dibenzylation. The conversion of amines into dibenzylamines, for example by treatment with benzyl bromide in a polar solvent such as acetonitrile or aqueous ethanol, in the presence of a base such as triethylamine or sodium carbonate, is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M Wuts, Wiley, Second Edition 1990, p. 364. The resultant protected benzyl alcohol **21.1** is converted into a halo derivative **21.2**, in which Ha is chloro or bromo. The conversion of alcohols into chlorides and bromides is described, for example, in

Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. For example, benzyl alcohols **21.2** can be transformed into the chloro compounds **21.3**, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in J. Am. Chem. Soc., 106, 3286, 1984. Benzyl alcohols can be transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc., 92, 2139, 1970. The resultant protected benzyl halide **21.3** is then converted into the corresponding benzylmagnesium halide **21.4** by reaction with magnesium metal in an ethereal solvent, or by a Grignard exchange reaction treatment with an alkyl magnesium halide. The resultant substituted benzylmagnesium halide **21.4** is then converted, using the sequence of reactions described above (Scheme **4**) for the preparation of the diacylated carbinol **4.11**, into the carbinol **21.5** in which the substituent XH is suitably protected.

The protecting group is then removed to afford the phenol, thiophenol or amine **21.6**. Deprotection of phenols, thiophenols and amines is described respectively in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978. N,N-dibenzyl amines can be converted into the unprotected amines by catalytic reduction in the presence of a palladium catalyst, as described above (Scheme **1**). The resultant phenol, thiophenol or amine **21.6** is then converted into the phosphonate ester **21.7** by reaction with an activated derivative of a dialkyl hydroxymethyl phosphonate **16.27**, in which Lv is a leaving group. The reaction is conducted under the same conditions as described above for the conversion of **16.5** to **16.11** (Scheme **16**).

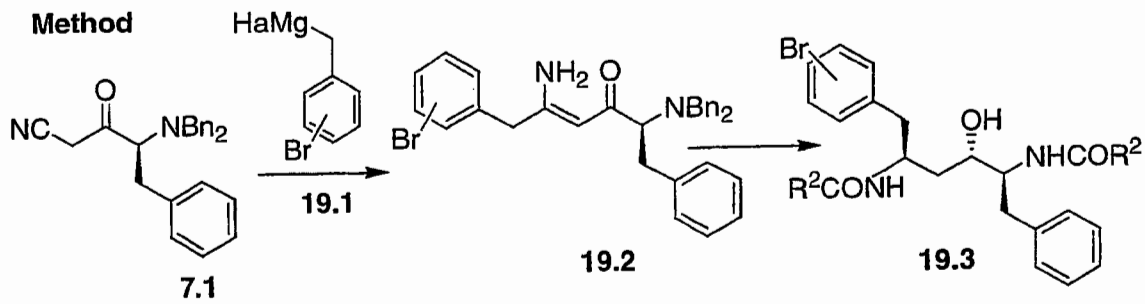
For example, 3-hydroxybenzyl alcohol **21.8** (Aldrich) is reacted with chlorotriisopropylsilane and imidazole in dimethylformamide, as described in Tet. Lett., 2865, 1964, to afford the silyl ether **21.9**. This compound is reacted with carbon tetrabromide and triphenylphosphine in dichloromethane, as described in J. Am. Chem. Soc., 109, 2738, 1987, to afford the brominated product **21.10**. This material is reacted with magnesium in ether to afford the Grignard reagent **21.11**, which is then subjected to the series of reaction shown in Scheme **4** to

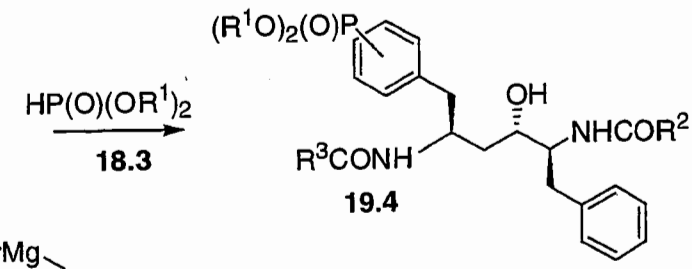
afford the carbinol **21.12**. The triisopropylsilyl protecting group is then removed by treatment of the ether **21.12** with tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Org. Chem., 51, 4941, 1986. The resultant phenol **21.13** is then reacted with a dialkyl trifluoromethanesulfonyloxymethylphosphonate **16.27**, prepared as described in Tet. Lett., 1986, 27, 1477, in dimethylformamide solution at 60°C in the presence of cesium carbonate, to afford the phosphonate product **21.14**.

Using the above procedures, but employing, in place of 3-hydroxybenzyl alcohol **21.8**, different hydroxy, mercapto or amino-substituted benzyl alcohols **21.1**, and/or different dialkyl trifluoromethanesulfonyloxymethyl phosphonates **16.27**, the corresponding products **21.7** are obtained.

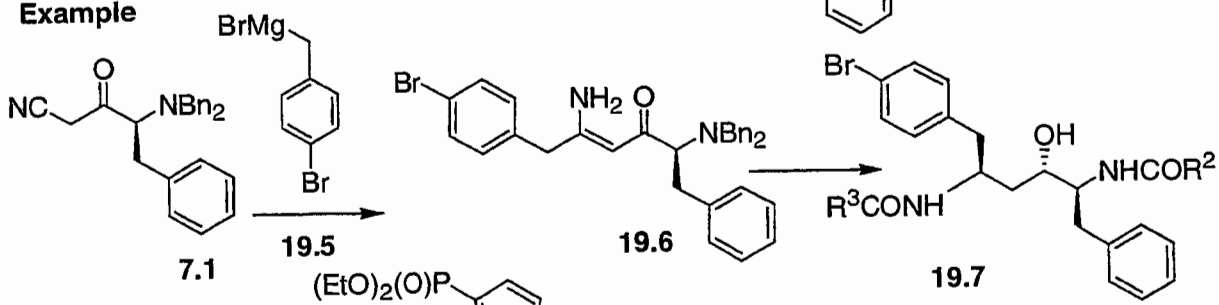
Scheme 19

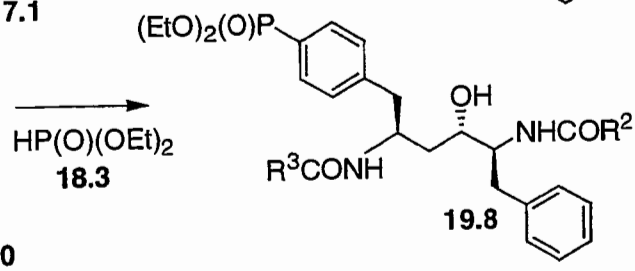
Method





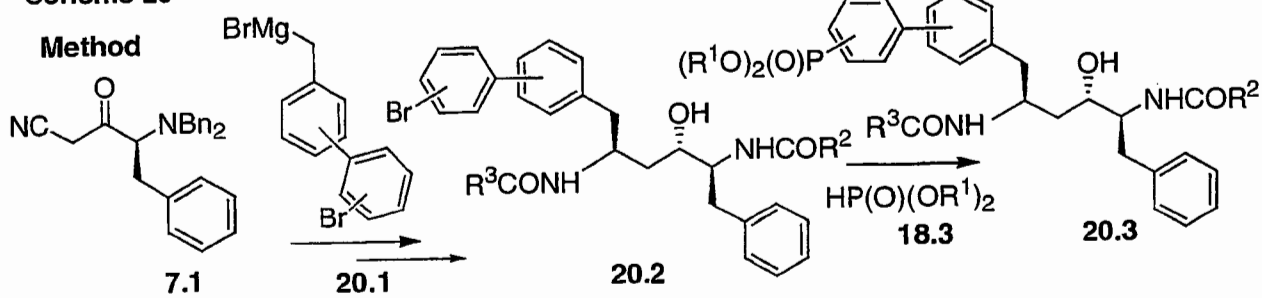
Example



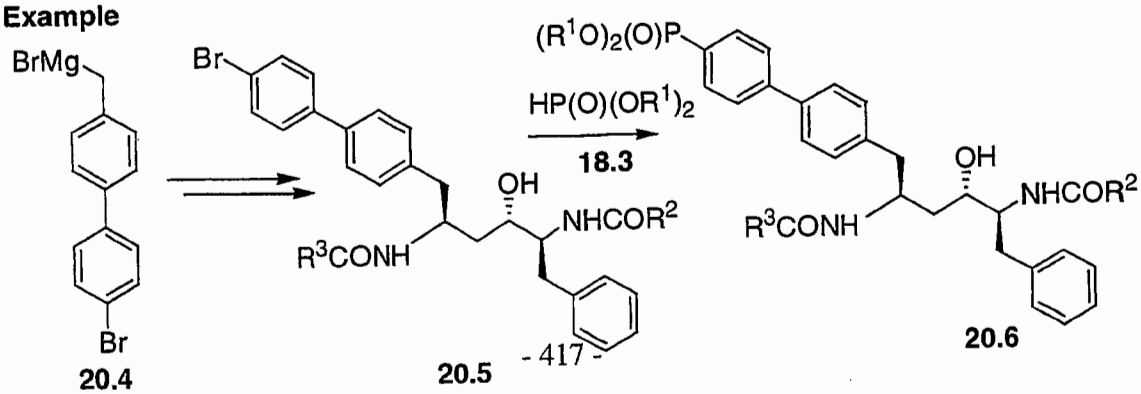


Scheme 20

Method

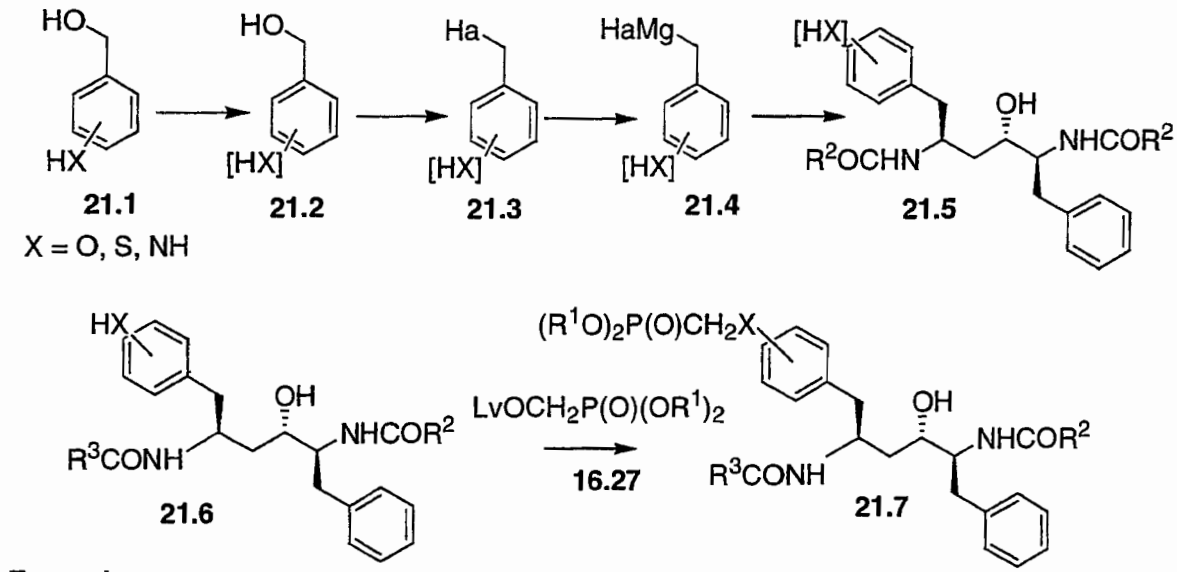


Example

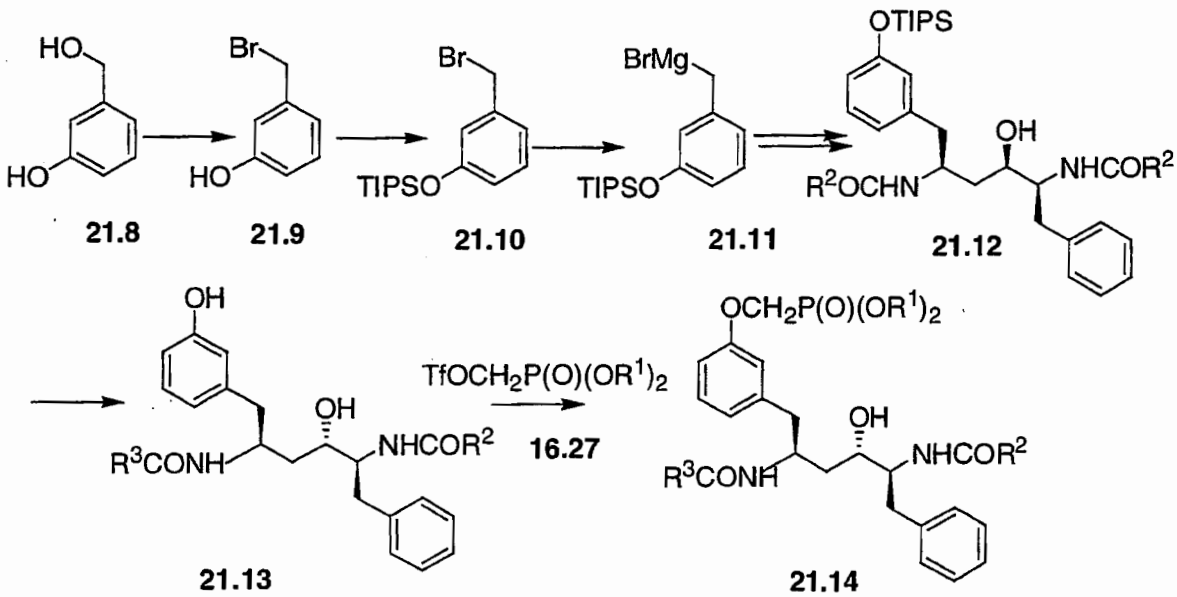


Scheme 21

Method



Example



Preparation of phosphonate-containing carboxylic acids 1.5.

Scheme **22** illustrates methods for the preparation of carboxylic acids **1.5**, in which A is Br, and methods for the conversion of the bromo substituent into various phosphonate-containing substituents.

In this procedure, 3-bromo-2-methylpropanamide **22.1** is substituted for the isobutyramide derivative **13.1** in the reaction sequence illustrated in Scheme **13**, so as to afford 2-{3-[2-(2-bromo-1-methyl-ethyl)-thiazol-4-ylmethyl]-3-methyl-ureido}-3-methyl-butyric acid methyl ester, **22.2**. The conditions required for the various reactions are the same as those described above (Scheme**13**). The bromo-substituted ester **22.2** is then subjected to various transformations so as to introduce phosphonate-containing substituents. For example, the ester **22.2** is reacted with a trialkyl phosphate **22.3** in an Arbuzov reaction, to afford the phosphonate ester **22.4**. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in Handb. Organophosphorus Chem., 1992, 115. The reaction is performed by heating the substrate at 100°C to 150°C with an excess of the trialkyl phosphite. The methyl ester group in the phosphonate product **22.4** is then hydrolyzed, using the procedures described above, (Scheme **13**) to prepare the carboxylic acid **22.5**.

For example, as shown in Scheme **22**, Example 1, the bromo compound **22.2** is heated at 120°C with a ten molar excess of tribenzyl phosphite **22.6** to afford the benzylphosphonate **22.7**. Hydrolysis of the methyl ester, as described above, then yields 2-(3-{2-[2-(bis-benzyloxy-phosphoryl)-1-methyl-ethyl]-thiazol-4-ylmethyl}-3-methyl-ureido)-3-methyl-butyric acid **22.8.**

Alternatively, the bromoester **22.2** is oxidized to the corresponding aldehyde **22.9**. Methods for the oxidation of bromo compounds to the corresponding aldehyde are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989 p. 599. The transformation can be effected by reaction of the aldehyde with dimethyl sulfoxide, optionally in the presence of a silver salt, as described in Chem. Rev., 67, 247, 1967. Alternatively, the bromo compound is reacted with trimethylamine oxide, as described in Ber., 94, 1360, 1961, to prepare 3-methyl-2-{3-methyl-3-[2-(1-methyl-2-oxo-ethyl)-thiazol-4-ylmethyl]-ureido}-butyric acid methyl ester **22.9**. The aldehyde is then reacted with a dialkyl aminoalkyl phosphonate **22.10** in a reductive amination reaction to afford the

aminophosphonate **22.11.** The conditions for the reductive amination reaction are the same as those described above for the preparation of the aminophosphonate **17.5**, (Scheme **17**). The methyl ester group present in the product **22.11** is then hydrolyzed, as described above, to yield the carboxylic acid **22.12.**

For example, as shown in Scheme **22**, Example 2, the bromo compound **22.2** is heated at 80°C in dimethylsulfoxide solution, in the presence of one molar equivalent of silver tetrafluoborate and triethylamine, as described in J. Chem. Soc., Chem. Comm., 1338, 1970, to afford the aldehyde **22.9**. Reductive amination of the product, in the presence of a dialkyl aminoethyl phosphonate **22.13**, the preparation of which is described in J. Org. Chem., 2000, 65, 676 and sodium triacetoxy borohydride, then affords the amino phosphonate **22.14**. Hydrolysis of the methyl ester, as described above, then afford the carboxylic acid **22.15**.

Alternatively, the bromo compound **22.2** is reacted with a dialkyl thioalkyl phosphonate **22.16** to effect displacement of the bromo substituent to afford the thioether **22.17**. The preparation of thioethers by the reaction of bromo compounds with thiols is described, for example, in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 787. The reactants are combined in the presence of a suitable base, such as sodium hydroxide, dimethylaminopyridine, potassium carbonate and the like, in a polar organic solvent such as dimethylformamide or ethanol, to afford the thioether **22.17**. The product is then subjected to hydrolysis, as described above, to afford the carboxylic acid **22.18**.

For example, as shown in Scheme **22**, Example 3, the bromo compound **22.2** is reacted with a dialkyl thioethylphosphonate **22.19**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990, and dimethylaminopyridine, in dimethylformamide solution at ambient temperature, to yield the thioether **22.20**. Hydrolysis of the methyl ester group, as described above, then afford the carboxylic acid **22.21**.

Scheme **23** illustrates the preparation of carboxylic acids **23.7** in which the phosphonate moiety is attached to the isopropyl group by means of a phenyl ring and a heteroatom. In this procedure, the hydroxy or mercapto substituent on a phenylbutanamide **23.1** is protected. Methods for the protection of hydroxyl and thiol groups are described above (Scheme **21**). The protected amide **23.2** is then subjected to the series of reactions illustrated in Scheme **13**, so as to afford the O- or S-protected ester **23.3**. The protecting group is then removed. Methods for the deprotection of phenols and thiophenols are described above (Scheme **16**).

The resultant phenol or thiophenol **23.4** is then reacted with a dialkyl bromoalkyl phosphonate **23.5**, to afford the ether or thioether compounds **23.6**. Conditions for the alkylation of phenols and thiophenols are described above (Scheme **16**). The ester groups present in the product **23.6** is then hydrolyzed, as described above, to afford the corresponding carboxylic acid **23.7**.

For example, 3-(4-hydroxyphenyl)butyric acid **23.8**, prepared as described in J. Med. Chem., 1992, 35, 548, is converted into the acid chloride by reaction with thionyl chloride. The acid chloride is then reacted with excess aqueous ethanolic ammonia to afford the amide **23.9**. This compound is converted into the tert. butyldimethylsilyl derivative **23.10** by treatment with tert-butylchlorodimethylsilane and imidazole in dichloromethane. The resultant amide **23.10** is then subjected to the series of reactions shown in Scheme **13**, so as to yield the ester **23.11**. Desilylation, by treatment with tetrabutylammonium fluoride in tetrahydrofuran, then affords the phenol **23.12**. This compound is reacted with a dialkyl bromoethyl phosphonate **23.13** (Aldrich) and potassium carbonate, in dimethylformamide at 80°C, to produce the ether **23.14**. Hydrolysis of the ester group, by treatment with aqueous methanolic lithium hydroxide, then affords the carboxylic acid **23.15**.

Using the above procedures, but employing, in place of the amide **23.9**, different hydroxy- or thio-substituted amides **23.23.1**, and/or different bromoalkylphosphonates **23.5**, the corresponding products **23.7** are obtained.

Scheme **24** and **25** describes the preparation of carboxylic acids **9.1** in which the phosphonate moiety is attached to the amine component. In this procedure, the chloromethylthiazole **14.1**, is reacted with a dialkyl aminoalkyl phosphonate **24.1** to produce the substituted amine **24.2**. The preparation of amines by reacting amines with alkyl halides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397. Typically, the components are reacted together in a polar solvent such as an alkanol or dimethylformamide and the like, to yield the substituted amine **24.2**. The latter compound is then converted into the carboxylic acid **24.3**, by means of the series of reactions shown in Scheme **14**.

For example, the chloromethyl thiazole **14.1** is reacted at 50°C in acetonitrile solution containing potassium carbonate, with one molar equivalent of a dialkyl aminomethyl phosphonate **24.4**, prepared as described in Bioorg. Chem., 2001, 29, 77, to afford the

substituted amine **24.5**. The product is then converted, using the reactions shown in Scheme **14**, into the carboxylic acid **24.6**.

Using the above procedures, but employing, in place of the dialkyl aminoethyl phosphonate **24.4**, different dialkyl aminoalkyl phosphonates **24.1**, the corresponding products **24.3** are obtained.

Scheme **25** illustrates the preparation of carboxylic acids **9.1** in which the phosphonate moiety is attached to the amine component by means of a saturated or unsaturated alkyl chain and a phenyl ring. In this procedure, the chloromethylthiazole **14.1** is reacted with allylamine **25.1**, using the procedures described above (Scheme **24**) to afford allyl-(2-isopropyl-thiazol-4-ylmethyl)-amine **25.2**. The ester amine is then converted, by means of the series of reactions shown in Scheme **14**, into 2-[3-allyl-3-(2-isopropyl-thiazol-4-ylmethyl)-ureido]-3-methyl-butyric acid methyl ester **25.3**. This material is coupled with a dialkyl bromo-substituted phenylphosphonate **25.4**, under the conditions of the palladium-catalyzed Heck reaction, to afford the coupled product **25.5**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Hydrolysis of the methyl ester, as described above, then yields the carboxylic acid **25.6**. Optionally, the double bond present in the product **25.6** is reduced to afford the dihydro analog **25.7**. The double bond is reduced in the presence of a palladium catalyst, such as, for example, 5% palladium on carbon, in a solvent such as methanol or ethanol, to afford the product **25.7**.

For example, the allyl-substituted urea **25.3** is reacted with a dialkyl 4-bromophenyl phosphonate **25.8**, prepared as described in J. Chem. Soc., Perkin Trans.,1977, 2, 789 in the presence of tetrakis(triphenylphosphine)palladium (0) and triethylamine, to afford the phosphonate ester **25.9**. Ester hydrolysis, as described above, then affords the carboxylic acid **25.10**. Hydrogenation, as described above, then affords the saturated analog **25.11**.

Using the above procedures, but employing, in place of the 4-bromophenyl phosphonate **25.8**, different bromophenyl phosphonates **25.4**, the corresponding products **25.6** and **25.7** are obtained.

Scheme **26** illustrates the preparation of carboxylic acids **11.1** in which the phosphonate moiety is attached to the valine substructure. In this procedure, 2-amino-4-bromo-3-methyl-butyric acid methyl ester **26.1**, prepared as described in U.S. Patent 5,346,898, is reacted with a chloroformate, for example 4-nitrophenyl chloroformate, to prepare the activated derivative **26.2** in which X is a leaving group. For example, the aminoester **26.1** is reacted with 4-nitrophenylchloroformate in dichloromethane at 0°C, as described in U.S. 5,484,801, to afford the product **26.2** in which X is 4-nitrophenoxy. The latter compound is reacted with (2-isopropyl-thiazol-4-ylmethyl)-methyl-amine **26.3**, prepared as described in U.S. 5,484,801, in the presence of a base such as triethylamine or dimethylaminopyridine, in an inert solvent such as dichloromethane or tetrahydrofuran, to afford 4-bromo-2-[3-(2-isopropyl-thiazol-4-ylmethyl)-3-methyl-ureido]-3-methyl-butyric acid methyl ester **26.4**. The bromo compound **26.4** is then oxidized to afford the aldehyde **26.5**. The oxidation of bromo compounds to afford the corresponding aldehydes is described above (Scheme **22**). In a typical procedure, the bromo compound is heated at 80°C in dimethylsulfoxide solution, optionally in the presence of silver salt such as silver perchlorate or silver tetrafluoborate, as described in J. Am. Chem. Soc., 81, 4113, 1959, to afford 2-[3-(2-isopropyl-thiazol-4-ylmethyl)-3-methyl-ureido]-3-methyl-4-oxo-butyric acid methyl ester **26.5**. The aldehyde is then subjected to a reductive amination procedure, in the presence of a dialkyl aminoalkyl phosphonate **26.6**, to afford the amine product **26.7**. The preparation of amines by means of reductive alkylation reactions is described above (Scheme **22**). Equimolar amounts of the aldehyde **26.5** and the amine **26.6** are reacted in the presence of a boron-containing reducing agent such as, for example, sodium triacetoxyborohydride, to yield the amine **26.7**. The methyl ester is then hydrolyzed, as described above, to yield the carboxylic acid **26.8**.

For example, 2-[3-(2-isopropyl-thiazol-4-ylmethyl)-3-methyl-ureido]-3-methyl-4-oxo-butyric acid methyl ester **26.5** is reacted with a dialkyl aminoethylphosphonate **26.9** and sodium cyanoborohydride, to afford the amine product **26.10**. The methyl ester is then hydrolyzed, as described above to yield the carboxylic acid **26.11**.

Using the above procedures, but employing, in place of the dialkyl aminoethylphosphonate **26.9**, different aminoalkyl phosphonates **26.6**, the corresponding products **26.8** are obtained.

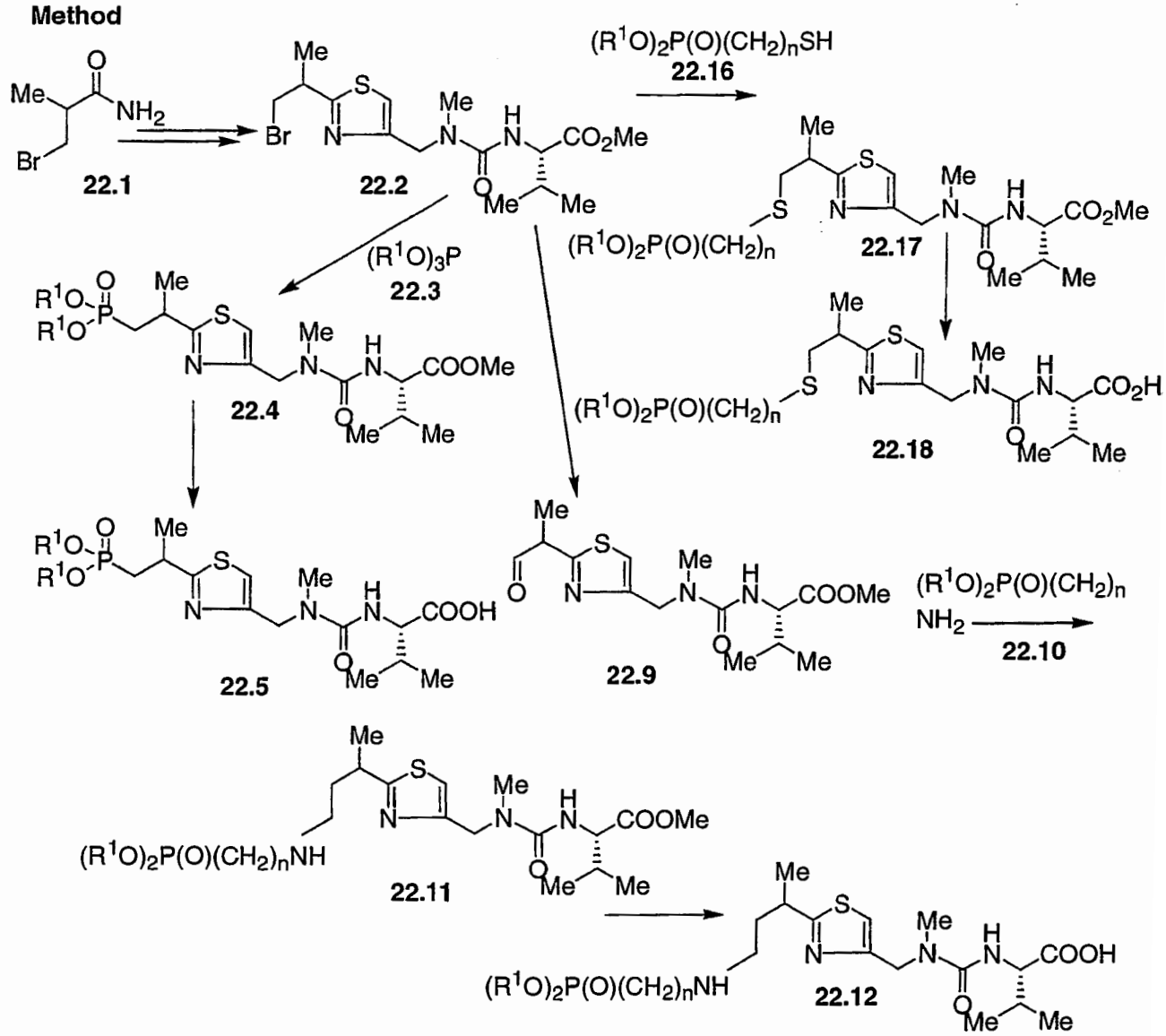
Alternatively, the bromo-substituted methyl ester **26.4** is then reacted with a dialkyl mercaptoalkyl phosphonate **26.12** to afford the thioether **26.13**. The preparation of thioethers by the reaction of bromo compounds with thiols is described, for example, in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 787. The reactants are combined in the presence of a suitable base, such as sodium hydroxide, dimethylamino pyridine, potassium or cesium carbonate and the like, in a polar organic solvent such as dimethylformamide or ethanol, to afford the thioether **26.13**. The methyl ester is then hydrolyzed, as described above to yield the carboxylic acid **26.14**.

For example, the bromo compound **26.4** is reacted with a dialkyl mercaptoethyl phosphonate **26.15**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990, in dimethylformamide solution, in the presence of cesium carbonate, to produce the thio ether product **26.16**. The methyl ester is then hydrolyzed, as described above, to yield the carboxylic acid **26.17**.

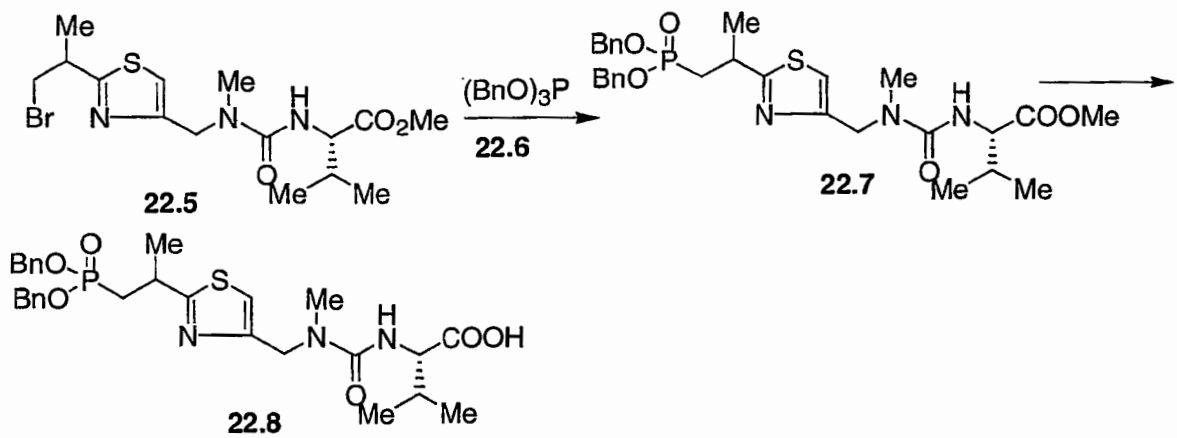
Using the above procedures, but employing, in place of the dialkyl mercaptoethyl phosphonate **26.15**, different mercaptoalkyl phosphonates **26.12**, the corresponding products **26.14** are obtained.

Scheme 22

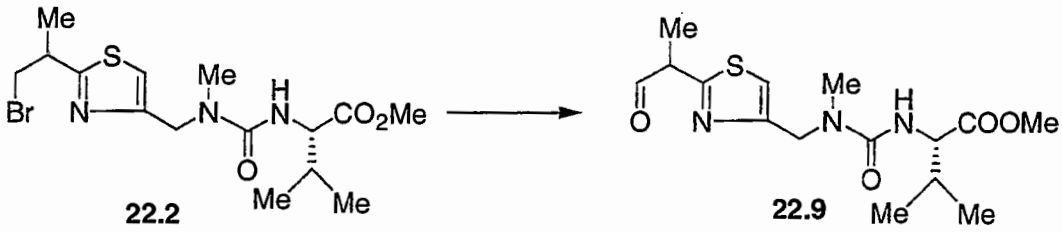
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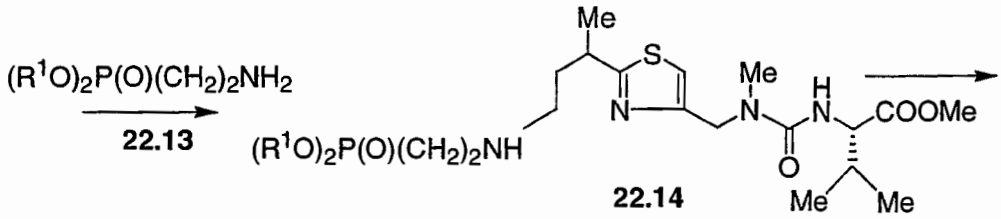


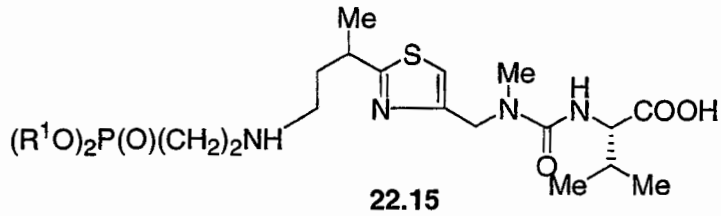
Example 1



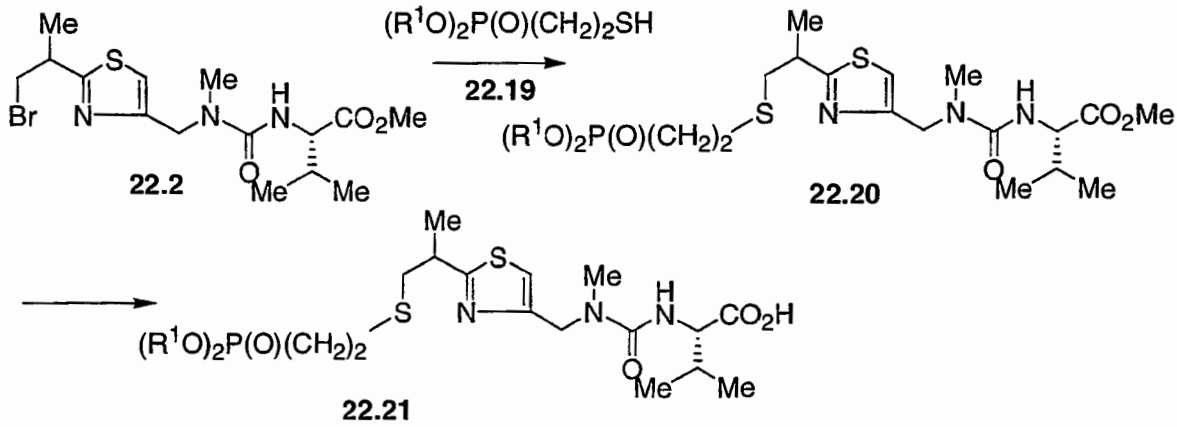
Example 2





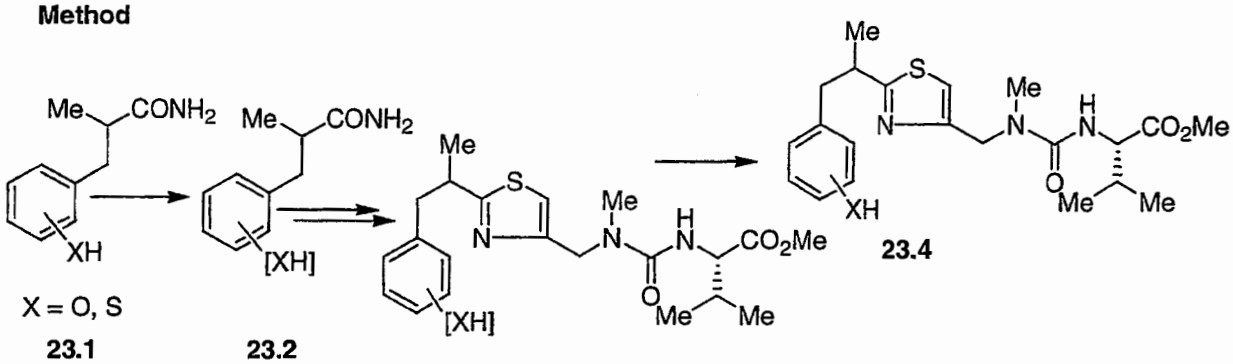


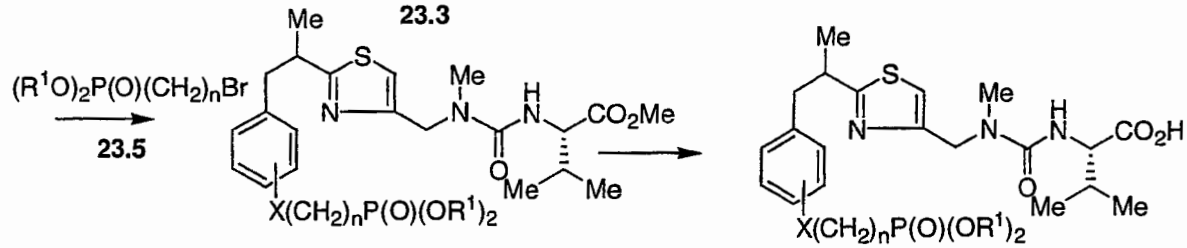
Example 3



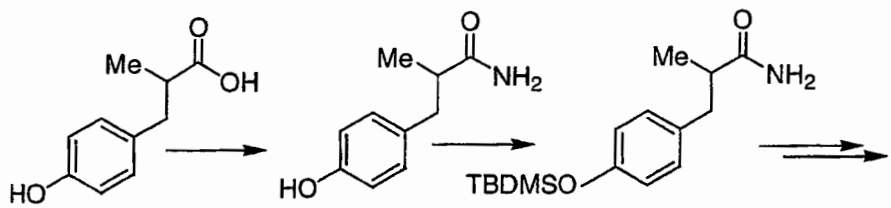
Scheme 23

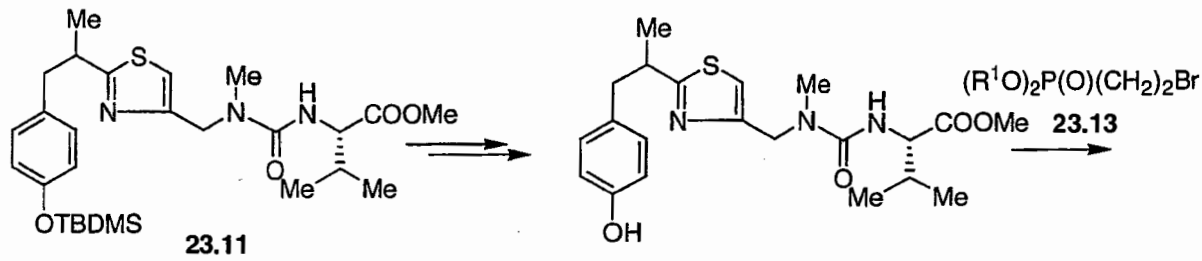
Method

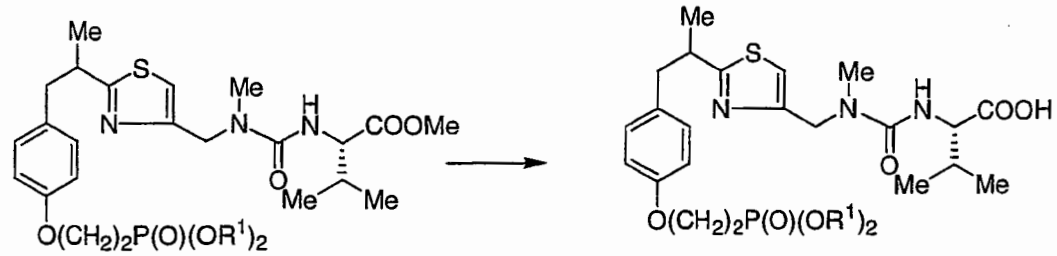




Example

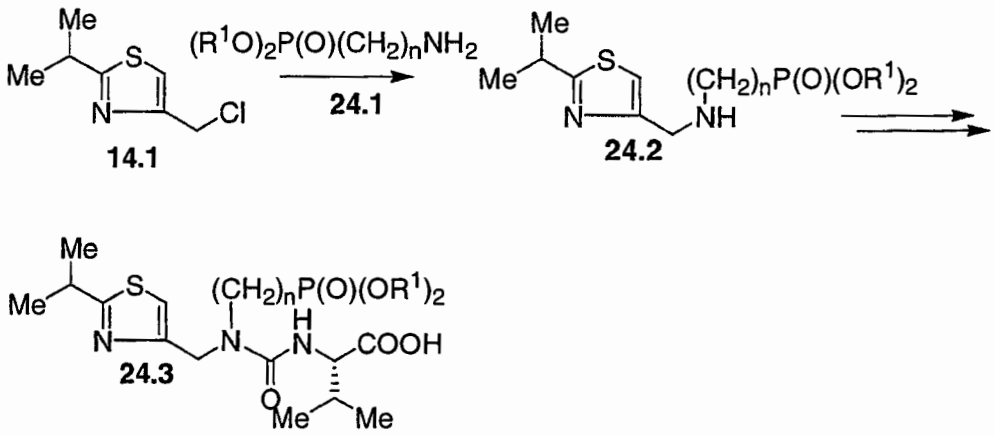




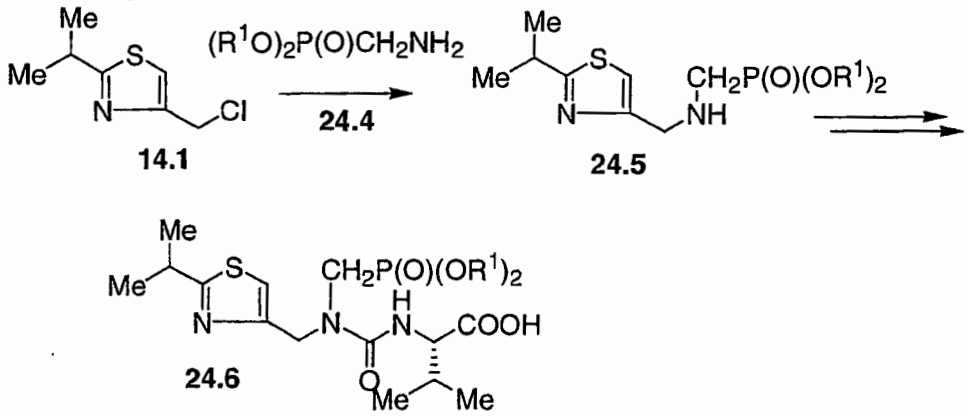


Scheme 24

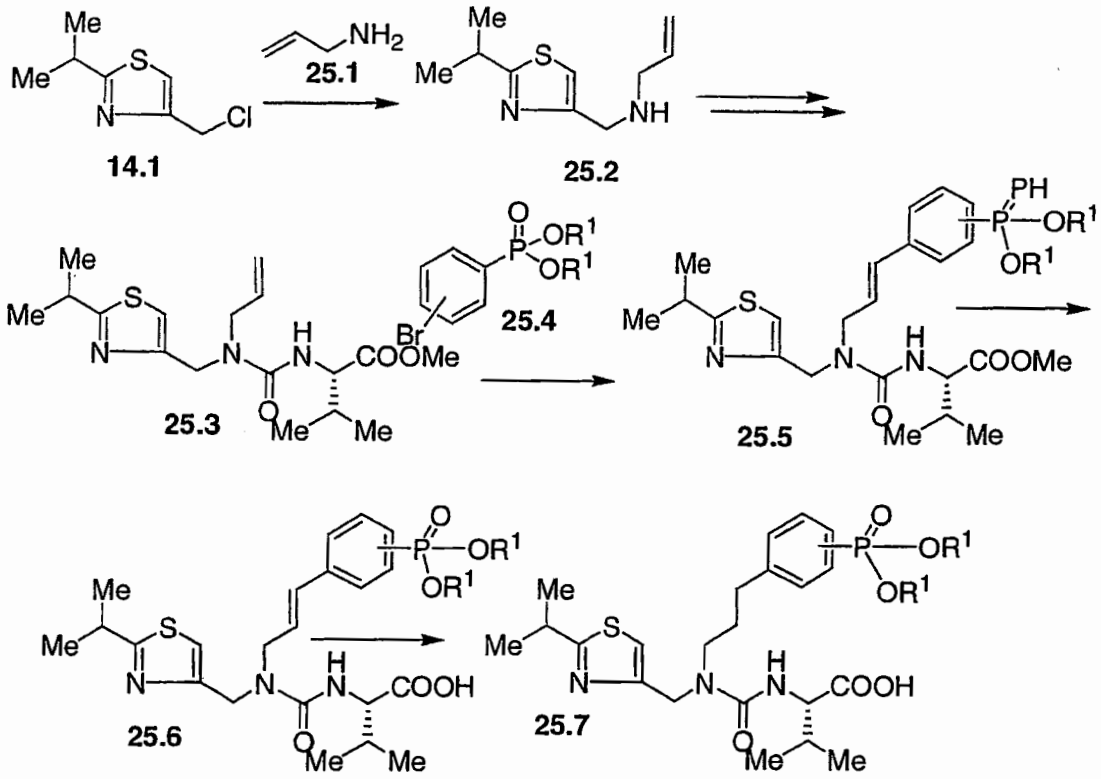
Method



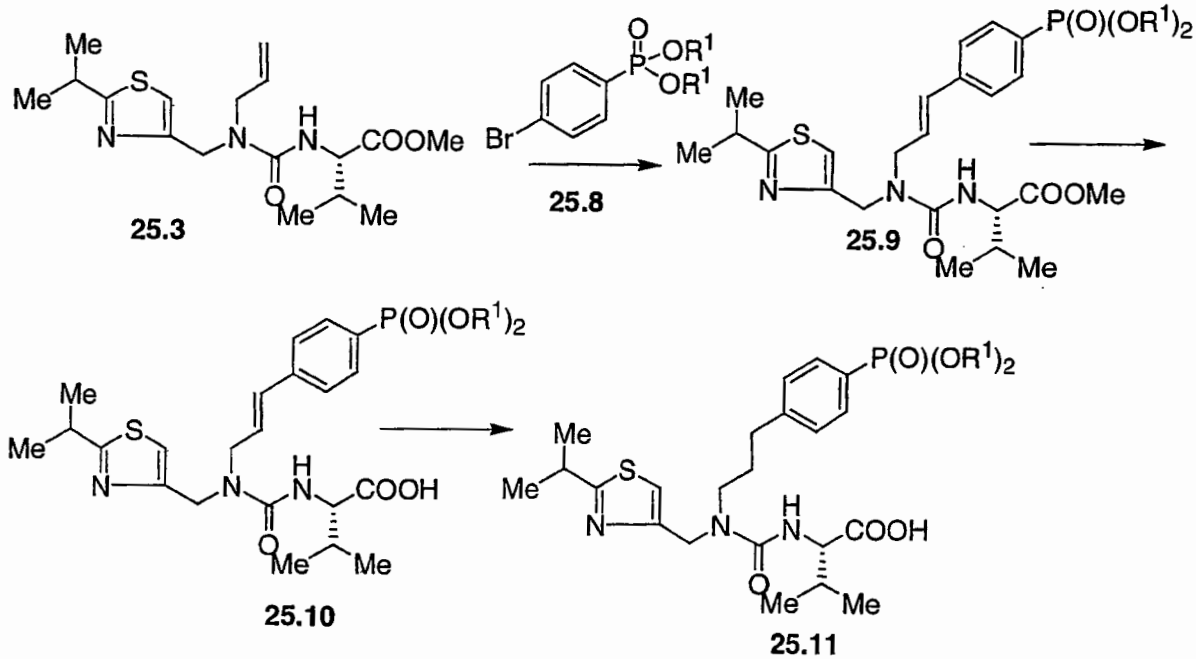
Example



Scheme 25
Method

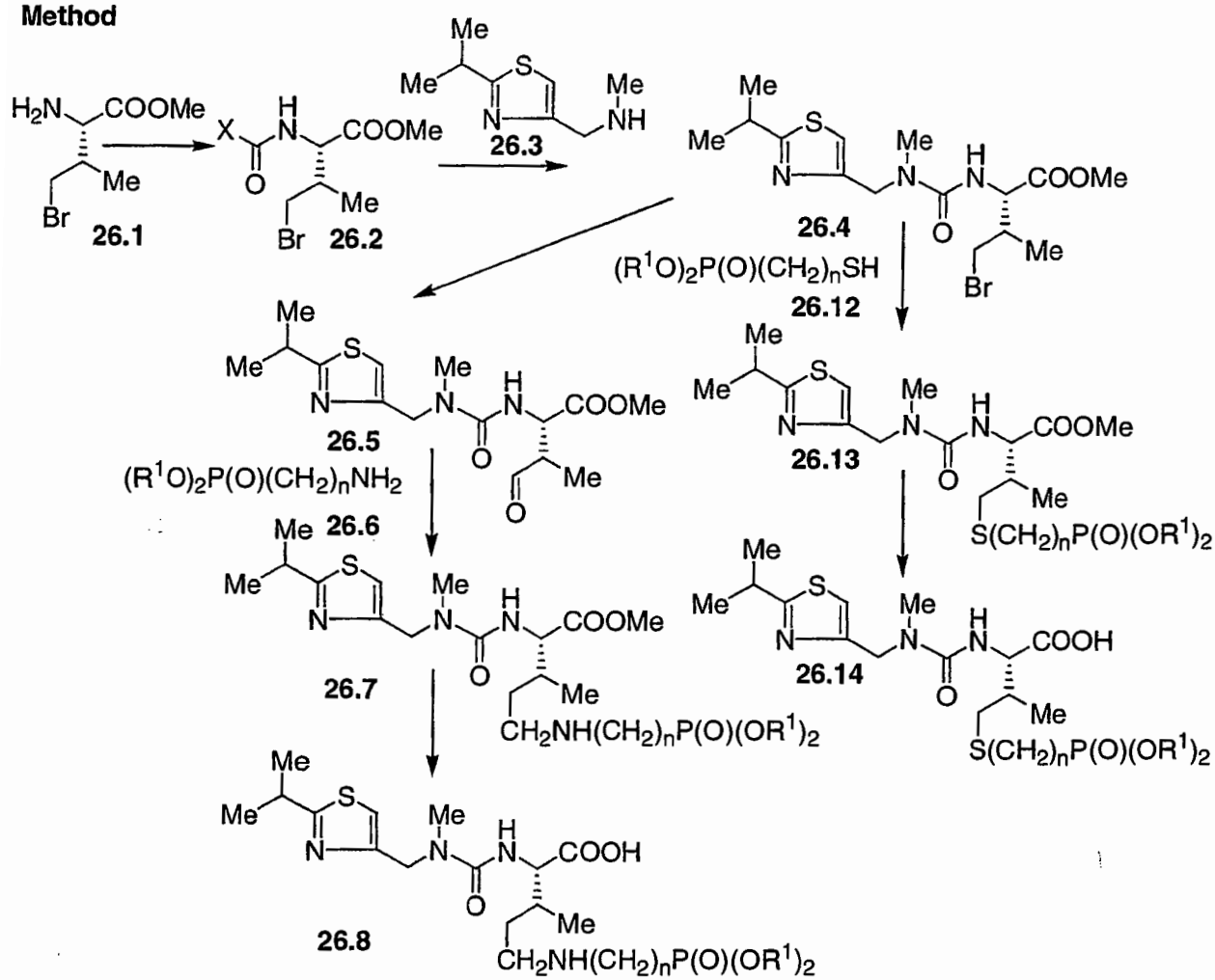


Example

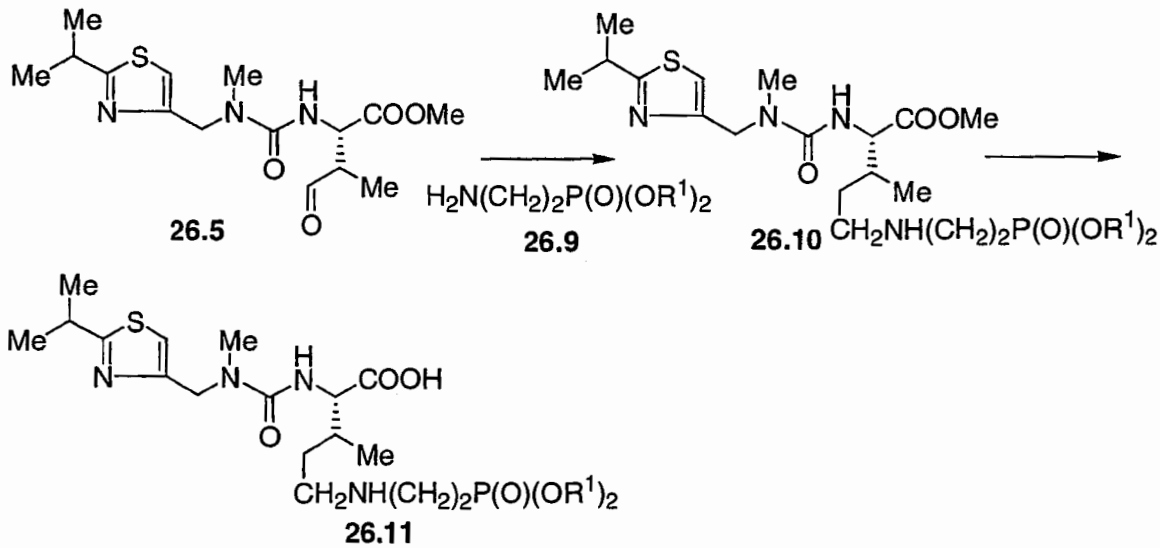


Scheme 26

Method



Example 1



Interconversions of the phosphonates R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH) and R-link-P(O)(OH)$_2$.

Schemes **1-26** described the preparations of phosphonate esters of the general structure R-link-P(O)(OR^1)$_2$, in which the groups R^1, the structures of which are defined in Chart **1**, may be the same or different. The R^{1}groups attached to a phosphonate esters **1-7**, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme **27**. The group R in Scheme **27** represents the substructure to which the substituent link-P(O)(OR^1)$_2$ is attached, either in the compounds **1-7** or in precursors thereto. The R^1 group may be changed, using the procedures described below, either in the precursor compounds, or in the esters **1-7**. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **27.1** into the corresponding phosphonate monoester **27.2** (Scheme **27**, Reaction 1) can be accomplished by a number of methods. For example, the ester **27.1** in which R^{1}is an aralkyl group such as benzyl, can be converted into the monoester compound **27.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester **27.1** in which R^{1}is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **27.2** can be effected by treatment of the ester **27.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.

Phosphonate diesters **27.1** in which one of the groups R^{1}is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **27.2** in which R^{1}is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^{1}are alkenyl, such as allyl, can be converted into the monoester **27.2** in which R^{1}is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by

using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **27.1** or a phosphonate monoester **27.2** into the corresponding phosphonic acid **27.3** (Scheme **27**, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **27.2** in which $R^1$is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **27.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **27.2** in which $R^1$is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **27.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **27.1** in which $R^1$is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **27.1** in which $R^1$is phenyl is described in J. Amer. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester **27.2** into a phosphonate diester **27.1** (Scheme **27**, Reaction 4) in which the newly introduced R^1group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **27.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **27.2** to the diester **27.1** can be effected by the use of the Mitsonobu reaction, as described above (Scheme **16**). The substrate is reacted with the hydroxy compound R^1OH, in the presence of

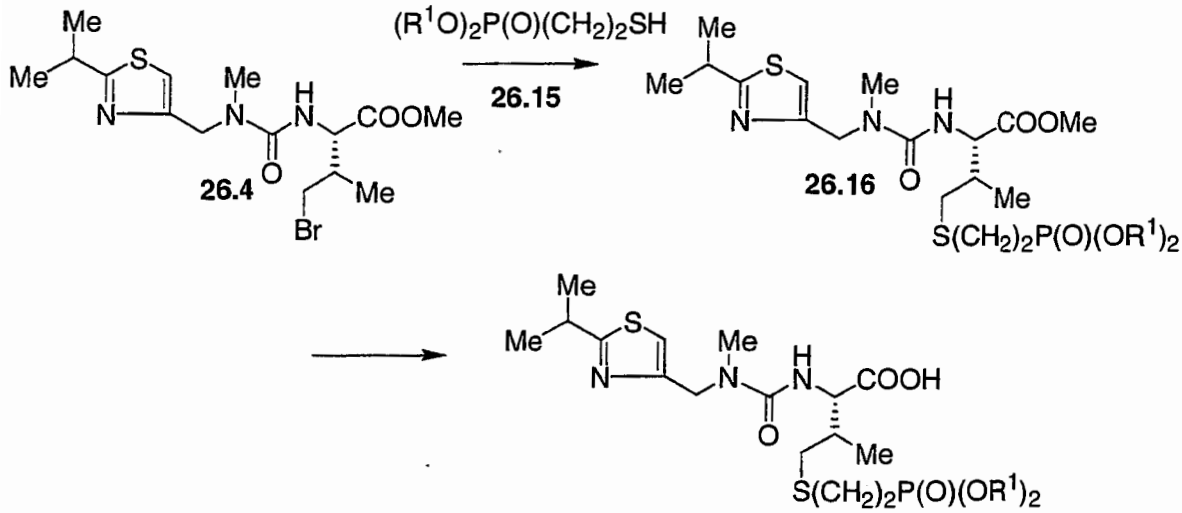
diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **27.2** can be transformed into the phosphonate diester **27.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **27.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **27.1**.

A phosphonic acid R-link-$P(O)(OH)_2$ can be transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **27**, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ **27.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

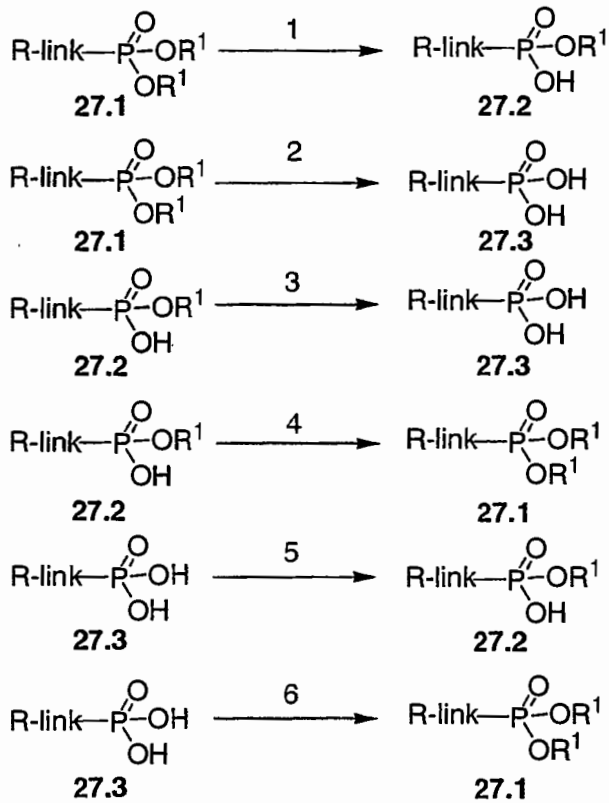
A phosphonic acid R-link-$P(O)(OH)_2$ **27.3** can be transformed into a phosphonate diester R-link-$P(O)(OR^1)_2$ **27.1** (Scheme **27**, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **27.3** can be transformed into phosphonic esters **27.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°C. Alternatively, phosphonic acids **27.3** can be transformed into phosphonic esters **27.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **27.1**.

Scheme 26

Example 2



Scheme 27



General applicability of methods for introduction of phosphonate substituents.

The procedures described above for the conversion of various functional groups into phosphonate moieties are of general application. For example, the methods described above for the introduction of phosphonate groups into the phenylalanine moiety, can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the thiazole compounds **1.5**, **9.1** and **11.1**, and for the preparation of the phosphonate esters **3**. Similarly, the methods described above for the introduction of phosphonate groups into the thiazole compounds **1.5**, **9.1** and **11.1** can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the phenylalanine intermediates **4.1** and for the preparation of the compounds **3**.

Phosphonate esters 1-7 incorporating carbamate moieties.

The phosphonate esters **1-7** in which the R^2CO or R^3CO groups are formally derived from the carboxylic acid synthons **14-16**, **19**, **21**, **22**, **25**, **34**, **51** or **52** as shown in Charts **2a**, **2b**, and **2c**, contain a carbamate moiety. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme **28** illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme **28**, in the general reaction generating carbamates, a carbinol **28.1** is converted into the activated derivative **28.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **28.2** is then reacted with an amine **28.3**, to afford the carbamate product **28.4**. Examples **1 – 7** in Scheme **28** depict methods by which the general reaction can be effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.

Scheme **28**, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **28.5**. In this procedure, the carbinol **28.5** is reacted with phosgene, in an inert solvent such as toluene, at about 0°C, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **28.6**. The latter compound is

then reacted with the amine component **28.3**, in the presence of an organic or inorganic base, to afford the carbamate **28.7**. cFor example, the chloroformyl compound **28.6** is reacted with the amine **28.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **28.7**. cAlternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme **28**, Example **2** depicts the reaction of the chloroformate compound **28.6** with imidazole, **28.7**, to produce the imidazolide **28.8**. The imidazolide product is then reacted with the amine **28.3** to yield the carbamate **28.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°C, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme **28** Example **3**, depicts the reaction of the chloroformate **28.6** with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester **28.10**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **28.19** - **28.24** shown in Scheme **28**, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **28.19**, N-hydroxysuccinimide **28.20**, or pentachlorophenol, **28.21**, the mixed carbonate **28.10** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **28.22** or 2-hydroxypyridine **28.23** can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme **28** Example **4** illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **28.8** is employed. In this procedure, a carbinol **28.5** is reacted with an equimolar amount of carbonyl diimidazole **28.11** to prepare the intermediate **28.8**. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **28.8** is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **28.7**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate **28.7**.

Scheme **28**, Example **5** illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **28.13**. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **28.12**, to afford the alkoxycarbonyl product **28.13**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine $R'NH_2$ to afford the carbamate **28.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80°C as described in Syn., 1977, 704.

Scheme **28**, Example **6** illustrates the preparation of carbamates in which a carbonate $(R''O)_2CO$, **28.14**, is reacted with a carbinol **28.5** to afford the intermediate alkyloxycarbonyl intermediate **28.15**. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate **28.7**. The procedure in which the reagent **28.15** is derived from hydroxybenztriazole **28.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **28.15** is derived from N-hydroxysuccinimide **28.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **28.15** is derived from 2-hydroxypyridine **28.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **28.15** is derived from 4-nitrophenol **28.24** is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate **28.14** is conducted in an inert organic solvent at ambient temperature.

Scheme **28**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides **28.16**. in this procedure, an alkyl chloroformate **28.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **28.16**. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **28.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme **28**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **28.7**.

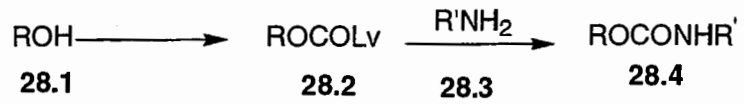
Scheme **28**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **28.18**. In this procedure, which is described in

Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **28.7**.

Scheme **28**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **28.7**.

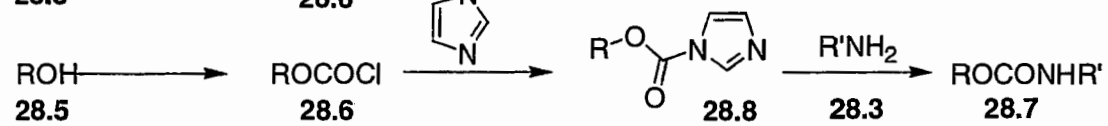
Scheme 28

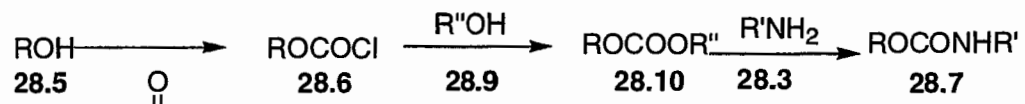
General reaction

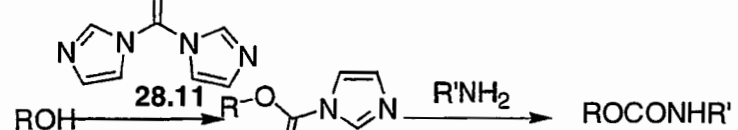


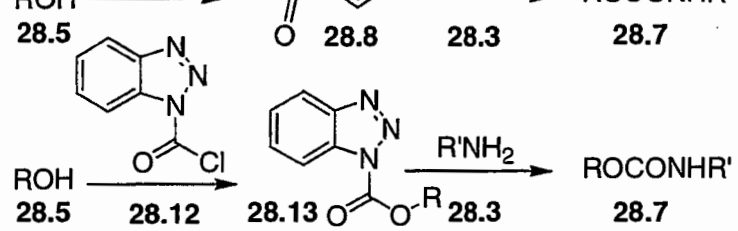
Examples

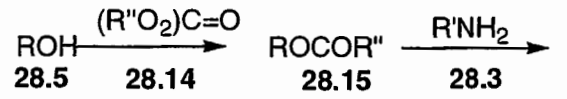
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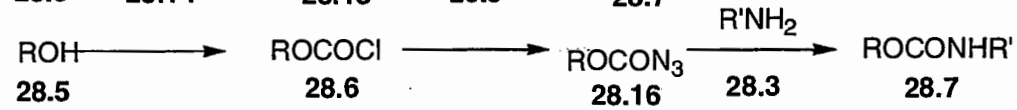

(2)


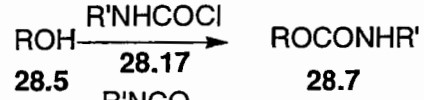
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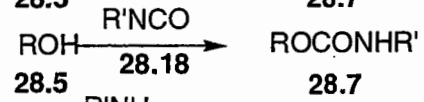
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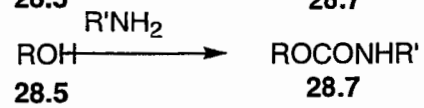
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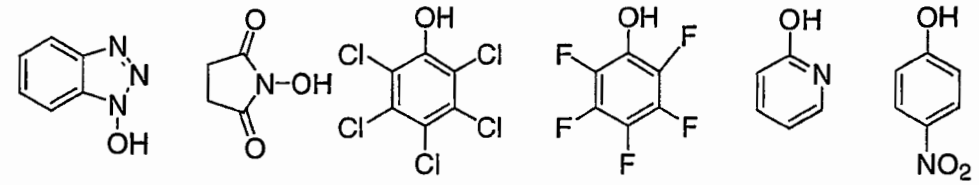
(6)


(7)


(8)


(9)


(10)


R"OH =


Preparation of phosphonate intermediates 6 and 7 with phosphonate moieties incorporated into the group R^2COOH and R^3COOH.

The chemical transformations described in Schemes **1-28** illustrate the preparation of compounds **1-5** in which the phosphonate ester moiety is attached to the thiazole substructure, (Schemes **1-3**, **9-10**, and **11-12**), the phenylalanine moiety (Schemes **4-6**), and the benzyl moiety (Schemes **7-8**).

The various chemical methods employed for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds R^2COOH and R^3COOH, as defined in Charts **2a**, **2b** and **2c**. The resultant phosphonate-containing analogs, designated as $R^{2a}COOH$ and $R^{3a}COOH$ can then, using the procedures described above, be employed in the preparation of the compounds **6** and **7**. The procedures required for the introduction of the phosphonate-containing analogs $R^{2a}COOH$ and $R^{3a}COOH$ are the same as those described above (Schemes **4**, **5**, and **28**) for the introduction of the R^2CO and R^3CO moieties.

Indinavir-like phosphonate protease inhibitors (ILPPI)

Preparation of the intermediate phosphonate esters 1-24.

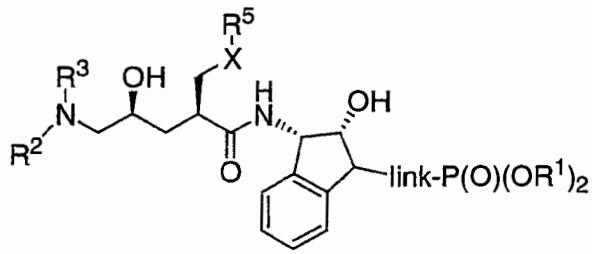
The structures of the intermediate phosphonate esters **1** to **22** and the structures of the component groups R^1, R^4, R^8, R^9, R^{11}, X and X' of this invention are shown in Charts **1 - 3**. The structures of the R^2R^3NH components are shown in Chart **4**; the structures of the amines components $R^7NHCH(R^6)CONHR^4$ are shown as the structures **A1 - A16** in Chart **4**. The structures of the R^5XCH_2 groups are shown in Chart **5**, and those of the $R^{10}CO$ components are illustrated in Chart **6**. The structures of the $R^7NHCH(R^6)COOH$ components are shown in Chart **10**.

Specific stereoisomers of some of the structures are shown in Charts **1 - 10**; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **24**. Subsequent chemical modifications to the compounds **1** to **24**, as described herein, permit the synthesis of the final compounds of this invention.

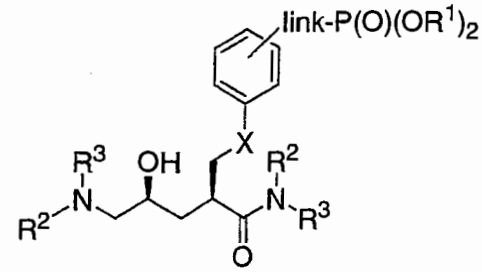
The intermediate compounds **1** to **24** incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **7**, **8** and **9** illustrate examples of the linking groups present in the structures **1** – **24**.

Schemes **1** - **207** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1** - **22**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **23** and **24**, in which a phosphonate moiety is incorporated into one of the groups R^2, R^3, R^5, R^{10} or R^{11} is also described below. In compounds **2**, **6**, **23** and **24** where two groups are the same Chart 4 it is noted that these groups may be independent or identical.

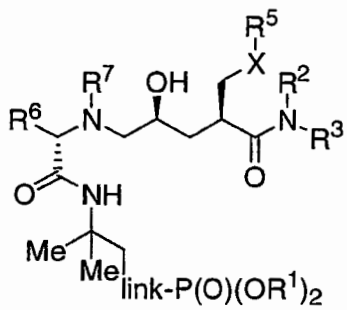
Chart 1



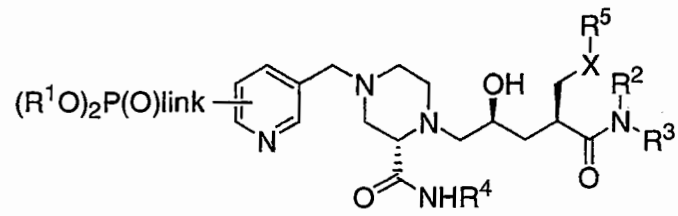
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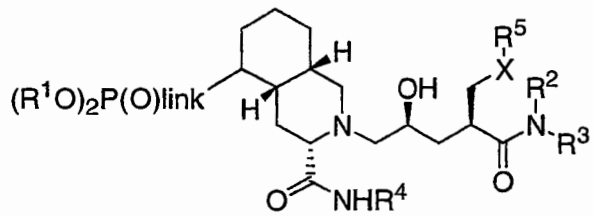
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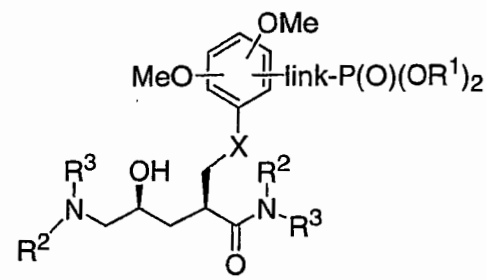
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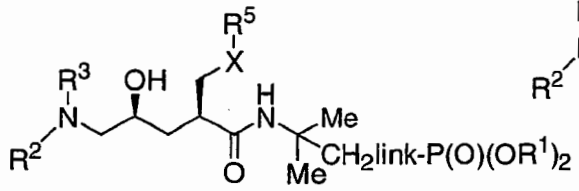
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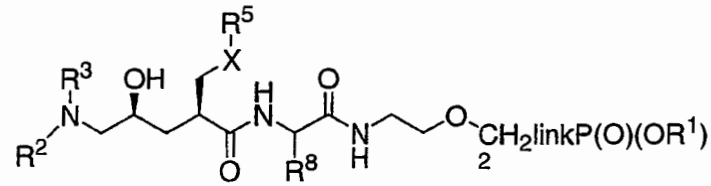
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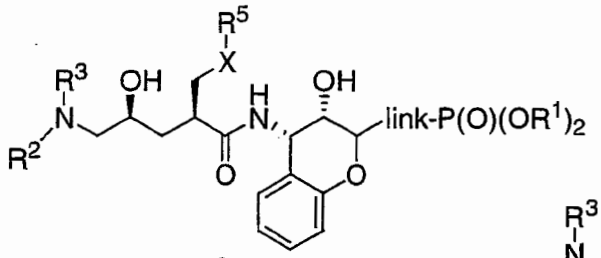


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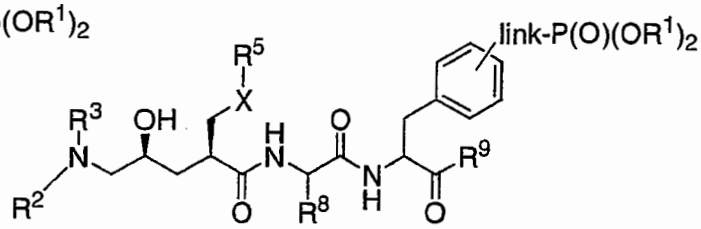
R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R^4 = $CH(CH_3)_3$; CH_2CF_3; $CH_2C_6H_4(CH_3)$-2; $CH_2C_6H_3(CH_3)_2$ 2,6

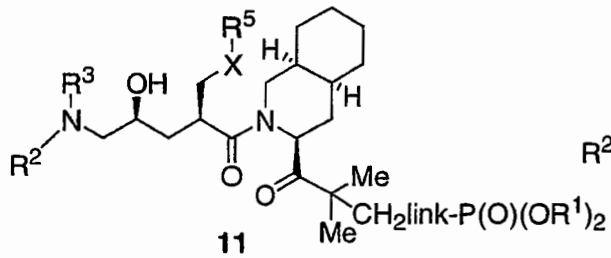
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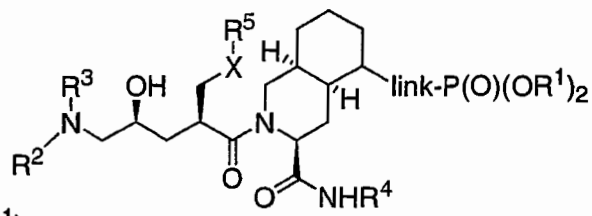
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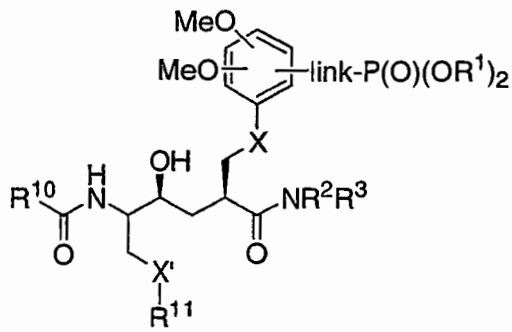
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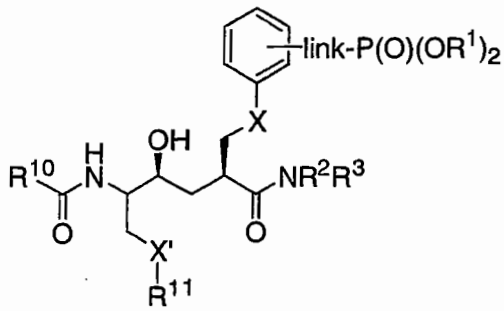
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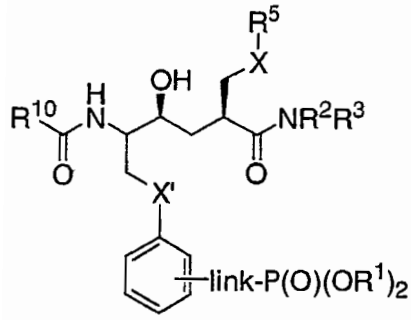
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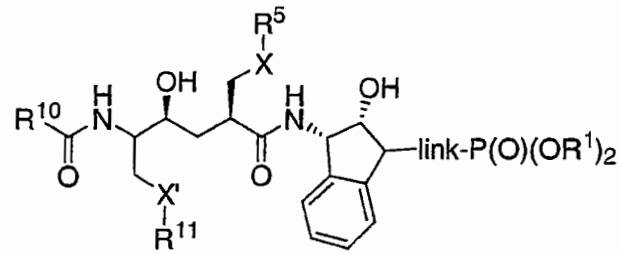
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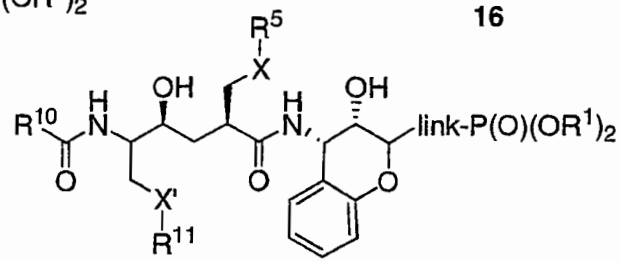
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15



16



17

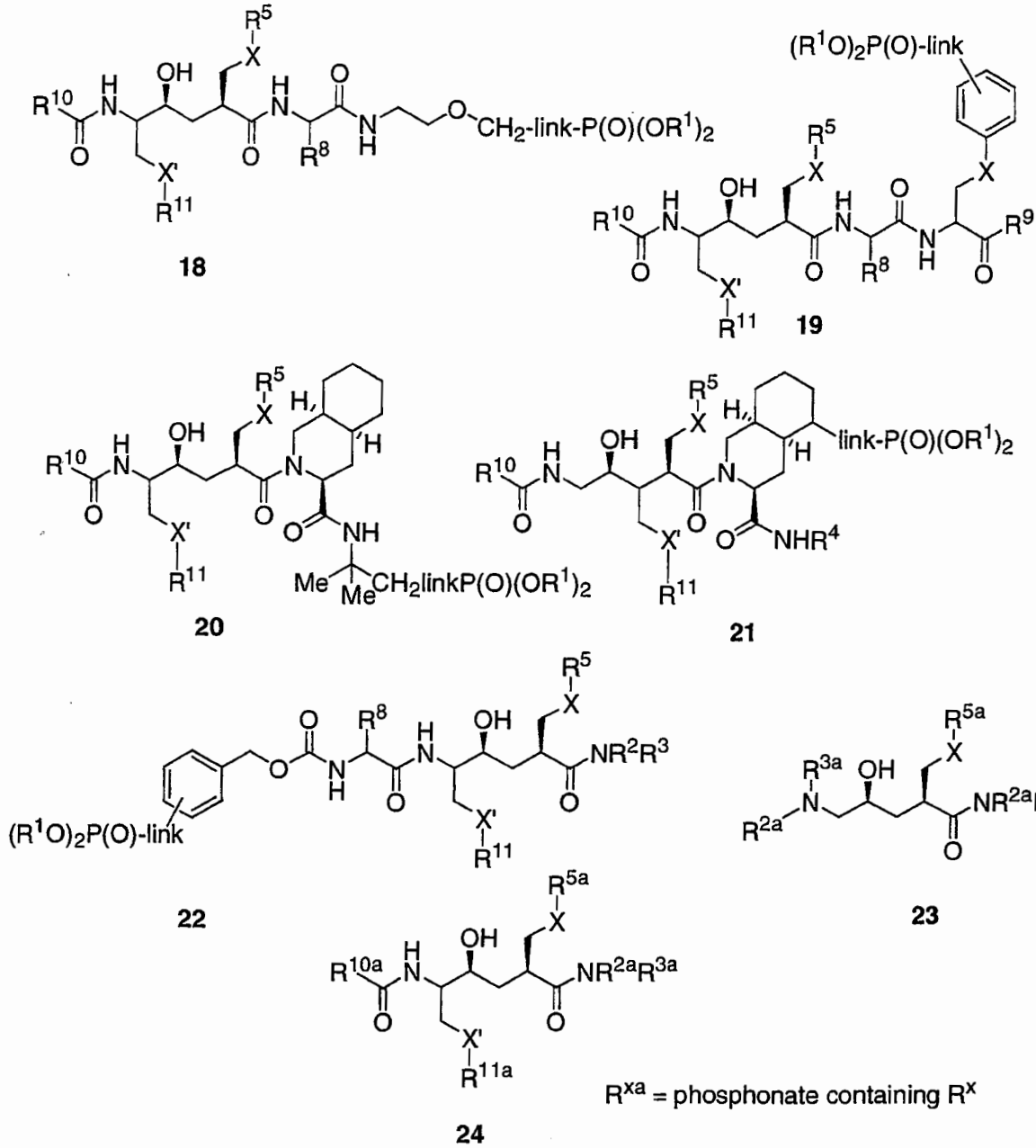
R^{11} = phenyl, alkyl

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R^4 = $CH(CH_3)_3$; CH_2CF_3; $CH_2C_6H_4(CH_3)$-2; $CH_2C_6H_3(CH_3)_2$ 2,6

R^9 = morpholino or methoxy

Chart 3



R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R^4 = $C(CH_3)_3$; CH_2CF_3; $CH_2C_6H_4(CH_3)$-2; $CH_2C_6H_3(CH_3)_2$ 2,6

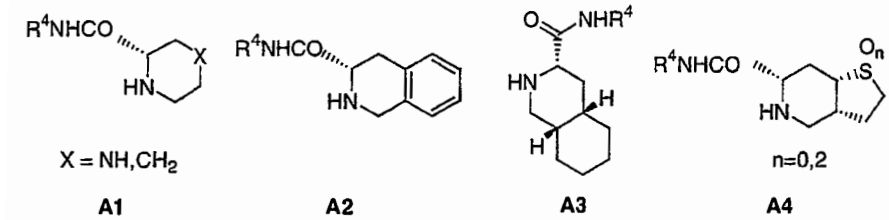
R^8 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

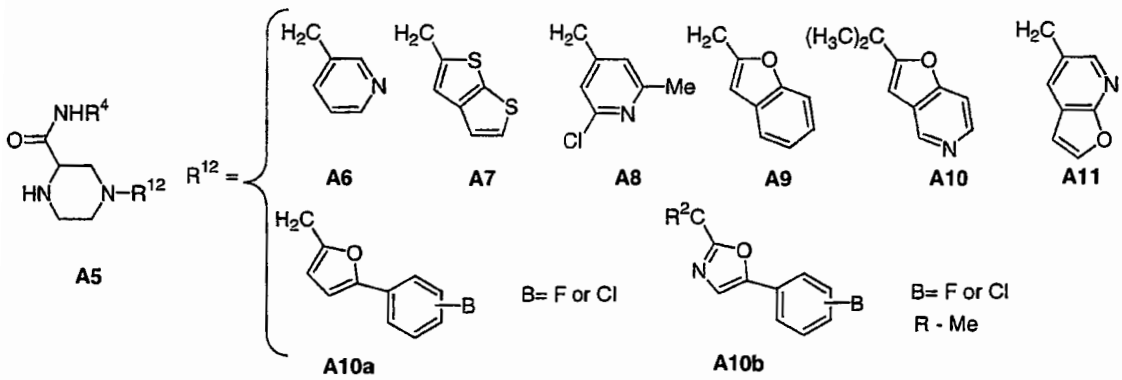
R^9= morpholino; alkoxy.

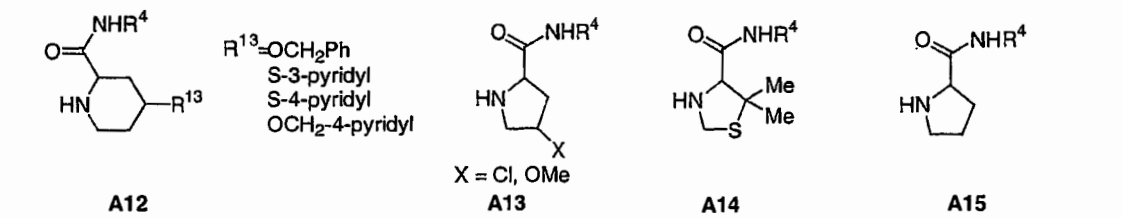
R^{11} = phenyl, alkyl

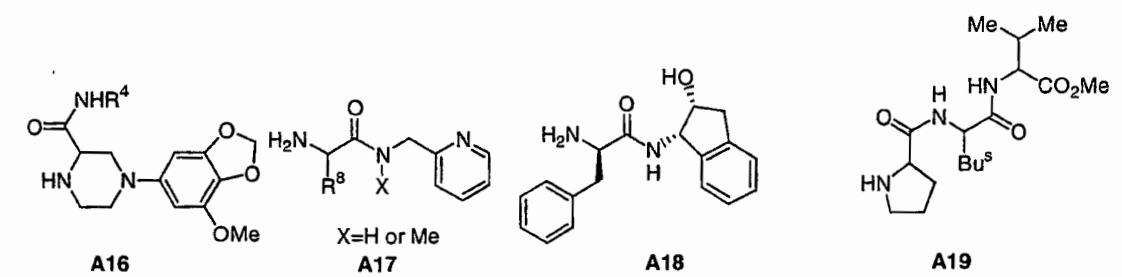
X, X' = S, direct bond

Chart 4 Structures of the R^2R^3NH components









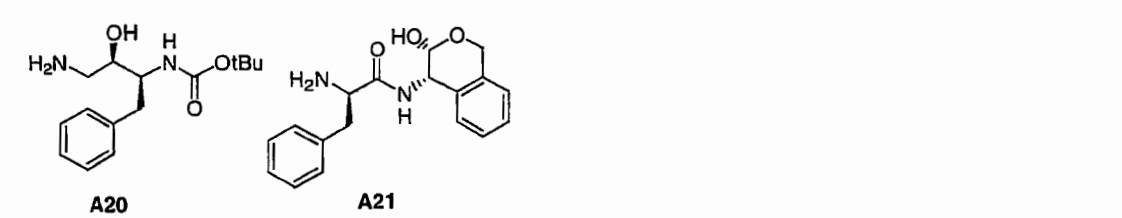
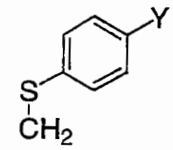
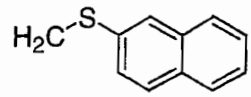


Chart 5. Structures of the R^5XCH_2 groups.

R^5SCH_2 =S-alkyl



24

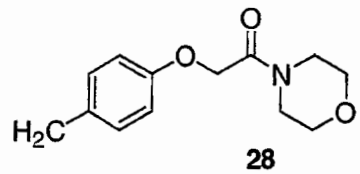


25 **26**

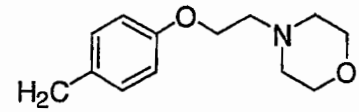
Y = H, F

R^5CH_2 = alkyl

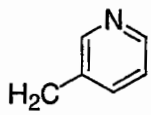
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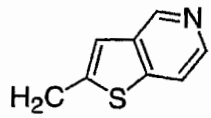
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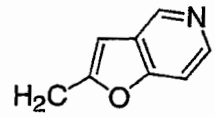
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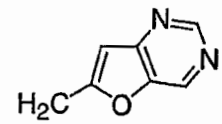
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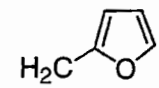
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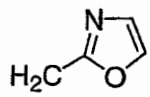
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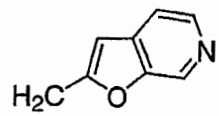
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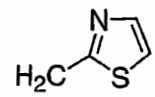
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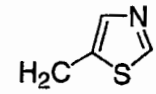
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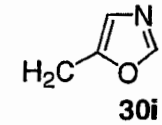
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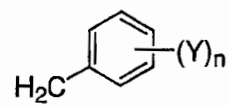
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30h



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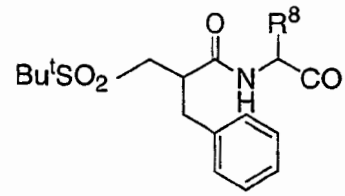


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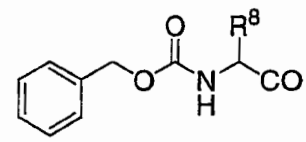
Y = H, OC_2H_5, $OCH_2C_6H_5$, MeO, $(MeO)_2$, $(MeO)_3$, CH_2CH_2OH, OH, Ha, CN, Ph, OCH_2O, OCH_2Ph

Chart 6. Structures of the $R^{10}CO$ components

$R^{10}CO$ =alkyl OCO

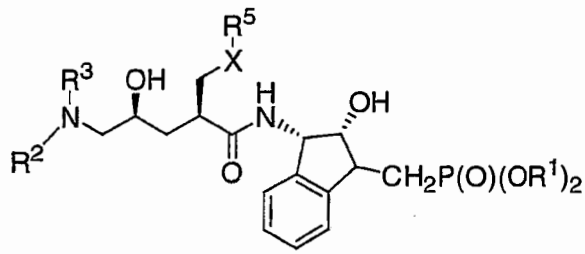


32 **33**

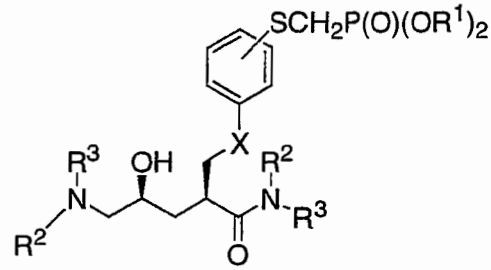


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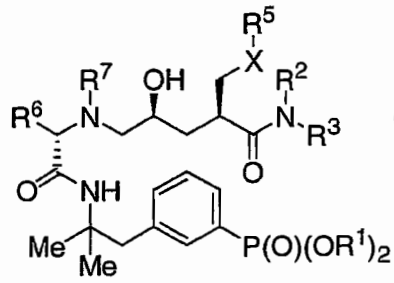
Chart 7. Examples of linking groups



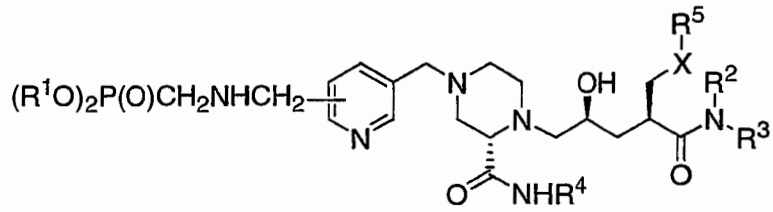
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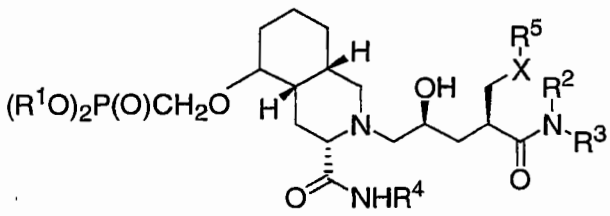
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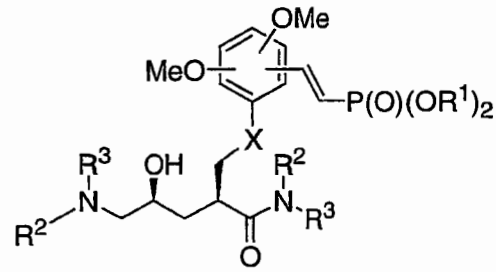
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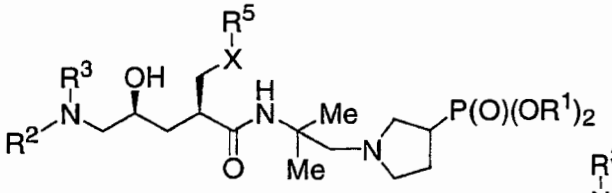
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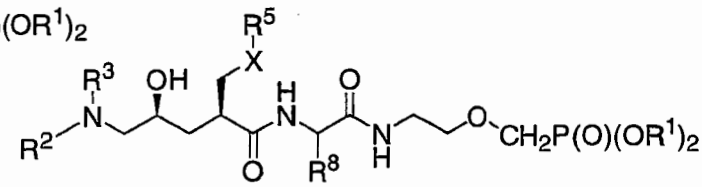
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L6

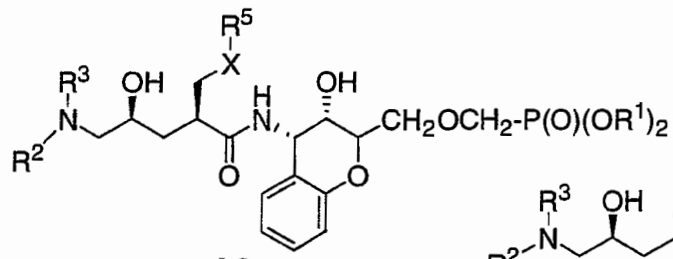


L7

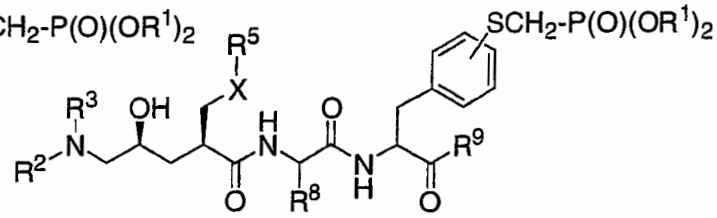


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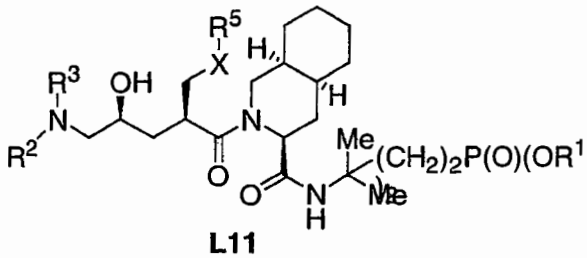
Chart 8. Examples of linking groups



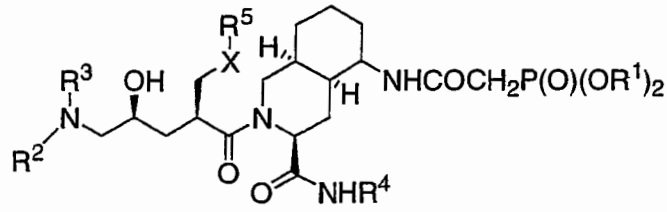
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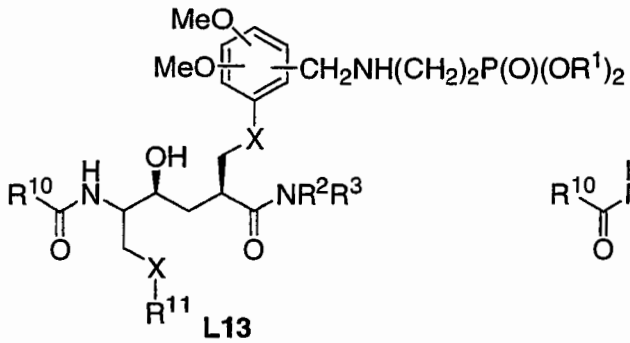
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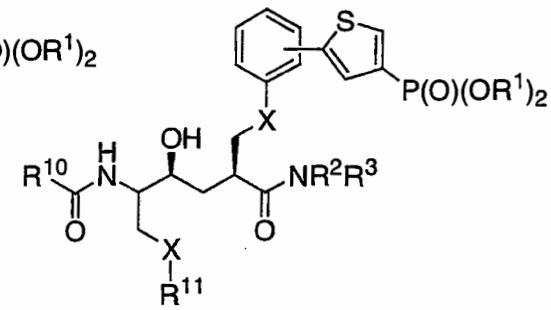
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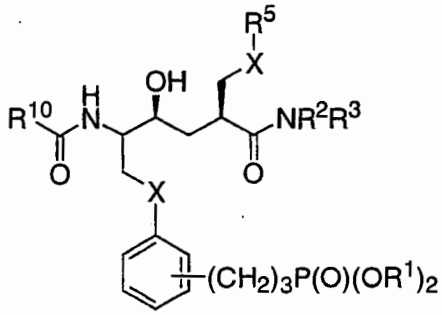
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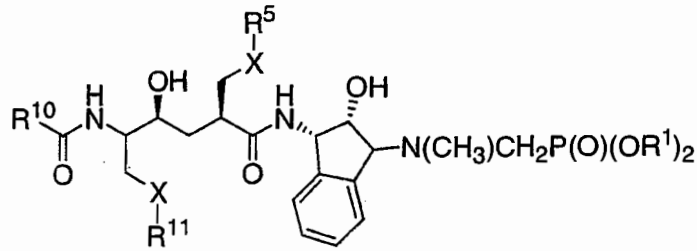
L13



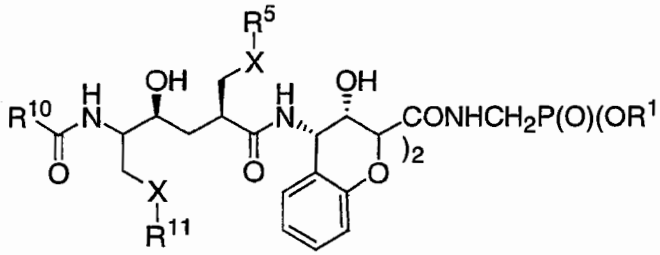
L14



L15

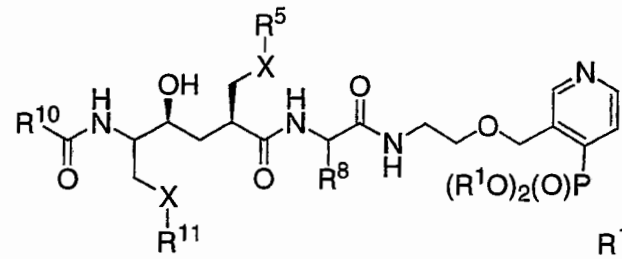


L16

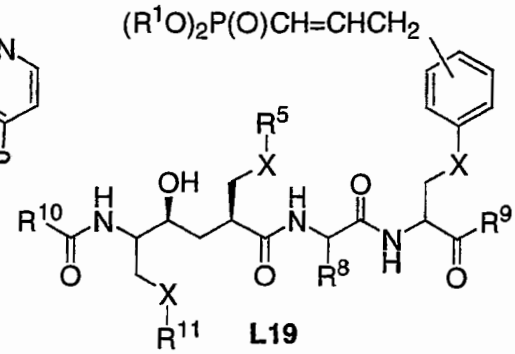


L17

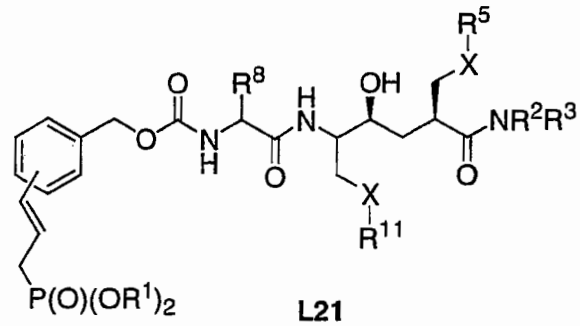
Chart 9. Examples of linking groups



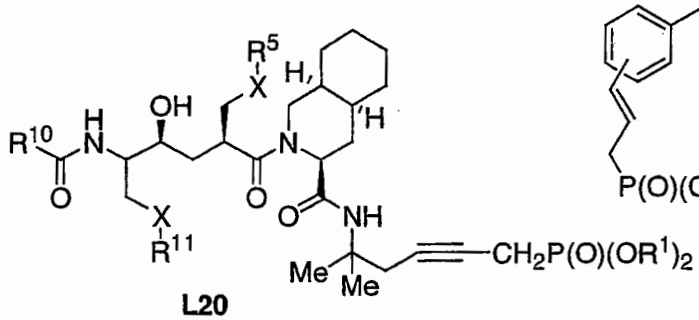
L18



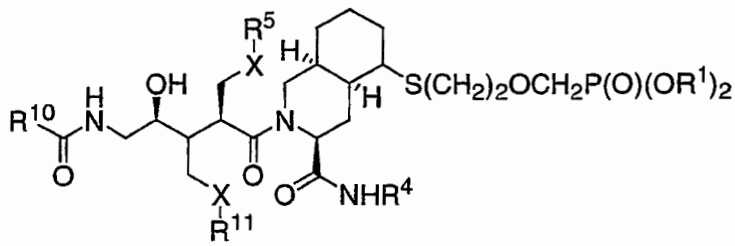
L19



L21

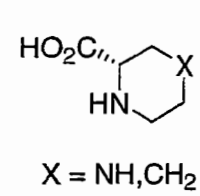


L20

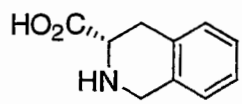


L22

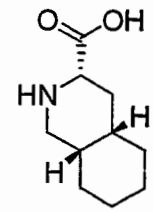
Chart 10. Structures of the $R^7NHCH(R^6)COOH$ components



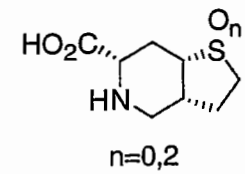
C1



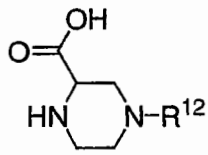
C2



C3

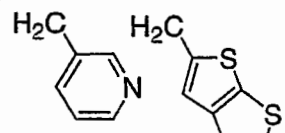


C4



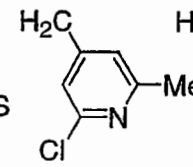
C5

R^{12} =

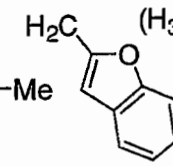


C6

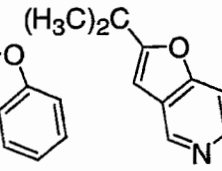
C7



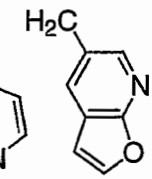
C8



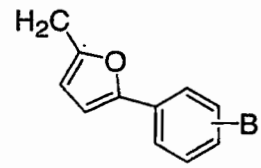
C9



C10

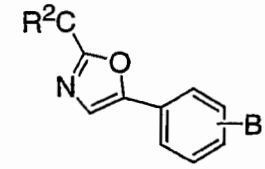


C11



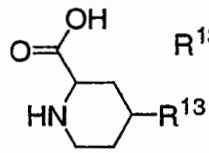
C10a

B= F or Cl



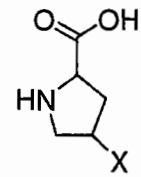
C10b

B= F or Cl
R - Me



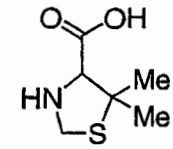
R^{13}= OCH_2Ph
S-3-pyridyl
S-4-pyridyl
OCH_2-4-pyridyl

C12

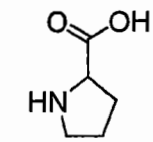


X = Cl, OMe

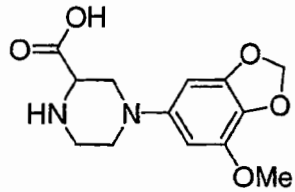
C13



C14



C!5



C16

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

The intermediate phosphonate esters **1**, in which the group A is attached to the aminoindanol moiety, are prepared as shown in Schemes **1** and **2**.

In this procedure, the propionic acid **1.1**, or an activated derivative thereof, is reacted with an aminoindanol derivative **1.2**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br, to afford the amide **1.3**. The preparation of the aminoindanol derivatives **1.2** is described in Schemes **133** - **137**.

The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride or anhydride, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid **1.1** is reacted with an equimolar amount of the amine **1.2** in the presence of dicyclohexylcarbodiimide and hydroxybenztriazole, in an aprotic solvent such as, for example, tetrahydrofuran, at about ambient temperature, so as to afford the amide product **1.3**. The amide is then reacted with 2-(S)glycidyl tosylate **1.4**, or an equivalent thereof, such as, for example, 2-(S) glycidyl p-nitrobenzenesulfonate, as described in Tet Lett., 35, 673, 1994. To effect the reaction, the amide **1.3** is first converted into the α-anion, by treatment with a strong base, such as, for example, sodium hydride, potassium tert. butoxide and the like. The anion is then reacted with the epoxide **1.4**, or an equivalent, as described above, in an inert solvent such as, for example, dimethylformamide, dioxan and the like. The reaction is conducted at a temperature of from 0°C to -100°C to yield the alkylated product **1.5**. Preferably, equimolar amounts of the amide **1.3** and the epoxide **1.4** are dissolved in tetrahydrofuran at about -50°C, and a slight excess of lithium hexamethyldisilylazide is added, as described in WO 9612492 and Tet. Lett., 35, 673, 1994. The temperature is raised to about -25°C to effect stereoselective alkylation and conversion to the epoxide **1.5**.

The thus-obtained epoxide **1.5** is then subjected to a regiospecific ring-opening reaction with the amine **1.6** to yield the hydroxyamine **1.7**. The preparation of hydroxyamines by the reaction between an amine and an epoxide is described, for example, in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1968, p. 357. The amine and the epoxide are reacted together in a polar organic solvent such as, for example, dimethylformamide or an alcohol, to effect the ring-opening reaction.

Preferably, equimolar amounts of the amine **1.6** and the epoxide **1.5** are heated in isopropanol at reflux for about 24 hours, to prepare the hydroxyamine product **1.7**, for example as described in WO 9628439 and Tet. Lett., 35, 673, 1994.

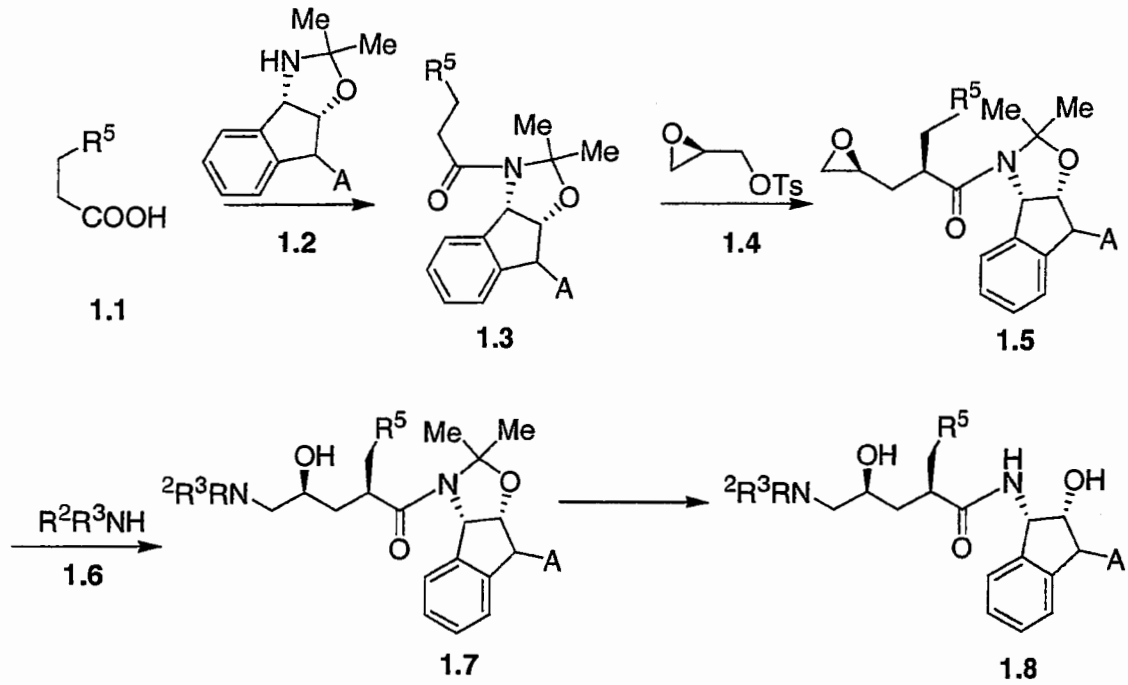
The hydroxyamine product **1.7** is then deprotected to remove the acetonide group and produce the compound **1.8** in which A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Acetonide protecting groups are removed by treatment with an acid, for example acetic acid or dilute hydrochloric acid, optionally in the presence of water and a water-miscible organic solvent such as, for example, tetrahydrofuran or an alcohol. Preferably, the acetonide protecting group is removed by treatment of the acetonide **1.7** with 6N hydrochloric acid in isopropanol at ambient temperature, as described in WO 9612492, to afford the indanol **1.8**.

The reactions shown in Scheme **1** illustrate the preparation of the compounds **1.8** in which A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **2** depicts the conversion of the compounds **1.8** in which A is [OH], [SH], [NH], Br, into the compounds **1** in which A is the group link-P(O)$(OR^1)_2$. In this procedure, the compounds **1.7** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **2.1**. Deprotection, by removal of the acetonide protecting group, as described above, then affords the intermediate phosphonate esters **1** in which X is a direct bond.

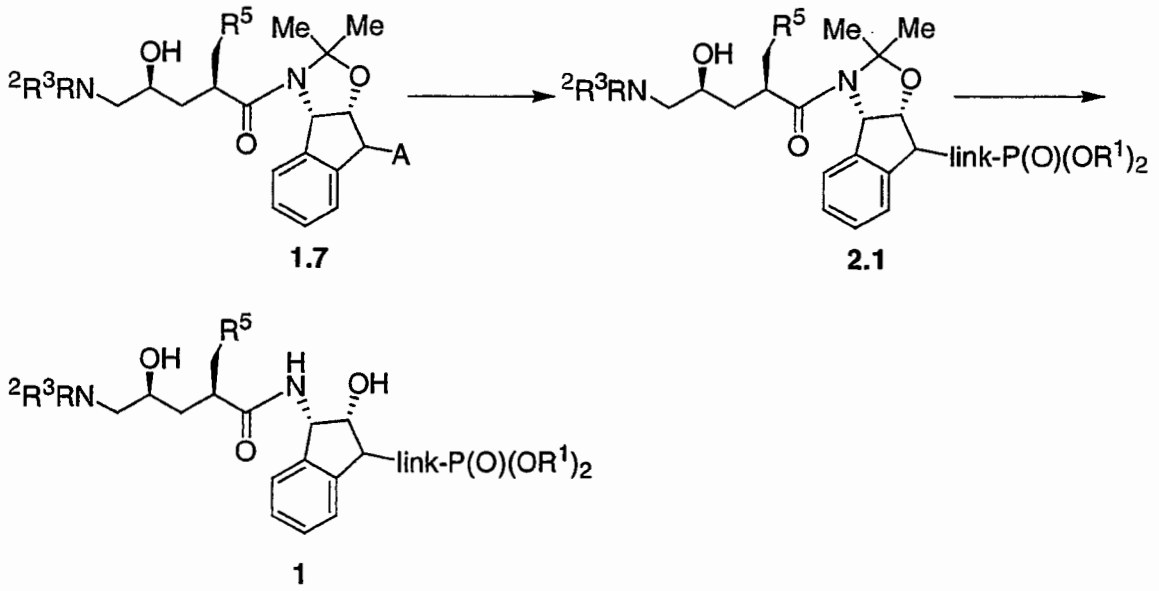
In the preceding and following schemes, the conversion of various substituents into the group link-P(O)$(OR^1)_2$ can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, during the introduction of the group link-P(O)$(OR^1)_2$.

In the preceding and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme **199**).

Scheme 1



Scheme 2



Preparation of the phosphonate ester intermediates 1 in which X is sulfur.

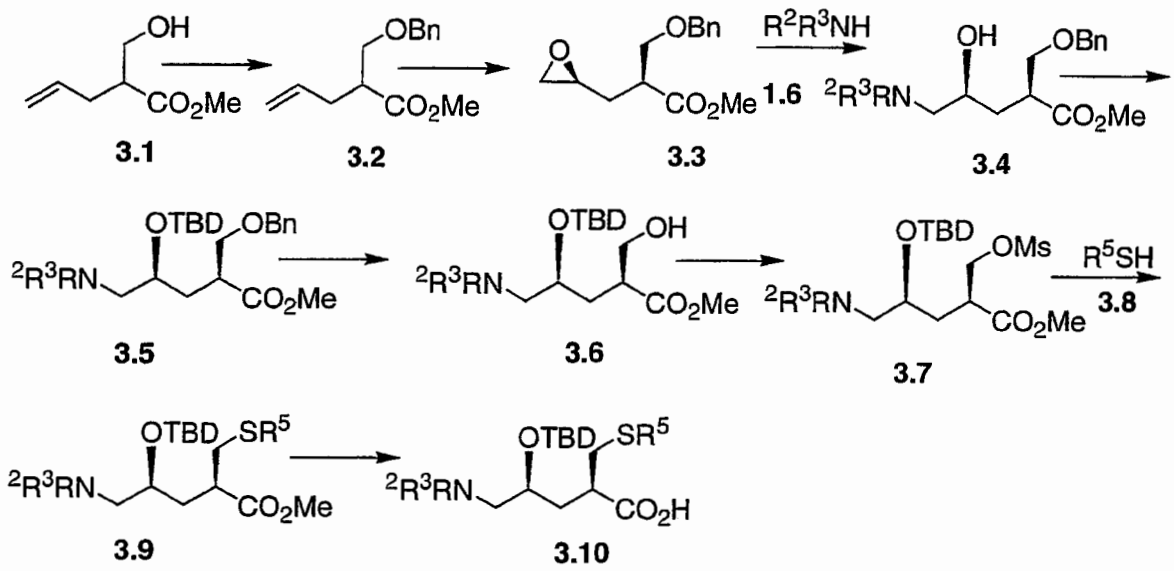
Schemes **3** and **4** illustrate the preparation of the phosphonate esters **1** in which X is sulfur. As shown in Scheme **3**, methyl 2-allyl-3-hydroxypropionate **3.1**, prepared as described in Tet. Lett., 1973, 2429, is converted into the benzyl ether **3.2**. The conversion of alcohols into

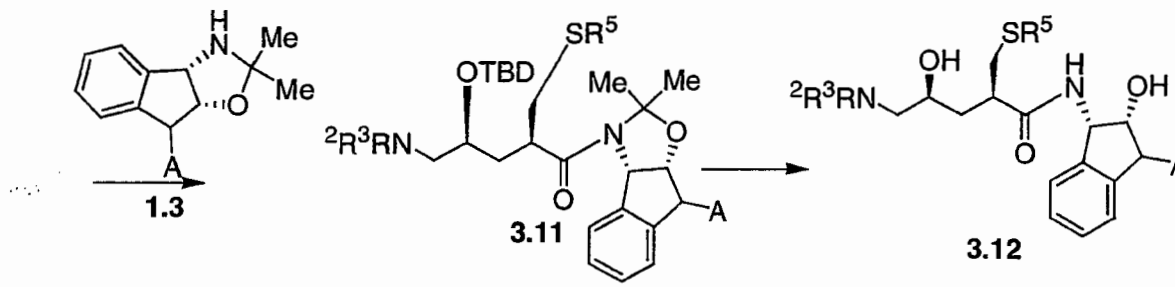
benzyl ethers is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 47. The reaction is effected by treatment of the carbinol with a benzyl halide, in the presence of a base such as potassium hydroxide, silver oxide, sodium hydride and the like, in an organic or aqueous organic solvent, optionally in the presence of a phase transfer catalyst. Preferably, the carbinol **3.1** is reacted with benzyl bromide and silver oxide in dimethylformamide at ambient temperature for 48 hours, to afford the product **3.2**. The benzyl ether is then subjected to an epoxidation reaction to produce the epoxide **3.3**. The conversion of olefins into epoxides is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 456. The reaction is performed by the use of a peracid such as peracetic acid, m-chloroperbenzoic acid or monoperphthalic acid, optionally in the presence of a base such as potassium carbonate or sodium bicarbonate, or by the use of tert. butyl hydroperoxide, optionally in the presence of a chiral auxiliary such as diethyl tartrate. Preferably, equimolar amounts of the olefin and m-chloroperbenzoic acid are reacted in dichloromethane in the presence of sodium bicarbonate, as described in Tet. Lett., 849, 1965, to afford the epoxide **3.3**. This compound is then reacted with the amine **1.6** to yield the hydroxyamine **3.4**. The reaction is performed as described above for the preparation of the hydroxyamine **1.7**. The hydroxyl substituent is then protected by conversion to the silyl ether **3.5**, in which OTBD is tert. butyldimethylsilyloxy. The preparation of silyl ethers is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 77. The reaction is effected by treatment of the carbinol with tert. butylchlorodimethylsilane and a base such as imidazole, dimethylaminopyridine or 2,6-lutidine, in an organic solvent such as dichloromethane or dimethylformamide. Preferably, equimolar amounts of the carbinol, tert. butylchlorodimethylsilane and imidazole are reacted in dimethylformamide at ambient temperature to give the silyl ether **3.5**. The benzyl ether is then removed to afford the carbinol **3.6**. The removal of benzyl protecting groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 49. The conversion is effected by means of catalytic hydrogenation over a palladium catalyst, with hydrogen or a hydrogen transfer agent, or by electrolytic reduction, by treatment with trimethylsilyl iodide, or by the use of a Lewis acid such as boron trifluoride or stannic chloride, or by oxidation with ferric chloride or ruthenium dioxide. Preferably, the benzyl ether is removed by reaction of the substrate with 5% palladium on carbon catalyst and ammonium formate in refluxing methanol, as described in Synthesis, 76, 1985. The resultant

carbinol **3.6** is then converted into the mesylate ester **3.7** by reaction with one molar equivalent of methanesulfonyl chloride or anhydride, in an organic solvent such as dichloromethane, and in the presence of a base such as dimethylaminopyridine or diisopropylethylamine. The product **3.7** is then reacted with the thiol R^5SH, to prepare the thioether **3.9**. The preparation of thioethers by alkylation of thiols is described in Synthetic Organic Chemistry, by R. B. Wagner, H. D. Zook, Wiley, 1953, p. 787. The reaction is effected by treatment of the thiol with a base such as sodium hydroxide, potassium carbonate or diazabicyclononene, in a solvent such as ethanol or dioxan, in the presence of the mesylate **3.7**, to afford the product **3.9**. The methyl ester moiety present in the latter compound is then hydrolyzed to give the carboxylic acid **3.10**. The transformation is effected hydrolytically, for example by the use of an alkali metal hydroxide in an aqueous organic solvent, or enzymically, for example by the use of porcine liver esterase, as described in J. Am. Chem. Soc., 104, 7294, 1982. Preferably, the ester group is hydrolyzed by treatment of the ester **3.9** with one molar equivalent of lithium hydroxide in aqueous methanol at ambient temperature, to give the carboxylic acid **3.10**. The latter compound is then reacted, as described above, with the aminoindanol acetonide **1.3** to give the amide **3.11**. Removal of the acetonide group, as described above, with concomitant desilylation, then affords the hydroxyamide **3.12**.

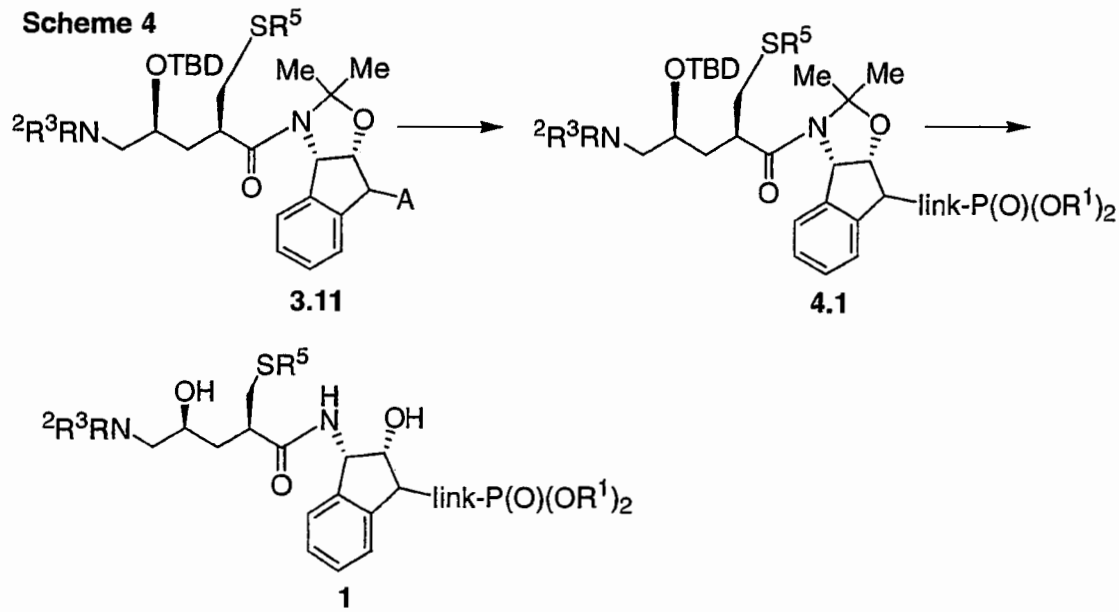
The reactions shown in Scheme **3** illustrate the preparation of the compounds **3.12** in which A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **4** depicts the conversion of the compounds **3.11** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **1** in which X is sulfur. In this procedure, the compounds **3.11** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **4.1**. Deprotection, by removal of the acetonide protecting group, as described above, then affords the intermediate phosphonate esters **1** in which X is sulfur.

Scheme 3





Scheme 4

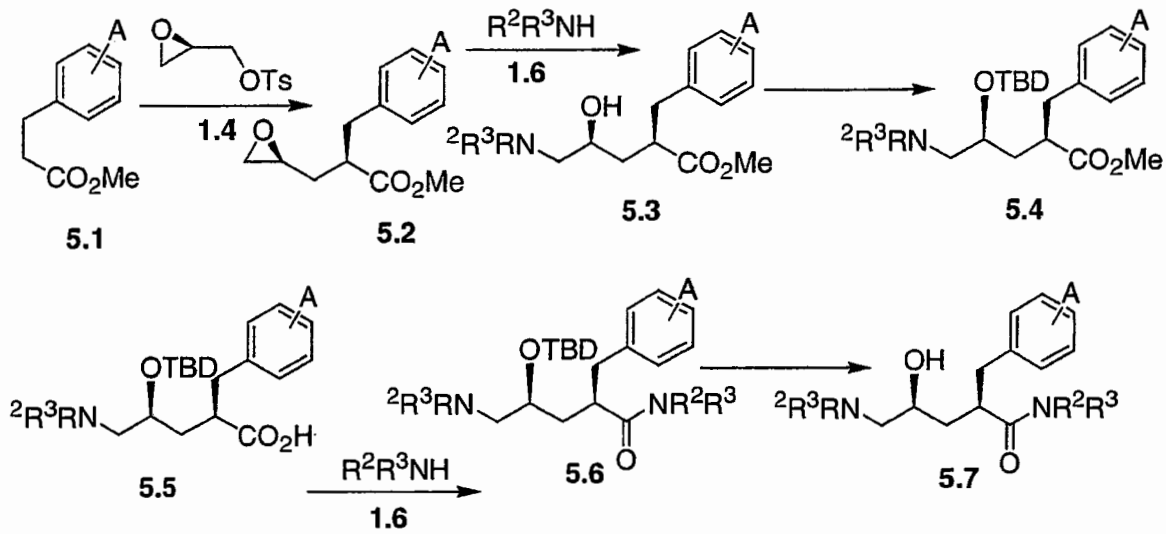


Preparation of the phosphonate ester intermediates 2 in which X is a direct bond.

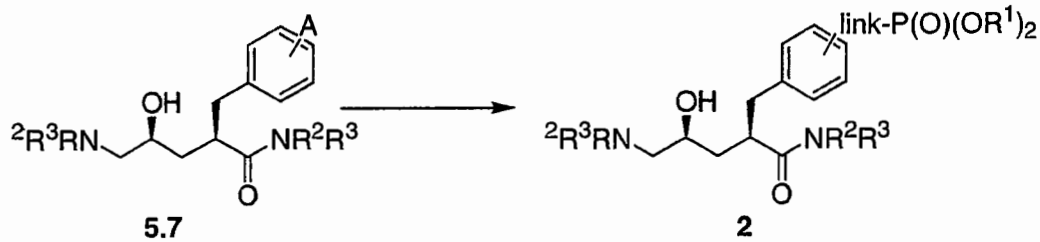
Schemes **5** and **6** illustrate the preparation of the phosphonate esters **2** in which X is a direct bond. As shown in Scheme **5**, the substituted phenyl propionic ester **5.1**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br, is reacted with the glycidyl tosylate **1.4** to afford the alkylated product **5.2**. The preparation of the phenylpropionic esters **5.1** is described below, (Schemes **138** - **143**). The reaction is performed as described above for the preparation of the oxirane **1.5**. The product **5.2** is then reacted with the amine R^2R^3NH (**1.6**) to yield the hydroxyamine **5.3**. The reaction is performed as described above for the preparation of the hydroxyamine **1.7**. The secondary hydroxy group is then protected, for example by conversion to the tert. butyldimethyl silyl ether **5.4**, using the conditions described above for the preparation of the silyl ether **3.5**. The methyl ester is then hydrolyzed to produce the carboxylic acid **5.5**, using the conditions described above for the hydrolysis of the methyl ester **3.9**. The carboxylic acid is then coupled with the amine **1.6** to give the amide **5.6**. The reaction is effected under the conditions described above for the preparation of the amide **1.3**. The product is desilylated, for example by treatment with 1M tetrabutyl ammonium fluoride in tetrahydrofuran, as described in J. Am. Chem. Soc., 94, 6190, 1972, to give the carbinol **5.7**.

The reactions shown in Scheme **5** illustrate the preparation of the compounds **5.7** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br, as described herein. Scheme **6** depicts the conversion of the compounds **5.7** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **2** in which X is a direct bond. In this procedure, the compounds **5.7** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **2**.

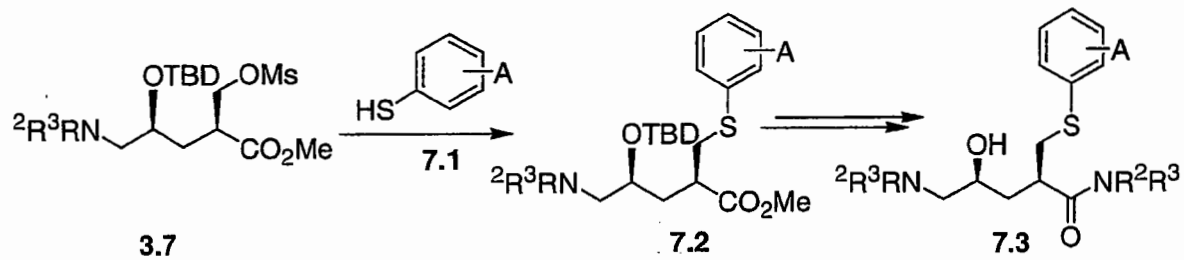
Scheme 5



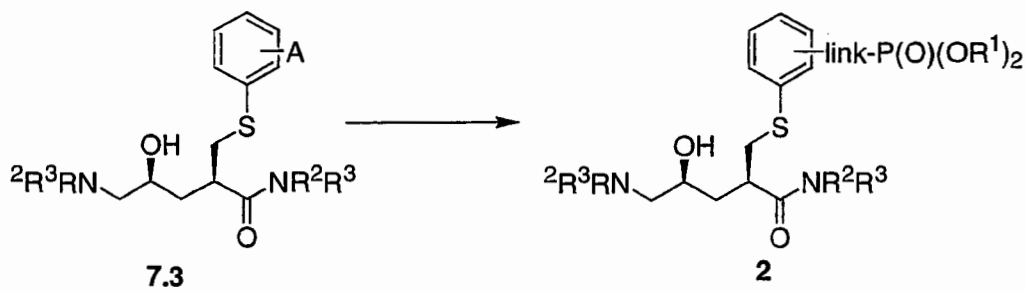
Scheme 6



Scheme 7



Scheme 8



Preparation of the phosphonate ester intermediates 2 in which X is sulfur.

Schemes **7** and **8** illustrate the preparation of the phosphonate esters **2** in which X is sulfur. As shown in Scheme **7**, the mesylate **3.7** is reacted with the thiophenol **7.1**, in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br, to afford the thioether **7.2**. The reaction is performed under the same conditions as described above for the preparation of the thioether **3.9**. The preparation of the thiophenols **7.2** is described in Schemes **144** - **153**. The product **7.2** is then transformed, using the sequence of reactions described above for the conversion of the ester **5.4** into the aminoamide **5.7**, into the aminoamide **7.3**.

The reactions shown in Scheme **7** illustrate the preparation of the compounds **7.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **8** depicts the conversion of the compounds **7.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **2** in which X is sulfur. In this procedure, the compounds **7.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **2**.

Preparation of the phosphonate ester intermediates 3 in which X is a direct bond.

Schemes **9** and **10** illustrate the preparation of the phosphonate esters **3** in which X is a direct bond. As shown in Scheme **9**, the methyl ester **9.1** is reacted, as described above, (Scheme **1**) with the epoxide **1.4** to afford the alkylated ester **9.2**. The product is then reacted with the amine **9.3**, in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor, to yield the hydroxyamine **9.4**. The preparation of the tert. butylamine derivatives **9.3** is described below, (Schemes **154** - **158**). The hydroxyamine is then transformed, using the sequence of reactions described above for the conversion of the aminoester **5.3** into the aminoamide **5.7**, into the aminoamide **9.5**.

The reactions shown in Scheme **9** illustrate the preparation of the compounds **9.5** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **10** depicts the conversion of the compounds **9.5** in which A is [OH], [SH], [NH],

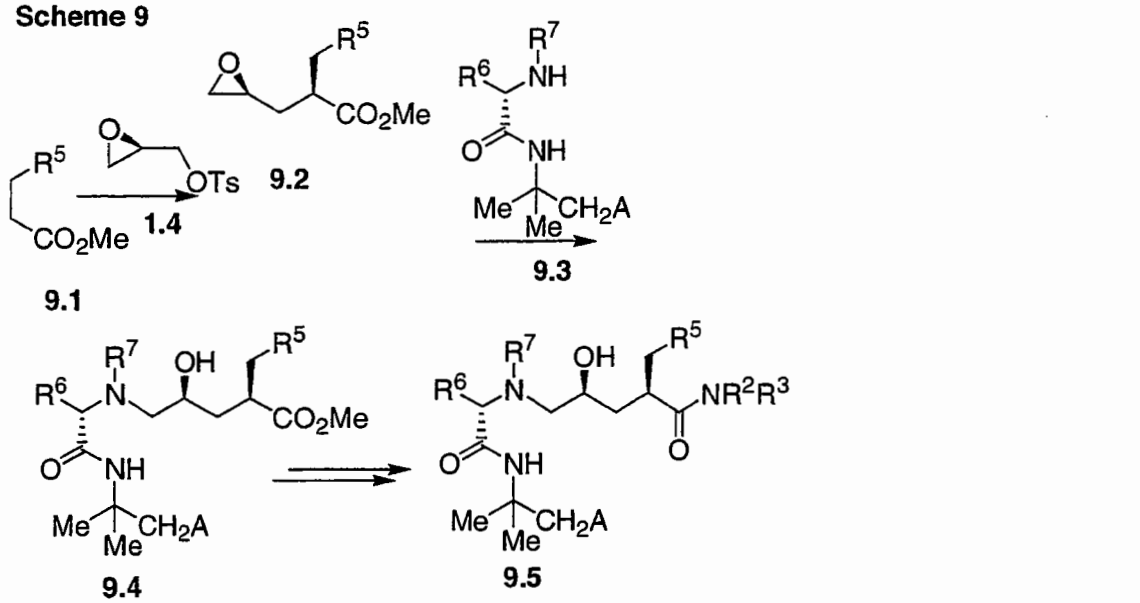
Br, into the phosphonate esters **3** in which X is a direct bond. In this procedure, the compounds **9.5** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **3**.

Preparation of the phosphonate ester intermediates 3 in which X is sulfur.

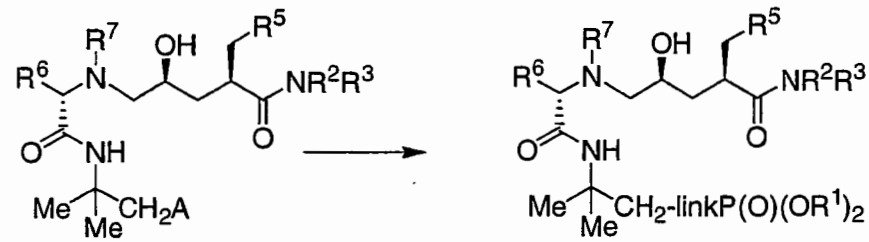
Schemes **11** and **12** illustrate the preparation of the phosphonate esters **3** in which X is sulfur. As shown in Scheme **11**, the benzyl-protected oxirane **3.3** is reacted, as described above, with the substituted tert. butylamine **9.3** to afford the hydroxyamine **11.1**. The product is then converted, using the sequence of reactions shown in Scheme **5** for the conversion of the hydroxyamine **5.3** into the aminoamide **5.7**, into the aminoamide **11.2**.

The reactions shown in Scheme **11** illustrate the preparation of the compounds **11.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **12** depicts the conversion of the compounds **11.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **3** in which X is sulfur. In this procedure, the compounds **11.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **3**.

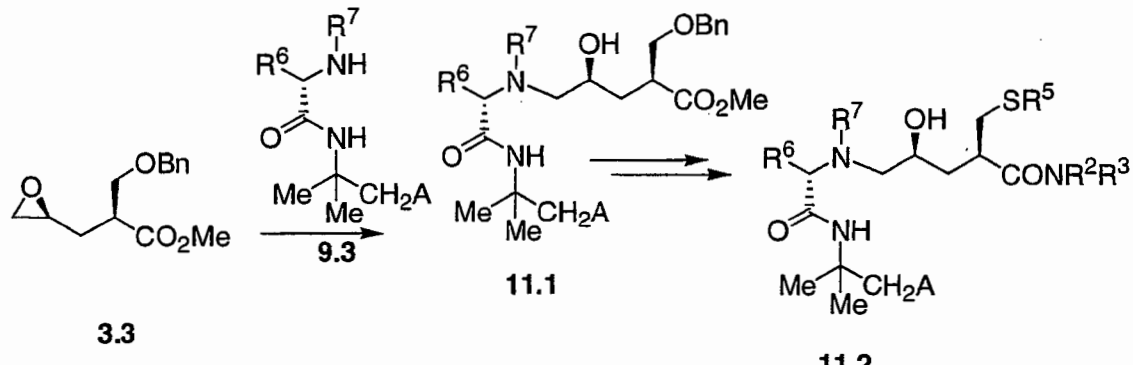
Scheme 9



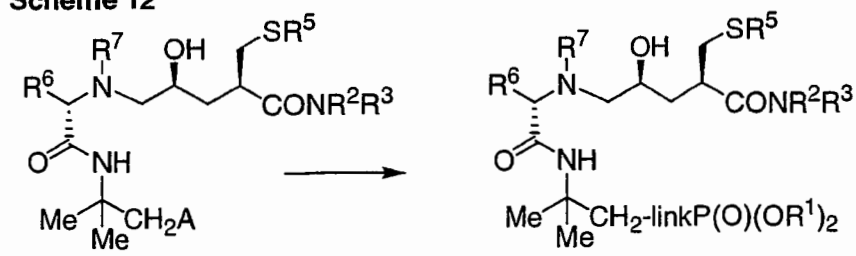
Scheme 10



Scheme 11



Scheme 12



Preparation of the phosphonate ester intermediates 4 in which X is a direct bond.

Schemes **13** and **14** illustrate the preparation of the phosphonate esters **4** in which X is a direct bond. As shown in Scheme **13**, the oxirane **9.2** is reacted, as described in Scheme **1**, with the pyridyl piperazine derivative **13.1** to produce the hydroxyamine **13.2**. The preparation of the pyridyl piperazine derivatives **13.1** is described in Schemes **159 – 164**. The product is then transformed, as described previously, (Scheme **5**) into the amide **13.3**.

The reactions shown in Scheme **13** illustrate the preparation of the compounds **13.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **12** depicts the conversion of the compounds **13.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **4** in which X is a direct bond. In this procedure, the compounds **13.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **4**.

Preparation of the phosphonate ester intermediates 4 in which X is sulfur.

Schemes **15** and **16** illustrate the preparation of the phosphonate esters **4** in which X is sulfur. As shown in Scheme **15**, the benzyl-protected oxirane **3.3** is reacted, as described above, with the pyridyl piperazine derivative **13.1** to afford the hydroxyamine **15.1**. The product is then converted, as described above (Scheme **5**) into the aminoamide **15.2**.

The reactions shown in Scheme **15** illustrate the preparation of the compounds **15.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **16** depicts the conversion of the compounds **15.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **4** in which X is sulfur. In this procedure, the compounds **15.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **4**.

Preparation of the phosphonate ester intermediates 5 in which X is a direct bond.

Schemes **17** and **18** illustrate the preparation of the phosphonate esters **5** in which X is a direct bond. As shown in Scheme **17**, the oxirane **9.2** is reacted, as described in Scheme **1**, with the decahydroisoquinoline derivative **17.1** to produce the hydroxyamine **17.2**. The preparation of the decahydroisoquinoline derivatives **17.1** is described in Schemes **192 – 197**. The product is then transformed, as described previously, (Scheme **3**) into the amide **17.3**.

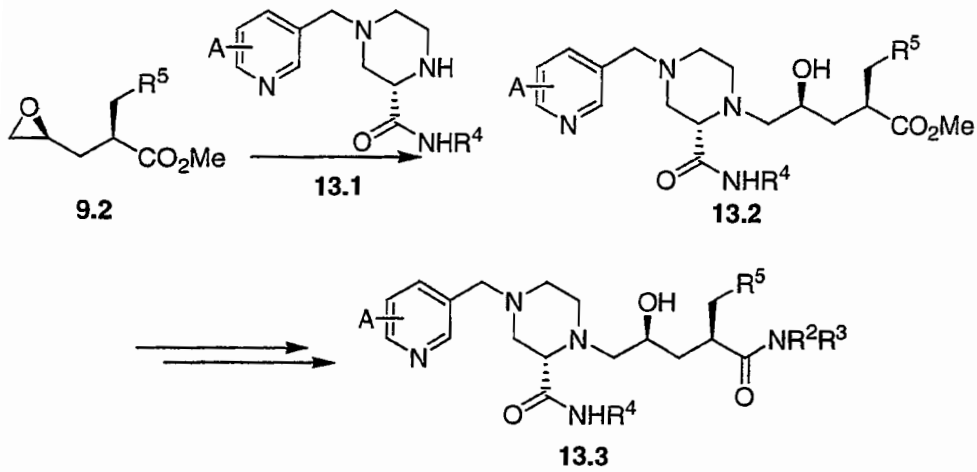
The reactions shown in Scheme **17** illustrate the preparation of the compounds **17.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **18** depicts the conversion of the compounds **17.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **5** in which X is a direct bond. In this procedure, the compounds **17.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **5**.

Preparation of the phosphonate ester intermediates 5 in which X is sulfur.

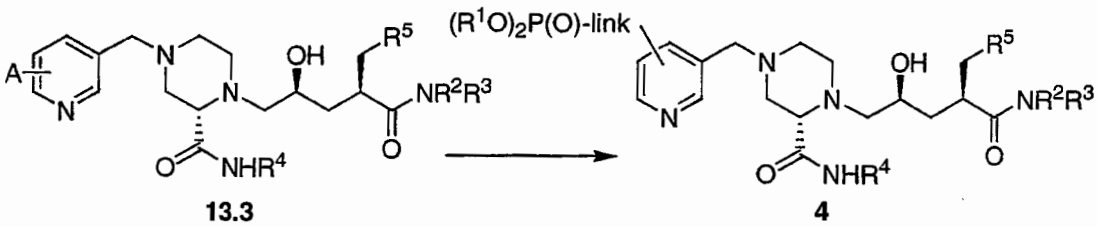
Schemes **19** and **20** illustrate the preparation of the phosphonate esters **5** in which X is sulfur. As shown in Scheme **19**, the benzyl-protected oxirane **3.3** is reacted, as described above, with the decahydroisoquinoline derivative **17.1** to afford the hydroxyamine **19.1**. The product is then converted, as described above (Scheme **5**) into the aminoamide **19.2**.

The reactions shown in Scheme **19** illustrate the preparation of the compounds **19.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **20** depicts the conversion of the compounds **19.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **5** in which X is sulfur. In this procedure, the compounds **19.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **5**.

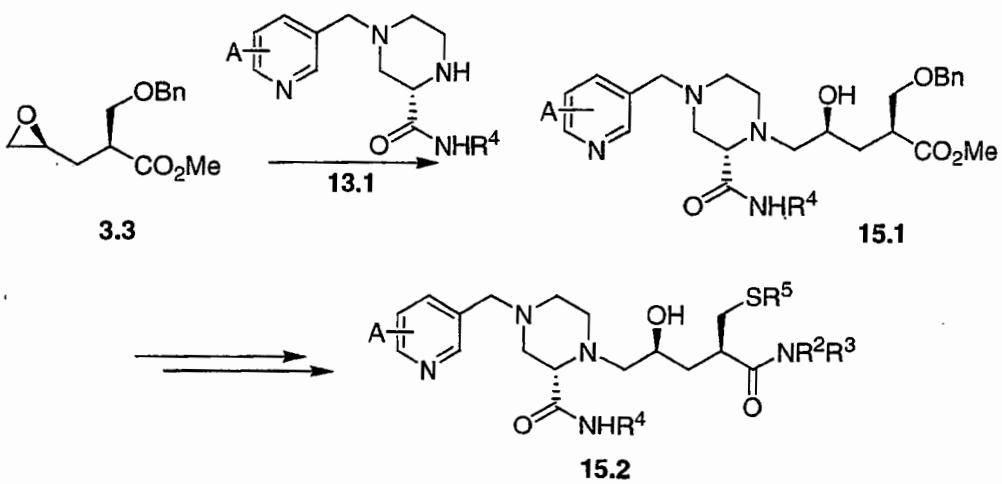
Scheme 13



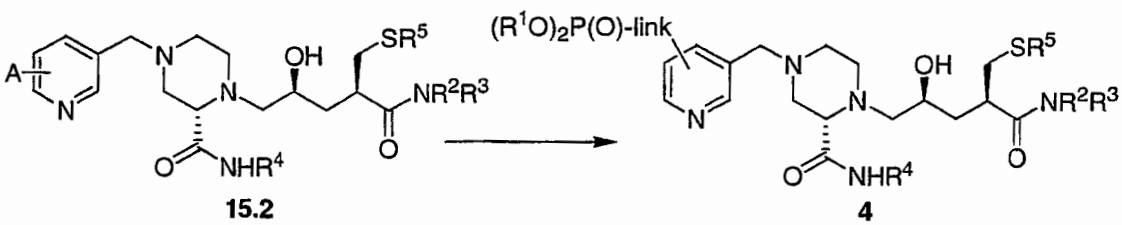
Scheme 14



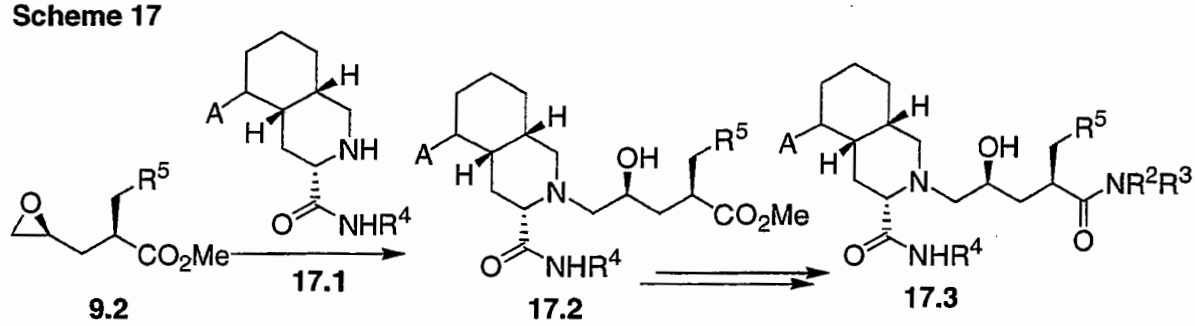
Scheme 15



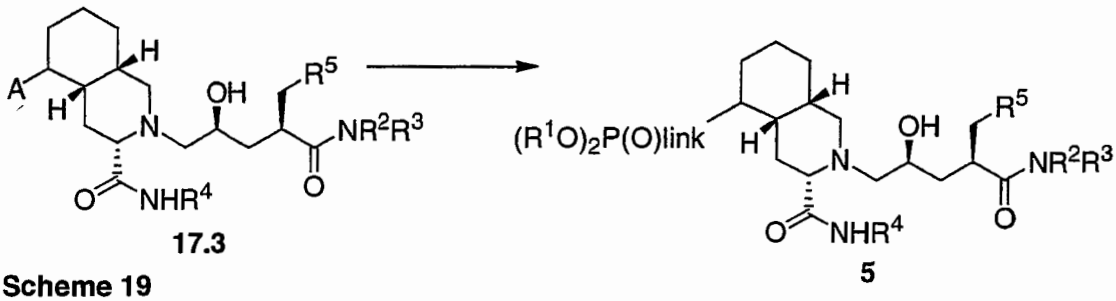
Scheme 16



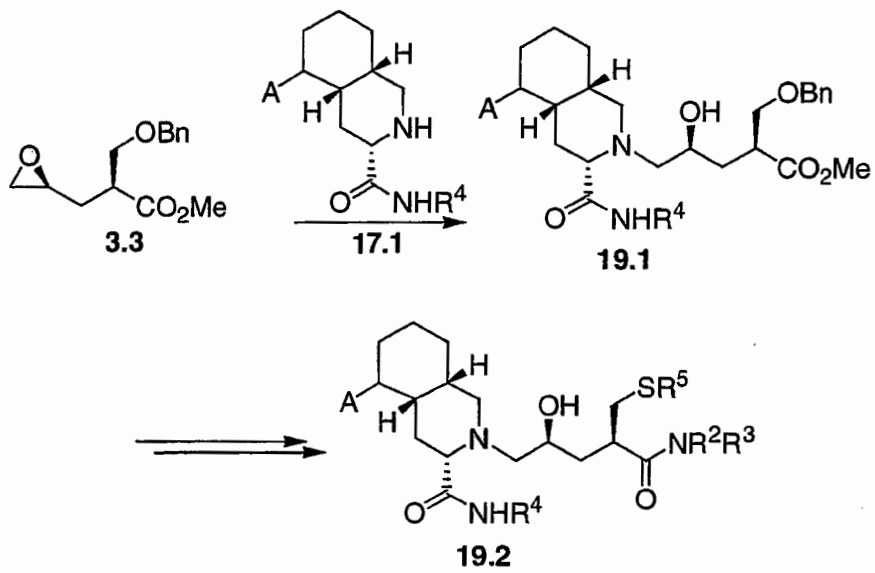
Scheme 17



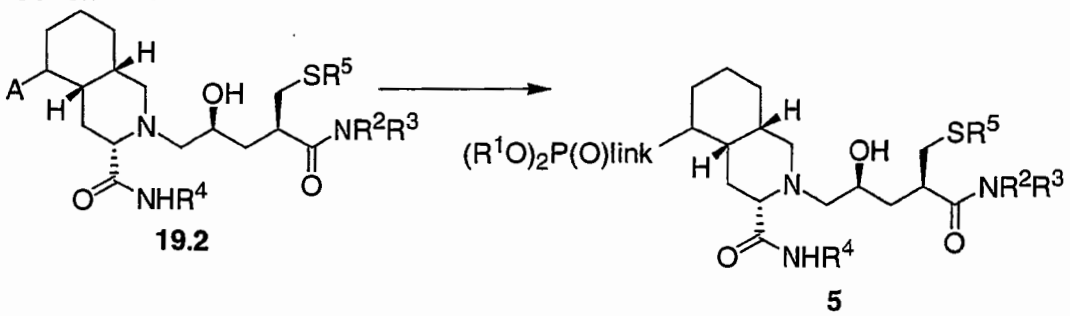
Scheme 18



Scheme 19



Scheme 20



Preparation of the phosphonate ester intermediates 6 in which X is a direct bond.

Schemes **21** and **22** illustrate the preparation of the phosphonate esters **6** in which X is a direct bond. As shown in Scheme **21**, the glycidyl tosylate **1.4** is reacted, as described in Scheme **5**, with the anion of the dimethoxyphenyl propionic ester **21.1** to afford the alkylated product **21.2**. The preparation of the dimethoxyphenyl propionic ester derivatives **21.1** is described in Scheme **186**. The product is then transformed, as described previously, (Scheme **5**) into the amide **21.3**.

The reactions shown in Scheme **21** illustrate the preparation of the compounds **21.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **22** depicts the conversion of the compounds **21.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **6** in which X is a direct bond. In this procedure, the compounds **21.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **6**.

Preparation of the phosphonate ester intermediates 6 in which X is sulfur.

Schemes **23** and **24** illustrate the preparation of the phosphonate esters **6** in which X is sulfur. As shown in Scheme **23**, the mesylate **3.7** is reacted, as described in Scheme **3**, with the dimethoxyphenyl mercaptan **23.1** to yield the thioether **23.2**. The preparation of the substituted thiols **23.1** is described below in Schemes **170 – 173**. The product is then converted, as described above (Scheme **5**) into the aminoamide **23.3**.

The reactions shown in Scheme **23** illustrate the preparation of the compounds **23.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **24** depicts the conversion of the compounds **23.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **6** in which X is sulfur. In this procedure, the compounds **23.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **6**.

Preparation of the phosphonate ester intermediates 7 in which X is a direct bond.

Schemes **25** and **26** illustrate the preparation of the phosphonate esters **7** in which X is a direct bond. As shown in Scheme **25**, the oxirane **9.2** is reacted, as described above (Scheme **1**) with the amine **1.6** to afford the hydroxyamine **25.1**. The product is then converted into the silyl ether **25.2**, using the procedures described in Scheme **3**. The methyl ester is then hydrolyzed to give the carboxylic acid **25.3**, and this compound is then coupled with the tert. butylamine derivative **25.4**, using the procedures described in Scheme **1**, to yield the amide **25.5**. The preparation of the tert. butylamine derivatives **25.4** is described in Schemes **154 – 157**. Desilylation then produces the hydroxyamide **25.6**.

The reactions shown in Scheme **25** illustrate the preparation of the compounds **25.6** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **26** depicts the conversion of the compounds **25.6** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **7** in which X is a direct bond. In this procedure, the compounds **25.6** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **7**.

Preparation of the phosphonate ester intermediates 7 in which X is sulfur.

Schemes **27** and **28** illustrate the preparation of the phosphonate esters **7** in which X is sulfur. As shown in Scheme **27**, the carboxylic acid **3.10** is coupled, as described in Scheme **3**, with the tert. butylamine derivative **25.4** to yield the amide product **27.1**. The product is then desilylated, as described above, to afford the amide **27.2**.

The reactions shown in Scheme **27** illustrate the preparation of the compounds **27.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **28** depicts the conversion of the compounds **27.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **7** in which X is sulfur. In this procedure, the compounds **27.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **7**.

Preparation of the phosphonate ester intermediates 8 in which X is a direct bond.

Schemes **29** and **30** illustrate the preparation of the phosphonate esters **8** in which X is a direct bond. As shown in Scheme **29**, the silylated carboxylic acid **25.3** is coupled, as described above, (Scheme **1**) with the amine **29.1** to afford the amide **29.2** which upon desilylation produces the hydroxyamide **29.3**. The preparation of the ethanolamine derivatives **29.1** is described in Schemes **174 – 178**.

The reactions shown in Scheme **29** illustrate the preparation of the compounds **29.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **30** depicts the conversion of the compounds **29.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **8** in which X is a direct bond. In this procedure, the compounds **29.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **8**.

Preparation of the phosphonate ester intermediates 8 in which X is sulfur.

Schemes **31** and **32** illustrate the preparation of the phosphonate esters **8** in which X is sulfur. As shown in Scheme **31**, the carboxylic acid **3.10** is coupled, as described previously, with the ethanolamine derivative **29.1** to yield the amide; the product is then desilylated, as described above, to afford the hydroxyamide **31.1**.

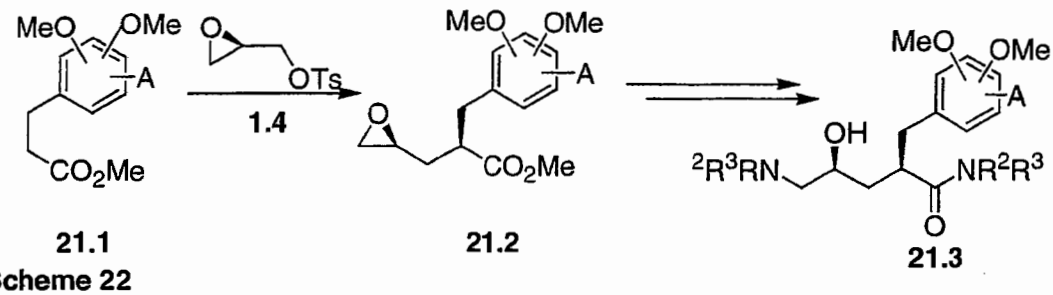
The reactions shown in Scheme **31** illustrate the preparation of the compounds **31.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **32** depicts the conversion of the compounds **31.1** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **8** in which X is sulfur. In this procedure, the compounds **31.1** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **8**.

Preparation of the phosphonate ester intermediates 9 in which X is a direct bond.

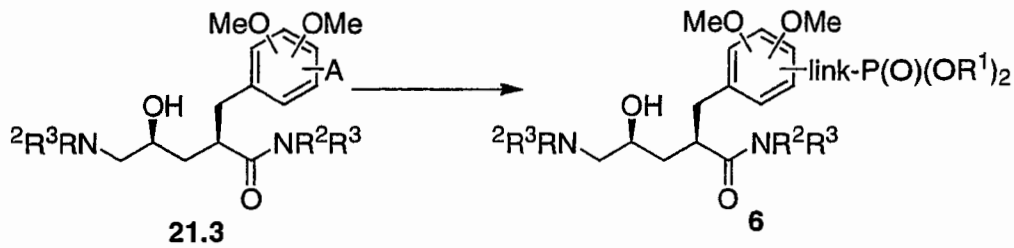
Schemes **33** and **34** illustrate the preparation of the phosphonate esters **9** in which X is a direct bond. As shown in Scheme **33**, the silylated carboxylic acid **25.3** is coupled, as described above, (Scheme **1**) with the chroman amine **33.1** to afford the corresponding amide, which upon desilylation produces the hydroxyamide **33.2**. The preparation of the chroman amines **33.1** is described in Schemes **179 – 181a**.

The reactions shown in Scheme **33** illustrate the preparation of the compounds **33.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **34** depicts the conversion of the compounds **33.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **9** in which X is a direct bond. In this procedure, the compounds **33.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **9**.

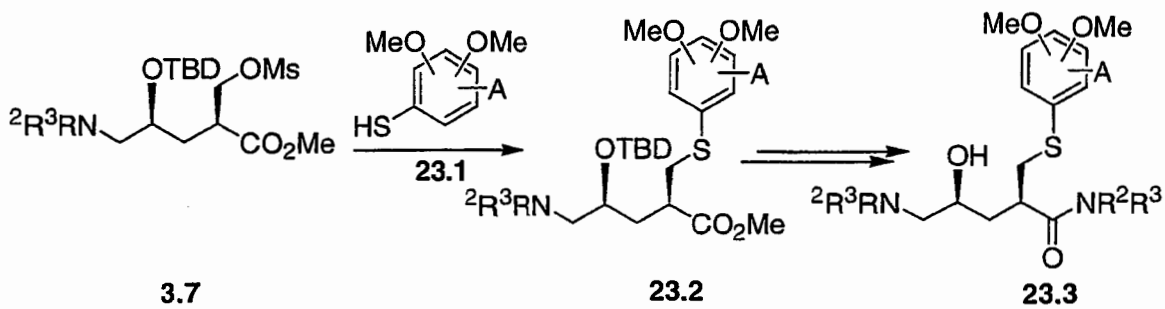
Scheme 21



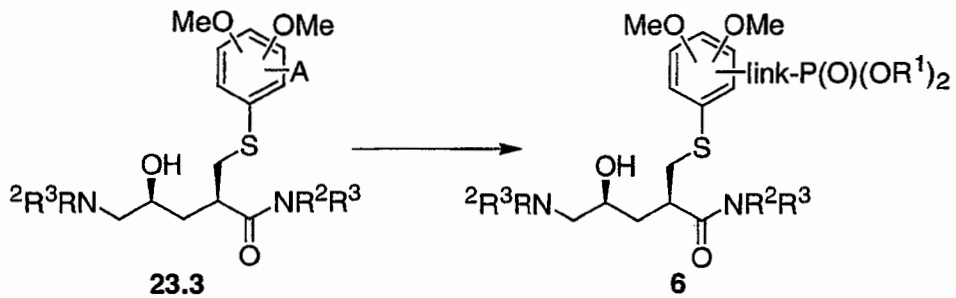
Scheme 22



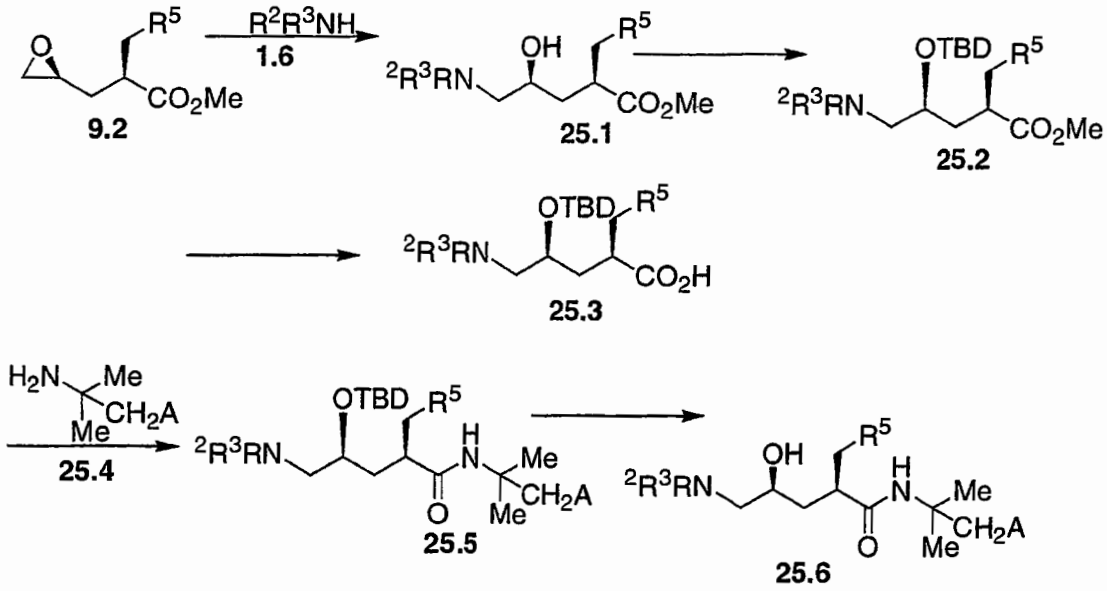
Scheme 23



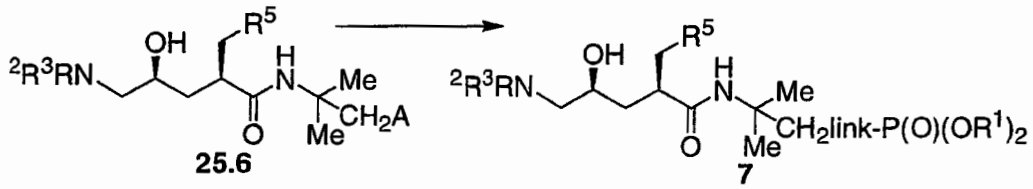
Scheme 24



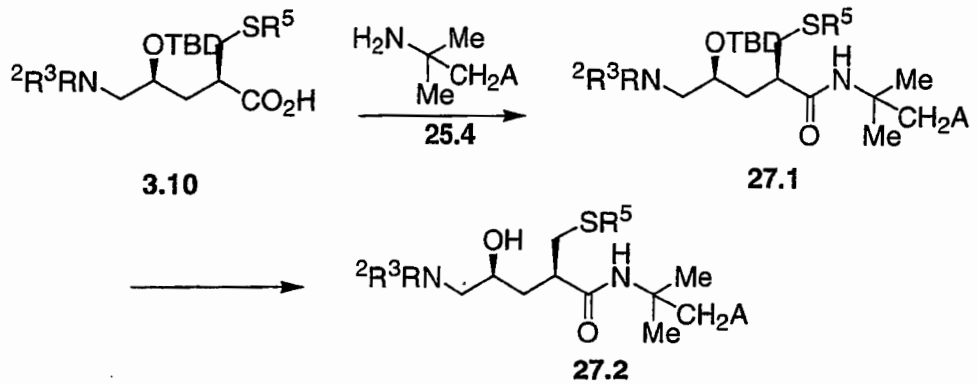
Scheme 25



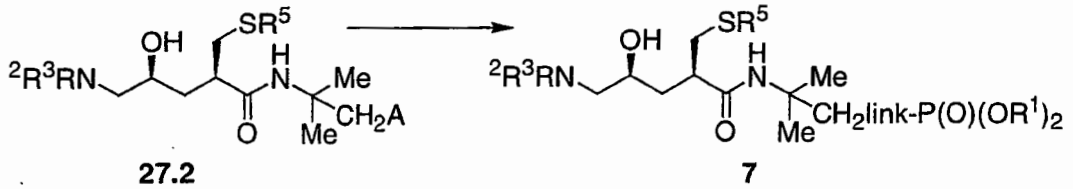
Scheme 26



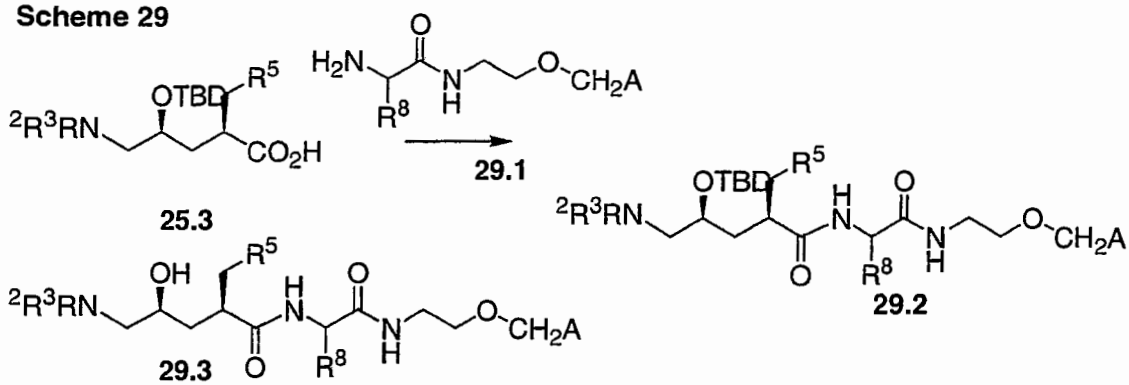
Scheme 27



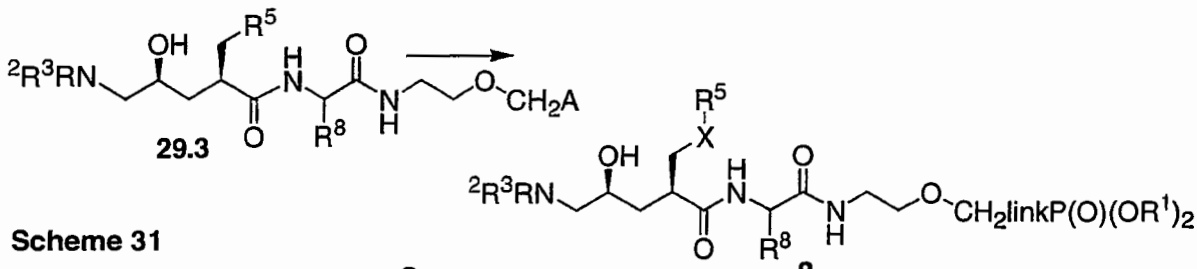
Scheme 28



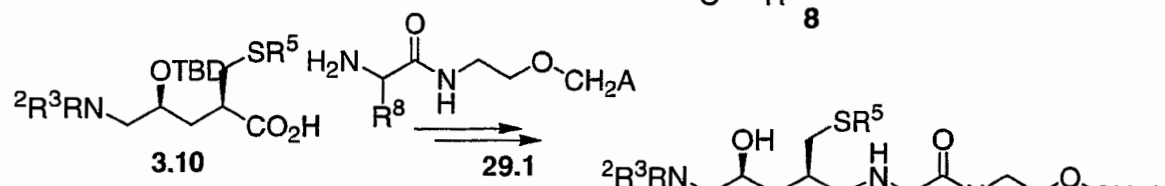
Scheme 29



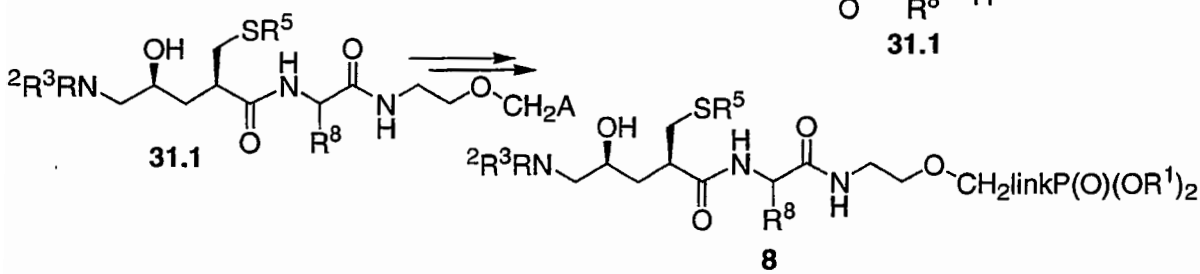
Scheme 30



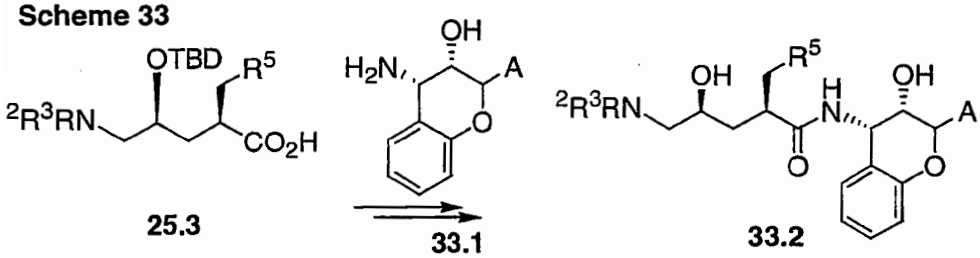
Scheme 31



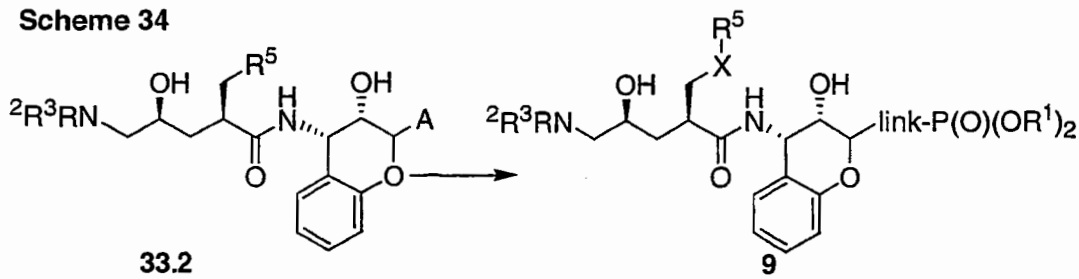
Scheme 32



Scheme 33



Scheme 34



Preparation of the phosphonate ester intermediates 9 in which X is sulfur.

Schemes **35** and **36** illustrate the preparation of the phosphonate esters **9** in which X is sulfur. As shown in Scheme **35**, the carboxylic acid **3.10** is coupled, as described previously, with the chroman amine **33.1** to yield the amide; the product is then desilylated, as described above, to afford the amide **35.1**.

The reactions shown in Scheme **35** illustrate the preparation of the compounds **35.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **36** depicts the conversion of the compounds **35.1** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **9** in which X is sulfur. In this procedure, the compounds **35.1** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **9**.

Preparation of the phosphonate ester intermediates 10 in which X is a direct bond.

Schemes **37** and **38** illustrate the preparation of the phosphonate esters **10** in which X is a direct bond. As shown in Scheme **37**, the silylated carboxylic acid **25.3** is coupled, as described above, (Scheme **1**) with the phenylalanine derivative **37.1** to afford the corresponding amide, which upon desilylation produces the hydroxyamide **37.2**. The preparation of the phenylalanine derivatives **37.1** is described in Schemes **182 – 185**.

The reactions shown in Scheme **37** illustrate the preparation of the compounds **37.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **38** depicts the conversion of the compounds **37.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **10** in which X is a direct bond. In this procedure, the compounds **37.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **10**.

Preparation of the phosphonate ester intermediates 10 in which X is sulfur.

Schemes **39** and **40** illustrate the preparation of the phosphonate esters **10** in which X is sulfur. As shown in Scheme **39**, the carboxylic acid **3.10** is coupled, as described previously, with the phenylalanine derivative **37.1** to yield the corresponding amide; the product is then desilylated, as described above, to afford the amide **39.1**.

The reactions shown in Scheme **39** illustrate the preparation of the compounds **39.1** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **40** depicts the conversion of the compounds **39.1** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **10** in which X is sulfur. In this procedure, the compounds **39.1** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **10**.

Preparation of the phosphonate ester intermediates 11 in which X is a direct bond.

Schemes **41** and **42** illustrate the preparation of the phosphonate esters **11** in which X is a direct bond. As shown in Scheme **41**, the silylated carboxylic acid **25.3** is coupled, as described above, (Scheme **1**) with the decahydroisoquinoline carboxamide **41.1**, prepared as described in Scheme **158**, to afford the corresponding amide, which upon desilylation produces the hydroxyamide **41.2**.

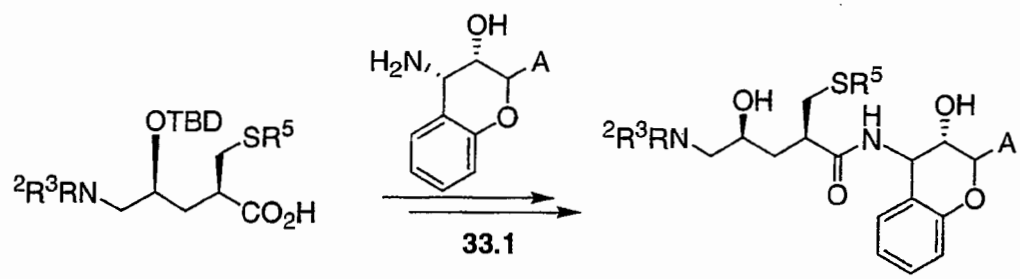
The reactions shown in Scheme **41** illustrate the preparation of the compounds **41.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **42** depicts the conversion of the compounds **41.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **11** in which X is a direct bond. In this procedure, the compounds **41.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compound

Preparation of the phosphonate ester intermediates 11 in which X is sulfur.

Schemes **43** and **44** illustrate the preparation of the phosphonate esters **11** in which X is sulfur. As shown in Scheme **43**, the carboxylic acid **3.10** is coupled, as described previously, with the decahydroisoquinoline carboxamide **41.1** to yield the corresponding amide; the product is then desilylated, as described above, to afford the amide **43.1**.

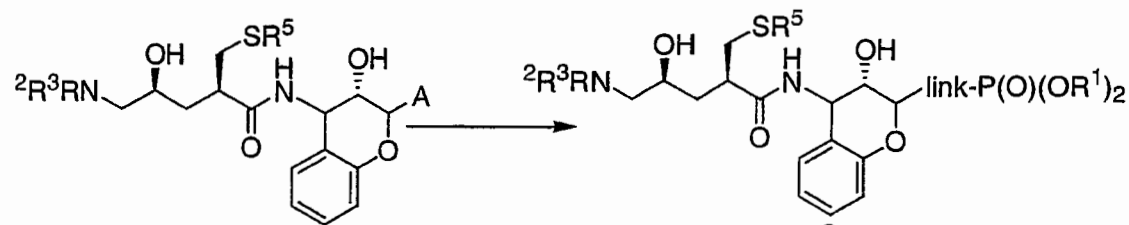
The reactions shown in Scheme **43** illustrate the preparation of the compounds **43.1** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **44** depicts the conversion of the compounds **43.1** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **11** in which X is sulfur. In this procedure, the compounds **43.1** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **11**.

Scheme 35



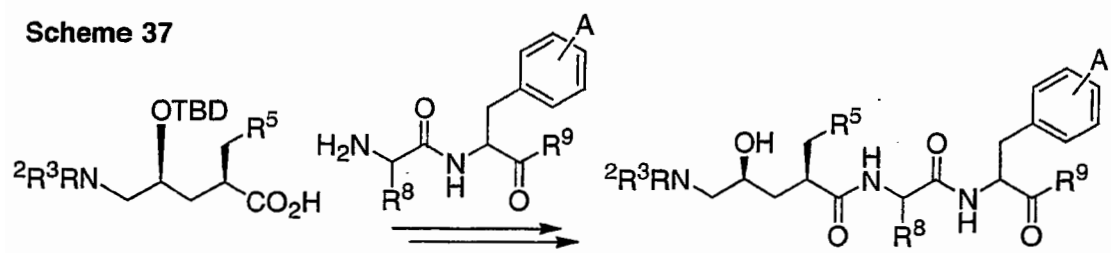
3.10 35.1

Scheme 36



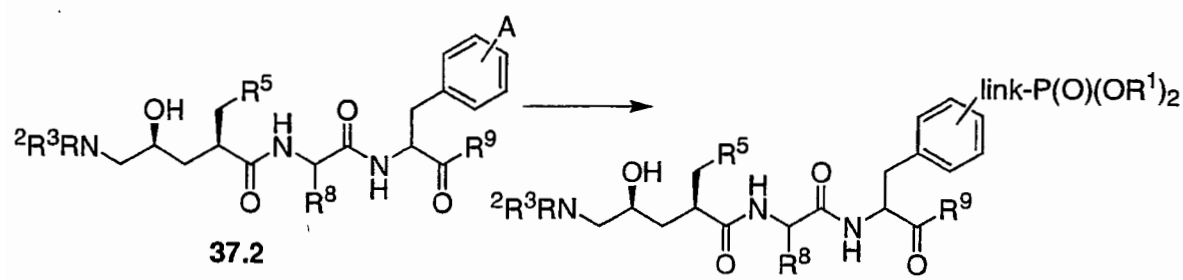
35.1 9

Scheme 37



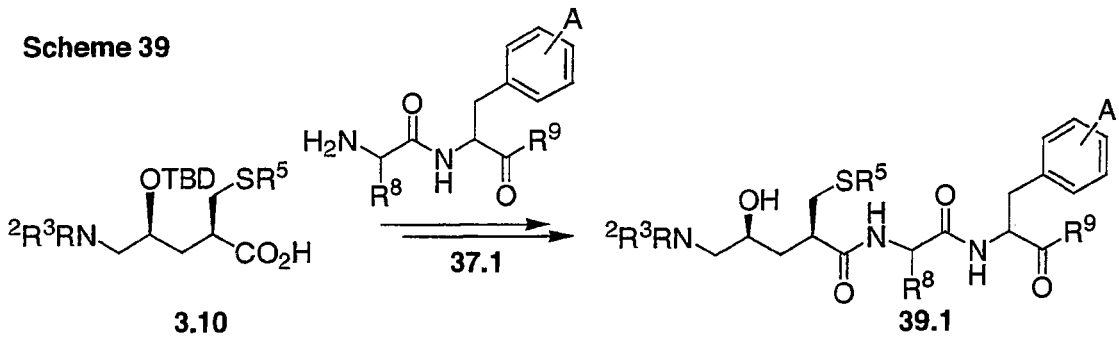
25.3 37.1 37.2

Scheme 38



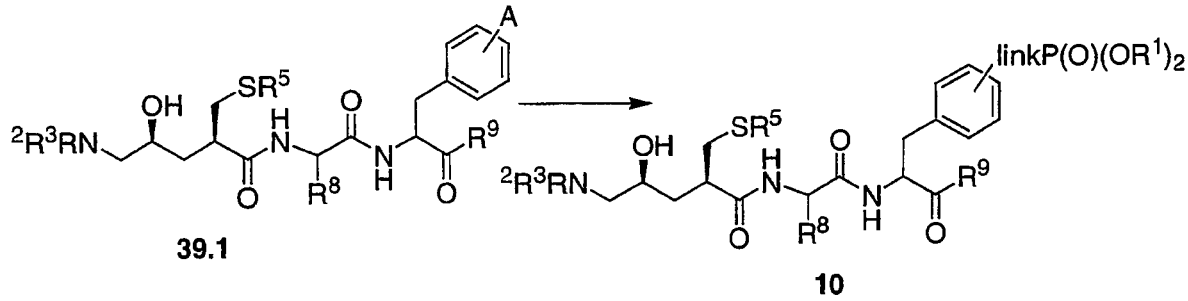
37.2 10

Scheme 39



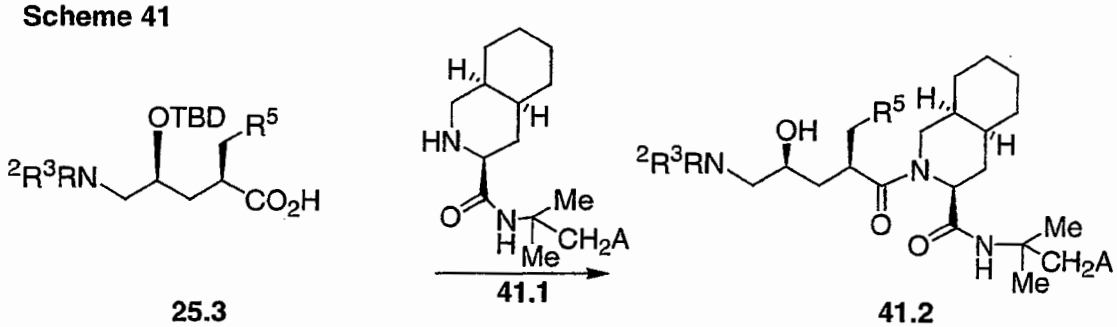
3.10 39.1

Scheme 40

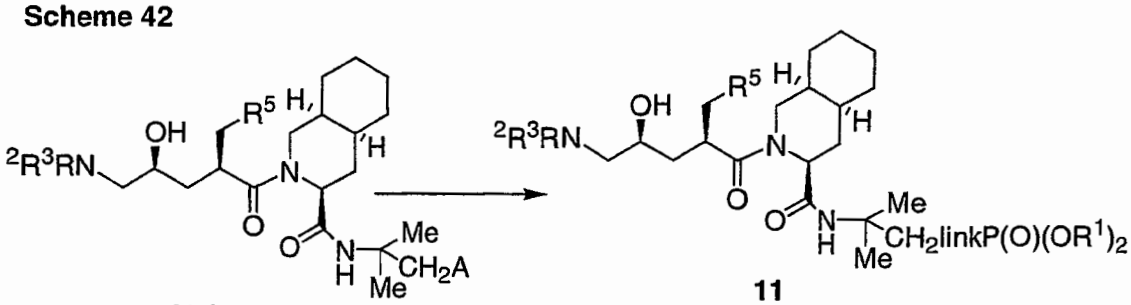


39.1 10

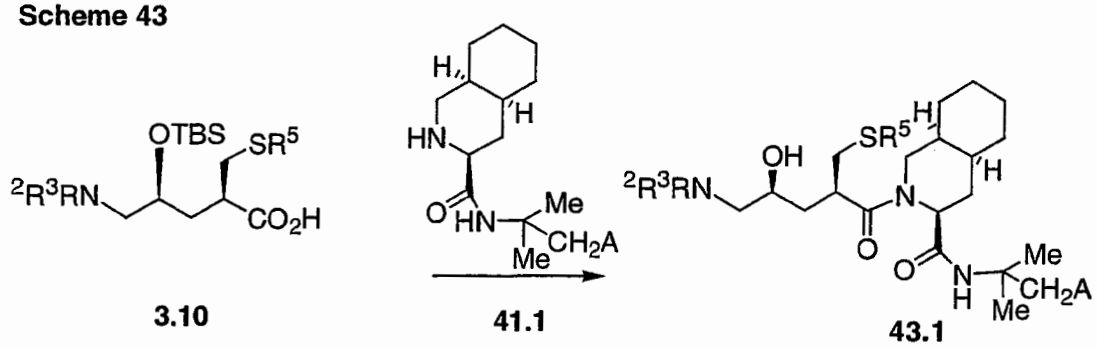
Scheme 41



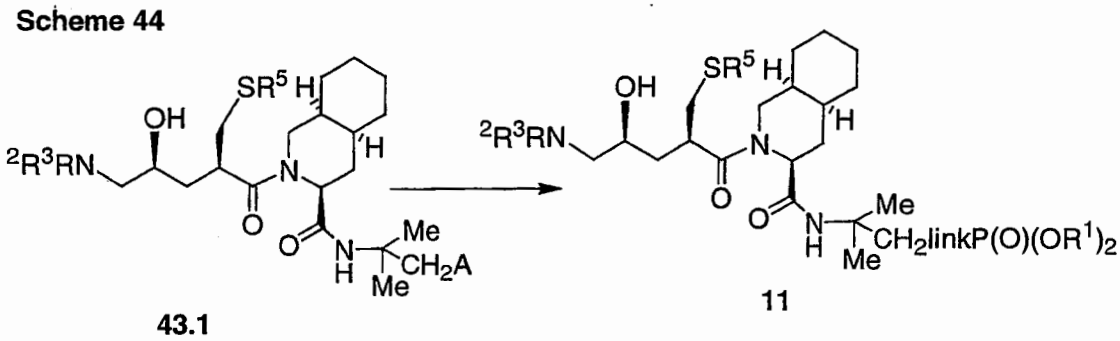
Scheme 42



Scheme 43



Scheme 44



Preparation of the phosphonate ester intermediates 12 in which X is a direct bond.

Schemes **45** and **46** illustrate the preparation of the phosphonate esters **12** in which X is a direct bond. As shown in Scheme **45**, the silylated carboxylic acid **25.3** is coupled, as described above, (Scheme **1**) with the decahydroisoquinoline derivative **45.1** to afford the

corresponding amide, which upon desilylation produces the hydroxyamide **45.2**. The preparation of the decahydroisoquinoline derivatives **45.1** is described in Schemes **192 – 197**.

The reactions shown in Scheme **45** illustrate the preparation of the compounds **45.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **46** depicts the conversion of the compounds **45.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **12** in which X is a direct bond. In this procedure, the compounds **45.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **12**.

Preparation of the phosphonate ester intermediates 12 in which X is sulfur.

Schemes **47** and **48** illustrate the preparation of the phosphonate esters **12** in which X is sulfur. As shown in Scheme **47**, the carboxylic acid **3.10** is coupled, as described previously, with the decahydroisoquinoline derivative **45.1** to yield the corresponding amide; the product is then desilylated, as described above, to afford the amide **47.1**.

The reactions shown in Scheme **47** illustrate the preparation of the compounds **47.1** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **48** depicts the conversion of the compounds **47.1** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **12** in which X is sulfur. In this procedure, the compounds **47.1** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **12**.

Preparation of the phosphonate ester intermediates 13 in which X and X' are direct bonds.

Schemes **49** and **50** illustrate the preparation of the phosphonate esters **12** in which X and X' are direct bonds. As shown in Scheme **49**, a BOC-protected aminoacid **49.1** is converted into the corresponding aldehyde **49.2**. A number of methods are known for the conversion of carboxylic acids and derivatives into the corresponding aldehydes, for example as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 619-627. The

conversion is effected by direct reduction of the carboxylic acid, for example employing diisobutyl aluminum hydride, as described in J. Gen. Chem. USSR., 34, 1021, 1964, or alkyl borane reagents, for example as described in J. Org. Chem., 37, 2942, 1972. Alternatively, the carboxylic acid is converted into an amide, such as the N-methoxy N-methyl amide, and the latter compound is reduced with lithium aluminum hydride, for example as described in J. Med. Chem., 1994, 37, 2918, to afford the aldehyde. Alternatively, the carboxylic acid is reduced to the corresponding carbinol which is then oxidized to the aldehyde. The reduction of carboxylic acids to carbinols is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 548ff. The reduction reaction is performed by the use of reducing agents such as borane, as described in J. Am. Chem. Soc., 92, 1637, 1970, or by lithium aluminum hydride, as described in Org. Reac., 6, 649, 1951. The resultant carbinol is then converted into the aldehyde by means of an oxidation reaction. The oxidation of a carbinol to the corresponding aldehyde is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. The conversion is effected by the use of oxidizing agents such as pyridinium chlorochromate, as described in J.Org. Chem., 50, 262, 1985, or silver carbonate, as described in Compt. Rend. Ser. C., 267, 900, 1968, or dimethyl sulfoxide/acetic anhydride, as described in J. Am. Chem. Soc., 87, 4214, 1965. Preferably, the procedure described in EP 708085 is employed. The carboxylic acid **49.1** is first reacted with equimolar amounts of isobutyl chloroformate and triethylamine in tetrahydrofuran, to afford a mixed anhydride which is then reduced by treatment with sodium borohydride in aqueous tetrahydrofuran at ambient temperature to afford the carbinol **49.2**. The carbinol is then oxidized to the aldehyde **49.3** by reaction with oxalyl chloride and dimethylsulfoxide in dichloromethane at -60°C, as described in EP708085. To transform the aldehyde into the hydroxyester **49.5**, ethyl 3-iodopropionate **49.4** is reacted first with a zinc-copper couple, prepared as described in Org. Syn. Coll. Vol. 5, 855, 1973, and the product is then reacted with trichlorotitanium isopropoxide, as described in EP 708085. The resultant reagent is then treated with the aldehyde **49.3** in dichloromethane at -20°C to yield the hydroxyester **49.5**. The hydroxyester is then cyclized to the lactone **49.6** by treatment with acetic acid in toluene at 100°C, as described in EP 708085. A number of alternative preparations of the lactone **49.6** are known, for example as described in J. Org. Chem., 1985, 50, 4615, J. Org. Chem., 1995, 60, 7927 and J. Org. Chem., 1991, 56, 6500. The lactone **49.6** is then reacted with a substituted benzyl iodide **49.7** to afford the alkylated product **49.8**.

The preparation of the benzyl halides **49.7** is described below, (Schemes **165 – 169**). The alkylation reaction is performed in an aprotic organic solvent such as dimethylformamide or tetrahydrofuran, in the presence of a strong base such as sodium hydride or lithium hexamethyl disilylazide. Preferably, the lactone is first reacted with lithium bis(trimethylsilyl)amide in a mixture of tetrahydrofuran and 1,3-dimethyltetrahydropyrimidinone, and then ethyl 3-iodopropioinate is added, as described in EP 708085, to prepare the alkylated lactone **49.8**. The lactone is then converted into the corresponding hydroxyacid **49.9** by alkaline hydrolysis, for example by treatment with lithium hydroxide in aqueous dimethoxyethane, as described in EP 708085. The hydroxyacid is then converted into the tert. butyldimethylsilyl ether **49.10**, by reaction with excess chloro tert. butyldimethylsilane and imidazole in dimethylformamide, followed by alkaline hydrolysis, employing potassium carbonate in aqueous methanolic tetrahydrofuran, as described in EP 708085, to yield the silyl ether **49.10**. The carboxylic acid is then coupled, as described above (Scheme **5**) with the amine R^2R^3NH to afford the amide product **49.11**. The BOC protecting group is then removed to give the free amine **49.12**. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC protecting group is removed by treatment of the substrate with 3M hydrogen chloride in ethyl acetate, as described in J. Org. Chem., 43, 2285, 1978, a procedure which also removes the silyl protecting group to afford the hydroxy amine **49.12**. The latter compound is then coupled with the carboxylic acid $R^{10}COOH$, or a functional equivalent thereof, to give the amide or carbamate product **49.13**. The preparation of amides by the reaction between amines and amides is described above (Scheme **1**). Compounds in which the group R^{10} is alkoxy are carbamates; the preparation of carbamates is described below (Scheme **198**)

The reactions shown in Scheme **49** illustrate the preparation of the compounds **49.13** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **50** depicts the conversion of the compounds **49.13** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **13** in which X and X' are direct bonds. In this procedure, the compounds **49.13** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **13**.

Preparation of the phosphonate ester intermediates 13 in which X is a direct bond and X' is sulfur.

Schemes **51** and **52** illustrate the preparation of the phosphonate esters **13** in which X is a direct bond and X' is sulfur. In this procedure, BOC serine methyl ester mesylate, **51.1**, the preparation of which is described in Synlett., 1997, 169, is reacted with the thiol **51.2**, employing the conditions described in Scheme **3**, to prepare the thioether **51.3**. The methyl ester group is then transformed into the corresponding aldehyde **51.4**. The reduction of esters to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 621. The conversion is effected by treatment with diisobutyl aluminum hydride, sodium aluminum hydride, lithium tri-tertiary butoxy aluminum hydride and the like. Preferably, the ester **51.3** is reduced to the aldehyde **51.4** by reaction with the stoichiometric amount of diisobutyl aluminum hydride in toluene at -80°C, as described in Syn., 617, 1975. The aldehyde is then transformed into the diamide **51.5**, using the sequence of reactions and reaction conditions described above (Scheme **49**) for the conversion of the aldehyde **49.3** into the diamide **49.13**.

The reactions shown in Scheme **51** illustrate the preparation of the compounds **51.5** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **52** depicts the conversion of the compounds **51.5** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **13** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **51.5** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **13**.

Preparation of the phosphonate ester intermediates 13 in which X and X' are sulfur.

Schemes **53**, **54** and **55** illustrate the preparation of the phosphonate esters **13** in which X and X' are sulfur. As shown in Scheme **53**, the aldehyde **51.4** is reacted with the dianion of N-methylmethacrylamide **53.1** to form the hydroxyamide **53.2**. The dianion is generated by treatment of N-methylmethacrylamide with two equivalents of an alkyllithium, for example n-butyllithium, in an organic solvent such as tetrahydrofuran or dimethoxyethane, as described in J. Org. Chem., 1986, 51, 3921. The dianion is then reacted with the aldehyde in the presence

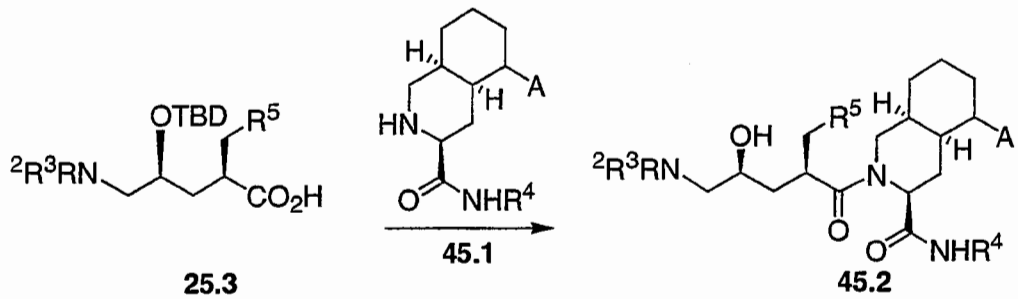
of chlorotitanium triisopropoxide, to afford the olefinic amide **53.2**. The product is cyclized to produce the methylene lactone **53.3** by heating in an inert solvent such as xylene, at reflux temperature, as described in J. Org. Chem., 1986, 51, 3921. The methylene lactone is then reacted with the thiol **53.4** to yield the thioether **53.5**. The preparation of the thiols **53.4** is described below, (Schemes **170 – 173**). The addition of thiols to methylene lactones analogous to the compound **53.3** is described in J. Org. Chem., 1986, 51, 3921. Equimolar amounts of the reactants are combined in an alcoholic solvent such as methanol at about 60°C, in the presence of a tertiary base such as triethylamine, to give the addition product **53.5**. The latter compound is then subjected to basic hydrolysis, for example by reaction with lithium hydroxide, as described above, (Scheme **49**) to produce the hydroxyacid **53.6**. The product is silylated, as described in Scheme **49**, to give the silylated carbinol **53.7**, and the product is then converted, as described in Scheme **49**, into the diamide **53.8**.

Scheme **54** illustrates an alternative method for the preparation of the diamides **53.8**. In this procedure, the anion of the lactone **54.1**, obtained as an intermediate in the conversion of the aldehyde **51.4** into the diamide **51.5**, (Scheme **51**) is reacted with formaldehyde or a functional equivalent thereof, to afford the hydroxymethyl compound **54.2**. The generation of the anion of lactones analogous to **54.1**, and alkylation thereof, is described above in Scheme **49**. Preferably, the anion is prepared by reaction of the lactone, in a solvent mixture composed of tetrahydrofuran and 1,3-dimethyltetrahydropyrimidinone, with lithium bis(trimethylsilyl)amide, as described in EP 708085, and formaldehyde, generated by pyrolysis of paraformaldehyde, is then introduced in an inert gas stream. The hydroxymethyl product is then converted into the corresponding mesylate **54.3**, by reaction with methanesulfonyl chloride in dichloromethane containing a tertiary base such as triethylamine or dimethylaminopyridine, and the mesylate is then reacted with the thiol reagent **53.4**, using the procedure described above for the preparation of the thioether **51.3**, to yield the thioether **53.5**. The product is then transformed, as described above, into the diamide **53.8**.

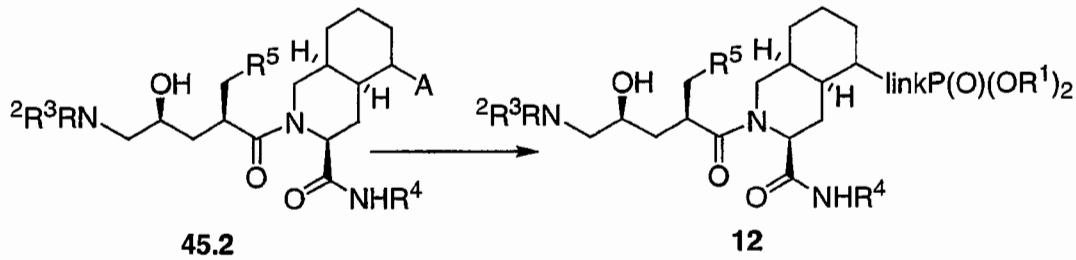
The reactions shown in Schemes **53** and **54** illustrate the preparation of the compounds **53.8** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **55** depicts the conversion of the compounds **53.8** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **13** in which X and X' are sulfur. In this

procedure, the compounds **53.8** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **13**.

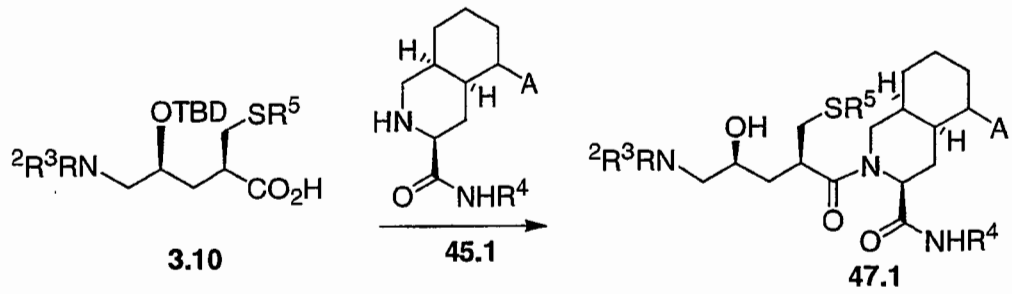
Scheme 45



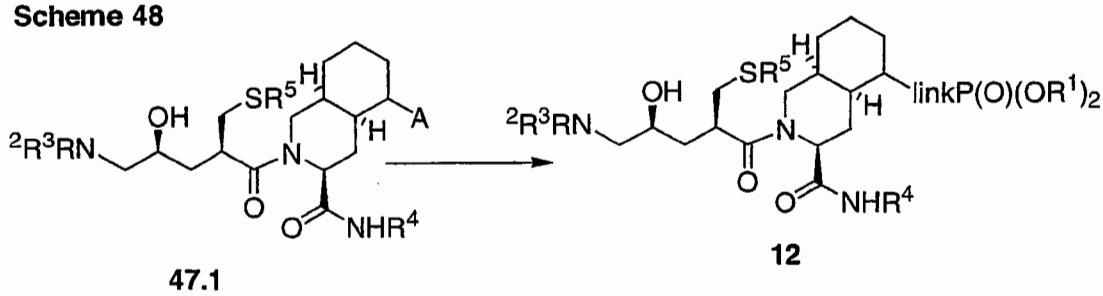
Scheme 46



Scheme 47

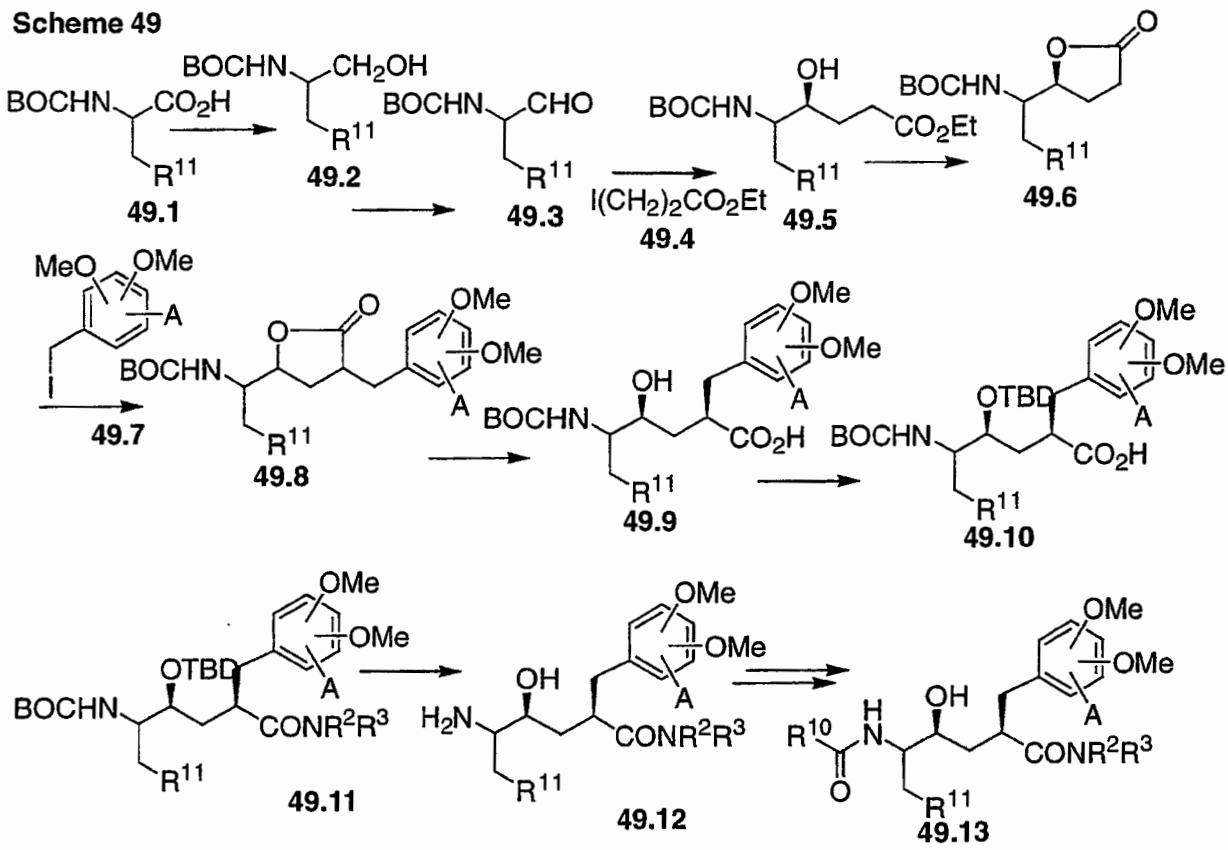


Scheme 48

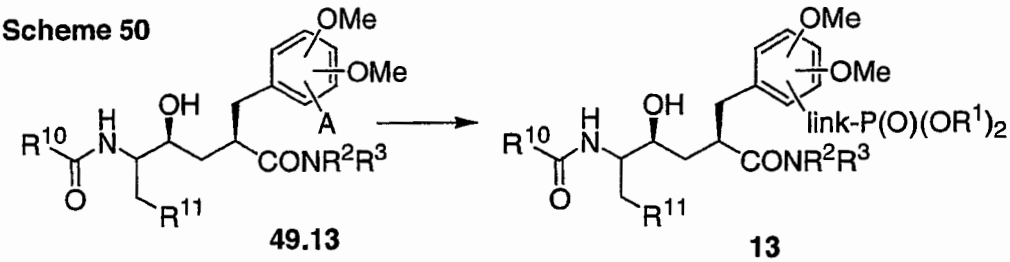


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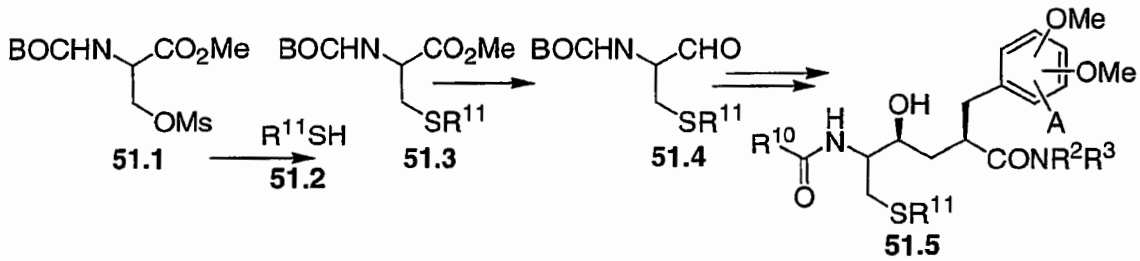
Scheme 49



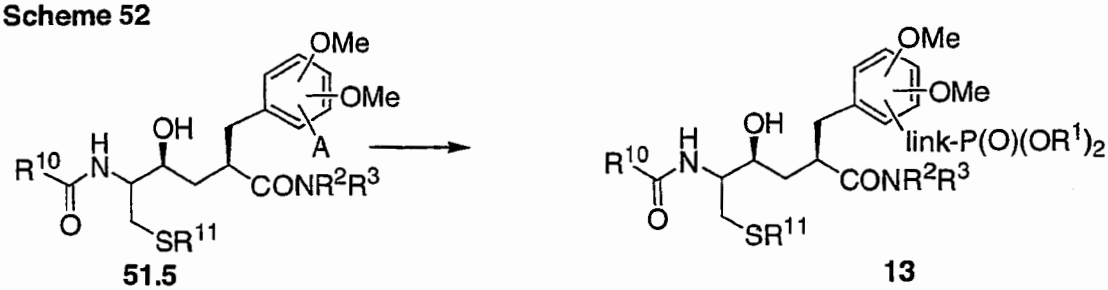
Scheme 50



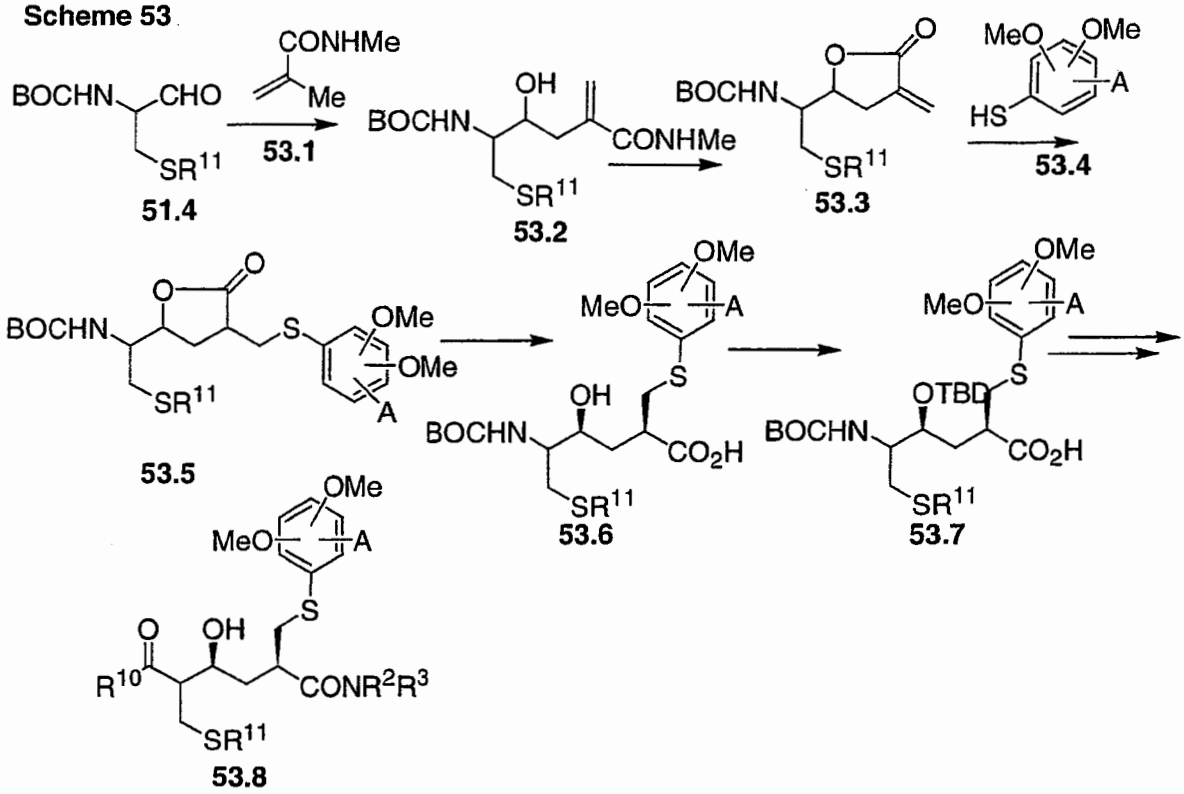
Scheme 51



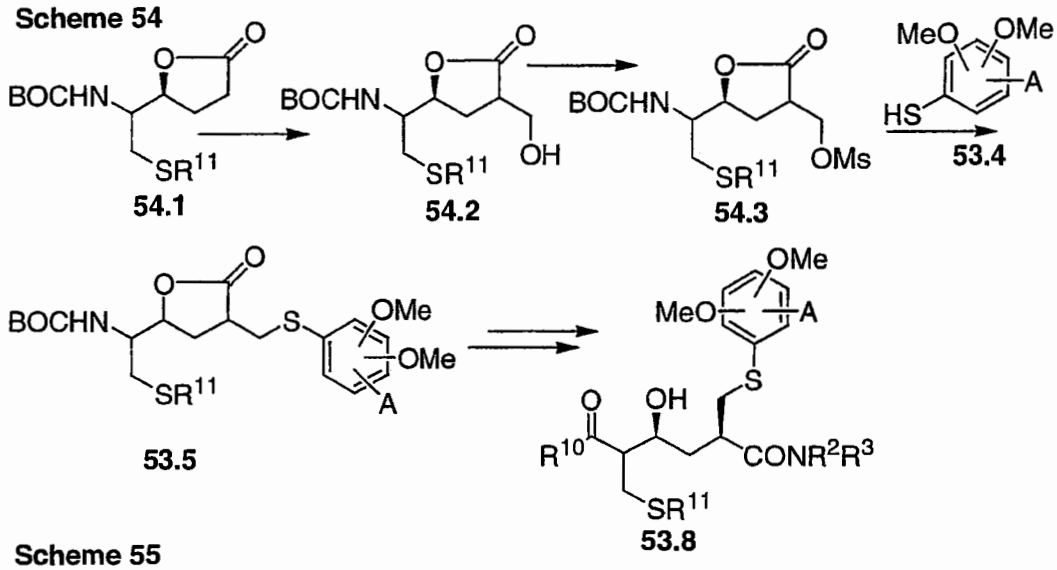
Scheme 52



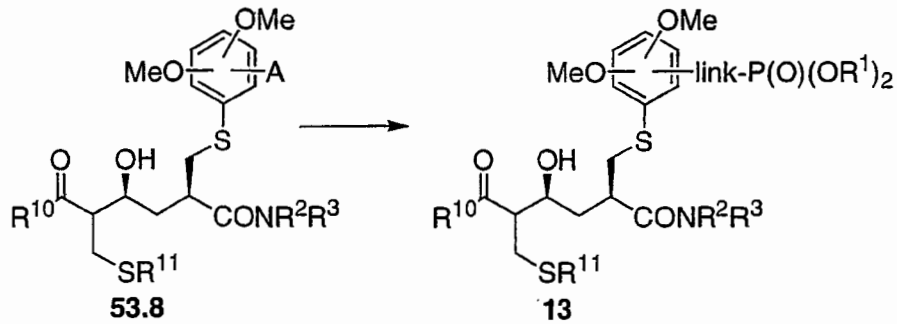
Scheme 53



Scheme 54



Scheme 55



Preparation of the phosphonate ester intermediates 13 in which X is sulfur and X' is a direct bond.

Schemes **56** and **57** illustrate the preparation of the phosphonate esters **13** in which X is sulfur and X' is a direct bond. In this procedure, the BOC-protected aldehyde **49.3** is converted, as described in Scheme **53**, into the methylene lactone **56.1**. The lactone is then reacted with the thiol **53.4** and a base, as described in Scheme **53**, to yield the thioether **56.2**. The thioether is then transformed, as described in Scheme **53**, into the diamide **56.3**.

The reactions shown in Scheme **56** illustrate the preparation of the compounds **56.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **57** depicts the conversion of the compounds **56.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **13** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **56.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **13**.

Preparation of the phosphonate ester intermediates 14 in which X and X' are direct bonds.

Schemes **58** and **59** illustrate the preparation of the phosphonate esters **14** in which X and X' are direct bonds. In this procedure, the lactone **49.6** is reacted, as described in Scheme **49**, with a substituted benzyl iodide **58.1**, to produce the alkylated compound **58.2**. The preparation of the benzyl iodides **58.1** is described in Schemes **187** - **191**. The product is then transformed, as described in Scheme **49**, into the diamide **58.3**.

The reactions shown in Scheme **58** illustrate the preparation of the compounds **58.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **59** depicts the conversion of the compounds **58.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **14** in which X and X' are direct bonds. In this procedure, the compounds **58.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **14**.

Preparation of the phosphonate ester intermediates 14 in which X is a direct bond and X' is sulfur.

Schemes **60** and **61** illustrate the preparation of the phosphonate esters **14** in which X is a direct bond and X' is sulfur. In this procedure, the lactone **54.1** is reacted, as described in Scheme **49**, with a substituted benzyl iodide **58.1**, to produce the alkylated compound **60.1**. The product is then transformed, as described in Scheme **49**, into the diamide **60.2**.

The reactions shown in Scheme **60** illustrate the preparation of the compounds **60.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **61** depicts the conversion of the compounds **60.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **14** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **60.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **14**.

Preparation of the phosphonate ester intermediates 14 in which X and X' are sulfur.

Schemes **62**, **63** and **64** illustrate the preparation of the phosphonate esters **14** in which X and X' are sulfur. As shown in Scheme **62**, the methylene lactone **53.3** is reacted, as described in Scheme **53**, with a substituted thiophenol **62.1** to produce the addition product **62.2**. The preparation of the substituted thiophenols **62.1** is described below, (Schemes **144 – 153**). The product is then transformed, as described in Scheme **53**, into the diamide **62.3**.

Scheme **63** illustrates an alternative method for the preparation of the diamide **62.3**. In this procedure, the mesylate **54.3** is reacted, as described in Scheme **54**, with the thiol **62.1** to afford the alkylation product **63.1**. The product is then transformed, as described in Scheme **53**, into the diamide **62.3**.

The reactions shown in Schemes **62** and **63** illustrate the preparation of the compounds **62.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **64** depicts the conversion of the compounds **62.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **14** in which X and X' are sulfur. In this procedure, the compounds **62.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **14**.

Preparation of the phosphonate ester intermediates 14 in which X is sulfur and X' is a direct bond.

Schemes **65** and **66** illustrate the preparation of the phosphonate esters **14** in which X is sulfur and X' is a direct bond. In this procedure, the methylene lactone **56.1** is reacted, as described in Scheme **53**, with a substituted thiophenol **62.1**, to produce the thioether **65.1**. The product is then transformed, as described in Scheme **53**, into the diamide **65.2**.

The reactions shown in Scheme **65** illustrate the preparation of the compounds **65.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **66** depicts the conversion of the compounds **65.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **14** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **65.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **14**.

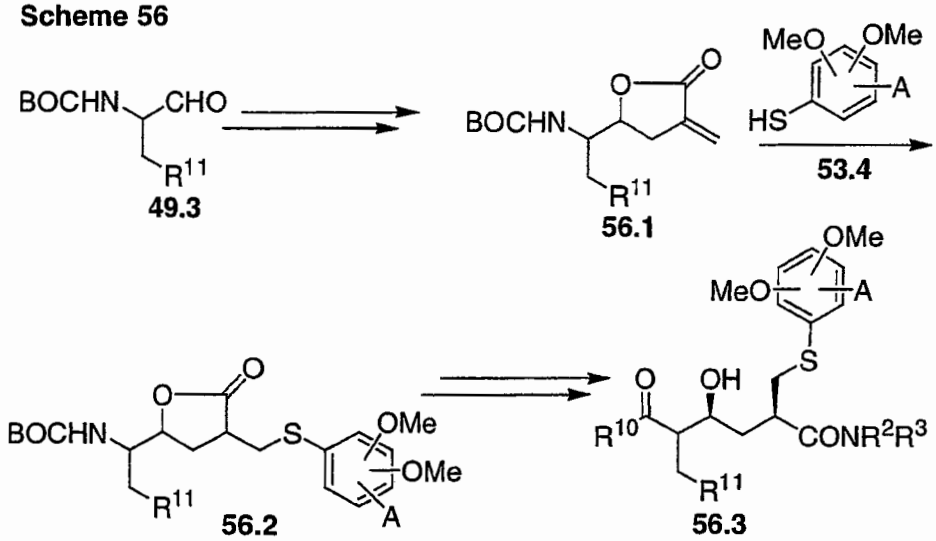
Preparation of the phosphonate ester intermediates 15 in which X and X' are direct bonds.

Schemes **67** and **68** illustrate the preparation of the phosphonate esters **15** in which X and X' are direct bonds. In this procedure, the BOC-protected phenylalanine derivative **67.1** is converted into the corresponding aldehyde **67.2**, using the procedures described above (Scheme **49**). The preparation of the phenylalanine derivatives **67.1** is described below, (Schemes **182 – 184**). The aldehyde is then converted, using the procedures described in Scheme **49**, into the lactone **67.3**. The latter compound is then alkylated, as described in Scheme **49**, with the reagent R^5CH_2I, (**67.4**), to afford the alkylated product **67.5**. This compound is then converted, as described in Scheme **49**, into the diamide **67.6**.

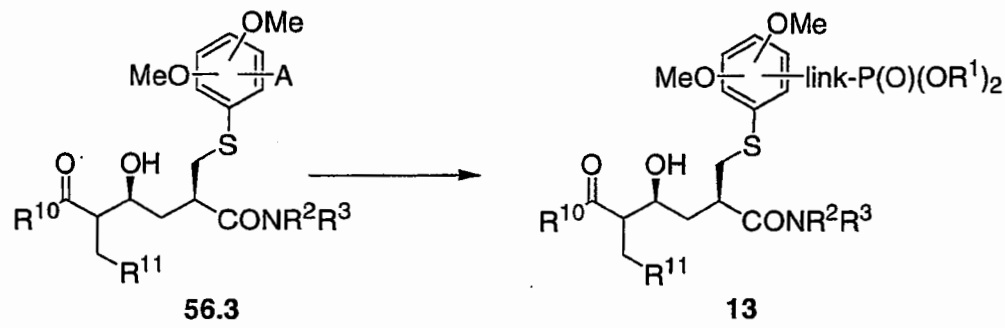
The reactions shown in Scheme **67** illustrate the preparation of the compounds **67.6** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **68** depicts the conversion of the compounds **67.6** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **15** in which X and X' are direct bonds. In this

procedure, the compounds **67.6** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **15**.

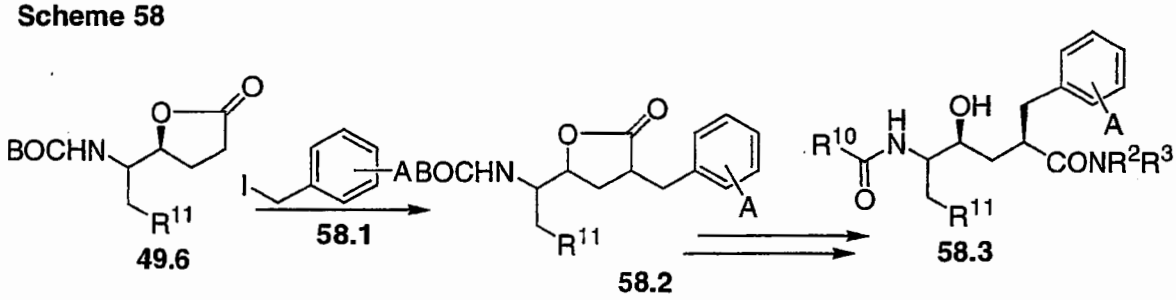
Scheme 56



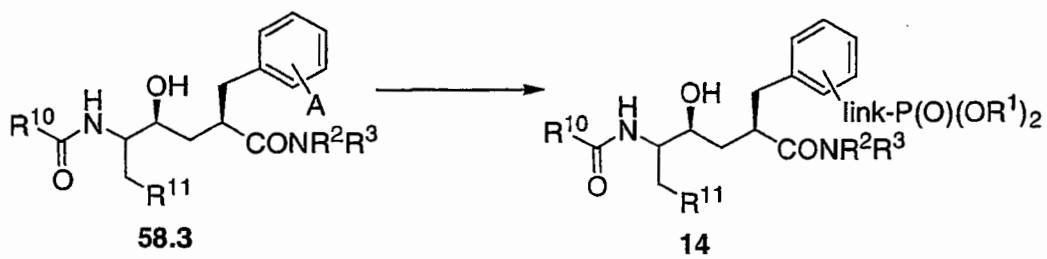
Scheme 57



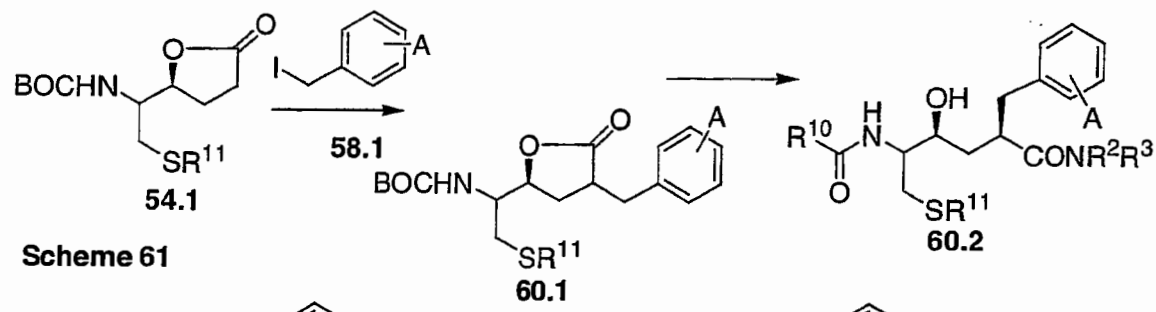
Scheme 58



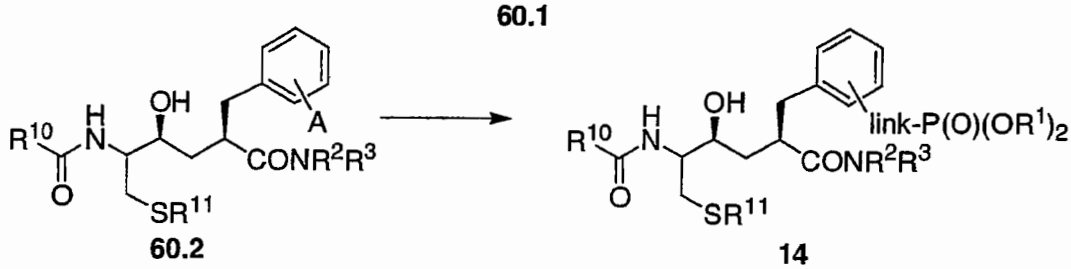
Scheme 59



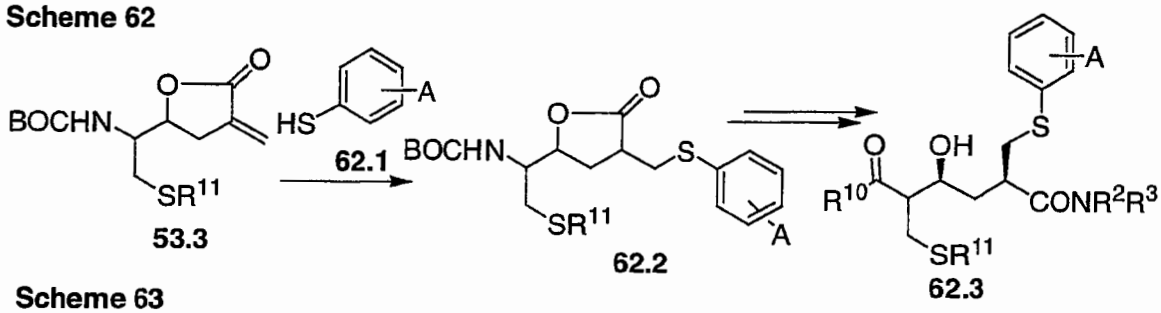
Scheme 60



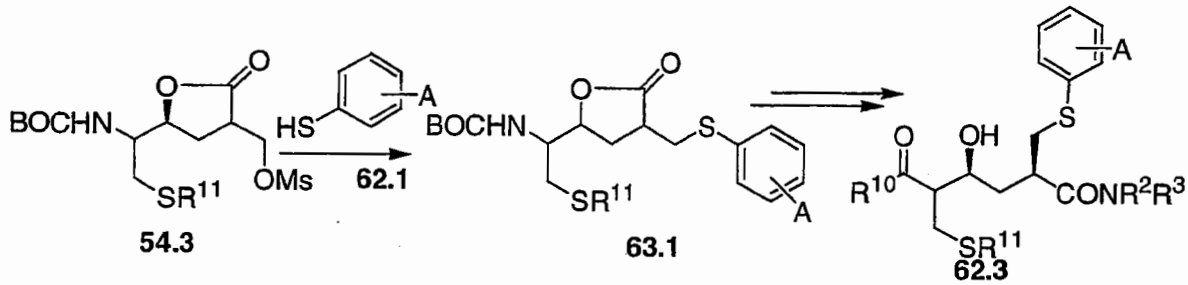
Scheme 61



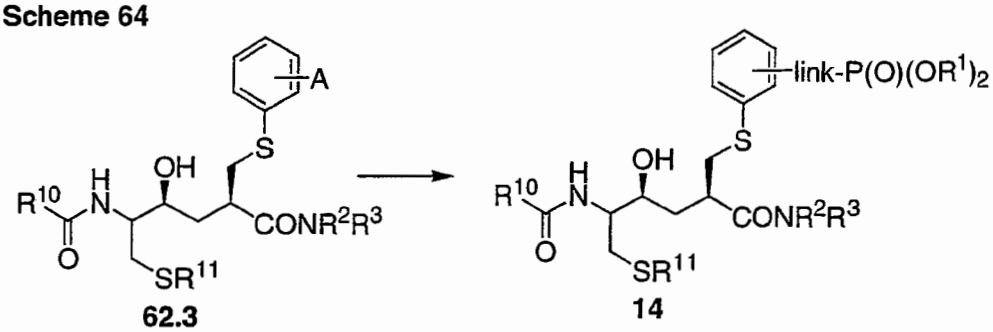
Scheme 62



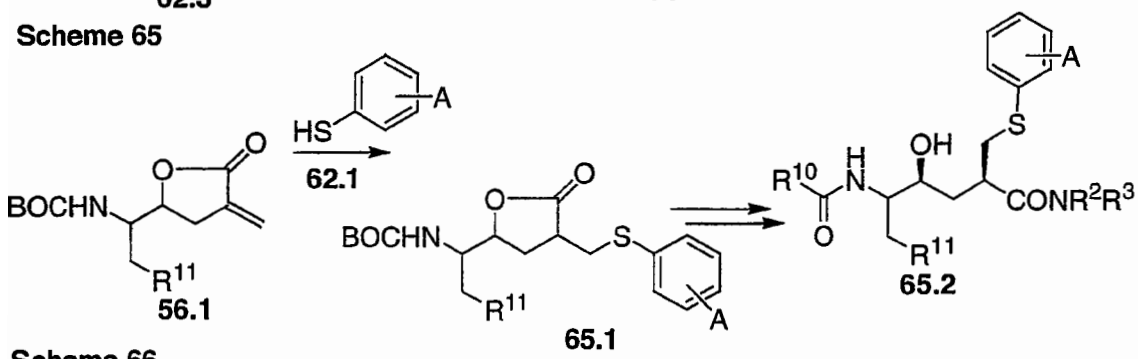
Scheme 63



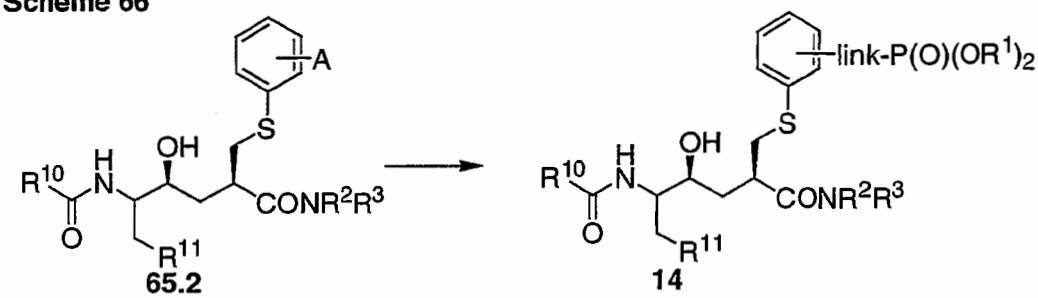
Scheme 64



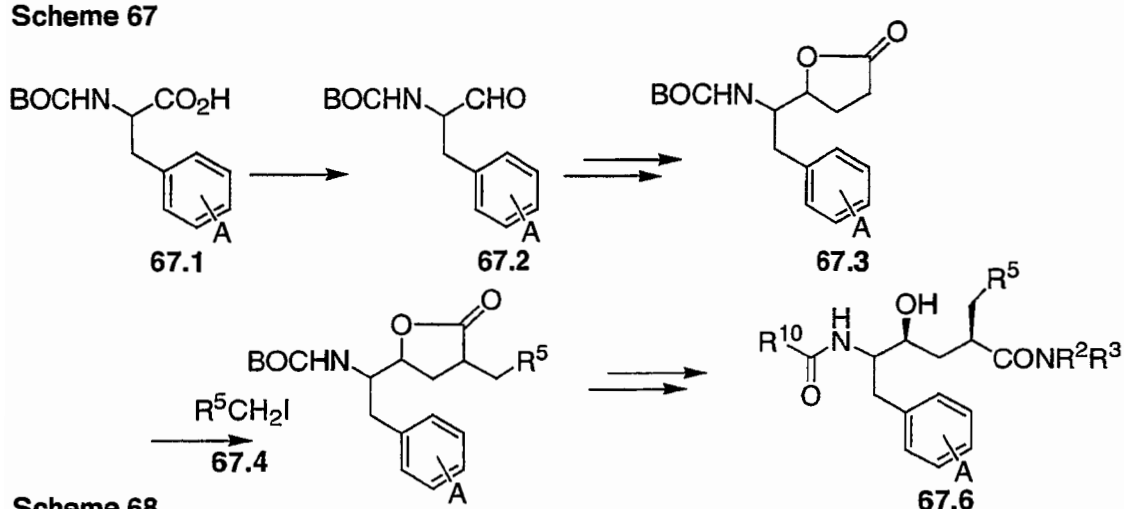
Scheme 65



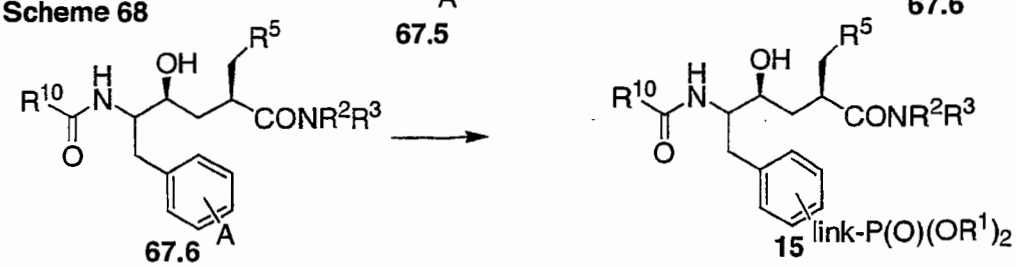
Scheme 66



Scheme 67



Scheme 68



Preparation of the phosphonate ester intermediates 15 in which X is a direct bond and X' is sulfur.

Schemes **69** and **70** illustrate the preparation of the phosphonate esters **15** in which X is a direct bond and X' is sulfur. In this procedure, the mesylate **51.1** is reacted, as described in Scheme **51**, with the thiophenol derivative **69.1**. The preparation of the thiophenol derivatives **69.1** is described below, Schemes **144 – 153**. The product is then converted, as described in Scheme **51**, into the corresponding aldehyde **69.3**, and the latter compound is then transformed, as described in Scheme **49**, into the lactone **69.4**. The lactone is then alkylated, as described in Scheme **49**, with the reagent R^5CH_2I, (**67.4**), to afford the alkylated product **69.5**. This compound is then converted, as described in Scheme **49**, into the diamide **69.6**.

The reactions shown in Scheme **69** illustrate the preparation of the compounds **69.6** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **70** depicts the conversion of the compounds **69.6** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **15** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **69.6** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **15**.

Preparation of the phosphonate ester intermediates 15 in which X and X' are sulfur.

Schemes **71**, **72** and **73** illustrate the preparation of the phosphonate esters **15** in which X and X' are sulfur. As shown in Scheme **71**, the aldehyde **69.3** is converted, as described in Scheme **53**, into the methylene lactone **71.1**. The lactone is then reacted, as described in Scheme **53**, with the thiol reagent **71.2** to yield the thioether product **71.3**. The product is then transformed, as described in Scheme **53**, into the diamide **71.4**.

Scheme **72** illustrates an alternative method for the preparation of the diamide **71.4**. In this procedure, the lactone **69.4** is reacted, as described in Scheme **54**, with formaldehyde or a formaldehyde equivalent, to afford the hydroxymethyl product **72.1**. The product is then transformed, by mesylation followed by reaction of the mesylate with the thiol reagent **71.2**, using the procedures described in Scheme **53**, into the thioether **71.3**.The latter compound is then converted, as described in Scheme **53**, into the diamide **71.4**.

The reactions shown in Schemes **71** and **72** illustrate the preparation of the compounds **71.4** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **73** depicts the conversion of the compounds **71.4** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **15** in which X and X' are sulfur. In this procedure, the compounds **71.4** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **15**.

Preparation of the phosphonate ester intermediates 15 in which X is sulfur and X' is a direct bond.

Schemes **74** and **75** illustrate the preparation of the phosphonate esters **15** in which X is sulfur and X' is a direct bond. In this procedure, the aldehyde **67.2** is converted, as described in Scheme **53**, into the methylene lactone **74.1**. The lactone is then reacted, as described in Scheme **53**, with the thiol **71.2** to afford the thioether **74.2**. This compound is then converted, as described in Scheme **53**, into the diamide **74.3**.

The reactions shown in Schemes **74** illustrate the preparation of the compounds **74.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **75** depicts the conversion of the compounds **74.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **15** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **74.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **15**.

Preparation of the phosphonate ester intermediates 16 in which X and X' are direct bonds.

Schemes **76** and **77** illustrate the preparation of the phosphonate esters **16** in which X and X' are direct bonds. In this procedure, the lactone **49.6** is reacted, as described in Scheme **49**, with the iodo compound **67.4** to yield the alkylated lactone **76.1**. The lactone is then converted, as described in Scheme **49**, into the carboxylic acid **76.2**. The carboxylic acid is then coupled, as described in Scheme **1**, with the aminoindanol derivative **1.2** to afford the amide **76.3**. The latter compound is then converted, as described in Scheme **49**, into the diamide **76.4**.

The reactions shown in Scheme **76** illustrate the preparation of the compounds **76.4** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **77** depicts the conversion of the compounds **76.4** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **16** in which X and X' are direct bonds. In this procedure, the compounds **76.4** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **16**.

Preparation of the phosphonate ester intermediates 16 in which X is a direct bond and X' is sulfur.

Schemes **78** and **79** illustrate the preparation of the phosphonate esters **16** in which X is a direct bond and X' is sulfur. In this procedure, the lactone **54.1** is reacted, as described in Scheme **49**, with the iodo compound **67.4**, to produce the alkylated compound **78.1**. This material is then transformed, as described in Scheme **49**, into the carboxylic acid **78.2**, which is then transformed, as described in Scheme **76**, into the diamide **78.3**.

The reactions shown in Scheme **78** illustrate the preparation of the compounds **78.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **79** depicts the conversion of the compounds **78.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **16** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **78.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **16**.

Preparation of the phosphonate ester intermediates 16 in which X and X' are sulfur.

Schemes **80**, **81** and **82** illustrate the preparation of the phosphonate esters **15** in which X and X' are sulfur. As shown in Scheme **80**, the methylene lactone **53.3** is reacted with the thiol **71.2** to produce the thioether **80.1**. The compound is then transformed, as described in Scheme **49**, into the silyl-protected carboxylic acid **80.2**. This material is then converted, as described in Scheme **76**, into the diamide **80.3**.

Scheme **81** illustrates an alternative method for the preparation of the compounds **80.2**. In this procedure, the mesylate **54.3** is reacted, as described in Scheme **54**, with the thiol **71.2**, to

prepare the thioether **80.1**. The product is then transformed, as described in Scheme **54**, into the diamide **80.3**.

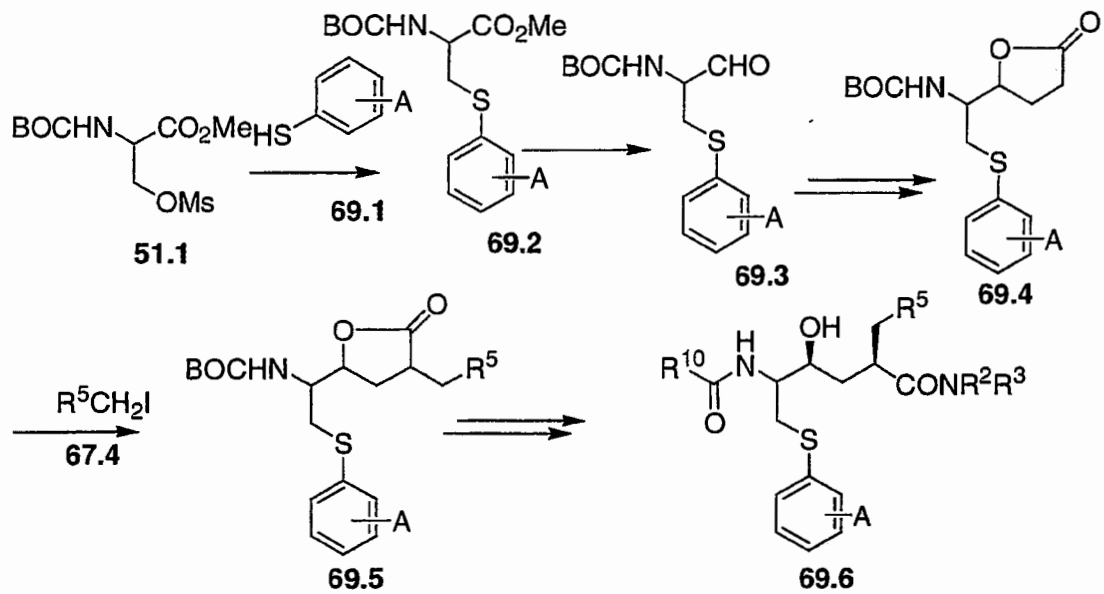
The reactions shown in Schemes **80** and **81** illustrate the preparation of the compounds **80.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **82** depicts the conversion of the compounds **80.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **16** in which X and X' are sulfur. In this procedure, the compounds **80.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **16**.

Preparation of the phosphonate ester intermediates 16 in which X is sulfur and X' is a direct bond.

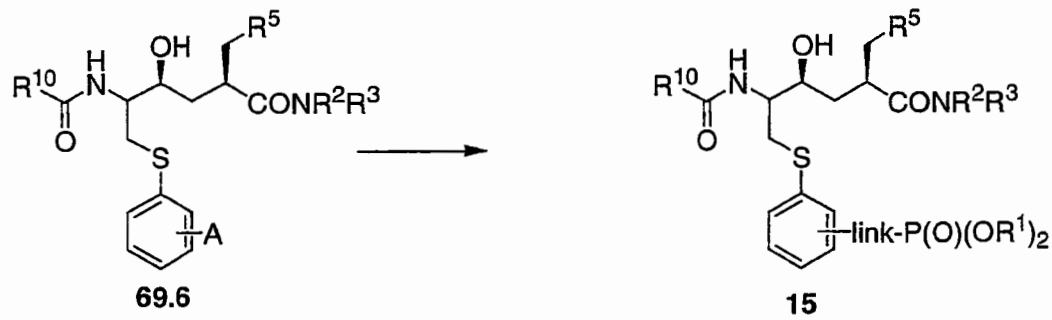
Schemes **83** and **84** illustrate the preparation of the phosphonate esters **16** in which X is sulfur and X' is a direct bond. In this procedure, the methylene lactone **53.3** is reacted, as described in Scheme **53**, with the thiol **71.2** to yield the thioether **83.1**. The product is then converted, as described in Scheme **76**, into the diamide **83.2**.

The reactions shown in Scheme **83** illustrate the preparation of the compounds **83.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **84** depicts the conversion of the compounds **83.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **16** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **83.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **16**.

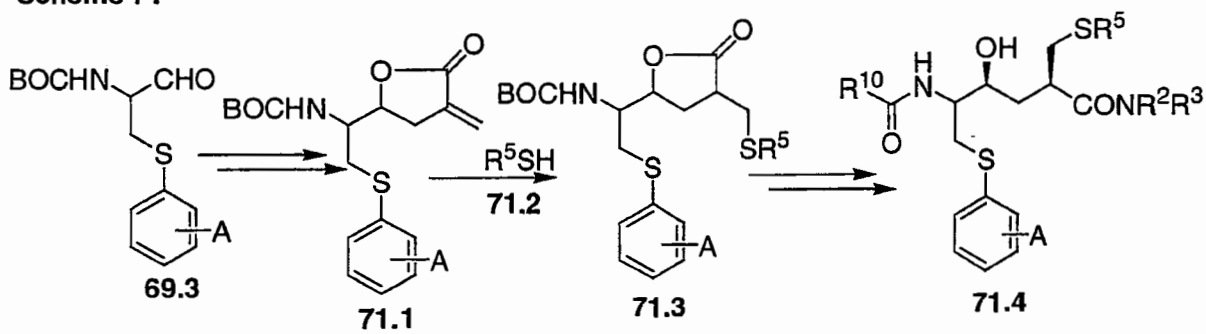
Scheme 69



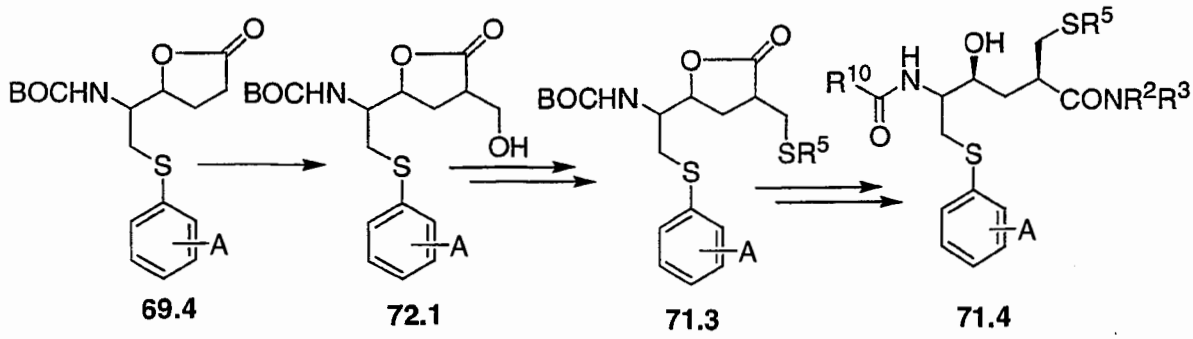
Scheme 70



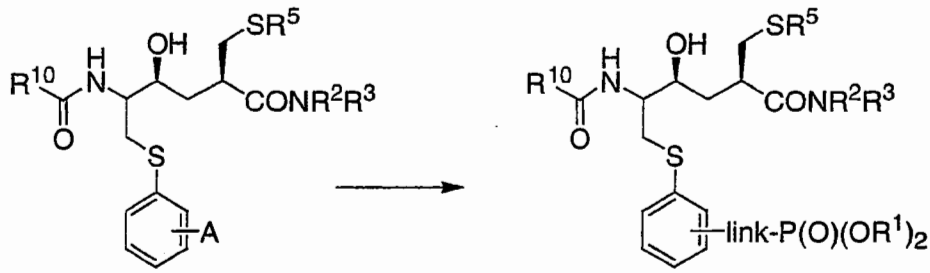
Scheme 71



Scheme 72

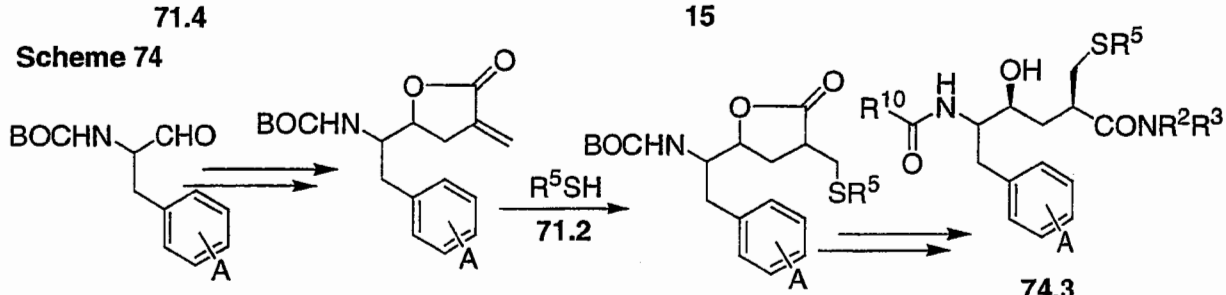


Scheme 73



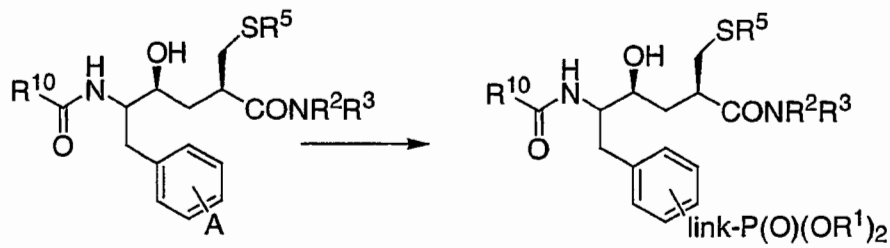
71.4 15

Scheme 74



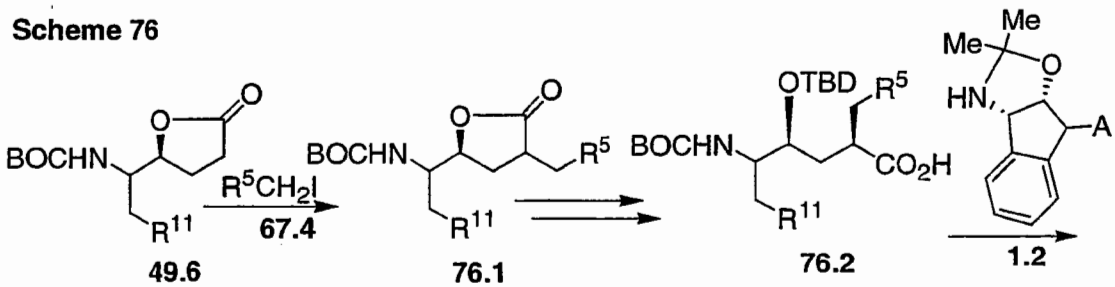
67.2 74.1 74.2 74.3

Scheme 75

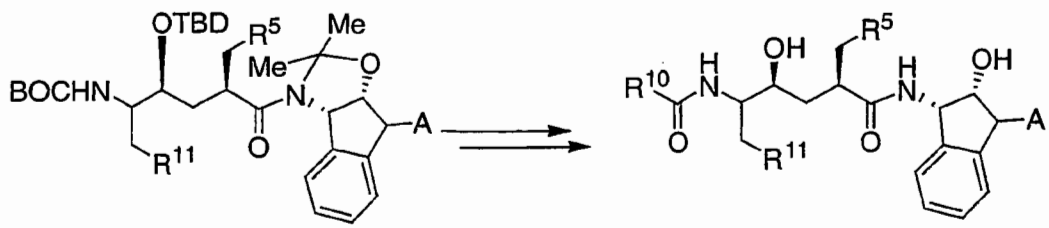


74.3 15

Scheme 76

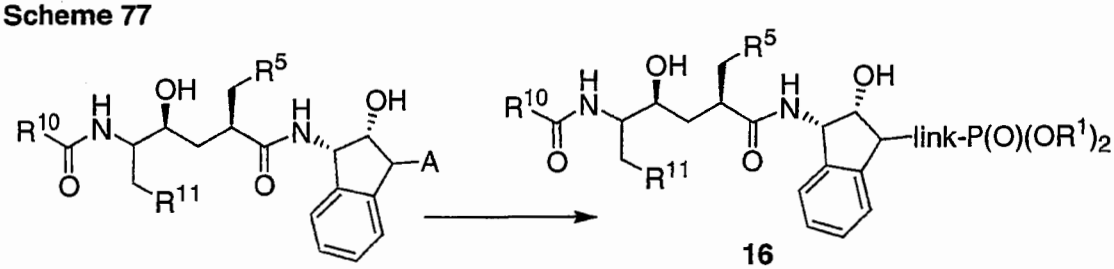


49.6 76.1 76.2



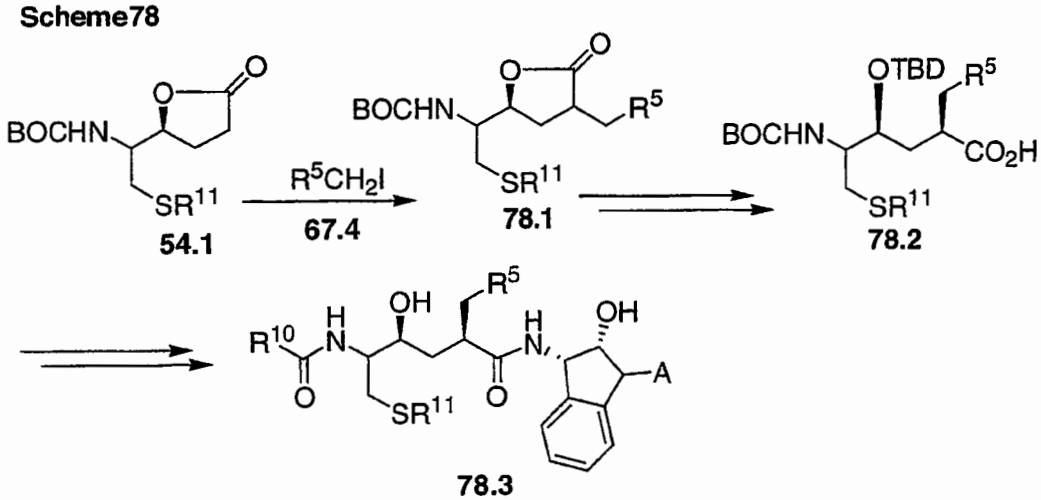
76.3 76.4

Scheme 77



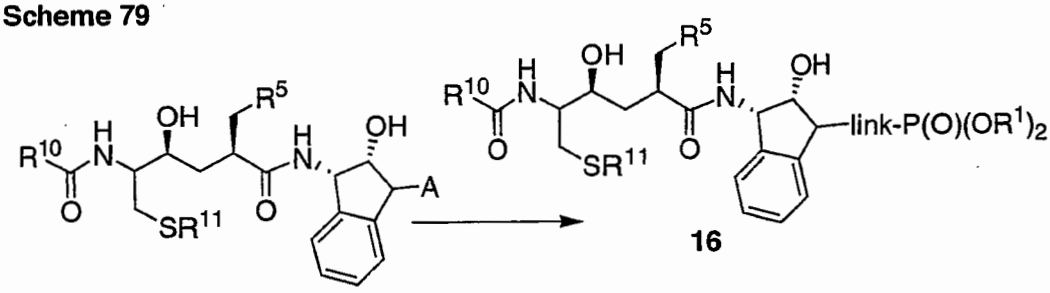
76.4 16

Scheme78



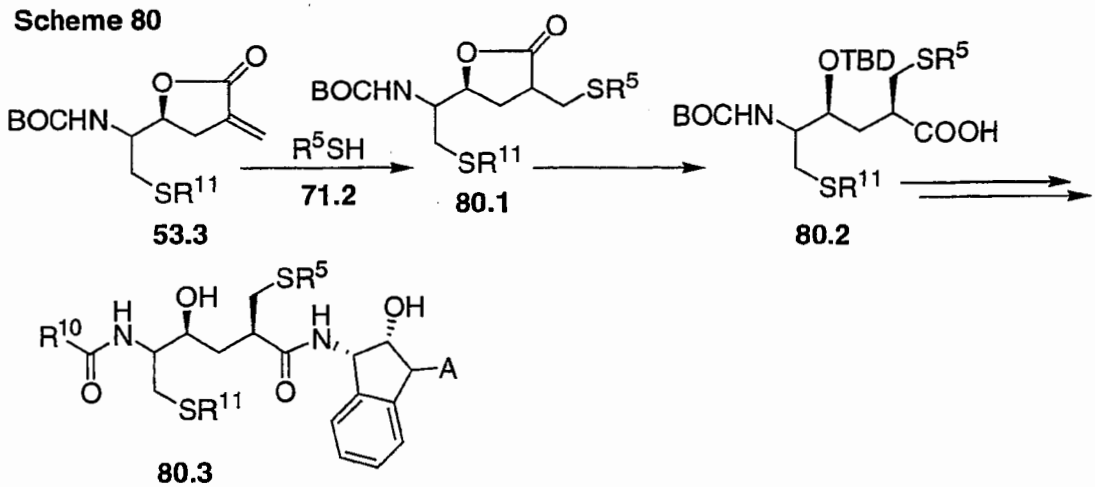
54.1 78.1 78.2 78.3

Scheme 79



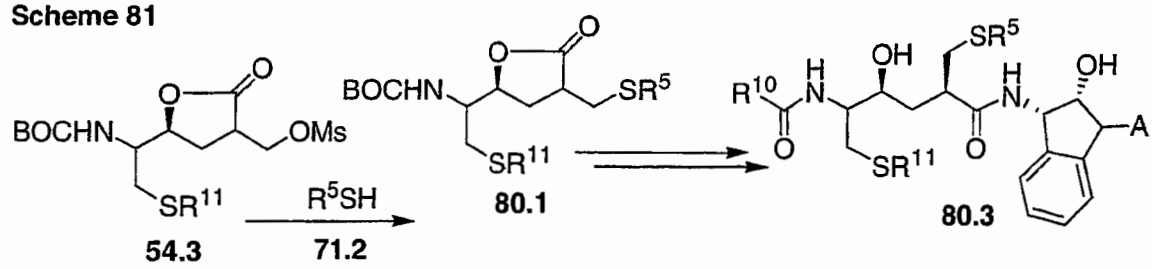
78.3

Scheme 80

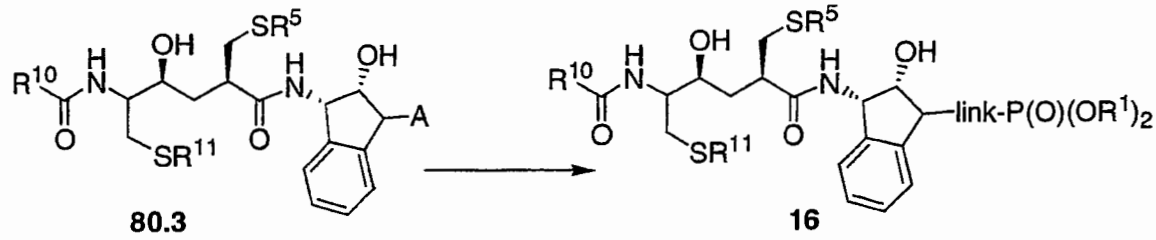


53.3 80.1 80.2 80.3

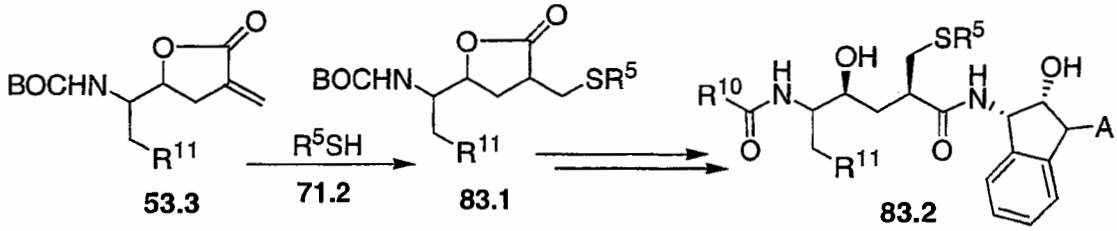
Scheme 81



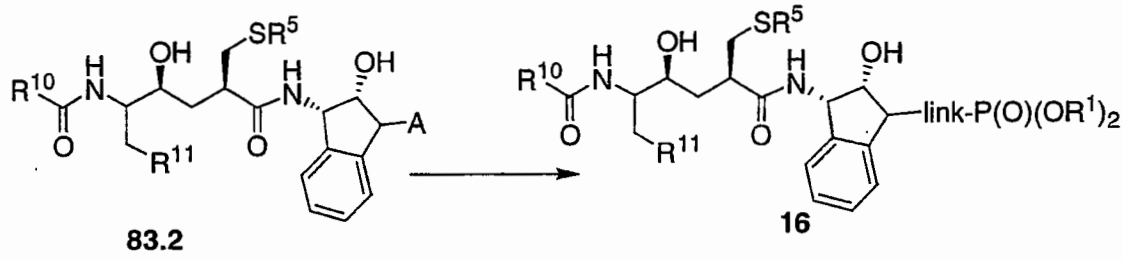
Scheme 82



Scheme 83



Scheme 84



Preparation of the phosphonate ester intermediates 17 in which X and X' are direct bonds.

Schemes **85** and **86** illustrate the preparation of the phosphonate esters **17** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **1**, with the aminochroman derivative **33.1** to afford the amide **85.1**. The product is then converted, as described in Scheme **49**, into the diamide **85.2**.

The reactions shown in Scheme **85** illustrate the preparation of the compounds **85.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **86** depicts the conversion of the compounds **85.2** in which A is [OH], [SH],

[NH], Br, into the phosphonate esters **17** in which X and X' are direct bonds. In this procedure, the compounds **85.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **17**.

Preparation of the phosphonate ester intermediates 17 in which X is a direct bond and X' is sulfur.

Schemes **87** and **88** illustrate the preparation of the phosphonate esters **17** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled with the amine **33.1** to afford the amide **87.1**. The product is then converted, as described in Scheme **49**, into the diamide **87.2**.

The reactions shown in Scheme **87** illustrate the preparation of the compounds **87.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **88** depicts the conversion of the compounds **87.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **17** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **87.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **17**.

Preparation of the phosphonate ester intermediates 17 in which X and X' are sulfur.

Schemes **89** and **90** illustrate the preparation of the phosphonate esters **17** in which X and X' are sulfur. As shown in Scheme **89**, the carboxylic acid **80.2** is coupled, as described in Scheme **1**, with the chroman amine **33.1** to give the amide **89.1**. The product is then transformed, as described in Scheme **49**, into the diamide **89.2**.

The reactions shown in Scheme **89** illustrate the preparation of the compounds **89.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **90** depicts the conversion of the compounds **89.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **17** in which X and X' are sulfur. In this procedure, the compounds **89.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **17**.

Preparation of the phosphonate ester intermediates 17 in which X is sulfur and X' is a direct bond.

Schemes **91** and **92** illustrate the preparation of the phosphonate esters **17** in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid **91.1**, which is an intermediate compound in the conversion of the lactone **83.1** into the diamide **83.2**, (Scheme **83**), is coupled, as described in Scheme **1**, with the chroman amine **33.1** to afford the amide **91.2**. The product is then converted, as described in Scheme **49**, into the diamide **91.3**.

The reactions shown in Scheme **91** illustrate the preparation of the compounds **91.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **92** depicts the conversion of the compounds **91.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **17** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **91.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **17**.

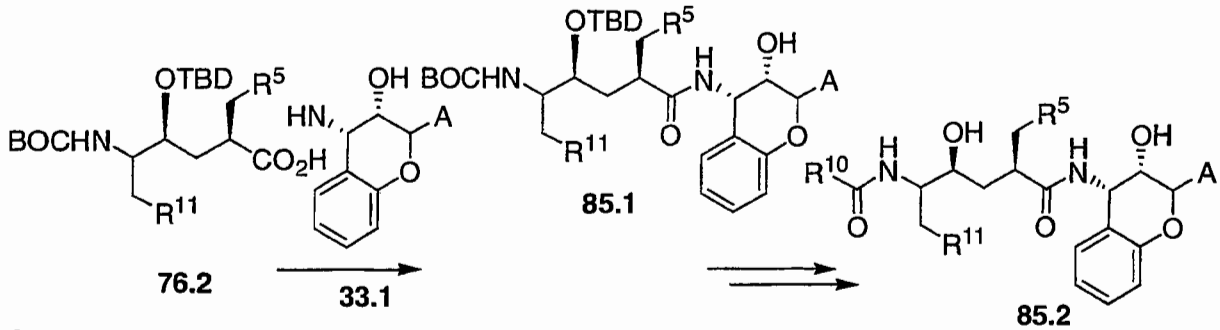
Preparation of the phosphonate ester intermediates 18 in which X and X' are direct bonds.

Schemes **93** and **94** illustrate the preparation of the phosphonate esters **18** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **1**, with the ethanolamine derivative **29.1** to afford the amide **93.1**. The product is then converted, as described in Scheme **49**, into the diamide **93.2**.

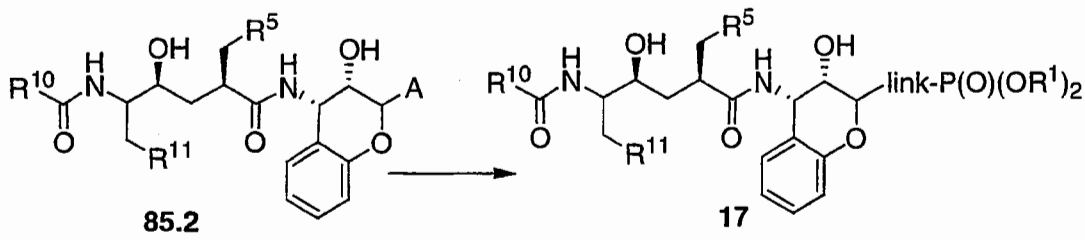
The reactions shown in Scheme **93** illustrate the preparation of the compounds **93.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **94** depicts the conversion of the compounds **93.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **18** in which X and X' are direct bonds. In this procedure, the compounds **93.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **18**.

Preparation of the phosphonate ester intermediates 18 in which X and X' are sulfur.

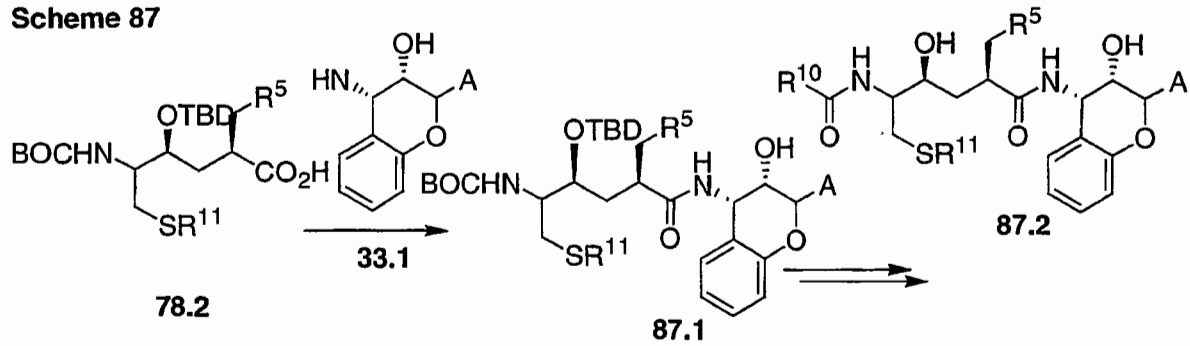
Scheme 85



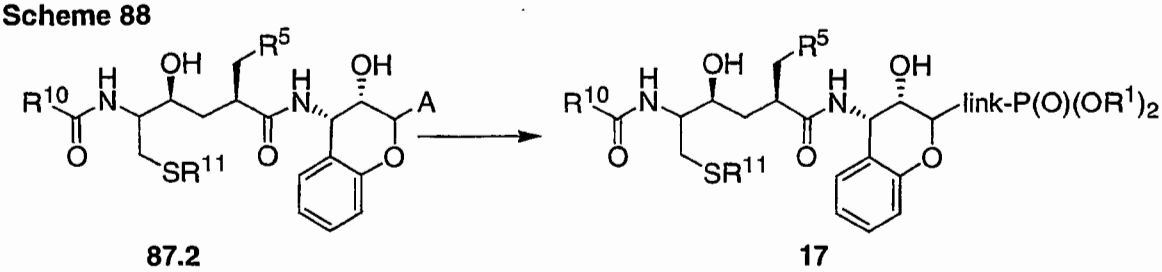
Scheme 86



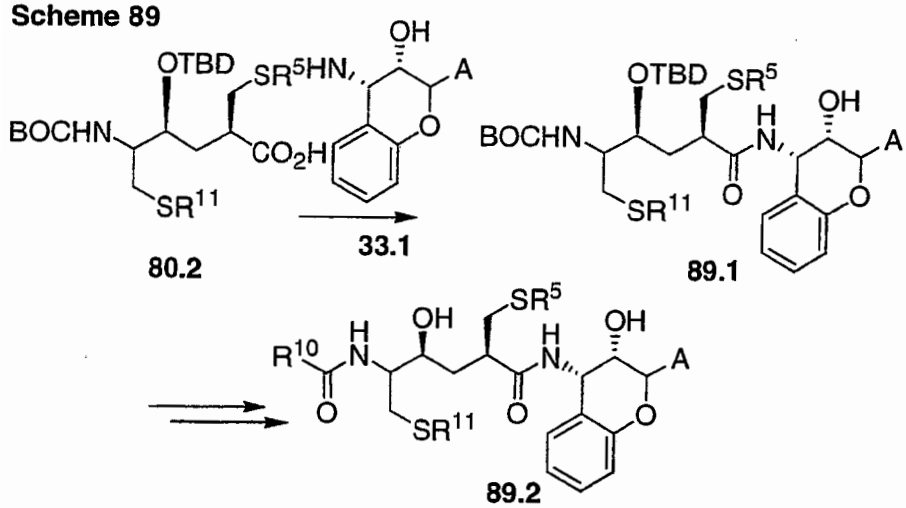
Scheme 87



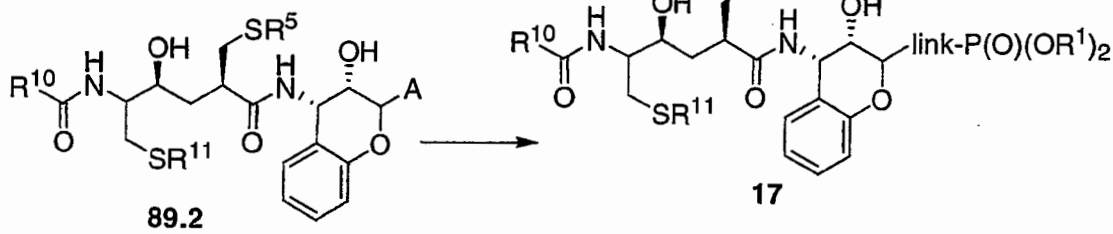
Scheme 88



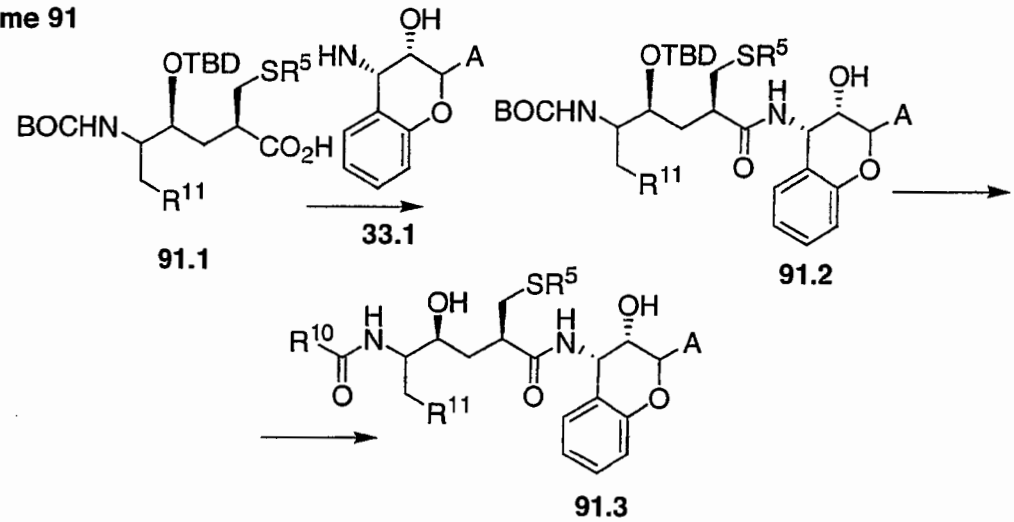
Scheme 89



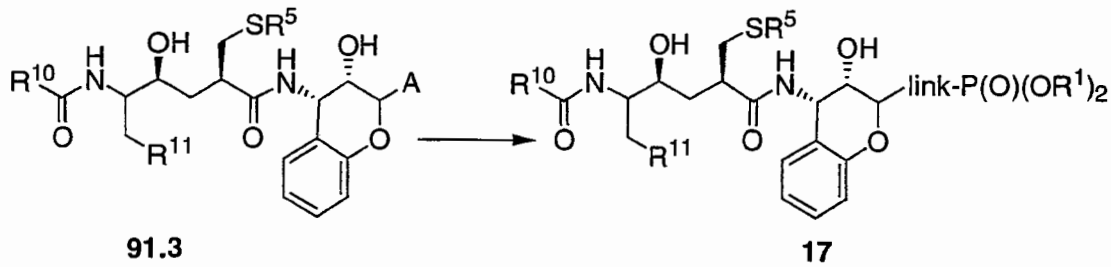
Scheme 90



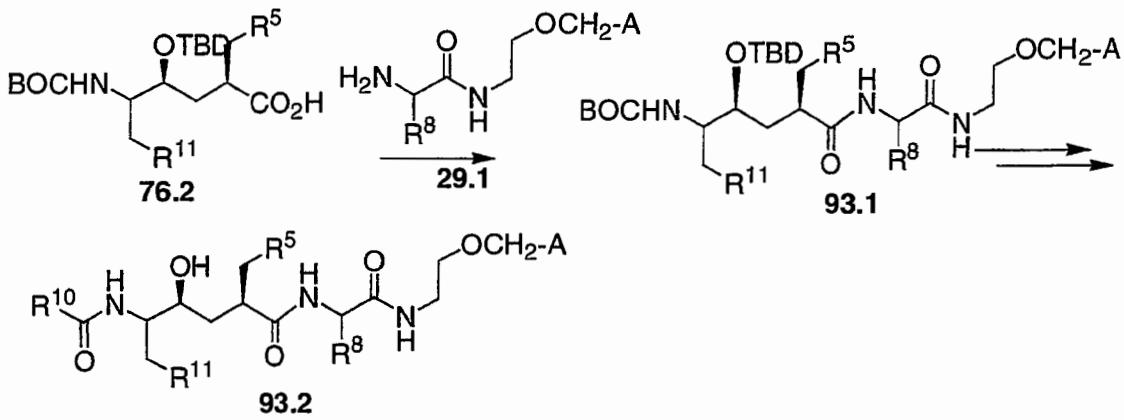
Scheme 91



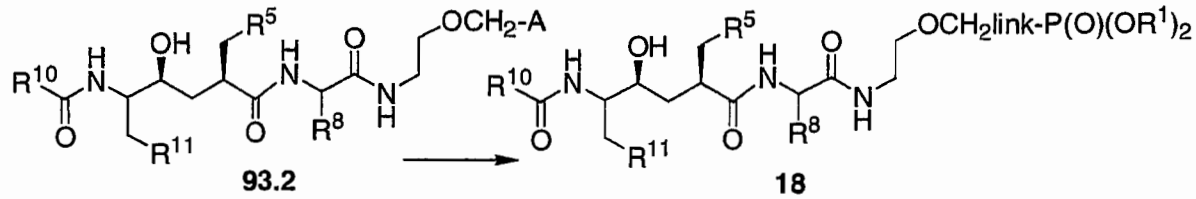
Scheme 92



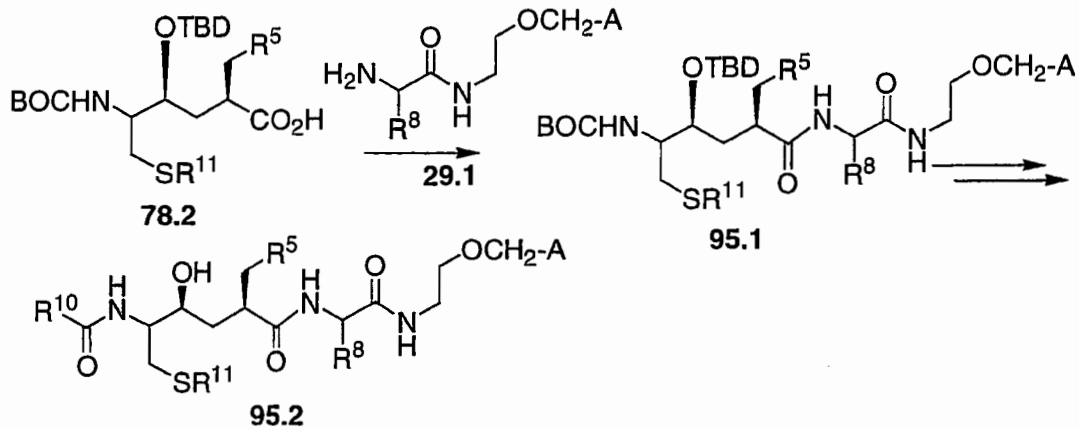
Scheme 93



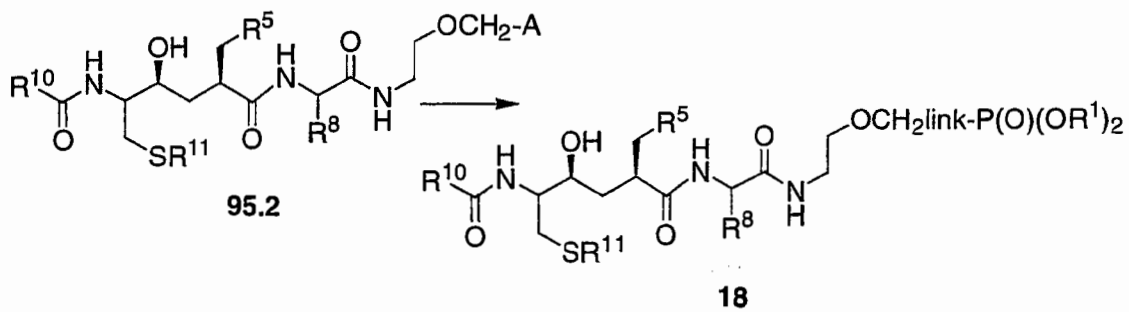
Scheme 94



Scheme 95



Scheme 96



Schemes **97** and **98** illustrate the preparation of the phosphonate esters **18** in which X and X' are sulfur. As shown in Scheme **97**, the carboxylic acid **80.2** is coupled, as described in Scheme **1**, with the ethanolamine derivative **29.1** to give the amide **97.1**. The product is then transformed, as described in Scheme **49**, into the diamide **97.2**.

The reactions shown in Scheme **97** illustrate the preparation of the compounds **97.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **98** depicts the conversion of the compounds **97.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **18** in which X and X' are sulfur. In this procedure, the compounds **97.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **18**.

Preparation of the phosphonate ester intermediates 18 in which X is sulfur and X' is a direct bond.

Schemes **99** and **100** illustrate the preparation of the phosphonate esters **18** in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid **91.1** is coupled, as described in Scheme **1**, with the ethanolamine derivative **29.1** to afford the amide **99.1**. The product is then converted, as described in Scheme **49**, into the diamide **99.2**.

The reactions shown in Scheme **99** illustrate the preparation of the compounds **99.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **100** depicts the conversion of the compounds **99.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **18** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **99.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **18**.

Preparation of the phosphonate ester intermediates 19 in which X and X' are direct bonds.

Schemes **101** and **102** illustrate the preparation of the phosphonate esters **19** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in

Scheme **1**, with the phenylalanine derivative **37.1** to afford the amide **101.1**. The product is then converted, as described in Scheme **49**, into the diamide **101.2**.

The reactions shown in Scheme **101** illustrate the preparation of the compounds **101.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **102** depicts the conversion of the compounds **101.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **19** in which X and X' are direct bonds. In this procedure, the compounds **101.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **19**.

Preparation of the phosphonate ester intermediates 19 in which X is a direct bond and X' is sulfur.

Schemes **103** and **104** illustrate the preparation of the phosphonate esters **19** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled, as described in Scheme **1**, with the amine **37.1** to afford the amide **103.1**. The product is then converted, as described in Scheme **49**, into the diamide **103.2**.

The reactions shown in Scheme **103** illustrate the preparation of the compounds **103.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **104** depicts the conversion of the compounds **103.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **19** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **103.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **19**.

Preparation of the phosphonate ester intermediates 19 in which X and X' are sulfur.

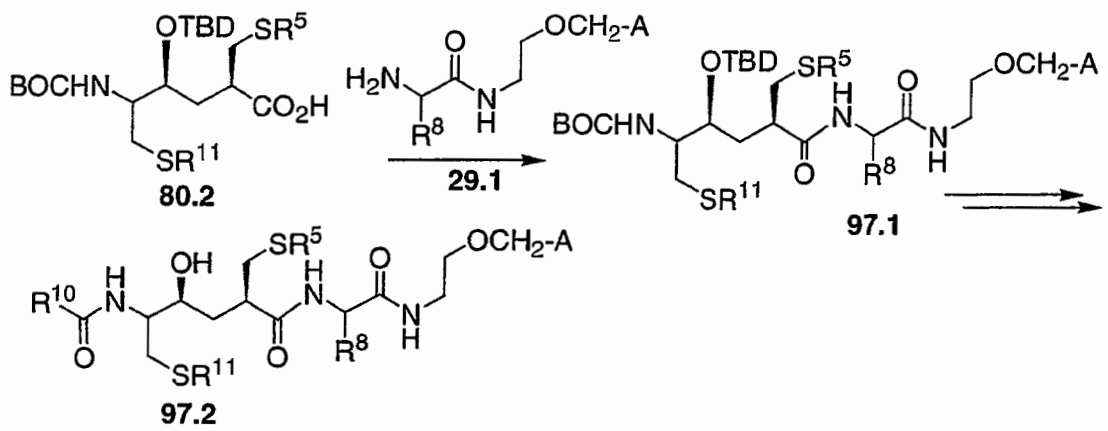
Schemes **105** and **106** illustrate the preparation of the phosphonate esters **19** in which X and X' are sulfur. As shown in Scheme **105**, the carboxylic acid **80.2** is coupled, as described in Scheme **1**, with the phenylalanine derivative **37.1** to give the amide **105.1**. The product is then transformed, as described in Scheme **49**, into the diamide **105.2**.

The reactions shown in Scheme **105** illustrate the preparation of the compounds **105.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH],

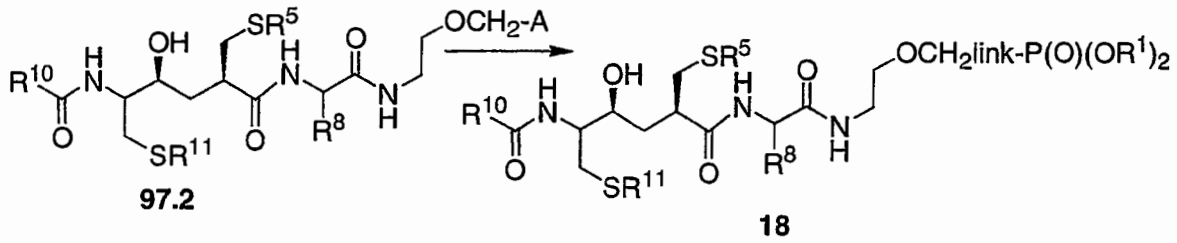
[SH], [NH], Br. Scheme **106** depicts the conversion of the compounds **105.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **19** in which X and X' are sulfur. In this procedure, the compounds **105.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **19**.

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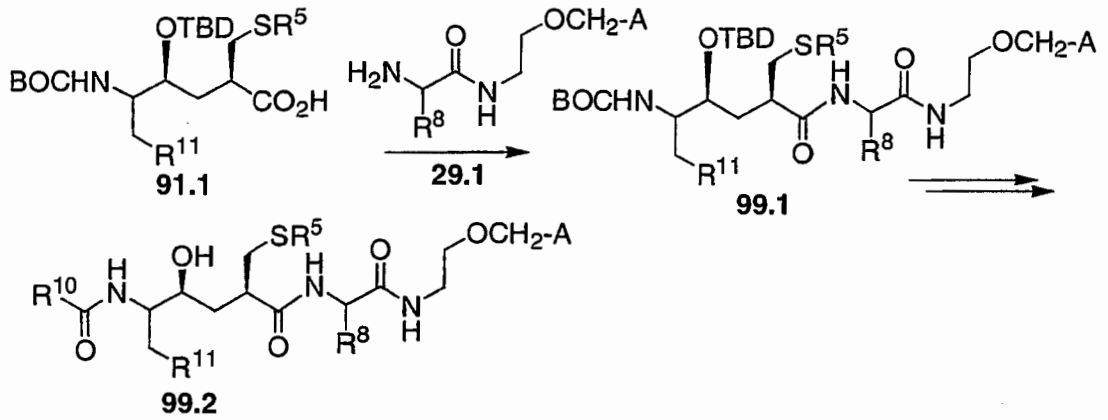
Scheme 97



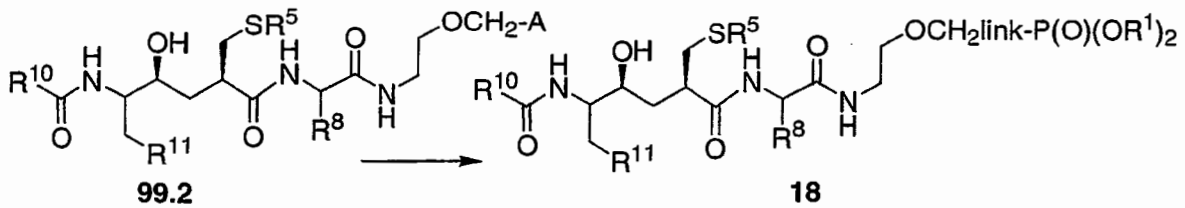
Scheme 98



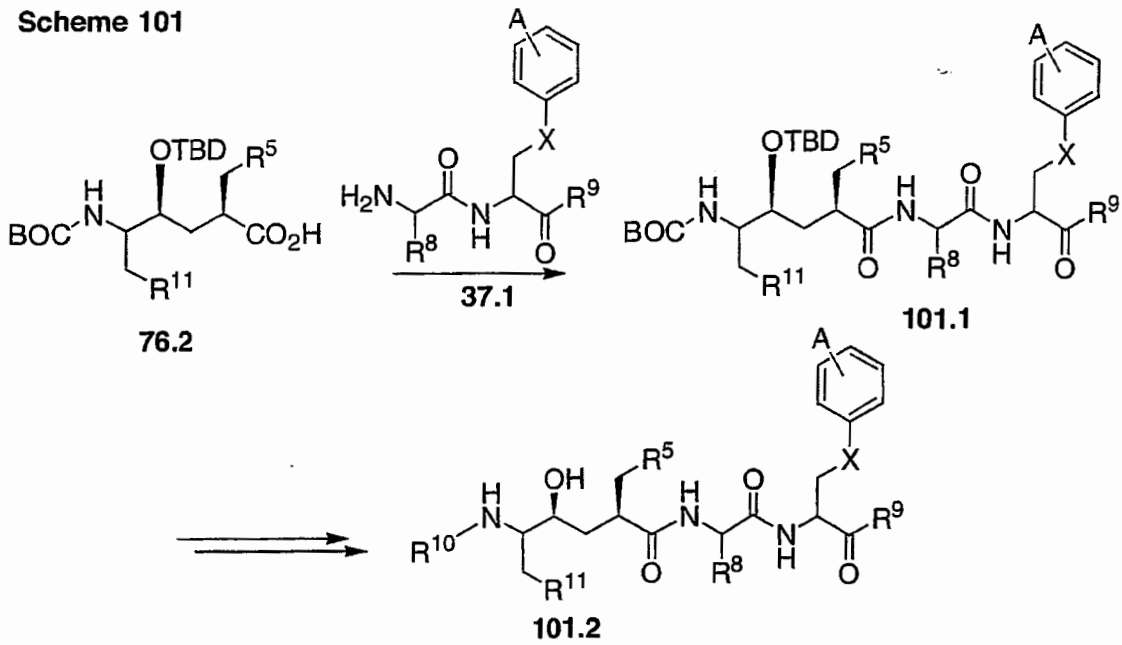
Scheme 99



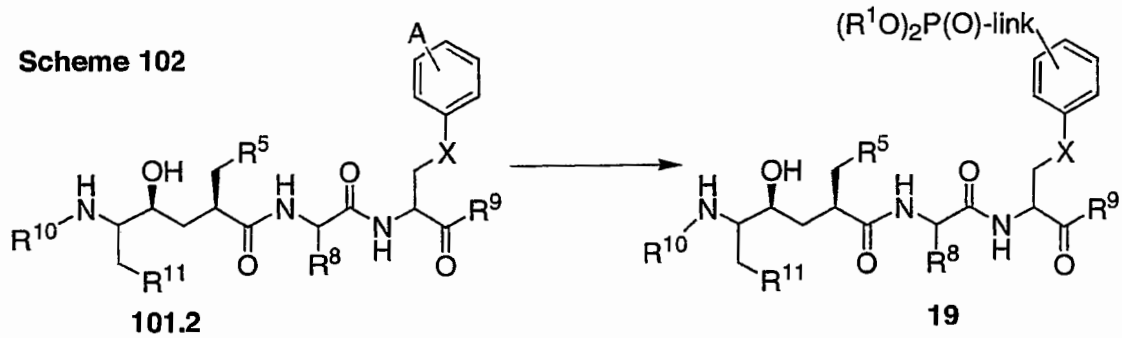
Scheme 100



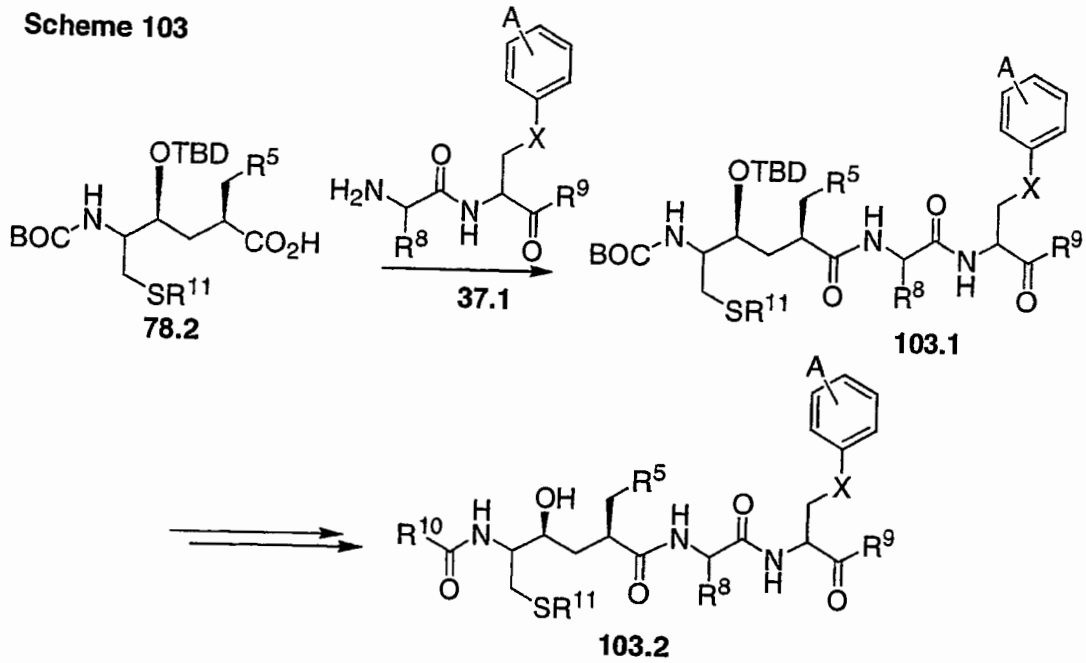
Scheme 101



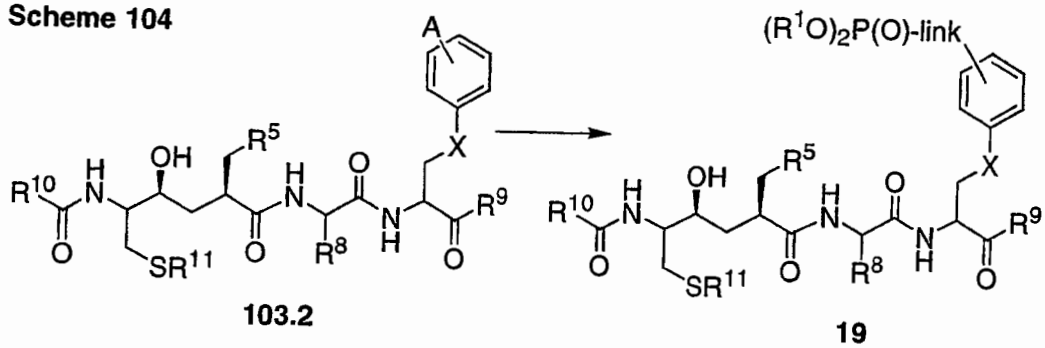
Scheme 102



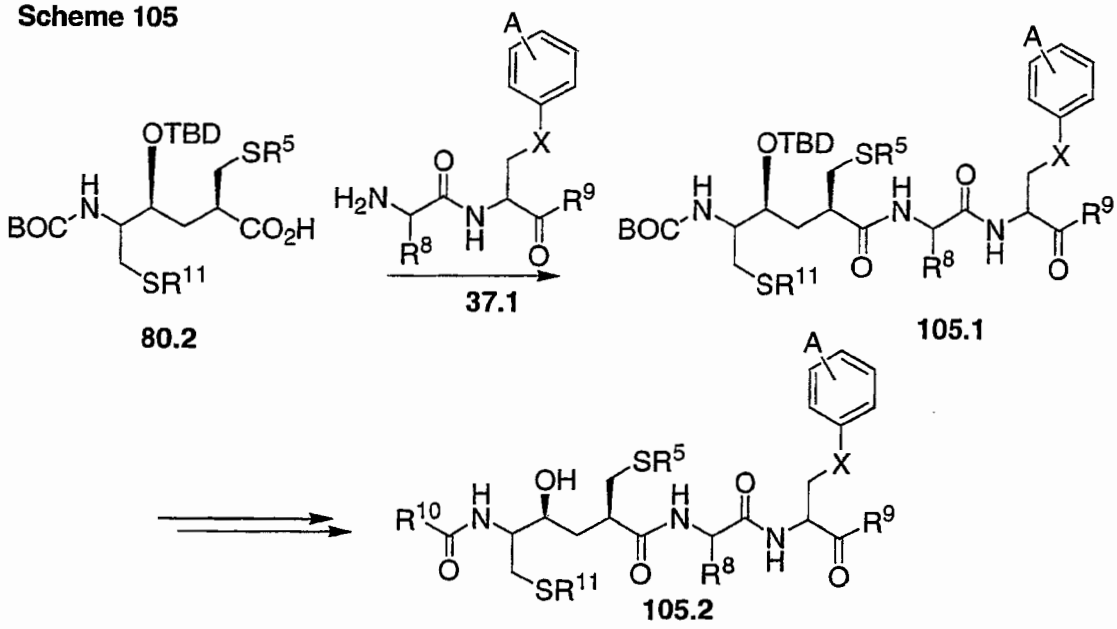
Scheme 103



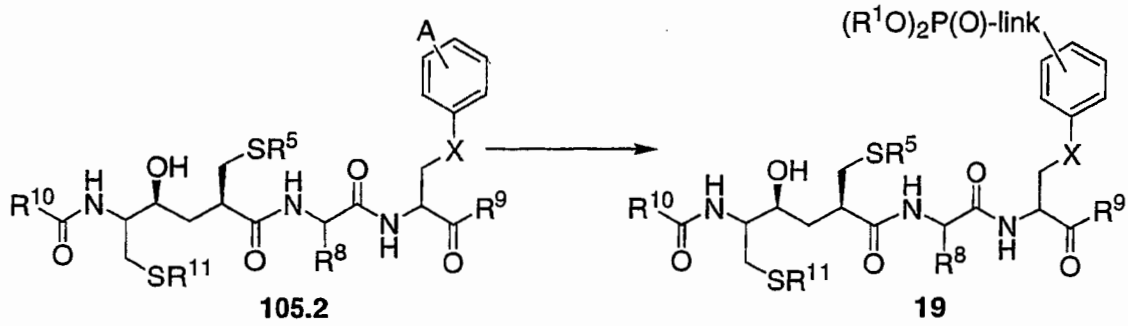
Scheme 104



Scheme 105



Scheme 106



Preparation of the phosphonate ester intermediates 19 in which X is sulfur and X' is a direct bond.

Schemes **107** and **108** illustrate the preparation of the phosphonate esters **19** in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid **91.1** is coupled, as described in Scheme **1**, with the phenylalanine derivative **37.1** to afford the amide **107.1**. The product is then converted, as described in Scheme **49**, into the diamide **107.2**.

The reactions shown in Scheme **107** illustrate the preparation of the compounds **107.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **108** depicts the conversion of the compounds **107.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **19** in which X is sulfur and X' is a direct

bond. In this procedure, the compounds **107.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **19**.

Preparation of the phosphonate ester intermediates 20 in which X and X' are direct bonds.

Schemes **109** and **110** illustrate the preparation of the phosphonate esters **20** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **1**, with the tert. butylamine derivative **41.1** to afford the amide **109.1**. The product is then converted, as described in Scheme **49**, into the diamide **109.2**.

The reactions shown in Scheme **109** illustrate the preparation of the compounds **109.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **110** depicts the conversion of the compounds **109.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X and X' are direct bonds. In this procedure, the compounds **109.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **20**.

Preparation of the phosphonate ester intermediates 20 in which X is a direct bond and X' is sulfur.

Schemes **111** and **112** illustrate the preparation of the phosphonate esters **20** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled, as described in Scheme **1**, with the amine **41.1** to afford the amide **111.1**. The product is then converted, as described in Scheme **49**, into the diamide **111.2**.

The reactions shown in Scheme **111** illustrate the preparation of the compounds **111.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **112** depicts the conversion of the compounds **111.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **111.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **20**.

Preparation of the phosphonate ester intermediates 20 in which X and X' are sulfur.

Schemes **113** and **114** illustrate the preparation of the phosphonate esters **20** in which X and X' are sulfur. As shown in Scheme **113**, the carboxylic acid **80.2** is coupled, as described in Scheme **1**, with the tert. butylamine derivative **41.1** to give the amide **113.1**. The product is then transformed, as described in Scheme **49**, into the diamide **113.2**.

The reactions shown in Scheme **113** illustrate the preparation of the compounds **113.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **114** depicts the conversion of the compounds **113.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X and X' are sulfur. In this procedure, the compounds **113.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **20**.

Preparation of the phosphonate ester intermediates 20 in which X is sulfur and X' is a direct bond.

Schemes **115** and **116** illustrate the preparation of the phosphonate esters **20** in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid **91.1** is coupled, as described in Scheme **1**, with the tert. butylamine derivative **41.1** to afford the amide **115.1**. The product is then converted, as described in Scheme **49**, into the diamide **115.2**.

The reactions shown in Scheme **115** illustrate the preparation of the compounds **115.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **116** depicts the conversion of the compounds **115.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **20** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **115.2** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **20**.

Preparation of the phosphonate ester intermediates 21 in which X and X' are direct bonds.

Schemes **117** and **118** illustrate the preparation of the phosphonate esters **21** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **1**, with the decahydroisoquinoline derivative **45.1** to afford the amide **117.1**. The product is then converted, as described in Scheme **49**, into the diamide **117.2**.

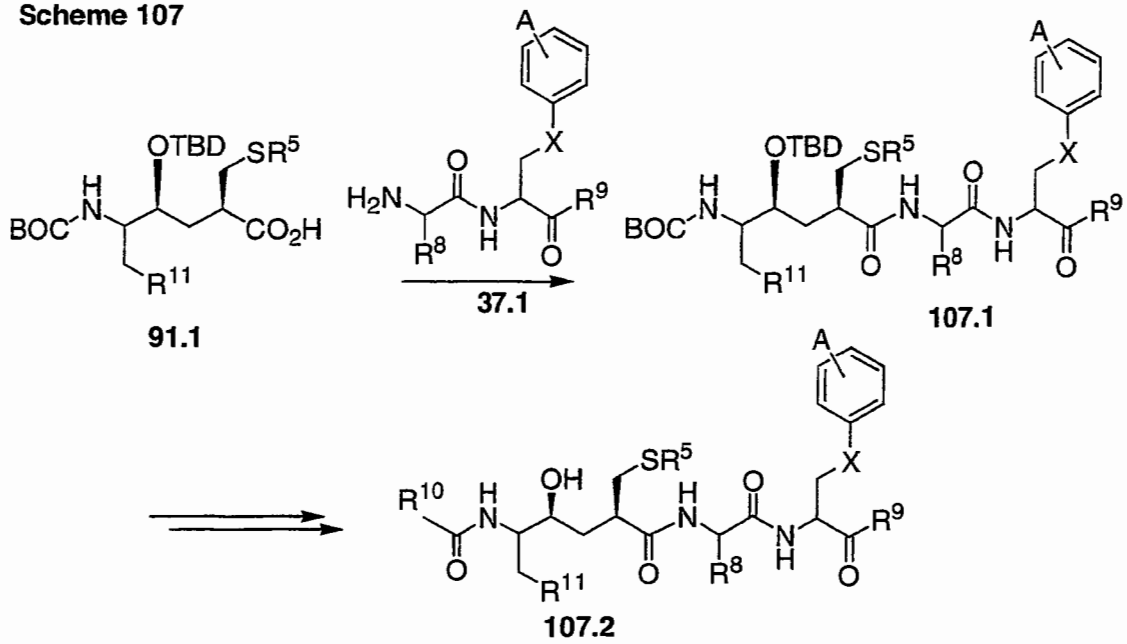
The reactions shown in Scheme **117** illustrate the preparation of the compounds **117.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **118** depicts the conversion of the compounds **117.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **21** in which X and X' are direct bonds. In this procedure, the compounds **117.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **21**.

Preparation of the phosphonate ester intermediates 21 in which X is a direct bond and X' is sulfur.

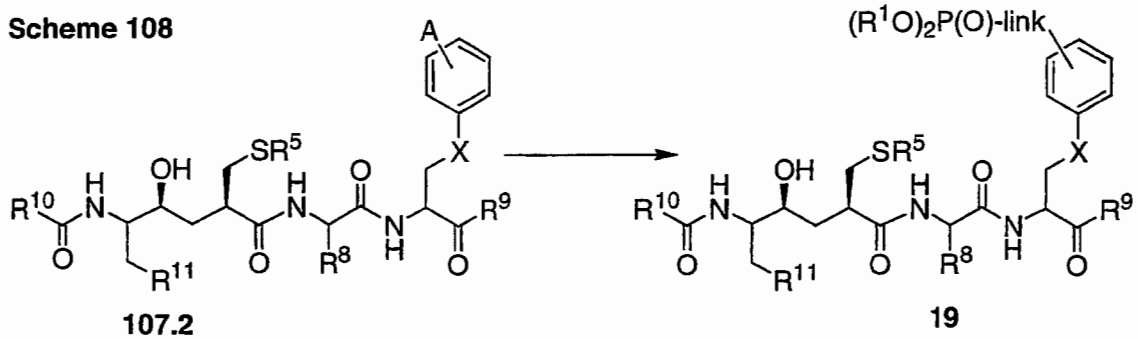
Schemes **119** and **120** illustrate the preparation of the phosphonate esters **21** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled, as described in Scheme **1**, with the amine **45.1** to afford the amide **119.1**. The product is then converted, as described in Scheme **49**, into the diamide **119.2**.

The reactions shown in Scheme **119** illustrate the preparation of the compounds **119.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **120** depicts the conversion of the compounds **119.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **21** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **119.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **21**.

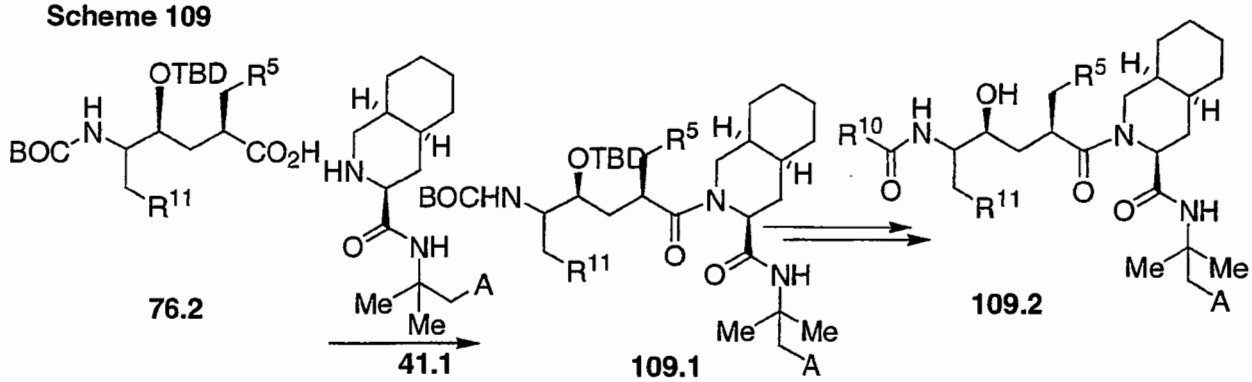
Scheme 107



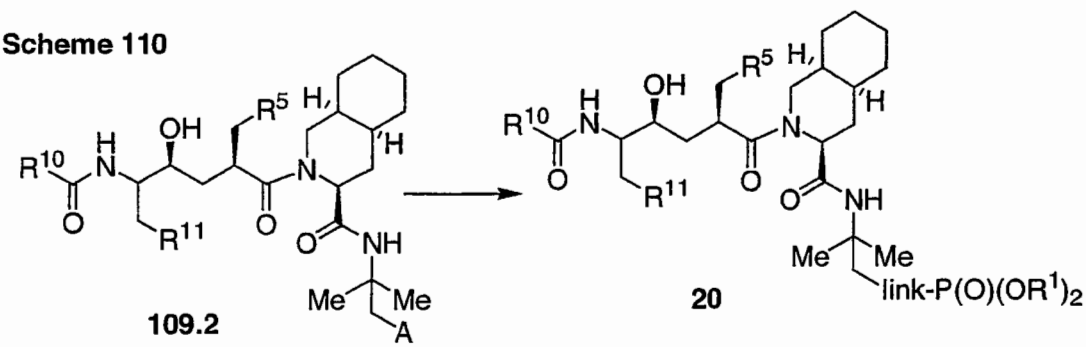
Scheme 108



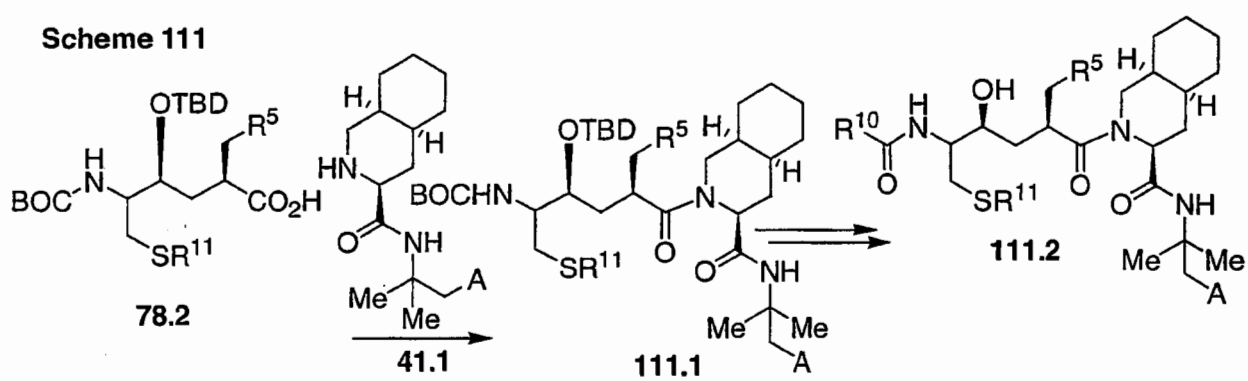
Scheme 109



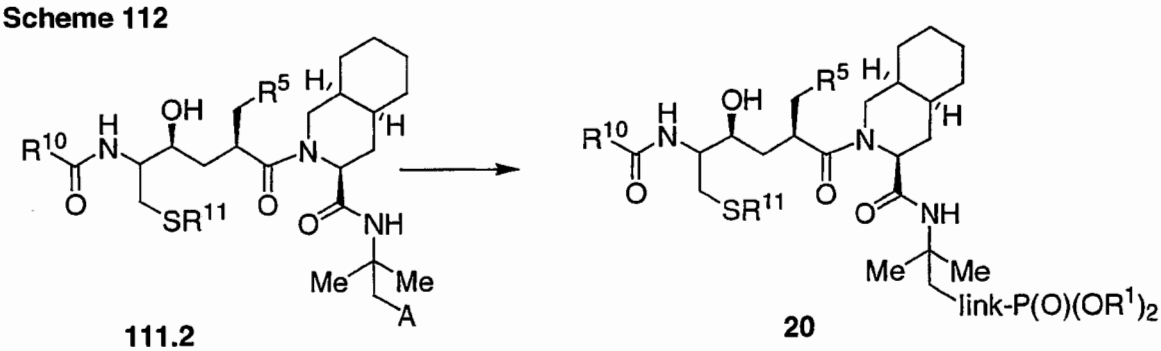
Scheme 110



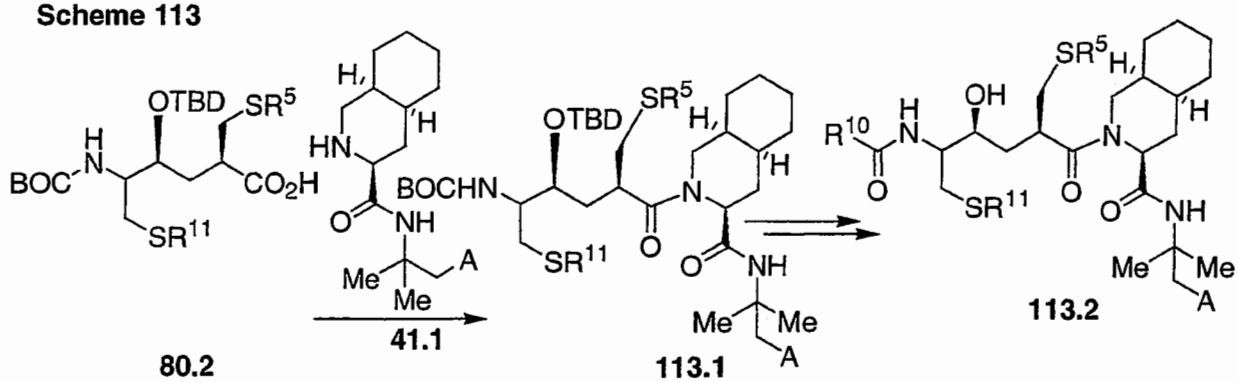
Scheme 111



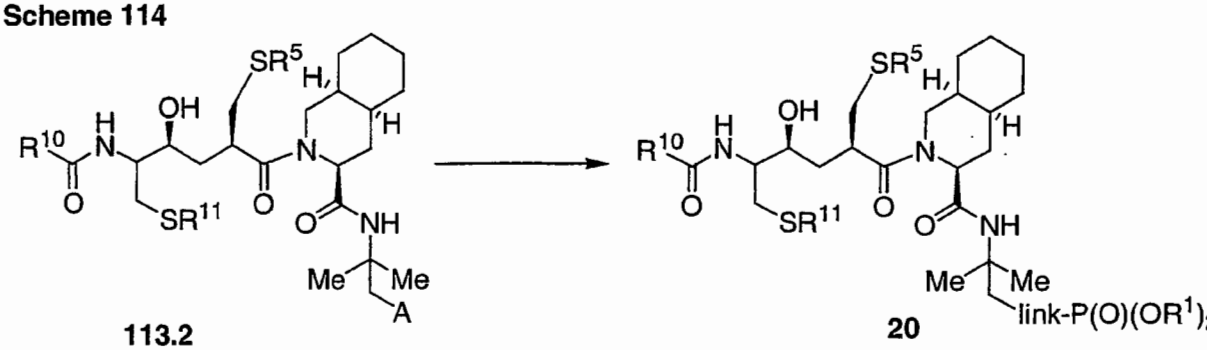
Scheme 112



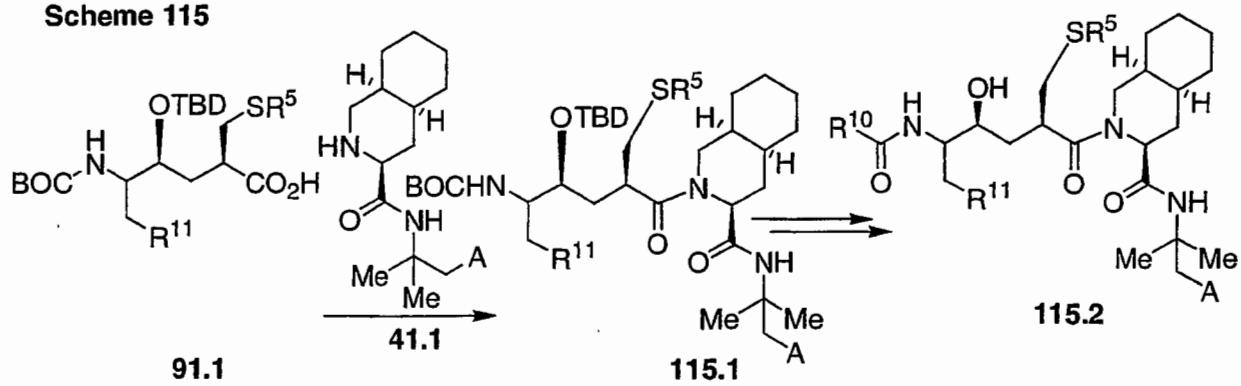
Scheme 113



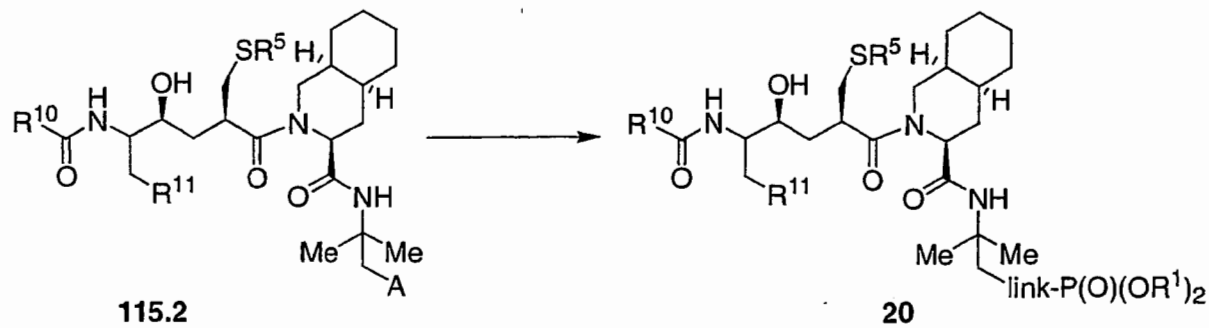
Scheme 114



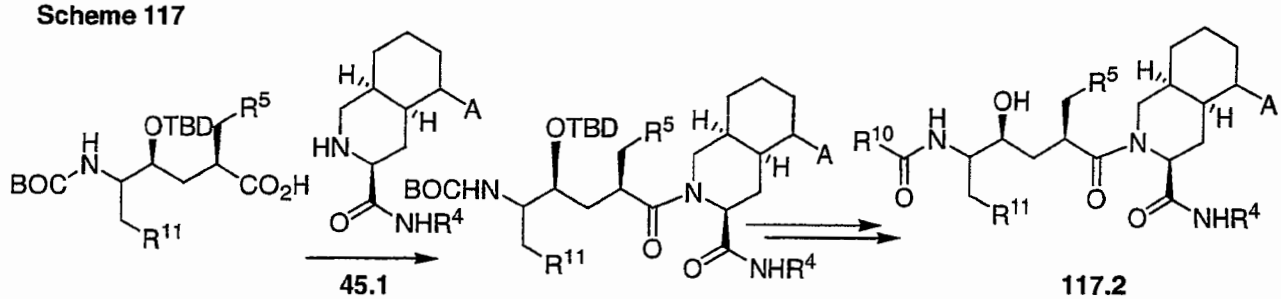
Scheme 115



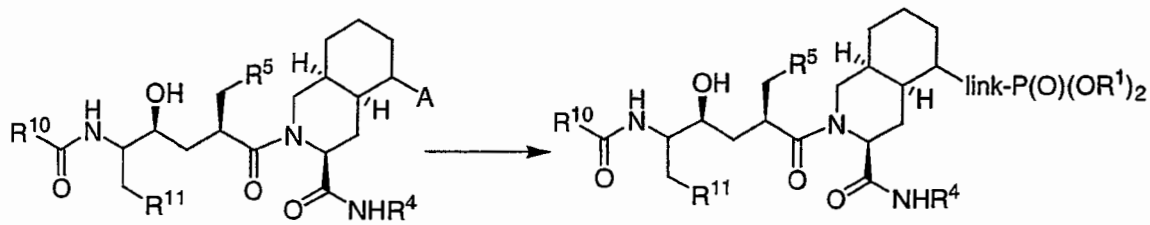
Scheme 116



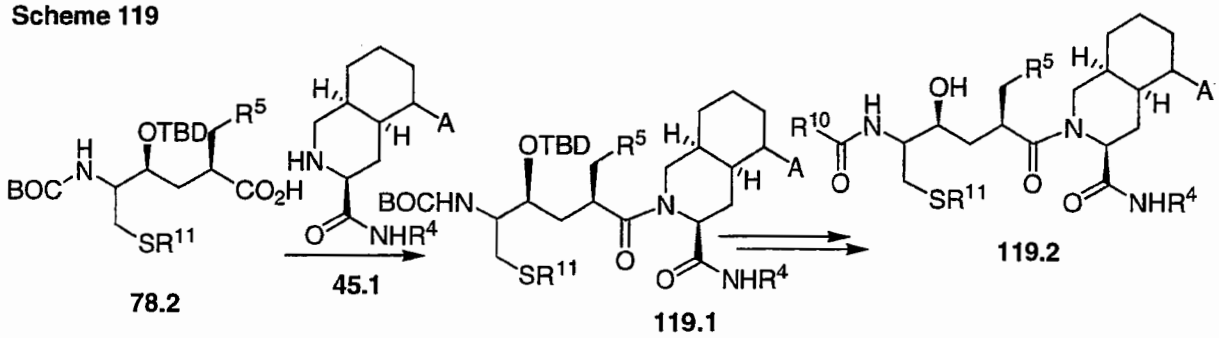
Scheme 117



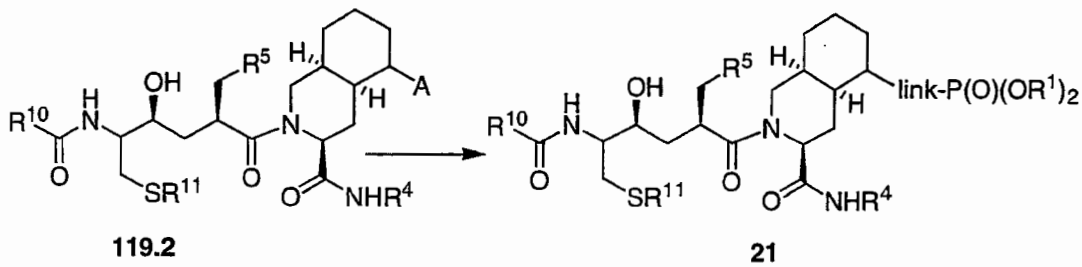
Scheme 118



Scheme 119



Scheme 120



Preparation of the phosphonate ester intermediates 21 in which X and X' are sulfur.

Schemes **121** and **122** illustrate the preparation of the phosphonate esters **21** in which X and X' are sulfur. As shown in Scheme **121**, the carboxylic acid **80.2** is coupled with the amine

45.1 to give the amide **121.1**. The product is then transformed, as described in Scheme **49**, into the diamide **121.2**.

The reactions shown in Scheme **121** illustrate the preparation of the compounds **121.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **122** depicts the conversion of the compounds **121.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **21** in which X and X' are sulfur. In this procedure, the compounds **121.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **21**.

Preparation of the phosphonate ester intermediates 21 in which X is sulfur and X' is a direct bond.

Schemes **123** and **124** illustrate the preparation of the phosphonate esters **21** in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid **91.1** is coupled, as described in Scheme **1**, with the amine **45.1** to afford the amide **123.1**. The product is then converted, as described in Scheme **49**, into the diamide **123.2**.

The reactions shown in Schemes **123** illustrate the preparation of the compounds **123.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **124** depicts the conversion of the compounds **123.2** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **21** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **123.2** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **21**.

Preparation of the phosphonate ester intermediates 22 in which X and X' are direct bonds.

Schemes **125** and **126** illustrate the preparation of the phosphonate esters **22** in which X and X' are direct bonds. In this procedure, the carboxylic acid **76.2** is coupled, as described in Scheme **5** with the amine **1.6**, to afford the amide **125.1**. The BOC protecting group is then removed, as described in Scheme **49**, to yield the amine **125.2**. The latter compound is then

coupled with the carboxylic acid **125.3** to produce the amide **125.4**. The preparation of the carboxylic acid reactant **125.3** is described in Scheme **191**.

The reactions shown in Scheme **125** illustrate the preparation of the compounds **125.4** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **126** depicts the conversion of the compounds **125.4** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **22** in which X and X' are direct bonds. In this procedure, the compounds **125.4** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **22**

Preparation of the phosphonate ester intermediates 22 in which X is a direct bond and X' is sulfur.

Schemes **127** and **128** illustrate the preparation of the phosphonate esters **22** in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid **78.2** is coupled, as described in Scheme **5** with the amine **1.6**, to afford the amide **127.1**. The BOC protecting group is then removed, as described in Scheme **49**, to yield the amine **127.2**. The latter compound is then coupled, as described in Scheme **1**, with the carboxylic acid **125.3** to produce the amide **127.3**.

The reactions shown in Scheme **127** illustrate the preparation of the compounds **127.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **128** depicts the conversion of the compounds **127.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **22,** in which X is a direct bond and X' is sulfur. In this procedure, the compounds **127.3** are converted, using the procedures described below, Schemes **133** - **197**, into the compounds **22**.

Preparation of the phosphonate ester intermediates 22 in which X and X' are sulfur.

Schemes **129** and **130** illustrate the preparation of the phosphonate esters **22** in which X and X' are sulfur. As shown in Scheme **129**, the carboxylic acid **80.2** is coupled, as described in Scheme **5**, with the amine **1.6**, to afford the amide **129.1**. The BOC protecting group is then

removed, as described in Scheme **49**, to yield the amine **129.2**. The latter compound is then coupled, as described in Scheme **1**, with the carboxylic acid **125.3** to produce the amide **129.3**.

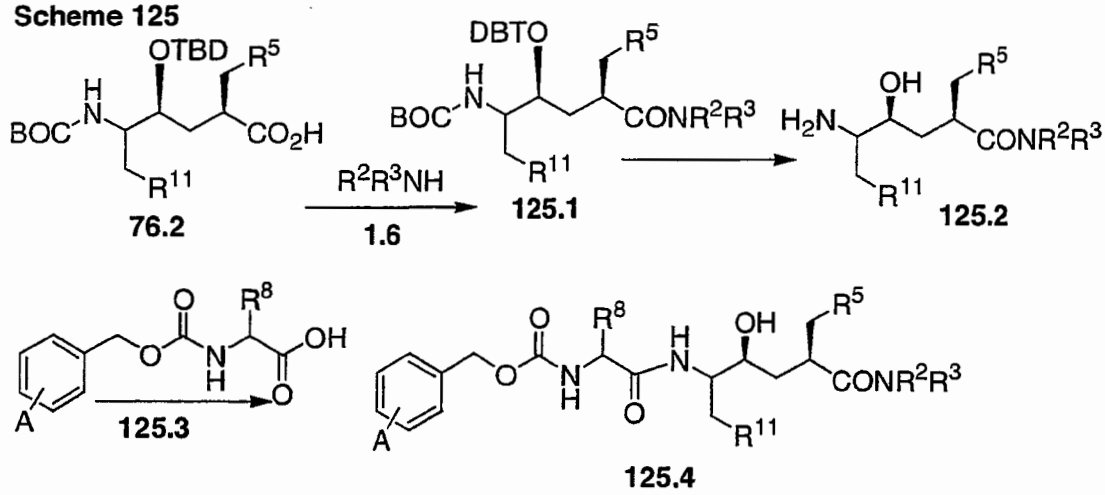
The reactions shown in Scheme **129** illustrate the preparation of the compounds **129.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **130** depicts the conversion of the compounds **129.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **22,** in which X and X' are sulfur. In this procedure, the compounds **129.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **22**.

Preparation of the phosphonate ester intermediates 22 in which X is sulfur and X' is a direct bond.

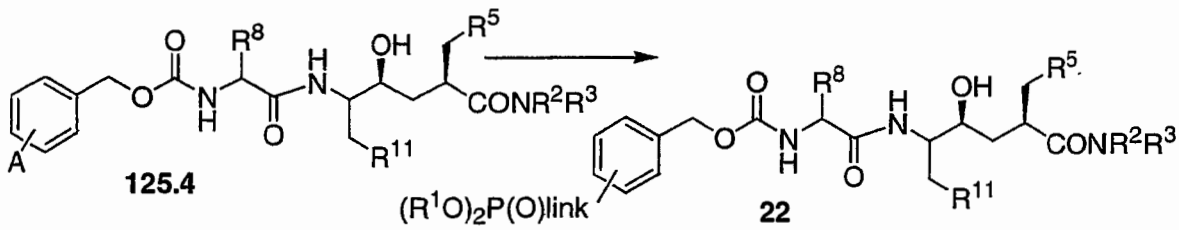
Schemes **131** and **132** illustrate the preparation of the phosphonate esters **22** in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid **91.1** is coupled, as described in Scheme **5**, with the amine **1.6**, to afford the amide **131.1**. The BOC protecting group is then removed, as described in Scheme **49**, to yield the amine **131.2**. The latter compound is then coupled, as described in Scheme **1**, with the carboxylic acid **125.3** to produce the amide **131.3**.

The reactions shown in Scheme **131** illustrate the preparation of the compounds **131.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme **132** depicts the conversion of the compounds **131.3** in which A is [OH], [SH], [NH], Br, into the phosphonate esters **22** in which X is sulfur and X' is a direct bond. In this procedure, the compounds **131.3** are converted, using the procedures described below, Schemes **133 - 197**, into the compounds **22**.

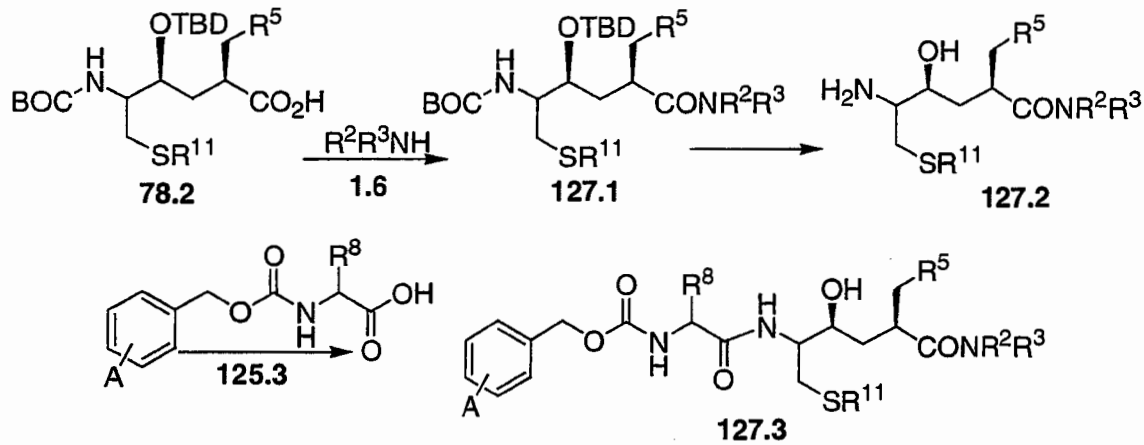
Scheme 125



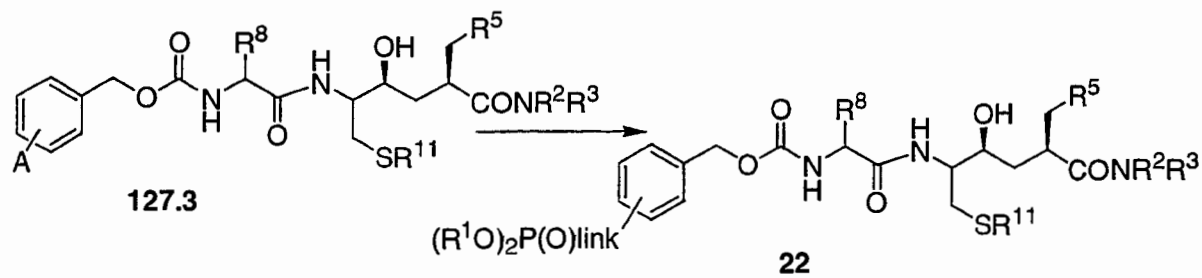
Scheme 126



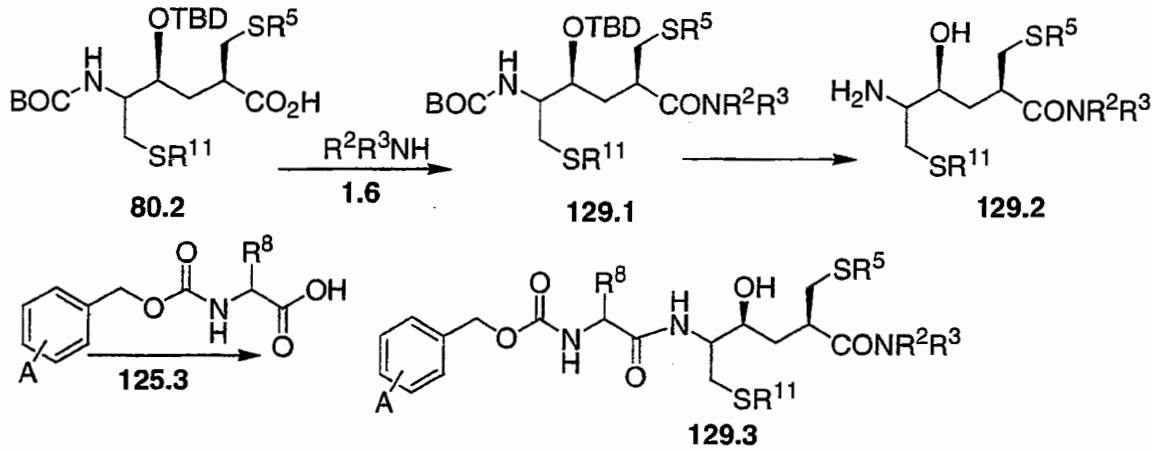
Scheme 127



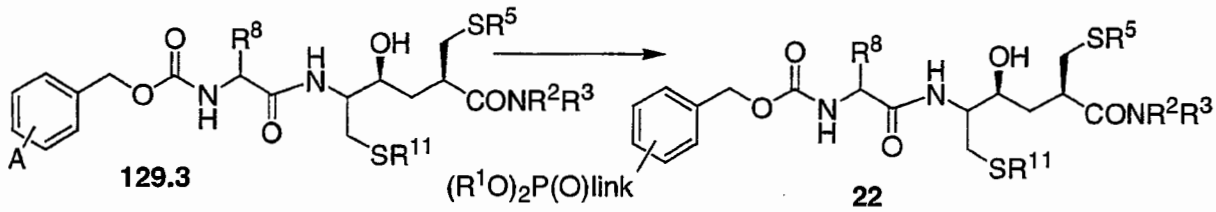
Scheme 128



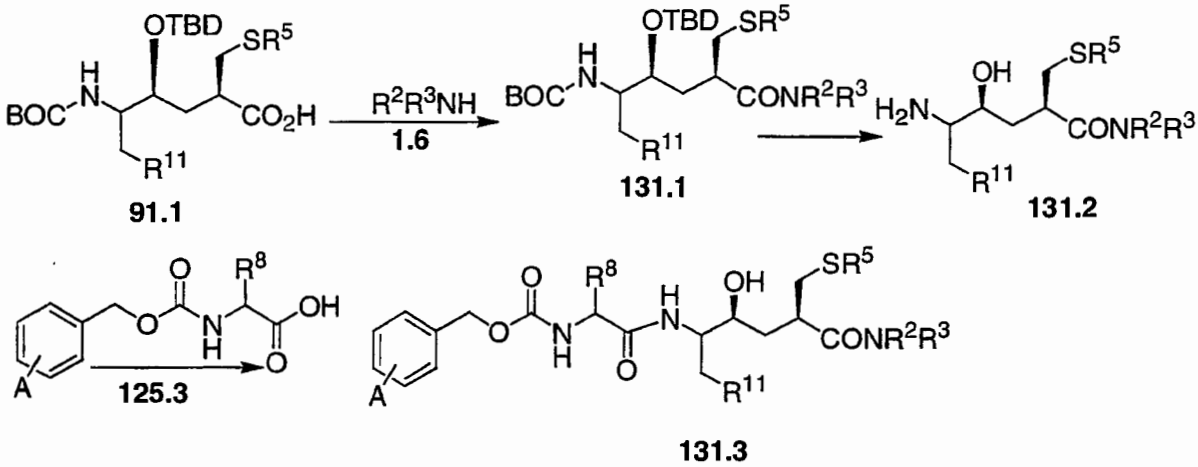
Scheme 129



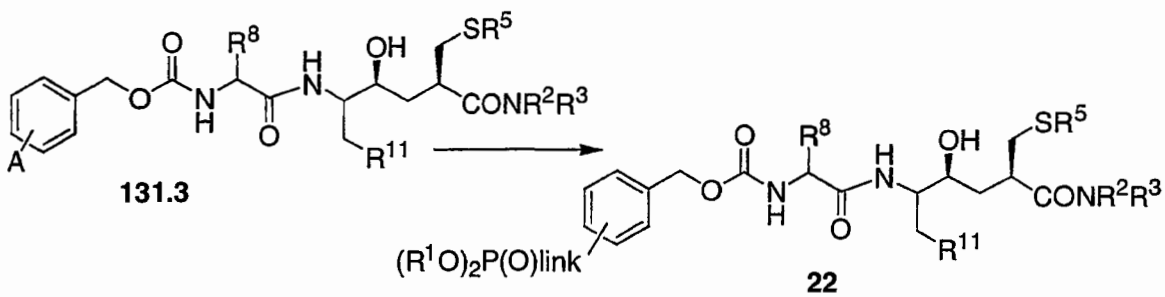
Scheme 130



Scheme 131



Scheme 132



Preparation of aminoindanol derivatives 1.2 incorporating phosphonate moieties.

Scheme **133** illustrates the preparation of variously substituted derivatives of 3-amino-indan-1,2-diol, the preparation of which is described in J. Med. Chem., 1991, 34, 1228. The alcohols, thiols, amines and bromo compounds shown in Scheme **133** can then be transformed into phosphonate-containing reactants **1.2**, as described below, (Schemes **134** - **137**). The reactants **1.2** are employed in the preparation of the phosphonate esters **1** and **16**.

In order to effect changes to the 1-substituent, the starting material **133.1** is transformed into the protected compound **133.2**. For example, the aminoalcohol **133.1** is treated with 2-methoxypropene in the presence of an acid catalyst, such as p-toluenesulfonic acid, in a solvent such as tetrahydrofuran, as described in WO9628439, to afford the acetonide-protected product **133.2**.

The amino group present in **133.2** is protected to afford the intermediate **133.3**, in which R^{12} is a protecting group, stable to the subsequent reactions. For example, R^{12} can be carbobenzyloxy (cbz), tert-butoxycarbonyl (BOC) and the like, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 309.

The free hydroxyl group present in the N-protected acetonide **133.3** is then converted into a suitable leaving group, such as, for example, trifluoromethylsulfonyloxy, p-toluenesulfonyloxy or, preferably, methanesulfonyloxy. This transformation is effected by treatment of **133.3** with a slight molar excess of the corresponding acid chloride or anhydride, in the presence of an organic base.

For example, treatment of **133.3** with methanesulfonyl chloride and pyridine in dichloromethane at ambient temperature affords the mesylate **133.4**.

The α-mesylate group in the product **133.4** is then subjected to displacement reactions with nitrogen, sulfur or oxygen nucleophiles, to effect introduction of the various heteroatoms with inversion of stereochemistry.

For example, the mesylate **133.4** is reacted with a nitrogen nucleophile such as potassium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 399, to afford the amine **133.9**.

Preferably, the mesylate **133.4** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such

as, for example, dimethylformamide, at ambient temperature, to afford the displacement product **133.5**, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the β-amine **133.9**.

The mesylate **133.4** is treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate group, followed by mild basic hydrolysis, for example by treatment with aqueous sodium bicarbonate or aqueous ammonia, to afford the β-thiol **133.12**.

Preferably, the mesylate **133.4** is reacted with one molar equivalent of potassium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **133.8**. The product then treated with a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the β-thiol **133.12**.

The mesylate **133.4** is transformed into the β-carbinol **133.7**, by treatment with an oxygen nucleophile. Conversion of sulfonate esters and related compounds to the corresponding carbinols is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 481. For example, the mesylate can be reacted with potassium superoxide, in the presence of a crown ether such as 18-crown-6, as described in Tet. Lett., 3183, 1975, to afford the β-carbinol **133.7**.

The carbinol **133.3** is also transformed into the β-bromo compound **133.6**. Methods for the conversion of carbinols to bromo compounds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 356.

For example, the α-carbinol **133.3** is reacted with hexabromoethane and triphenylphosphine, in an aprotic solvent such as ethyl acetate, as described in Syn., 139, 1983, to afford the β-bromo compound **133.6**.

Using the above described procedures for the conversion of the α-carbinol **133.3** into the β-oriented amine **133.9**, thiol **133.12** and bromo compound **133.6**, the β-carbinol **133.7** is transformed into the α-oriented amine or thiol **133.11** or the bromo compound **133.10**.

Schemes **134** - **137** illustrate the preparation of aminoindanol derivatives incorporating the group link-P(O)(OR^1)$_2$, derived from the intermediates whose syntheses are described above (Scheme **133**).

Scheme **134** depicts the preparation of phosphonate esters linked to the aminoindanol nucleus by means of a carbon chain and a heteroatom O, S or N. In this procedure, the hetero-substituted indanol **134.1** is reacted with a bromoalkylphosphonate **134.2**, in the presence of a suitable base. The base required for this transformation depends on the nature of the heteroatom X. For example, if X is N or S, an excess of an inorganic base such as, for example, potassium carbonate, in the presence of an organic solvent such as dimethylformamide, is suitable. The reaction proceeds at from ambient temperature to about 80°C to afford the displacement products **134.3**. If X is O, an equimolar amount of a strong base, such as, for example, lithium hexamethyldisilylazide and the like, is employed, in the presence of a solvent such as tetrahydrofuran. Deprotection, by removal of the group R^{12}, then affords the amine **134.4**.

For example, the β-thiol **133.12** is reacted with an equimolar amount of dialkyl 4-bromobutyl phosphonate **134.5**, the preparation of which is described in Synthesis, 1999, 9, 909, in dimethylformamide containing excess potassium carbonate, at ca 60°C to afford the thioether phosphonate product **134.6**. Deprotection then affords the amine **134.7.**

Using the above procedures, but employing, in place of the thiol **133.12**, different carbinols, thiols or amines **134.1**, and/or different bromoalkylphosphonates **134.2**, the corresponding products **134.4** are obtained.

Scheme **135** illustrates the preparation of aminoindanol derivatives in which the phosphonate ester group is attached by means of a nitrogen atom and a carbon chain. In this method, the aminoindanol **135.1** is reacted with a formyl-substituted phosphonate ester, utilizing a reductive amination procedure. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component **135.1** and the aldehyde component **135.2** are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product **135.3**. Deprotection, by removal of the R^{12} group, then affords the amine **135.4**.

For example, equimolar amounts of the amine **133.11** and a dialkylformylphosphonate **135.5**, prepared as described in US 3784590, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in J. Am. Chem. Soc., 91, 3996, 1969, to afford the product **135.6** which is then deprotected to produce the amine **135.7**.

Using the above procedures, but employing, in place of the α-amine **133.11**, the β-amine **133.9**, and/or different formyl-substituted phosphonates **135.2**, the corresponding products **135.4** are obtained.

Scheme **136** depicts the preparation of aminoindanol phosphonates in which the phosphonate moiety is attached to the nucleus by means of a heteroatom and one carbon. In this procedure, a carbinol, thiol or amine **136.1** is reacted with a dialkyl trifluoromethylsulfonyloxy phosphonate **136.2**, in the presence of a suitable base, to afford the alkylation product **136.3**. Deprotection of the product **136.3** then yields the amine **136.4**. The base required for this reaction between **136.1** and **136.2** depends on the nature of the heteroatom X. For example, if X is N or S, an excess of inorganic base such as, for example, potassium carbonate, cesium carbonate or the like, in the presence of an organic solvent such as dimethylformamide, is suitable. The reaction proceeds at from ambient temperature to about 80° to afford the displacement products **136.3**. If X is O, an equimolar amount of a strong base, such as, for example, lithium hexamethyldisilylazide, sodium hydride or the like, is employed, in the presence of a solvent such as tetrahydrofuran.

For example, the α-carbinol **133.3** is reacted with one equivalent of lithium hexamethyl disilylazide in tetrahydrofuran, followed by addition of an equimolar amount of a dialkyl trifluoromethylsulfonyloxymethyl phosphonate **136.5**, the preparation of which is described in Tet. Lett., 1986, 27, 1497, to afford the ether product **136.6**. Deprotection, by removal of the R^{12} group, then affords the amine **136.7**.

Using the above procedures, but employing, in place of the α-carbinol **133.3**, different carbinols, thiols or amines **136.1**, and /or different dialkyl trifluoromethylsulfonyloxymethyl phosphonates **136.2**, the corresponding products **136.4** are obtained.

Scheme **137** illustrates the preparation of aminoindanol phosphonate esters in which the phosphonate group is attached directly to the aminoindanol nucleus.

In this procedure, the bromoindanol derivative **137.1** is reacted with a sodium dialkyl phosphite, in a suitable aprotic polar solvent such as dimethyl formamide or N-methylpyrrolidinone. Displacement of the bromo substituent occurs to yield the phosphonate **137.3.** Deprotection, by removal of the R^{12} group, then affords the amine **137.4.**

For example, equimolar amounts of the α-bromo compound **133.10** and the dialkyl sodium phosphite **137.2**, are dissolved in dimethylformamide and the mixture is heated at ca. 60°C, as described in J. Med. Chem., 35, 1371, 1992, to afford the β-phosphonate **137.5.**

Alternatively, the phosphonate compound **137.5** is obtained by means of an Arbuzov reaction between the bromo compound **133.10** and a trialkyl phosphite $P(OR^1)_3$. In this procedure, as described in Handb. Organophosphorus Chem., 1992, 115, the reactants are heated together at ca. 100°C to afford the product **137.5.** Deprotection of the latter compound affords the amine **137.6.**

Using the above procedures, but employing, in place of the α-bromo compound **133.10**, the β-bromo compound **133.6**, and/or different phosphites **137.2**, the corresponding phosphonates **137.4** are obtained.

Preparation of phenylpropionic acid intermediates 5.1 incorporating phosphonate moieties.

Phenylpropionic acid derivatives incorporating the substituent link-$P(O)(OR^1)_2$ are prepared by the reactions illustrated in Schemes **139-143**, using as starting materials variously substituted phenylpropionic acids. The phenylpropionic acid derivatives **5.1** are employed in the preparation of the phosphonate esters **2** in which X is a direct bond.

A number of the substituted phenylpropionic acids required for the reactions shown in Schemes **139-143** are commercially available; in addition, the syntheses of variously substituted phenylpropionic acids have been reported. For those substituted phenylpropionic acids which are not commercially available, and whose syntheses have not been reported, a number of well-established synthetic routes are available. Representative methods for the synthesis of substituted phenylpropionic acids from commercially available starting materials are shown in Scheme **138.**

For example, variously substituted benzaldehydes **138.1** are subjected to a Wittig reaction with carboethoxymethylenetriphenylphosphorane **138.2**, as described in Ylid Chemistry, by A. W.

Johnson, Academic Press, 1966, p. 132, to afford the corresponding cinnamate esters **138.3**. Equimolar amounts of the reactants **138.1** and **138.2** are heated in an inert solvent such as dioxan or dimethylformamide, at ca 50°C, to afford the product **138.3**. Reduction of the double bond in the product **138.3** then afford the saturated ester **138.6**, (X =H) which upon hydrolysis yields the phenylpropionic acid intermediate **138.10**.

Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 6. Typical of the available reduction methods are catalytic hydrogenation, for example using palladium catalysts, as described in Hydrogenation Methods, by P. N. Rylander, Academic Press, New York, 1985, hydroboration-protonolysis, as described in J. Am. Chem. Soc., 81, 4108, 1959, or diimide reduction, as described in J. Org. Chem., 52, 4665, 1987. The choice of a particular reduction method is made by one skilled in the art, depending on the nature of the substituent groups attached to the cinnamic acid ester **138.3.**

Alternatively, the cinnamic esters **138.3** are obtained by means of a palladium-catalyzed Heck reaction between an appropriately substituted bromobenzene **138.5** and ethyl acrylate **138.4**. In this procedure, a substituted bromobenzene **138.5** is reacted with ethyl acrylate in the presence of a palladium (II) catalyst, as described in J. Med. Chem., 35, 1371, 1992, to afford the cinnamate ester **138.3**. Equimolar amounts of the reactants **138.4** and **138.5** are dissolved in a polar aprotic solvent such as dimethylformamide or tetrahydrofuran, at a temperature of about 60°C, in the presence or ca. 3 mol % of, for example, bis(triphenylphosphine)palladium (II) chloride and triethylamine, to afford the product **138.3**.

Alternatively, the substituted phenylpropionic acid intermediates are obtained from the correspondingly substituted methylbenzenes **138.7**. In this procedure, the methylbenzene **138.7** is subjected to free-radical bromination, for example by reaction with an equimolar amount of N-bromosuccinimide, as described in Chem. Rev., 63, 21, 1963, to afford the bromomethyl derivative **138.8**. The latter compound is then reacted with a salt of an ester of malonic acid, for example the sodium salt of diethyl malonate **138.9**, as described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 489, to afford the displacement product **138.6**, (X = COOEt). The latter compound is subjected to hydrolysis and decarboxylation, for example by treatment with aqueous alkali or dilute aqueous acid, to afford the phenylpropionic acid **138.10**.

Scheme **139** illustrates the preparation of phosphonate-containing phenylpropionic acids in which the phosphonate moiety is attached to the phenyl ring by means of an aromatic group. In this procedure, the carboxyl group of a bromo-substituted phenylpropionic acid **139.1** is protected. Methods for the protection of carboxylic acids are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224. The product **139.2** is then subjected to halogen-methyl exchange, for example by reaction with an alkyllithium, to afford the product **139.3** in which M is Li. The latter compound is subjected to palladium (II) or palladium (0) catalyzed coupling, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. Compound **139.3** is first converted into the boronic acid **139.4**, by reaction with a trialkyl borate, and the boronic acid product is coupled with a dialkyl bromophenylphosphonate **139.5** to yield the product **139.6**. Deprotection then affords the intermediate phosphonate-substituted phenylpropionic acid **139.7**.

For example, 4-bromophenylpropionic acid **139.8**, prepared as described in U.S. 4,032,533, is converted into the acid chloride, by treatment with thionyl chloride, oxalyl chloride and the like. The acid chloride is then reacted with 3-methyl-3-oxetanemethanol **139.9** (Aldrich), in the presence of a tertiary organic base such as pyridine, in a solvent such as dichloromethane, to afford the ester **139.10**. This product is then rearranged by treatment with boron trifluoride etherate in dichloromethane, at about -15°C as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 268, to yield the orthoester **139.11**, known as an OBO ester. The latter product is then reacted with one molar equivalent of n-butyllithium, in a solvent such as ether, at about -80°C, to afford the lithio derivative, which is reacted with a trialkyl borate, as described in J. Organomet. Chem., 1999, 581, 82, to yield the boronate **139.12**. This material is coupled, in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0), and an inorganic base such as sodium carbonate, with a dialkyl 4-bromophenylphosphonate **139.13**, prepared as described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, to give the coupled product **139.14**. Deprotection, for example by treatment with aqueous pyridine p-toluenesulfonate, as described in Can. J. Chem., 61, 712, 1983, then affords the carboxylic acid **139.15**.

Using the above procedures, but employing, in place of the 4-bromophenylpropionic acid **139.8**, different bromophenylpropionic acids **139.1**, and/or different dialkyl bromophenyl phosphonates **139.5**, the corresponding products **139.7** are obtained.

Scheme **140** depicts the preparation of phenylpropionic acids in which a phosphonate ester is attached to the phenyl ring by means of a heteroatom. In this procedure, a suitably protected hydroxy, thio or amino-substituted phenyl propionic acid **140.1** is reacted with a derivative of a hydroxymethyl dialkylphosphonate **140.2**, in which Lv is a leaving group such as methanesulfonyloxy and the like. The reaction is conducted in a polar aprotic solvent, in the presence of an organic or inorganic base, to afford the displacement product **140.3**. Deprotection then affords the carboxylic acid **140.4**.

For example, trichloroethyl 3-hydroxyphenylpropionic acid **140.5**, prepared by reaction of 3-hydroxyphenylpropionic acid (Fluka) with trichloroethanol and dicyclohexylcarbodiimide, as described in J. Am. Chem. Soc., 88, 852, 1966, is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **140.6**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product **140.7**. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C, to afford the product **140.7**. Removal of the trichloroethyl ester group, for example by treatment with zinc in acetic acid at 0°C, as described in J. Am. Chem. Soc., 88, 852, 1966, then yields the carboxylic acid **140.8**. Using the above procedures, but employing, in place of the phenol **140.5**, different phenols, thiols or amines **140.1**, and/or different phosphonates **140.2**, the corresponding products **140.4** are obtained.

Scheme **141** illustrates the preparation of phenylpropionic acids in which a phosphonate moiety is attached by means of a chain incorporating a heteroatom. In this procedure, a carboxyl protected halomethyl substituted phenylpropionic acid **141.1** is reacted with a dialkyl hydroxy, thio or amino-substituted alkylphosphonate **141.2**. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant **141.2**. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed.

For example, 4-bromomethyl phenylpropionic acid, prepared as described in U.S. 4,032,533, is converted into the methoxymethyl ester **141.5**, by reaction with methoxymethyl chloride and

triethylamine in dimethylformamide, as described in J. Chem. Soc, 2127, 1965. Equimolar amounts of the ester **141.5** and a dialkyl 2-aminoethyl phosphonate **141.6**, prepared as described in J. Org. Chem., 2000, 65, 676, are reacted in dimethylformamide at ca 80°C, in the presence of potassium carbonate, to afford the displacement product **141.7**. Deprotection, for example by treatment with trimethylsilyl bromide and a trace of methanol, as described in Aldrichimica Acta, 11, 23, 1978, then yields the carboxylic acid **141.8**.
Using the above procedures, but employing, in place of the amine **141.6**, different amines, alcohols or thiols **141.2** and/or different halomethyl-substituted phenylpropionic acids **141.1**, the corresponding products **141.4** are obtained.

Scheme **142** illustrates the preparation of phosphonate esters attached to the phenyl ring by means of an oxygen or sulfur link, by means of a Mitsonobu reaction. In this procedure, a protected hydroxy- or thio-substituted phenylpropionic acid **142.1** is reacted with a dialkyl hydroxyalkyl phosphonate **142.2**. The condensation reaction between **142.1** and **142.2** is effected in the presence of a triaryl phosphine and diethyl azodicarboxylate, as described in Org. React., 1992, 42, 335. The product **142.3** is then deprotected to afford the carboxylic acid **142.4**.
For example, 3-mercaptophenylpropionic acid (Apin Chemicals) is converted into the tert. butyl ester **142.5**, by treatment with carbonyl diimidazole, tert. butanol and diazabicycloundecene, as described in Synthesis, 833, 1982. The ester is reacted with a dialkyl hydroxymethylphosphonate **142.6**, prepared as described in Synthesis, 4, 327, 1998, in the presence of triphenyl phosphine, triethylamine and diethyl azodicarboxylate, to afford the thioether **142.7**. The tert. butyl group is removed by treatment with formic acid at ambient temperature, as described in J. Org. Chem., 42, 3972, 1977, to yield the carboxylic acid **142.8**.
Using the above procedures, but employing, in place of the thiol **142.5**, different phenols or thiols **142.1** and/or different hydroxyalkyl phosphonates **142.2**, the corresponding products **142.4** are obtained.

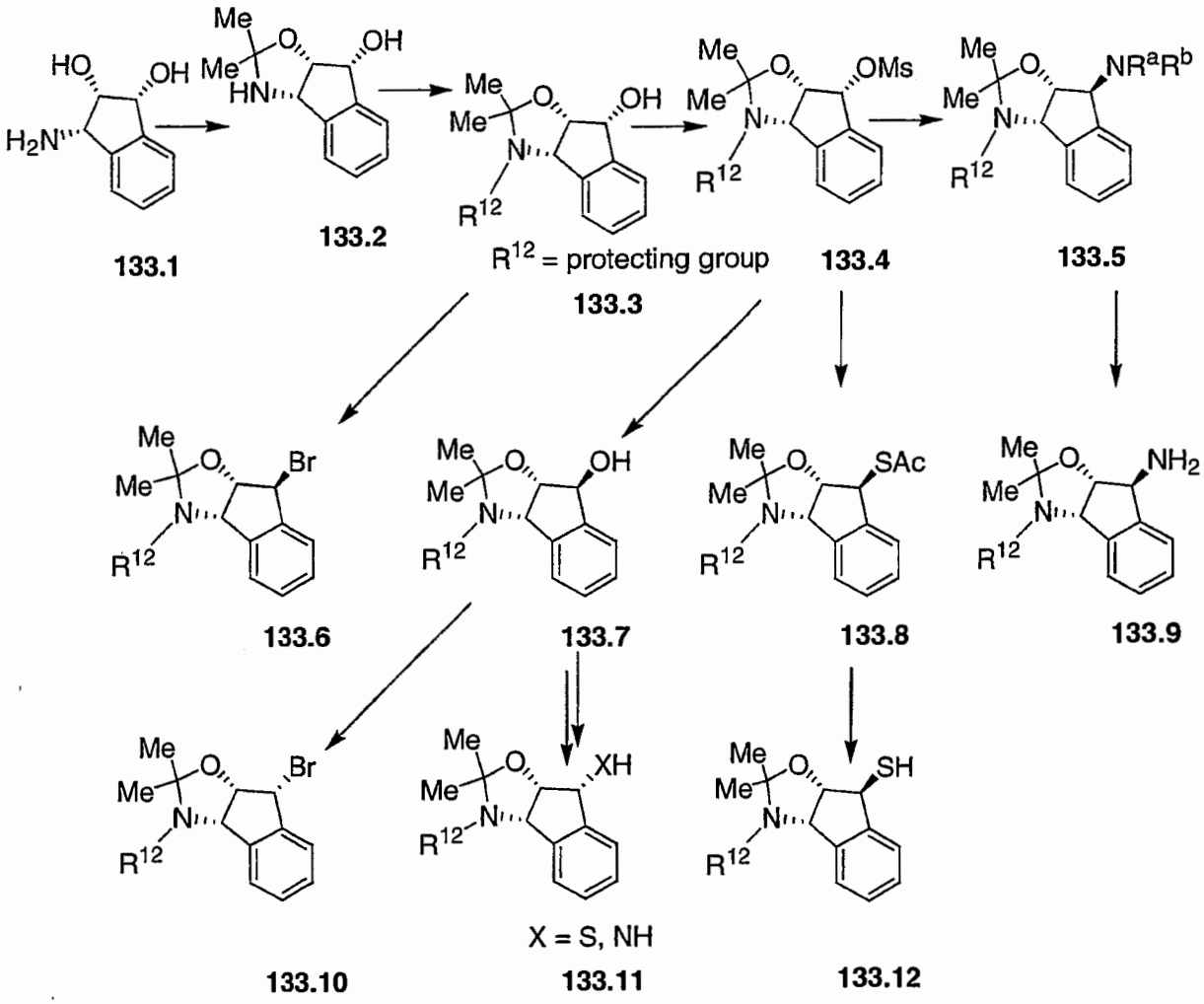
Scheme **143** depicts the preparation of phenylpropionic acids linked to a phosphonate ester by means of an aromatic or heteroaromatic ring. The products **143.3** are obtained by means of an alkylation reaction in which a bromomethyl aryl or heteroaryl phosphonate **143.1** is reacted with a carboxyl-protected hydroxy, thio or amino-substituted phenylpropionic acid **140.1**. The

reaction is conducted in the presence of a base, the nature of which is determined by the substituent X in the reactant **140.1**. For example, if X is O, a strong base such as lithium hexamethyldisilylazide or sodium hydride is employed. If X is S or N, an organic or inorganic base, such as diisopropylethylamine or cesium carbonate is employed. The alkylated product **143.2** is then deprotected to afford the carboxylic acid **143.3**.

For example, 3-(4-aminophenyl)propionic acid (Aldrich) is reacted with tert. butyl chlorodimethylsilane and imidazole in dimethylformamide, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 262, to afford the silyl ester **143.4**. This compound is reacted with a an equimolar amount of a dialkyl 4-bromomethylbenzylphosphonate **143.5**, prepared as described in Tet. Lett., 1998, 54, 9341, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the product **143.6**. The silyl ester is removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to give the carboxylic acid **143.7**.

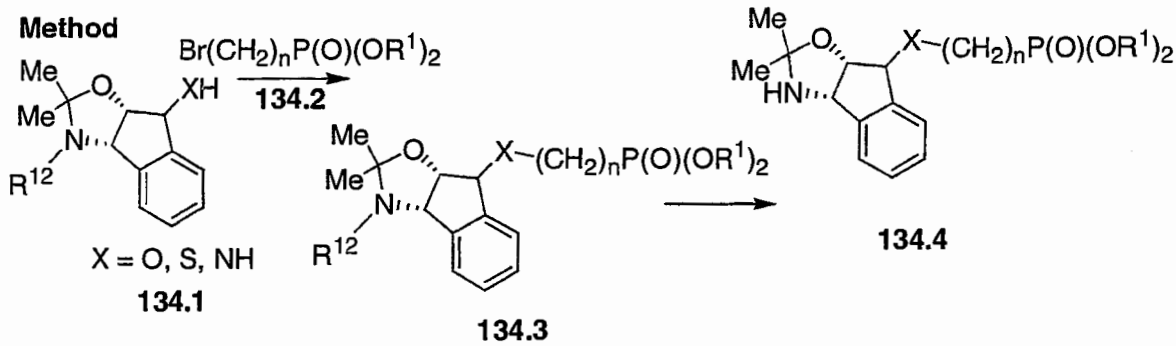
Using the above procedures, but employing, in place of the amino compound **143.4**, different phenols, mercaptans or amines **140.1**, and/or different halomethyl phosphonates **143.1**, the corresponding products **143.3** are obtained.

Scheme 133

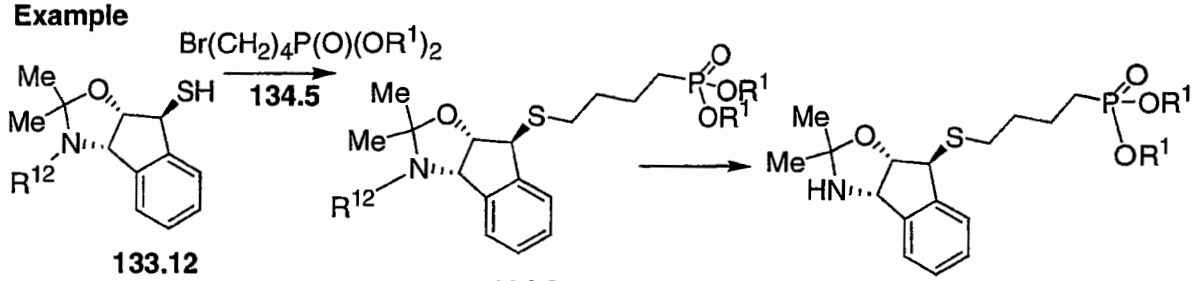

133.1
133.2
133.3
R12 = protecting group
133.4
133.5
133.6
133.7
133.8
133.9
133.10
133.11
X = S, NH
133.12

Scheme 134

Method

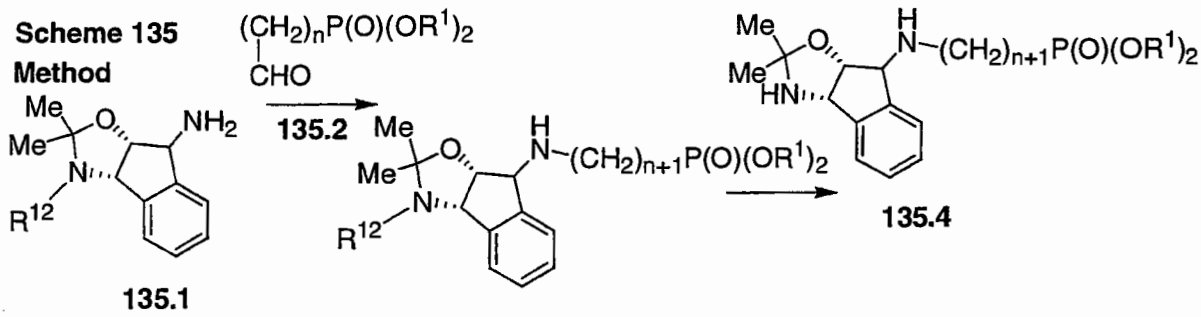


Example

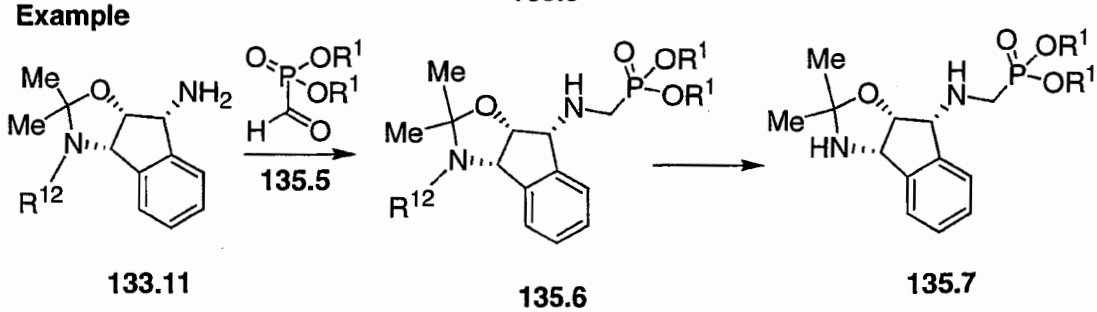


Scheme 135

Method

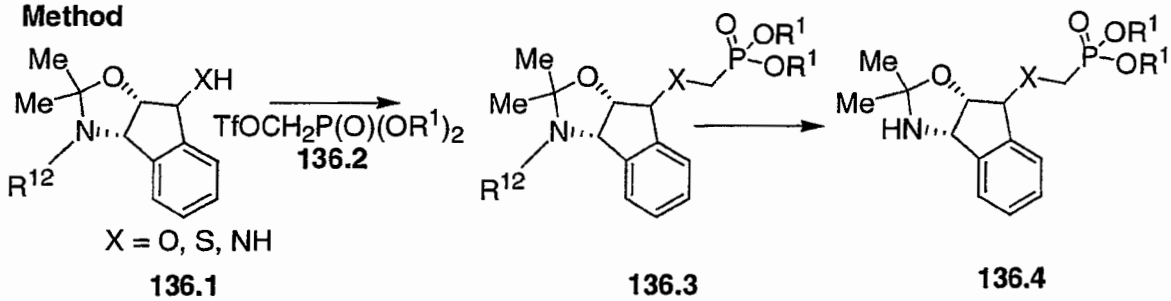


Example

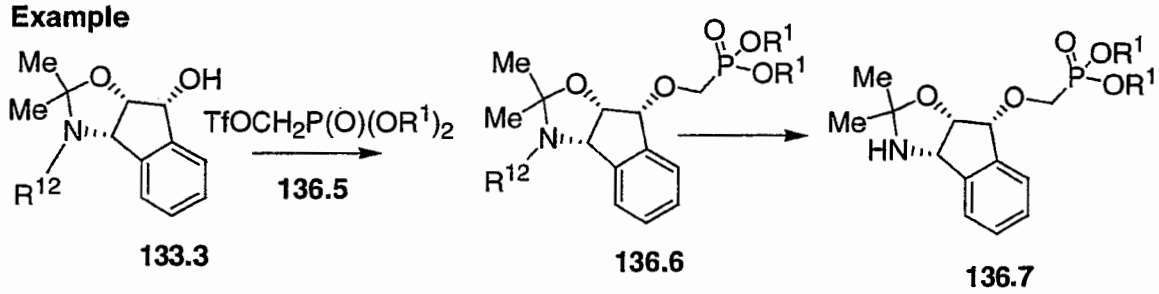


Scheme 136

Method

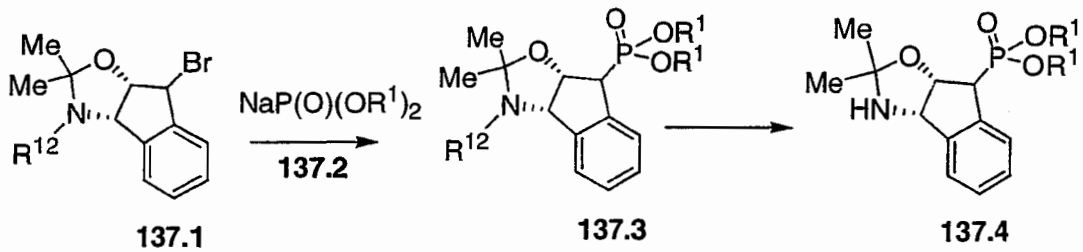


Example

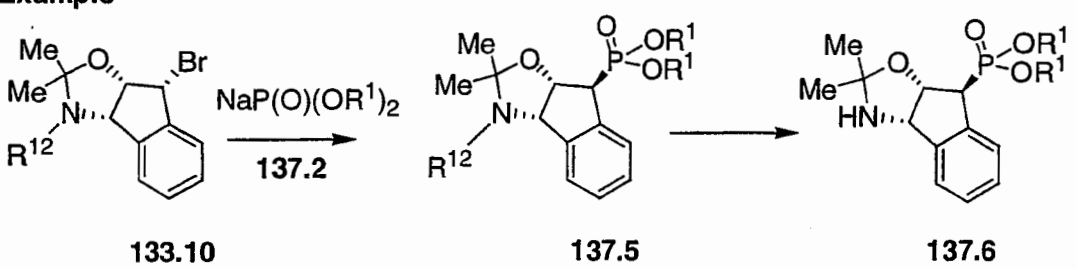


Scheme 137

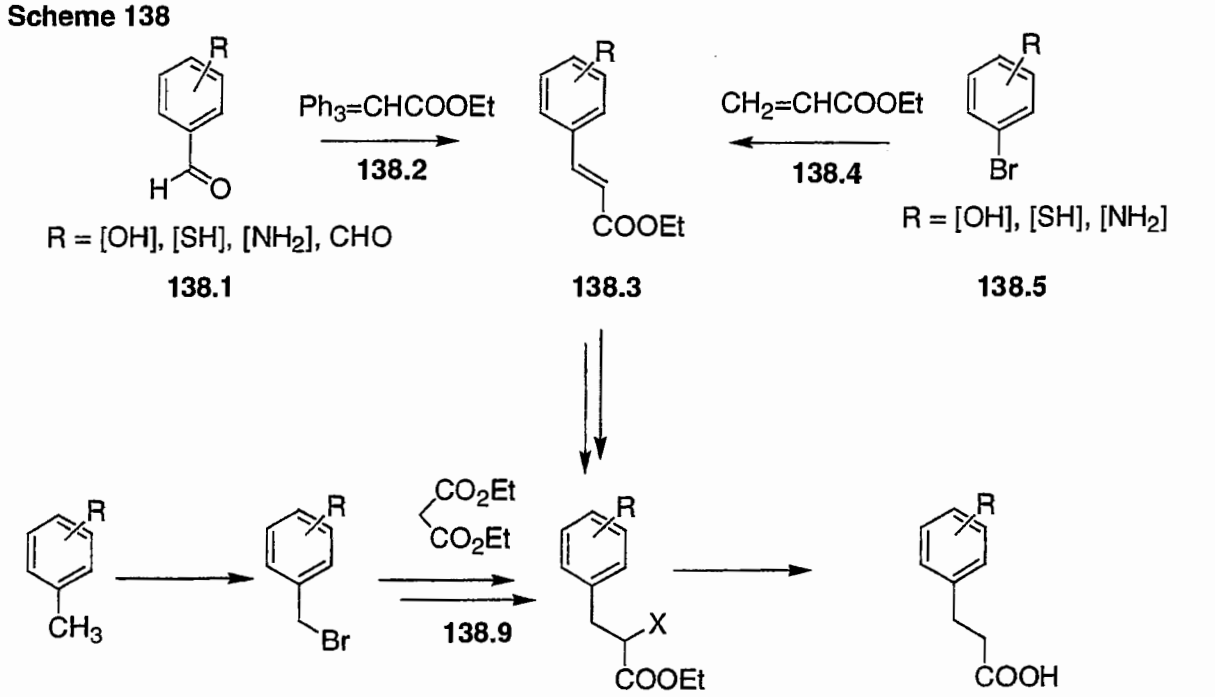
Method



Example

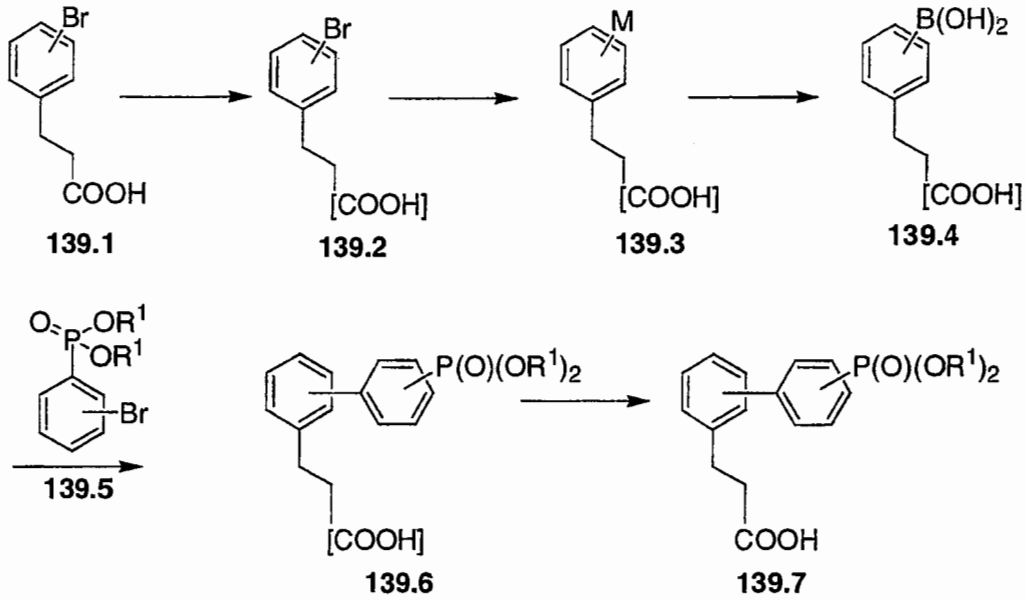


Scheme 138

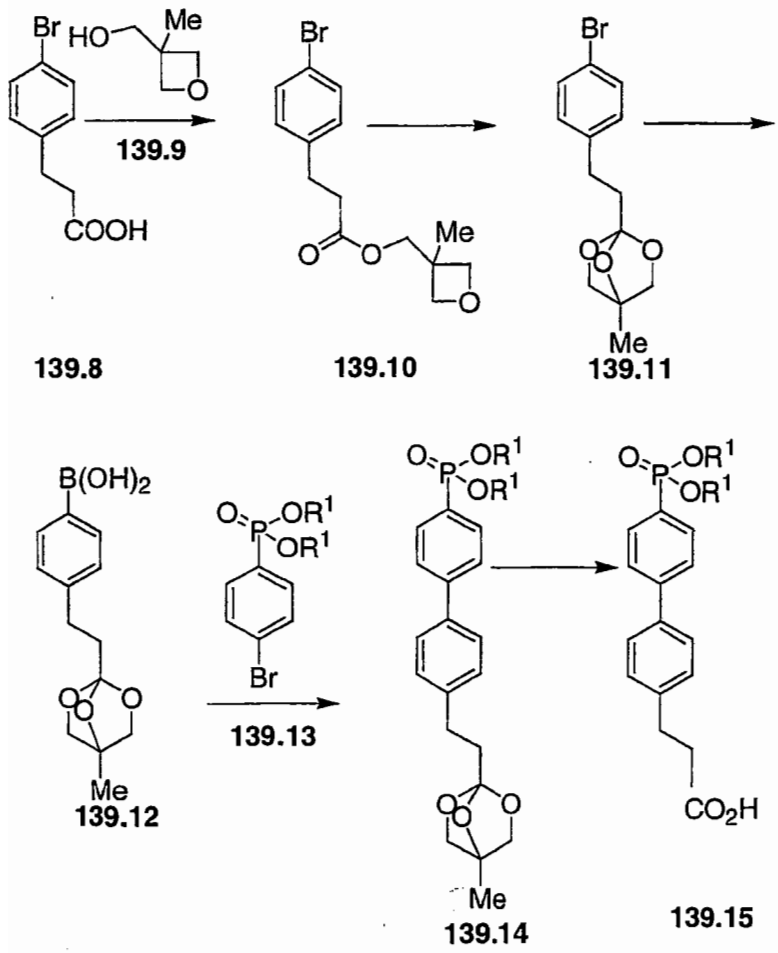

R
H
O
Ph3=CHCOOEt
138.2
CH2=CHCOOEt
138.4
Br
COOEt
R = [OH], [SH], [NH2], CHO
138.1
138.3
R = [OH], [SH], [NH2]
138.5
CH3
CO2Et
CO2Et
138.9
X
COOEt
COOH
R = [OH], [SH], [NH2], [NH]alkyl, CH2Ha
138.7
138.8
X = COOEt or H
138.6
R = [OH], [SH], [NH2] [NH]alkyl, CH2Ha
138.10

Scheme 139

Method

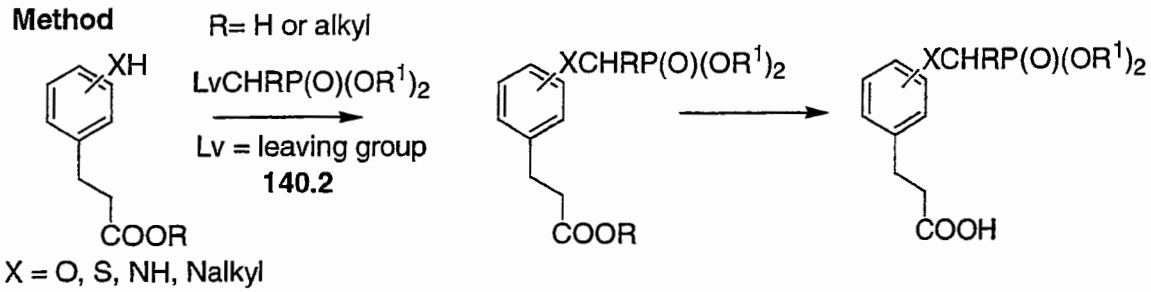


Example



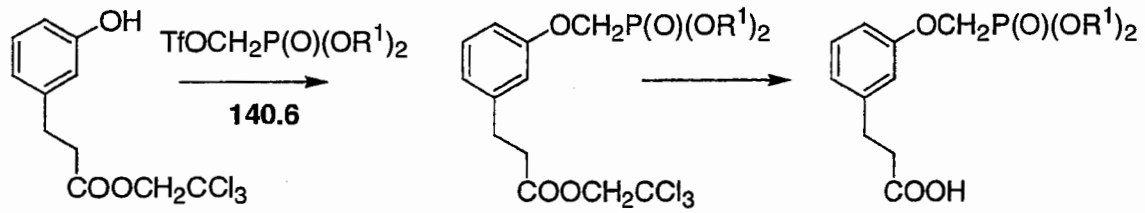
Scheme 140

Method



140.1 **140.3** **140.4**

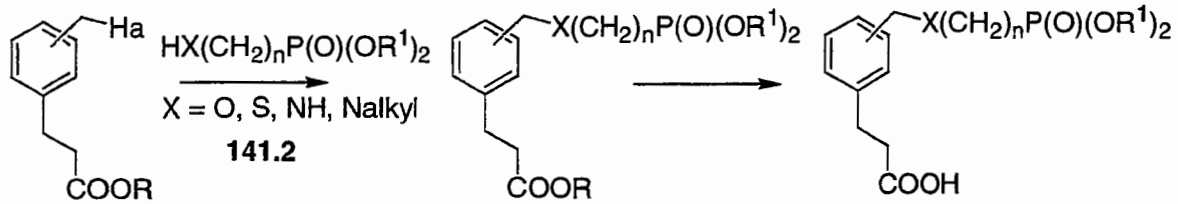
Example



140.5 **140.7** **140.8**

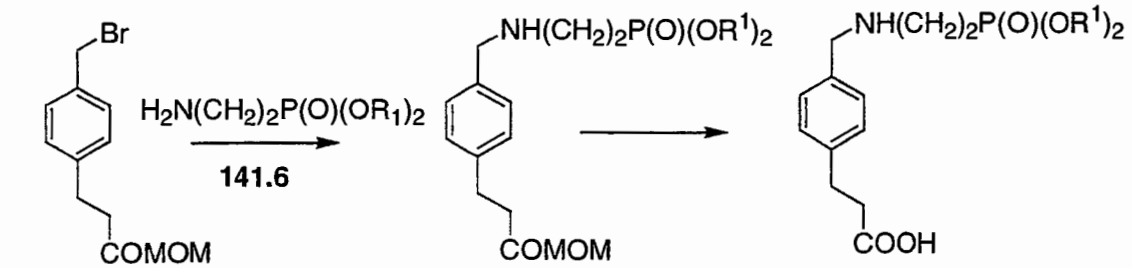
Scheme 141

Method



141.1 **141.3** **141.4**

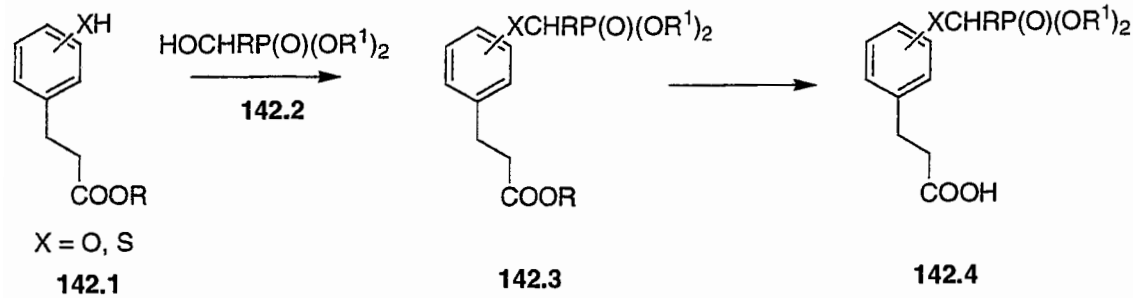
Example



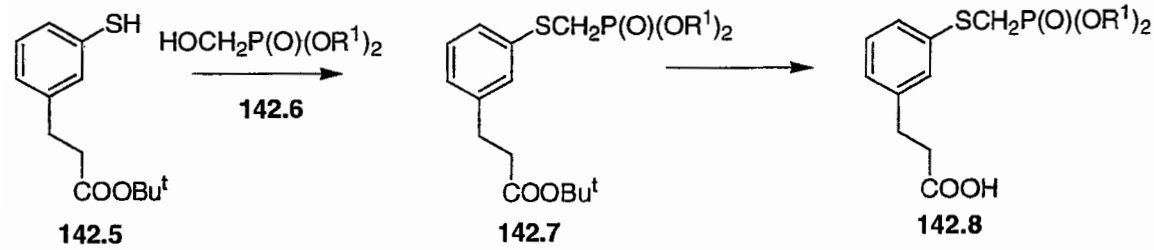
141.5 **141.7** **141.8**

Scheme 142

Method

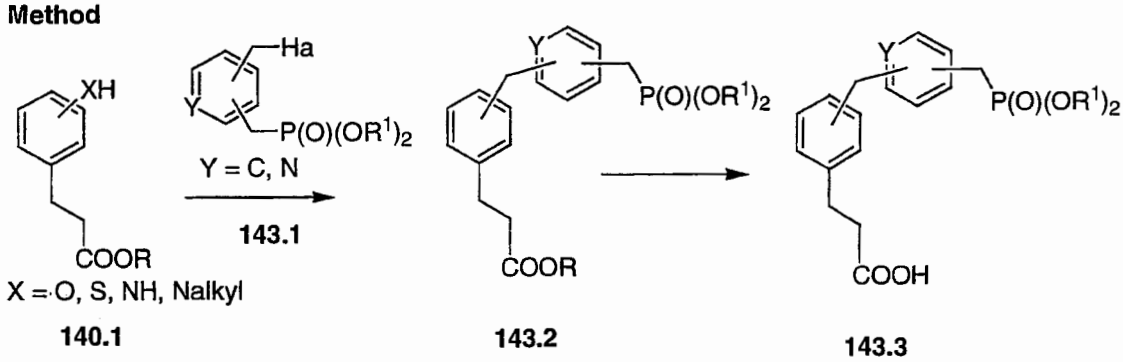


Example

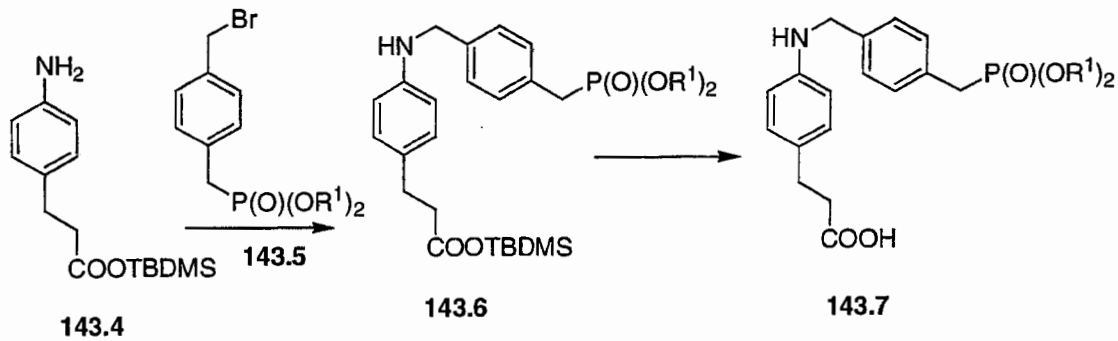


Scheme 143

Method



Example



Preparation of the phosphonate-containing thiophenol derivatives 7.1.

Schemes **144** - **153** describe the preparation of phosphonate-containing thiophenol derivatives **7.1** which are employed in the preparation of the phosphonate ester intermediates **2**, **14** and **19** in which X is sulfur, and of the intermediate **15** in which X' is sulfur.

Scheme **144** depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol **144.1** is protected to afford the product **144.2**. The protection and deprotection of thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277. For example, thiol substituents are protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a chlorotrialkylsilane and a base such as imidazole. Alternatively, thiol substituents are protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The product is then coupled, in the presence of a palladium catalyst, with a dialkyl phosphite **144.3**, to afford the phosphonate ester **144.4**. The preparation of arylphosphonates by the coupling of aryl halides with dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The thiol protecting group is then removed, as described above, to afford the thiol **144.5**.
For example, 3-bromothiophenol **144.6** is converted into the 9-fluorenylmethyl (Fm) derivative **144.7** by reaction with 9-fluorenylmethyl chloride and diisopropylethylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite **144.3** to afford the phosphonate ester **144.8**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The compound **144.7** is reacted, in toluene solution at reflux, with a dialkyl phosphite **144.3**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product **144.8**. The Fm protecting group is then removed by treatment of the product with piperidine in dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol **144.9**.

Using the above procedures, but employing, in place of 3-bromothiophenol **144.6**, different thiophenols **144.1**, and/or different dialkyl phosphites **144.3**, the corresponding products **144.5** are obtained.

Scheme **145** illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol **145.2** is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative **145.3**. The latter compound is reacted with a halodialkyl phosphite **145.4** to afford the product **145.5**; deprotection then affords the thiophenol **145.6**

For example, 4-bromothiophenol **145.7** is converted into the S-triphenylmethyl (trityl) derivative **145.8**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 287. The product is converted into the lithium derivative **145.9** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorophosphite **145.10** to afford the phosphonate **145.11**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **145.12**.

Using the above procedures, but employing, in place of the bromo compound **145.7**, different halo compounds **145.1**, and/or different halo dialkyl phosphites **145.4**, there are obtained the corresponding thiols **145.6**.

Scheme **146** illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol **146.1** is subjected to free-radical bromination to afford a bromomethyl product **146.2**. This compound is reacted with a sodium dialkyl phosphite **146.3** or a trialkyl phosphite, to give the displacement or rearrangement product **146.4**, which upon deprotection affords the thiophenol **146.5**.

For example, 2-methylthiophenol **146.5** is protected by conversion to the benzoyl derivative **146.7**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **146.8**. This material is reacted with a sodium dialkyl phosphite **146.3**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **146.9**.

Alternatively, the bromomethyl compound **146.8** is converted into the phosphonate **146.9** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **146.8** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100°C to produce the phosphonate **146.9**. Deprotection of the phosphonate **146.9**, for example by treatment with aqueous ammonia, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiol **146.10**.

Using the above procedures, but employing, in place of the bromomethyl compound **146.8**, different bromomethyl compounds **146.2**, there are obtained the corresponding thiols **146.5**.

Scheme **147** illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **147.1** is reacted with a dialkyl hydroxyalkylphosphonate **147.2** under the conditions of the Mitsonobu reaction, for example as described in Org. React., 1992, 42, 335, to afford the coupled product **147.3**. Deprotection then yields the O- or S-linked products **147.4**.

For example, 3-hydroxythiophenol, **147.5**, is converted into the monotrityl ether **147.6**, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **147.7** in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound **147.8**. Removal of the trityl protecting group, as described above, then affords the thiophenol **147.9**.

Using the above procedures, but employing, in place of the phenol **147.5**, different phenols or thiophenols **147.1**, there are obtained the corresponding thiols **147.4**.

Scheme **148** illustrates the preparation of thiophenols **148.4** bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **148.1** is reacted with an activated ester, for example the trifluoromethanesulfonate **148.2**, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product **148.3**. Deprotection then affords the thiol **148.4**.

For example, 4-methylaminothiophenol **148.5** is reacted in dichloromethane solution with one equivalent of acetyl chloride and a base such as pyridine, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 298, to afford the S-acetyl product **148.6**. This material is then reacted with a dialkyl

trifluoromethanesulfonyloxymethyl phosphonate **148.7**, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product **148.8**. Preferably, equimolar amounts of the phosphonate **148.7** and the amine **148.6** are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product **148.8**. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiophenol **148.9**.

Using the above procedures, but employing, in place of the thioamine **148.5**, different phenols, thiophenols or amines **148.1**, and/or different phosphonates **148.2**, there are obtained the corresponding products **148.4**.

Scheme **149** illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate **149.2**. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol **149.1** is reacted with a dialkyl bromoalkyl phosphonate **149.2** to afford the product **149.3**. Deprotection then affords the free thiophenol **149.4.**

For example, 3-hydroxythiophenol **149.5** is converted into the S-trityl compound **149.6**, as described above. This compound is then reacted with a dialkyl 4-bromobutyl phosphonate **149.7**, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°C to yield the ether product **149.8**. Deprotection, as described above, then affords the thiol **149.9**.

Using the above procedures, but employing, in place of the phenol **149.5**, different phenols, thiophenols or amines **149.1**, and/or different phosphonates **149.2**, there are obtained the corresponding products **149.4**.

Scheme **150** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **150.2** is coupled with an aromatic bromo compound **150.1**. The coupling of aryl halides with olefins

by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **150.3**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **150.4**, or the saturated analog **150.6**.

For example, 3-bromothiophenol is converted into the S-Fm derivative **150.7**, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate **150.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **150.9**. Deprotection, as described above, then affords the thiol **150.10**. Optionally, the initially formed unsaturated phosphonate **150.9** is subjected to catalytic or chemical reduction, for example using diimide, as described in Scheme **138**, to yield the saturated product **150.11**, which upon deprotection affords the thiol **150.12**.

Using the above procedures, but employing, in place of the bromo compound **150.7**, different bromo compounds **150.1**, and/or different phosphonates **150.2**, there are obtained the corresponding products **150.4** and **150.6**

Scheme **151** illustrates the preparation of an aryl-linked phosphonate ester **151.4** by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **151.1** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product **151.3** which is deprotected to yield the thiol **151.4**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic

Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **151.5**. This material is reacted with a dialkyl 4-bromophenylphosphonate **151.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **151.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **151.8**. Using the above procedures, but employing, in place of the boronate **151.5**, different boronates **151.1**, and/or different phosphonates **151.2**, there are obtained the corresponding products **151.4**.

Scheme **152** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **152.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **152.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **152.3** is then deprotected to afford the thiol **152.4**.
For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **152.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **152.5** is then reacted with a dialkyl 4-(bromomethyl)phenylphosphonate, **152.6**, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C. The thioether product **152.7** thus obtained is deprotected, as described above, to afford the thiol **152.8**.
Using the above procedures, but employing, in place of the thiophenol **152.5**, different phenols, thiophenols or amines **152.1**, and/or different phosphonates **152.2**, there are obtained the corresponding products **152.4**.

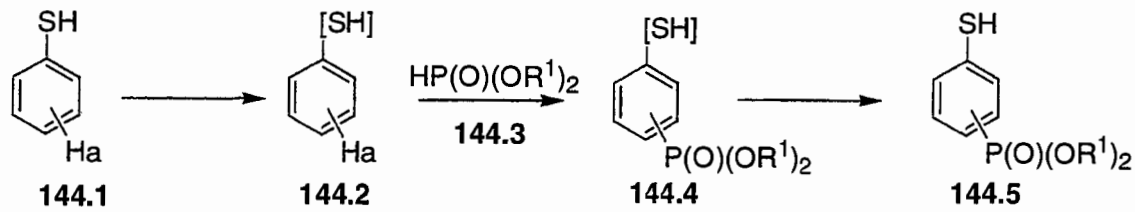
Scheme **153** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

In this procedure, a suitably protected thiophenol **153.1**, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **153.2**, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **153.3**. Deprotection, as described above, then affords the thiol **153.4**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines are also obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines are also obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p. 707. For example, 2,3-dihydro-1H-indole-5-thiol, **153.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **153.6**, as described above, and the ester is then reacted with the trifluoromethanesulfonate **153.7**, using the conditions described above for the preparation of the phosphonate **148.8**, (Scheme **148**), to yield the phosphonate **153.8**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **153.9**.

Using the above procedures, but employing, in place of the thiol **153.5**, different thiols **153.1**, and/or different triflates **153.2**, there are obtained the corresponding products **153.4**.

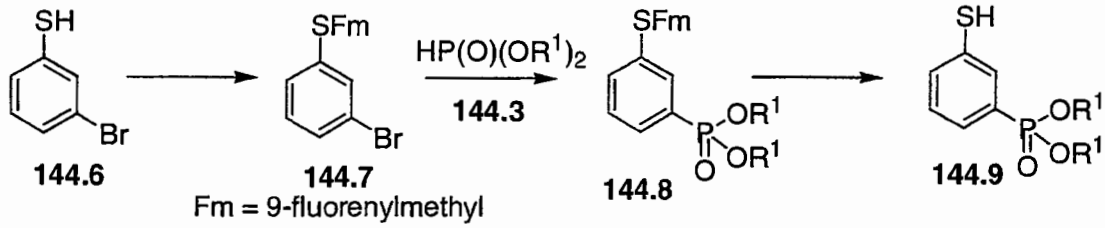
Scheme 144

Method



144.1 144.2 144.4 144.5

Example

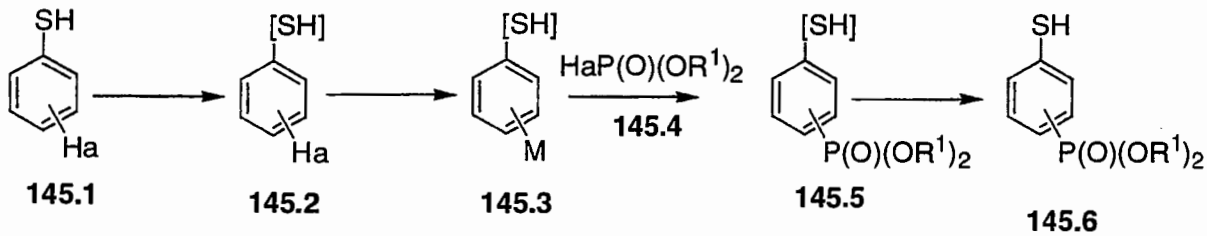


144.6 144.7 144.8 144.9

Fm = 9-fluorenylmethyl

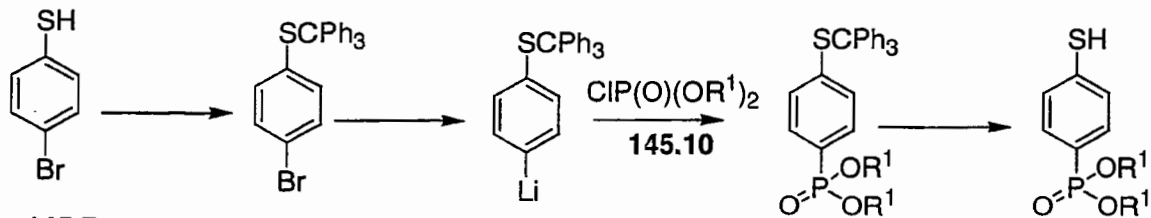
Scheme 145

Method



145.1 145.2 145.3 145.5 145.6

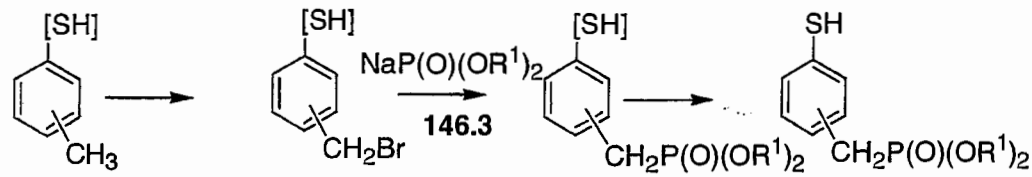
Example



145.7 145.8 145.9 145.11 145.12

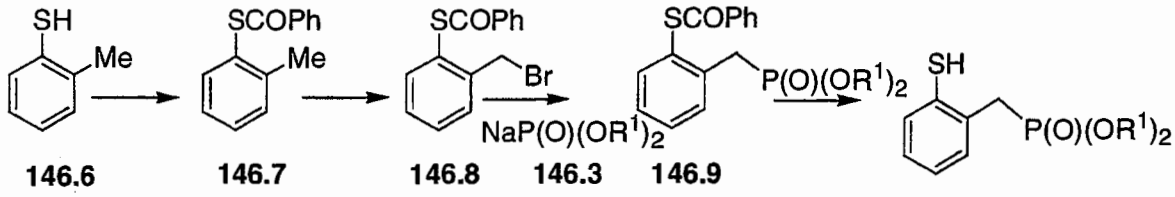
Scheme 146

Method



146.1 146.2 146.4 146.5

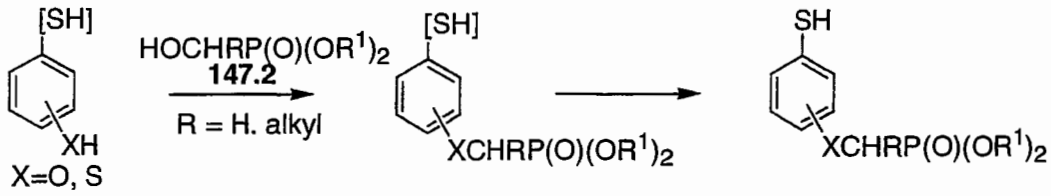
Example



146.6 146.7 146.8 146.3 146.9 146.10

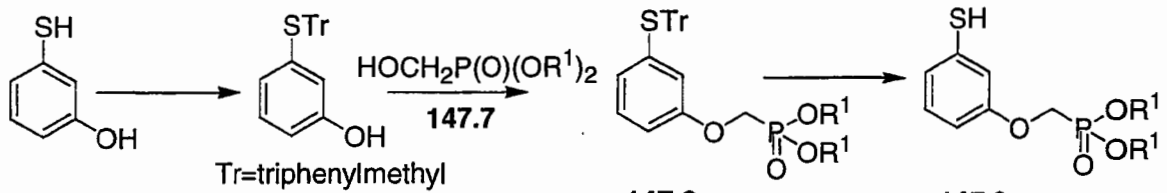
Scheme 147

Method



147.1 147.3 147.4

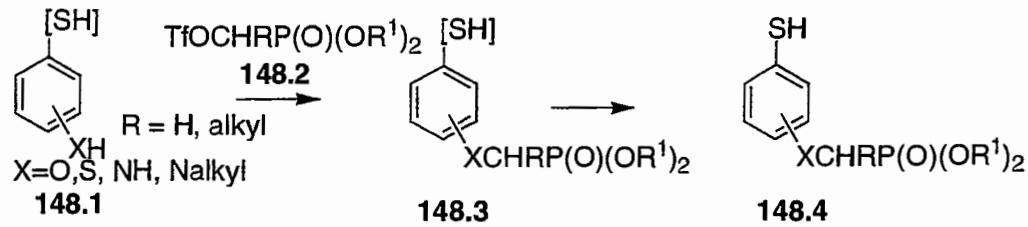
Example



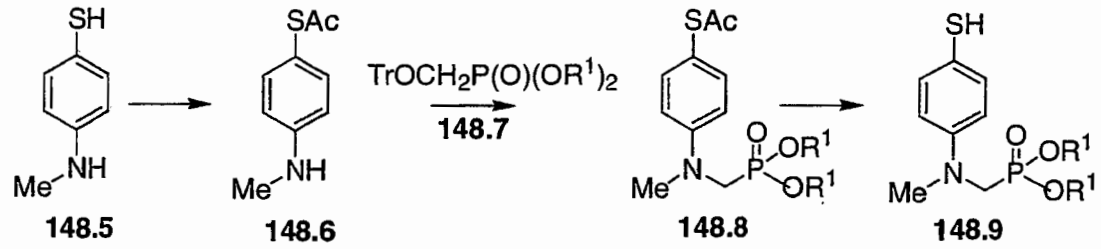
147.5 147.6 147.8 147.9

Scheme 148

Method

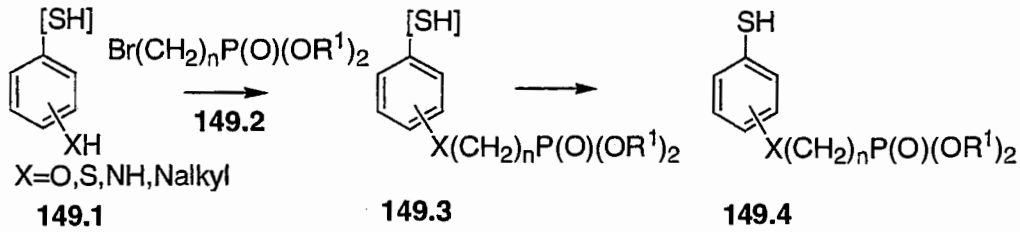


Example

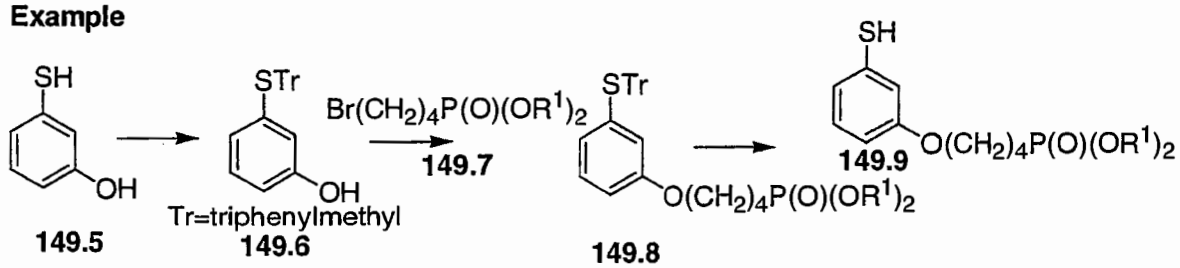


Scheme 149

Method

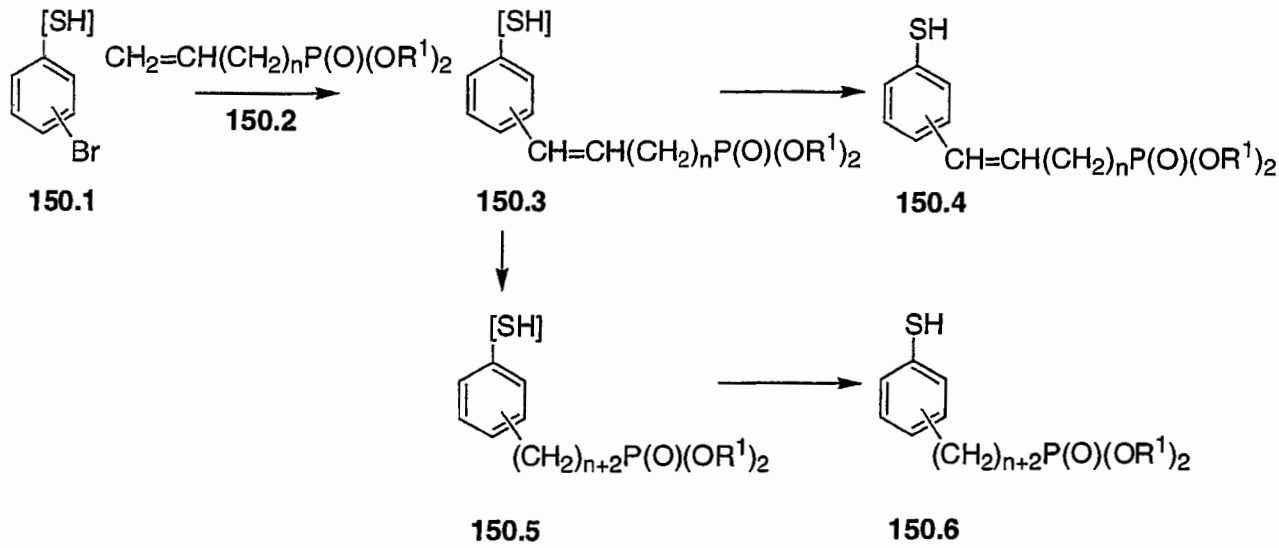


Example

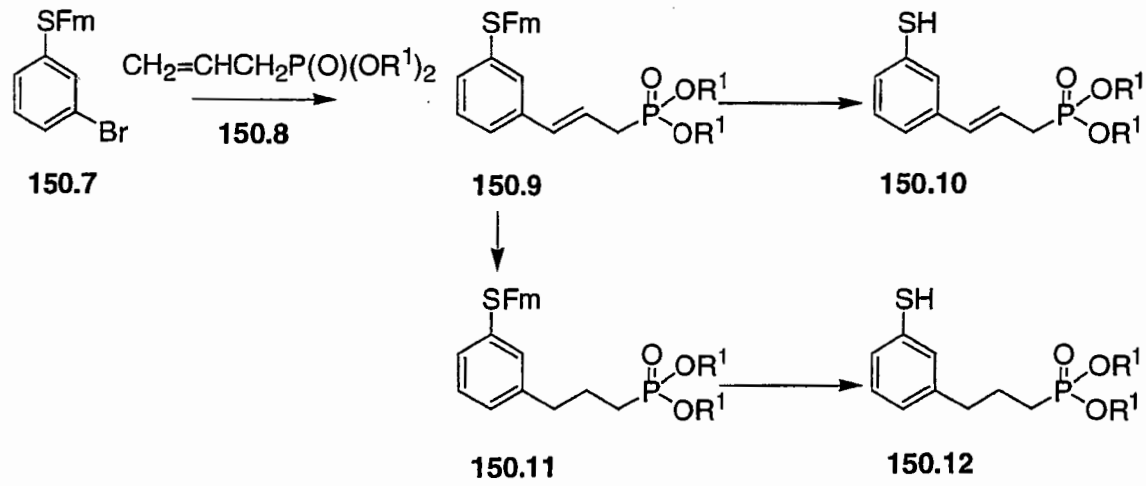


Scheme 150

Method

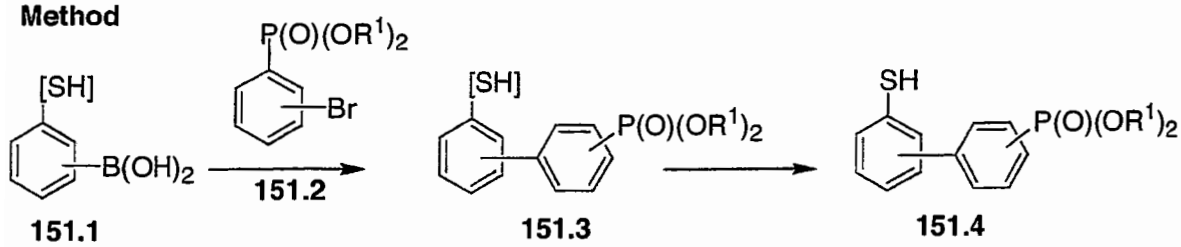


Example



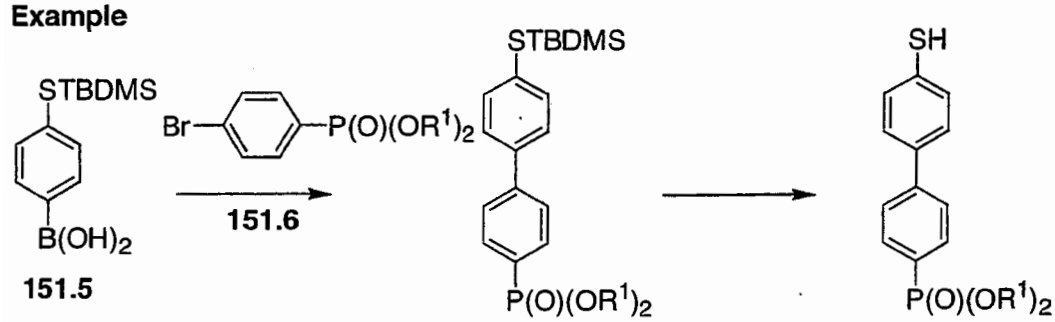
Scheme 151

Method



151.1 151.3 151.4

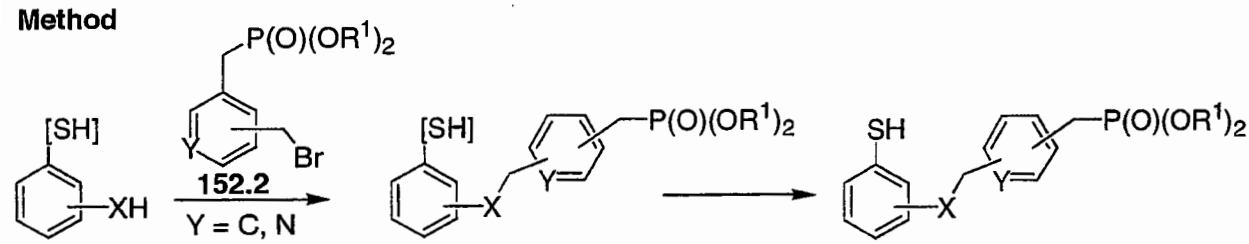
Example



151.5 151.7 151.8

Scheme 152

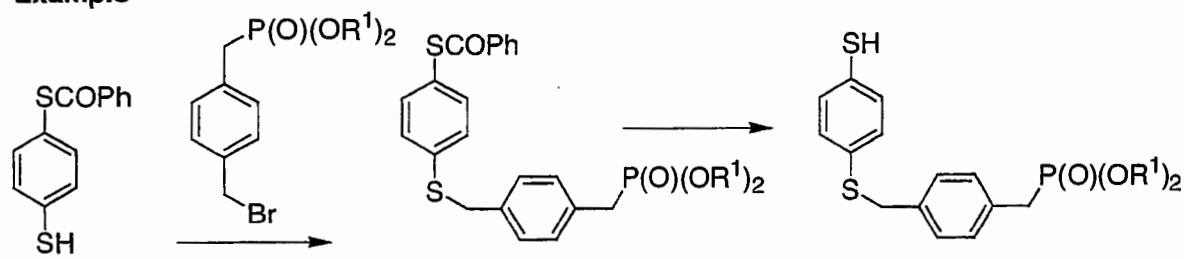
Method



X =O, S, NH, Nalkyl

152.1 152.3 152.4

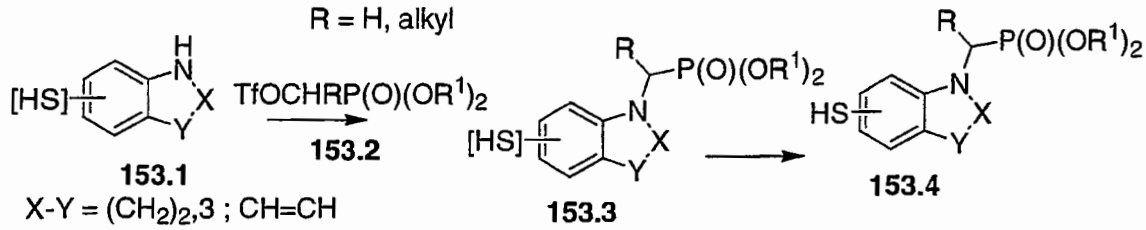
Example



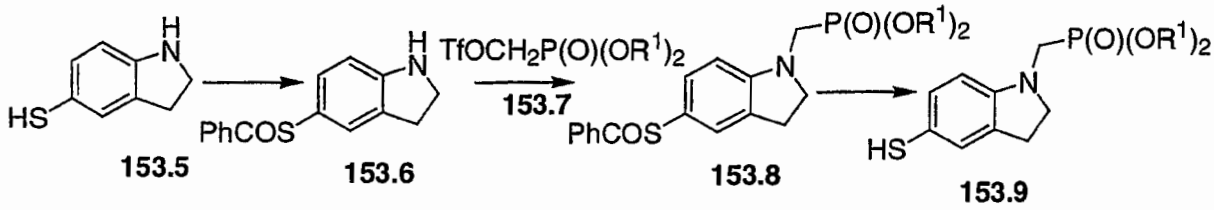
152.5 152.7 152.8

Scheme 153

Method



Example



Preparation of tert-butylamine derivatives 9.3 and 25.4 incorporating phosphonate groups.

Schemes **154 – 158** illustrate the preparation of the tert. butylamine derivatives **9.3** and **25.4** in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor, such as [OH], [SH], Br, which are employed in the preparation of the intermediate phosphonate esters **3**, **7**, **11** and **20**.

Scheme **154** describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2.2-dimethyl-2-aminoethyl bromide **154.1** is reacted with a trialkyl phosphite **154.2**, under the conditions of the Arbuzov reaction, as described in Scheme **137**, to afford the phosphonate **154.3**, which is then deprotected to give the amine **154.4.**

For example, the cbz derivative of 2,2-dimethyl-2-aminoethyl bromide **154.6**, is heated with a trialkyl phosphite at ca 150°C to afford the product **154.7**. Deprotection then affords the free amine **154.8**. The removal of carbobenzyloxy substituents to afford the corresponding amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The conversion is effected by the use of catalytic hydrogenation, in the presence of hydrogen or a hydrogen donor and a palladium catalyst. Alternatively, the cbz group is removed by treatment of the substrate with triethylsilane,

triethylamine and a catalytic amount of palladium (II) chloride, as described in Chem. Ber., 94, 821, 1961, or by the use of trimethylsilyl iodide in acetonitrile at ambient temperature, as described in J. Chem. Soc., Perkin Trans. I, 1277, 1988. The cbz group is also removed by treatment with Lewis acid such as boron tribromide, as described in J. Org. Chem., 39, 1247, 1974, or aluminum chloride, as described in Tet. Lett., 2793, 1979.

Using the above procedures, but employing different trialkyl phosphites, there are obtained the corresponding amines **154.4**.

Scheme **155** illustrates the preparation of phosphonate esters attached to the tert butylamine by means of a heteroatom and a carbon chain. A protected alcohol or thiol **155.1** is reacted with a dialkyl bromoalkylphosphonate **155.2,** to afford the displacement product **155.3**. Deprotection, if needed, then yields the amine **155.4**.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol **155.5** is reacted with a dialkyl 4-bromobutyl phosphonate **155.6**, prepared as described in Synthesis, 1994, 9, 909, in dimethylformamide containing potassium carbonate and a catalytic amount of potassium iodide, at ca 60° to afford the phosphonate **155.7** Deprotection, by hydrogenation over a palladium catalyst, then affords the free amine **155.8**.

Using the above procedures, but employing different alcohols or thiols **155.1**, and/or different bromoalkylphosphonates **155.2**, there are obtained the corresponding ether and thioether products **155.4**.

Scheme **156** describes the preparation of carbon-linked tert. butylamine phosphonate derivatives, in which the carbon chain is unsaturated or saturated.

In the procedure, a terminal acetylenic derivative of tert-butylamine **156.1** is reacted, under basic conditions, with a dialkyl chlorophosphite **156.2**, to afford the acetylenic phosphonate **156.3**. The coupled product **156.3** is deprotected to afford the amine **156.4.** Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products **156.5** and **156.6** respectively.

For example, 2-amino-2-methylprop-1-yne **156.7**, the preparation of which is described in WO 9320804, is converted into the N-phthalimido derivative **156.8**, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide

in tetrahydrofuran at -78°C. The resultant anion is then reacted with a dialkyl chlorophosphite **156.2** to afford the phosphonate **156.9**. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine **156.10**. Partial catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p. 566, produces the olefinic phosphonate **156.11**, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p. 3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate **156.12**. Using the above procedures, but employing different acetylenic amines **156.1**, and/or different dialkyl halophosphites, there are obtained the corresponding products **156.4**, **156.5** and **156.6**.

Scheme **157** illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.
In this method, an aminopropyl-substituted cyclic amine **157.1** is reacted with a limited amount of a bromoalkyl phosphonate **157.2**, using, for example, the conditions described above (Scheme **149**) to afford the displacement product **157.3**.
For example, 3-(1-amino-1-methyl)ethylpyrrolidine **157.4**, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with one molar equivalent of a dialkyl 4-bromobutyl phosphonate **157.5**, prepared as described in Synthesis, 1994, 9, 909, to afford the displacement product **157.6**.
Using the above procedures, but employing, in place of 3-(1-amino-1-methyl)ethylpyrrolidine **157.4**, different cyclic amines **157.1**, and/or different bromoalkylphosphonates **157.2**, there are obtained the corresponding products **157.3**.

Scheme **158** illustrates the preparation of the amides **9.3** which are employed in the preparation of the phosphonate esters **3**. In this procedure, the carboxylic acids **158.1**, the structures of which are illustrated in Chart **10**, compounds **C1** - **C16**, are converted into the BOC-protected derivatives **155.8**. Methods for the conversion of amines into the BOC derivative are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 327. For example, the amine is reacted with di-tert-butoxycarbonylanhydride (BOC anhydride) and a base, or with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), and the like. The carboxylic acid

158.2 is then coupled, as described in Scheme **1**, with the tert. butylamine derivatives **25.4**, or precursors thereto, the preparation of which is described in Schemes **154** - **157**, to afford the amide **158.3**. The BOC group is then removed to yield the amine **9.3**. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection is effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preparation of pyridine intermediates 13.1 incorporating phosphonate substituents.

Schemes **159** - **163**, described the preparation of chloromethyl or formyl pyridine derivatives incorporating phosphonate moieties. Scheme **164** illustrates the conversion of the above compounds into the piperazine derivatives **13.1** which are employed in the preparation of the phosphonate esters **4**.

Scheme **159** illustrates the preparation of chloromethyl-substituted pyridines in which a phosphonate moiety is directly attached to the pyridine ring.
In this procedure, a halo-substituted methylpyridine **159.1** is reacted with a dialkyl phosphite **159.2**, to afford the phosphonate product **159.3**. The coupling reaction is conducted in the presence of a palladium (0) catalyst, for example as described in J. Med. Chem., 35, 1371, 1992. The product **159.3** is then converted into the chloromethyl derivative **159.4** by means of a chlorination reaction. The chlorination of benzylic methyl groups is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 313. A variety of free-radical chlorinating agents are employed.
For example, 3-bromo-5-methylpyridine, **159.5** (ChemPacific) is reacted with an equimolar amount of a dialkyl sodium phosphite, **13.2** in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, in toluene at reflux, to yield the phosphonate **159.6**. The latter compound is then chlorinated, for example by the use of one molar equivalent of phenyliodonium dichloride, as described in J. Org. Chem., 29, 3692, 1964, to prepare the chloromethyl compound **159.7**.
Using the above procedures, but employing, in place of the bromomethyl pyridine **159.5**, different halomethyl pyridines **159.1**, and/or different dialkyl phosphites **159.2** the corresponding products **159.4** are obtained.

Scheme **160** depicts the preparation of chloromethyl pyridines incorporating a phosphonate group attached to the pyridine ring by means of a carbon link. In this procedure, a bis(chloromethyl)pyridine **160.1** is reacted with a sodium dialkyl phosphite **146.3**, employing, for example, procedures described in J. Med. Chem., 35, 1371, 1992, to afford the displacement product **160.2**.

For example, 3,5-bis(chloromethyl)pyridine **160.3**, the preparation of which is described in Eur. J. Inorg. Chem., 1998, 2, 163, is reacted with one molar equivalent of a dialkyl sodium phosphite **146.3** in tetrahydrofuran, at ambient temperature, to afford the product **160.4**. Using the above procedures, but employing, in place of the bis(chloromethyl) compound **160.3**, different bis(chloromethyl) pyridines **160.1**, and/or different dialkyl sodium phosphites **146.3** the corresponding products **160.2** are obtained.

Scheme **161** illustrates the preparation of pyridine aldehydes incorporating a phosphonate group linked to the pyridine nucleus by means of a saturated or unsaturated carbon chain. In this procedure, a suitably protected halo-substituted pyridine carboxaldehyde **161.1** is coupled, by means of a palladium-catalyzed Heck reaction, as described in Scheme **150**, with a dialkyl alkenyl phosphonate **161.2**. Methods for the protection of aldehydes are described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 175. The protected aldehyde **161.1** is reacted with an olefinic phosphonate **161.2**, in the presence of a palladium (0) catalyst, to afford the coupled product **161.3**. Deprotection of the aldehyde group then affords the product **161.6**. Alternatively, the unsaturated compound **161.3** is reduced to afford the saturated analog **161.5**, which upon deprotection yields the saturated analog **161.7**. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, and chemical reduction, the latter for example employing diborane or diimide.

For example, 5-bromopyridine-3-carboxaldehyde **161.8** (ChemPacific) is converted into the dimethyl acetal, by reaction with methanolic ammonium chloride, as described in J. Org. Chem., 26, 1156, 1961. The acetal **161.9** is then reacted with a dialkyl butenyl phosphonate **161.10**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of bis(triphenylphosphine) palladium(II) chloride, as described in J. Med. Chem., 1992, 35, 1371, to afford the coupled product **161.11**. Deprotection, for example by treatment with formic acid in pentane, as described in Synthesis, 651, 1983, yields the free aldehyde **161.13**.

The product is reduced, for example by reaction with diimide, as described in J. Org. Chem., 30, 3965, 1965, to afford the saturated product **161.12.**

Using the above procedures, but employing, in place of the aldehyde **161.8**, different aldehydes **161.1**, and/or different phosphonates **161.2,** the corresponding products **161.6** and **161.7** are obtained.

Scheme **162** illustrates the preparation of pyridine aldehydes incorporating a phosphonate group linked to the pyridine by a heteroatom and a carbon chain. In this procedure, a 2- or 4-halo-substituted pyridine aldehyde **162.1** is reacted with a dialkyl hydroxy- or thio-alkylphosphonate **162.2.** The preparation of alkoxypyridines by the reaction of alkoxides with halopyridines is described, for example, in J. Am. Chem. Soc., 82, 4414, 1960. The preparation of pyridine thioethers by reaction of halopyridines with thiols is described, for example, in Chemistry of Heterocyclic Compounds, Pyridine and its derivatives, E. Klingsberg, Ed, part 4, p. 358. The alcohols and thiols are transformed into metal salts, for example sodium or potassium salts, and then reacted with the halopyridine substrates at elevated temperatures, optionally in the presence of copper powder catalyst, to afford the ether or thioether products **162.3.**
For example, a tetrahydrofuran solution of 2-bromo-pyridine-5-aldehyde **162.4**, prepared as described in Tet. Lett., 2001, 42, 4841, is heated at reflux with an equimolar amount of a dialkyl 2-mercaptoethylphophonate **162.5**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990, in the presence of sodium carbonate, to afford the thioether product **162.6**.

Using the above procedures, but employing, in place of the haloaldehyde **162.4**, different haloaldehydes **162.1**, and/or different hydroxy or thio-alkyl phosphonates **162.2**, the corresponding products **162.3** are obtained.

Scheme **163** depicts the preparation of pyridine aldehydes **163.3** in which the phosphonate group is attached to the pyridine nucleus by means of a chain incorporating a nitrogen atom. In this procedure, a pyridine dicarboxaldehyde **163.1** is reacted with a dialkyl aminoalkyl phosphonate **163.2**, in the presence of a reducing agent, so as to effect a reductive amination reaction, yielding the product **163.3**. The preparation of amines by means of reductive amination of aldehydes is described, for example, in Advanced Organic Chemistry, F. A.

Carey, R. J. Sundberg, Plenum, 2001, part B, p. 269. The reactants are combined in an inert solvent such as an alcohol or ether, and treated with a reducing agent such as, for example, sodium cyanoborohydride or sodium triacetoxy borohydride, so as to yield the amine product **163.3**.

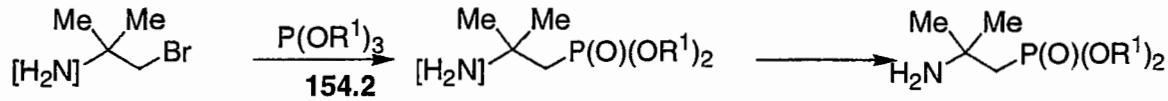
For example, equimolar amounts of pyridine 3,5-dicarboxaldehyde **163.4**, prepared as described in Tet. Lett., 1994, 35, 6191, and a dialkyl 2-aminoethyl phosphonate **163.5** prepared as described in J. Org. Chem., 2000, 65, 676, are reacted with sodium cyanoborohydride in isopropanol containing acetic acid, at ambient temperature, so as to produce the amine product **163.6**

Using the above procedures, but employing, in place of the dicarboxaldehyde **163.4**, different dicarboxaldehydes **163.1**, and/or different aminoalkyl phosphonates **163.2**, the corresponding products **163.3** are obtained.

Scheme **164** illustrates the incorporation of the formyl or chloromethyl pyridines, the syntheses of which are described above, into the piperazine reagent **13.1**. Compounds **164.2** in which Z is chloromethyl are reacted with the mono-protected piperazine derivatives **164.1**, the preparation of which are described in WO 9711698, to afford the alkylated product **164.3**. The preparation of amines by means of alkylation reactions is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 397. Equimolar amounts of the reactants **164.1** and the halomethyl pyridine compound **164.2**, are combined in a organic solvent such as an alcohol or dimethylformamide, in the presence of a base such as triethylamine or potassium carbonate, to give the alkylated products **164.3**. The alkylation of a piperazine derivative by a 3-chloromethylpyridine is described in WO9628439. Alternatively, the amine **164.1** is reacted with the aldehyde **164.2** to afford the product **164.3** in a reductive alkylation reaction. The preparation of amines by means of reductive amination procedures is described in Scheme **163**. In this procedure, the amine component and the aldehyde component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The reductive alkylation reaction between 3-pyridinecarboxaldehyde and a substituted piperazine is described in WO9628439. Deprotection of the product **164.3** then yields the free amine **13.1**.

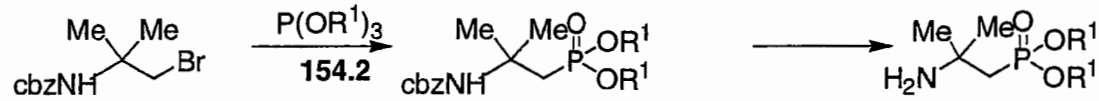
Scheme 154

Method



154.1 **154.3** **154.4**

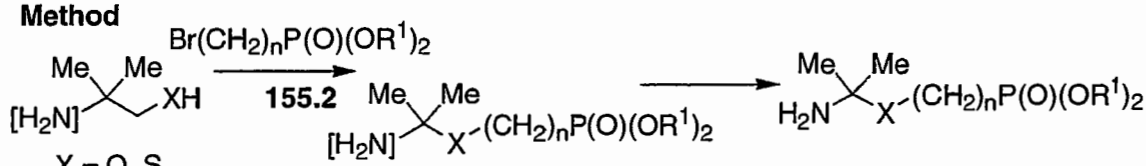
Example



154.6 **154.7** **154.8**

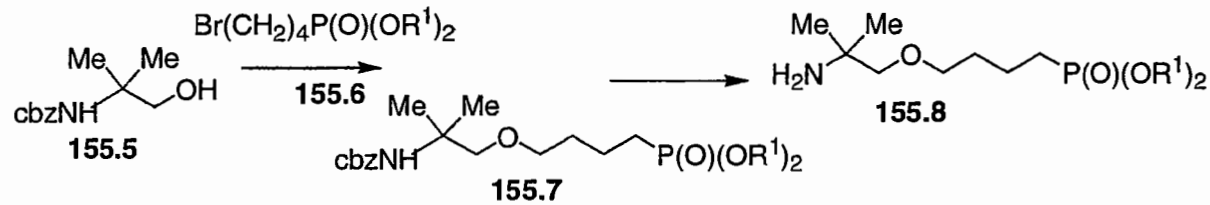
Scheme155

Method



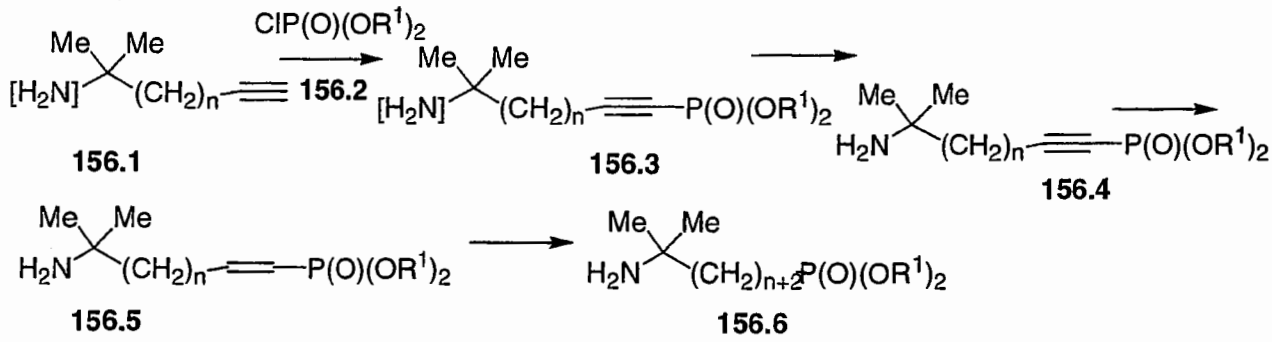
155.1 **155.3** **155.4**

Example

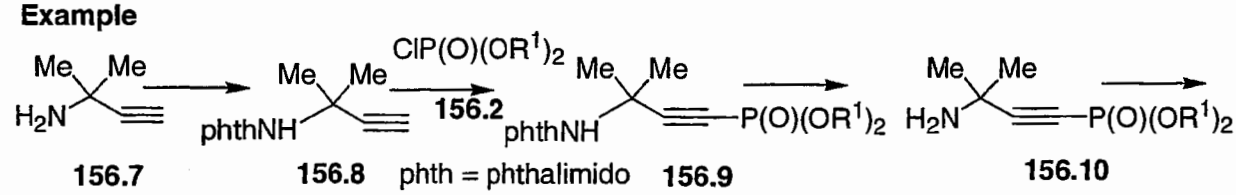


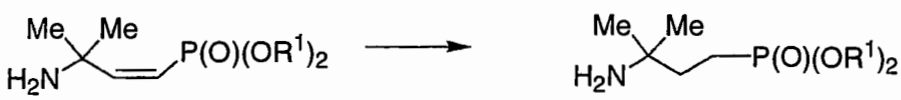
155.5 **155.7** **155.8**

Scheme156
Method

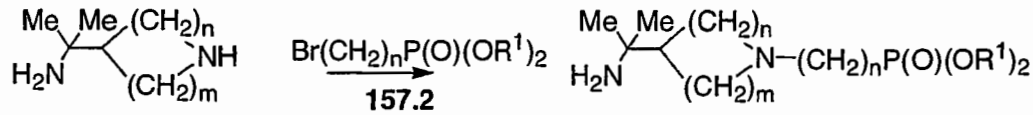


Example

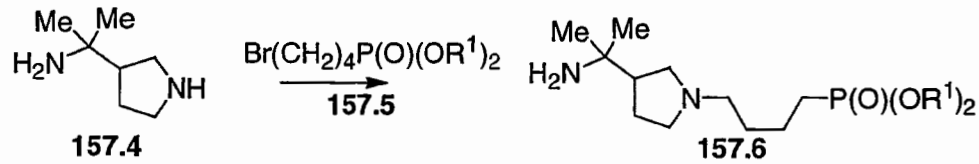




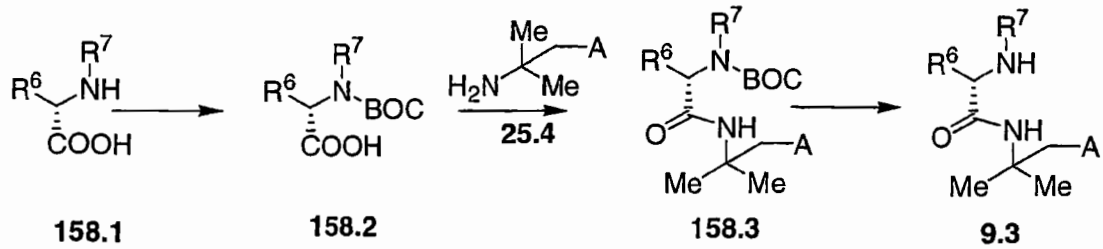
Scheme 157
Method



Example

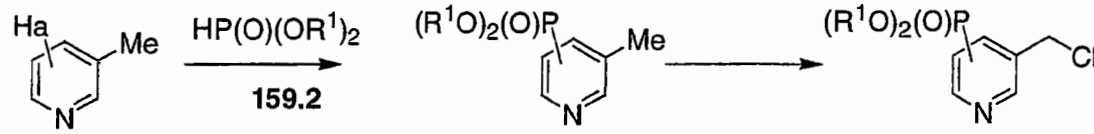


Scheme 158



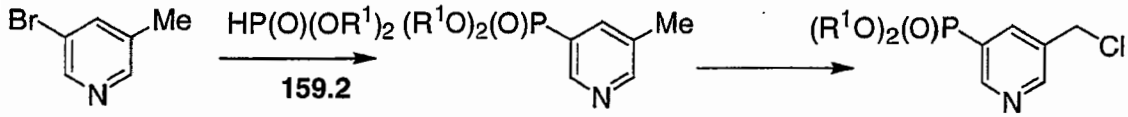
Scheme 159

Method



159.1 **159.3** **159.4**

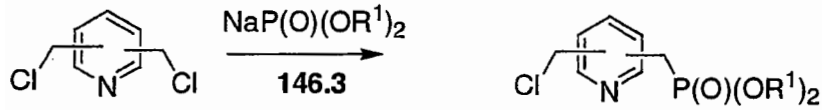
Example



159.5 **159.6** **159.7**

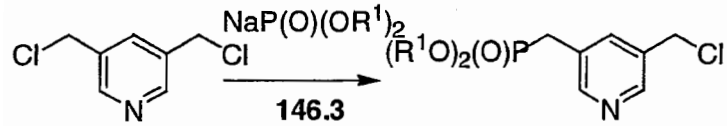
Scheme 160

Method



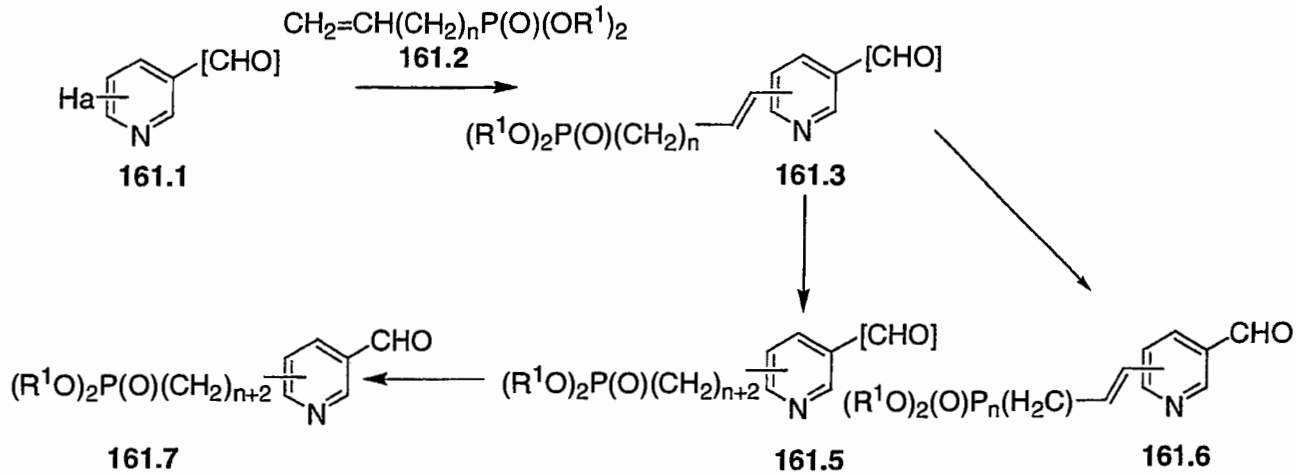
160.1 **160.2**

Example

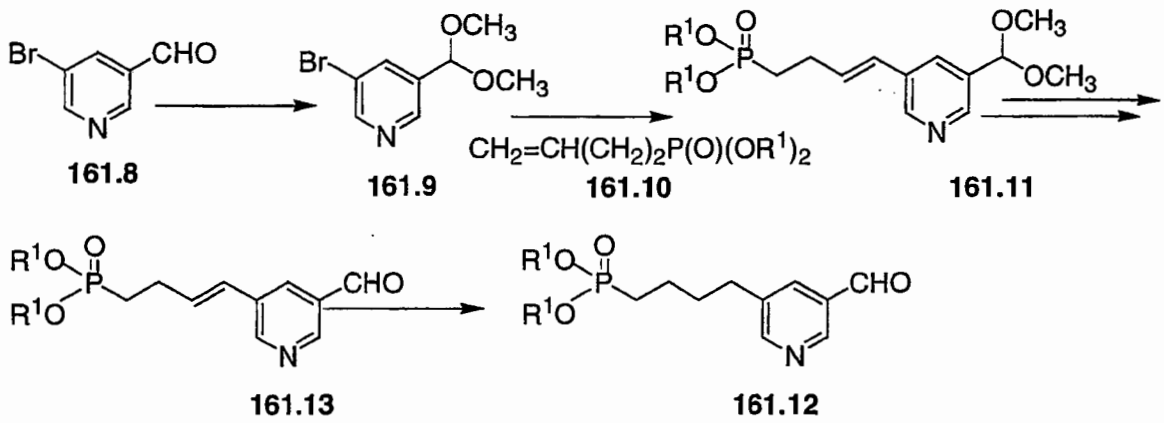


160.3 **160.4**

Scheme 161
Method

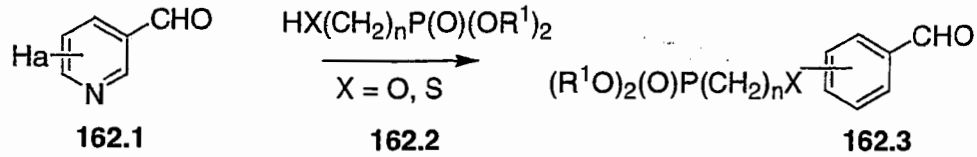


Example



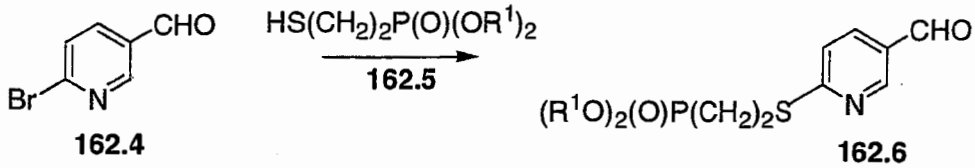
Scheme 162

Method



162.1 **162.2** **162.3**

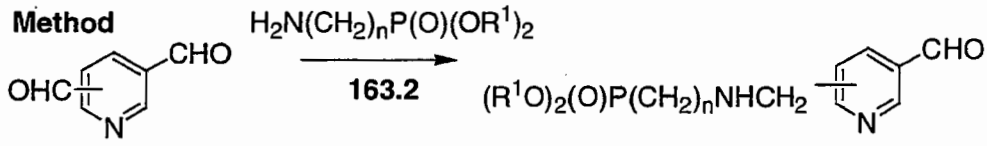
Example



162.4 **162.5** **162.6**

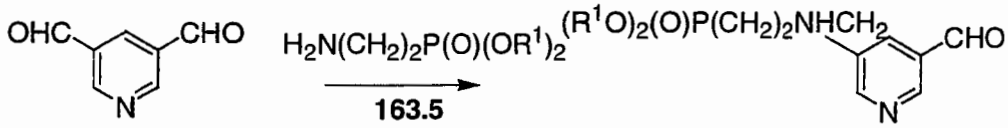
Scheme 163

Method



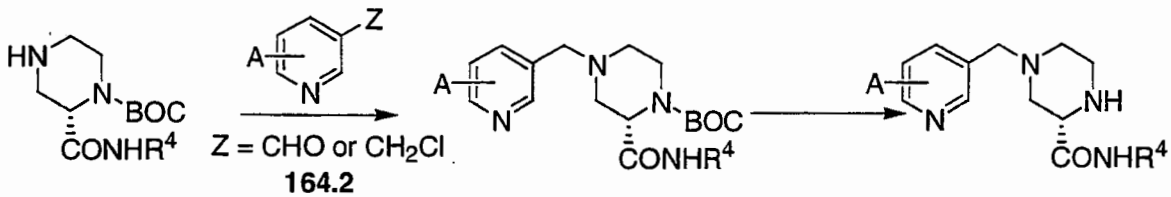
163.1 **163.2** **163.3**

Example



163.4 **163.5** **163.6**

Scheme 164



164.1 **164.2** **164.3** **13.1**

Preparation of dimethoxybenzyl halides 49.7 incorporating phosphonate groups.

Schemes **165** - **169** illustrate the preparation of dimethoxybenzyl halides **49.7** incorporating phosphonate groups, which are employed in the synthesis of the phosphonate esters **6** and **13**.

Scheme **165** depicts the preparation of dimethoxybenzyl alcohols in which the phosphonate group is attached either directly to the phenyl ring or by a saturated or unsaturated alkylene

chain. In this procedure, a bromo-substituted dimethoxy benzyl alcohol is coupled, in the presence of a palladium catalyst, with a dialkyl alkenyl phosphonate **165.2**, to afford the coupled product **165.3**. The reaction is conducted under the conditions described in Scheme **150**. The product **165.3** is then reduced, for example by treatment with diimide, as described in Scheme **150**, to yield the saturated analog **165.4**. Alternatively, the bromo compound **165.1** is coupled, in the presence of a palladium catalyst, as described in Scheme **144**, with a dialkyl phosphite **165.5**, to afford the phosphonate **165.6**.

For example, 4-bromo-3,5-dimethoxybenzyl alcohol **165.7**, the preparation of which is described in J. Med. Chem., 1977, 20, 299, is coupled with a dialkyl allyl phosphonate **165.8** (Aldrich) in the presence of bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **165.9**. The product is reduced, for example by treatment with diimide, as described in J. Org. Chem., 52, 4665, 1987, to yield the saturated compound **165.10**.

Using the above procedures, but employing, in place of the dimethoxy bromobenzyl alcohol **165.7**, different benzyl alcohols **165.1**, and/or different alkenyl phosphonates **165.2**, the corresponding products **165.3** and **165.4** are obtained.

As a further example, 3-bromo-4,5-dimethoxybenzyl alcohol **165.11**, the preparation of which is described in J. Org. Chem., 1978, 43, 1580, is coupled, in toluene solution at reflux, with a dialkyl phosphite **165.5**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to yield the phenyl phosphonate **165.12**.

Using the above procedures, but employing, in place of the dimethoxy bromobenzyl alcohol **165.11**, different benzyl alcohols **165.1**, and/or different dialkyl phosphites **165.5**, the corresponding products **165.6** are obtained.

Scheme **166** illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an amide group. In this procedure, a carboxy-substituted dimethoxybenzyl alcohol **166.1** is coupled, as described in Scheme **1**, with a dialkyl aminoalkyl phosphonate **166.2** to prepare the amide **166.3**.

For example, 2,6-dimethoxy-4-(hydroxymethyl)benzoic acid **166.4**, the preparation of which is described in Chem. Pharm. Bull., 1990, 38, 2118, is coupled in dimethylformamide solution, in

the presence of dicyclohexylcarbodiimide, with a dialkyl aminoethyl phosphonate **166.5**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, to afford the amide **166.6**. Using the above procedures, but employing, in place of the dimethoxybenzoic acid **166.4**, different benzoic acids **166.1**, and/or different aminoalkyl phosphites **166.2**, the corresponding products **166.3** are obtained.

Scheme **167** illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an aminoalkyl or an amide group. In this procedure, an amino-substituted dimethoxybenzyl alcohol **167.1** is reacted, under reductive amination conditions, as described in Scheme **163**, with a dialkyl formylalkylphosphonate **167.2** to yield the aminoalkyl product **167.3**. Alternatively, the amino-substituted dimethoxybenzyl alcohol **167.1** is coupled, as described in Scheme **1**, with a dialkyl carboxyalkyl phosphonate **167.4**, to produce the amide **167.5**.

For example, 3-amino-4,5-dimethoxybenzyl alcohol **167.6**, the preparation of which is described in Bull. Chem. Soc. Jpn., 1972, 45, 3455, is reacted, in the presence of sodium triacetoxyborohydride, with a dialkyl formylmethyl phosphonate **167.7**, as described in Scheme **135**, to afford the aminoethyl phosphonate **167.8**.

Using the above procedures, but employing, in place of the amine **167.6**, different amines **167.1**, and/or different formylalkyl phosphites **167.2**, the corresponding products **167.3** are obtained.

As a further example, 4-amino-3,5-dimethoxybenzyl alcohol **167.9**, the preparation of which is described in Bull. Chem. Soc. Jpn., 1972, 45, 3455, is coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl phosphonoacetic acid **167.10**, (Aldrich) to afford the amide **167.11**.

Using the above procedures, but employing, in place of the amine **167.6**, different amines **167.1**, and/or different carboxyalkyl phosphonates **167.4**, the corresponding products **167.5** are obtained.

Scheme **168** illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an alkoxy group. In this procedure, a dimethoxyhydroxy benzyl alcohol **168.1** is reacted with a dialkyl alkylphosphonate **168.2** with a terminal leaving group to afford the alkoxy product **168.3**. The alkylation reaction is

effected in a polar organic solvent such as dimethylformamide in the presence of a base such as dimethylaminopyridine or cesium carbonate.

For example, 4-hydroxy-3,5-dimethoxybenzyl alcohol **168.4**, the preparation of which is described in J. Med. Chem. 1999, 43, 3657, is reacted in dimethylformamide at 80°C with an equimolar amount of a dialkyl bromopropyl phosphonate **168.5**, prepared as described in J. Am. Chem. Soc., 2000, 122, 1554, and cesium carbonate, to give the alkylated product **168.6**. Using the above procedures, but employing, in place of the phenol **168.4**, different phenols **168.1**, and/or different alkyl phosphonates **168.2**, the corresponding products **168.3** are obtained.

As a further example, 4,5-dimethoxy-3-hydroxybenzyl alcohol **168.7**, prepared as described in J. Org. Chem., 1989, 54, 4105, is reacted, as described above, with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **168.8**, prepared as described in Tet. Lett., 1986, 27, 1477, to produce the alkylated product **168.9**.

Using the above procedures, but employing, in place of the phenol **168.7**, different phenols **168.1**, and/or different alkyl phosphonates **168.2**, the corresponding products **168.3** are obtained.

Scheme **169** illustrates the conversion of the benzyl alcohols **169.1**, in which the substituent A is the group link-$P(O)(OR^1)_2$, or a precursor, prepared as described above, into the corresponding halides **169.2**. The conversion of alcohols into chlorides, bromides and iodides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff, p. 356ff and p. 358ff. For example, benzyl alcohols are transformed into the chloro compounds, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in J. Am. Chem. Soc., 106, 3286, 1984. Benzyl alcohols are transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc., 92, 2139, 1970. Benzyl alcohols are transformed into iodides by reaction with sodium iodide and boron trifluoride etherate, as described in Tet. Lett., 28, 4969, 1987, or by reaction with diphosphorus tetraiodide, as described in Tet. Lett., 1801, 1979. Benzylic chlorides or bromides are transformed into the corresponding iodides by reaction with sodium iodide in acetone or methanol, for example as described in EP 708085.

Preparation of dimethoxythiophenols 23.1 incorporating phosphonate groups.

Schemes **170 - 173** illustrate the preparation of the dimethoxythiophenols **23.1** incorporating phosphonate groups, which are used in the synthesis of the phosphonate esters **6** and **13**.

Scheme **170** illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached by means of an amide group. In this procedure, a dimethoxyamino-substituted benzoic acid **170.1** is converted into the corresponding thiol **170.2**. The conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoborate, is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to afford the thiol **170.2**. The product is then coupled, as described above, with a dialkyl aminoalkyl phosphonate **170.3**, to yield the amide **170.4**.

For example, 5-amino-2,3-dimethoxybenzoic acid **170.5**, the preparation of which is described in JP 02028185, is converted, as described above, into 2,3-dimethoxy-5-mercaptobenzoic acid **170.6**. The product is then coupled, as described in Scheme **1**, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminopropyl phosphonate **170.7**, (Acros) to afford the amide **170.8**.

Using the above procedures, but employing, in place of the amine **170.5**, different amines **170.1**, and/or different aminoalkyl phosphonates **170.3**, the corresponding products **170.4** are obtained.

Scheme **171** illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromodimethoxyaniline **171.1** is converted, as described in Scheme **170**, into the corresponding thiophenol **171.2**. The thiol group is then protected to give the derivative **171.3**. The protection and deprotection of thiol groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277. For example, thiol substituents are protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a chlorotrialkylsilane and a base such as imidazole. Alternatively, thiol substituents are protected by conversion to tert-butyl or

adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The product **171.3** is then coupled, in the presence of a palladium catalyst, as described in Scheme **165**, with a dialkyl alkenyl phosphonate **171.4**, to give the alkenyl product **171.5**. Deprotection then yields the thiol **171.6**. Reduction of the double bond, for example by reaction with diimide, as described in J. Org. Chem., 52, 4665, 1987, affords the saturated product **171.7**.

For example, 4-bromo-3,5-dimethoxyaniline **171.8**, prepared as described in WO9936393, is converted, by diazotization, into 4-bromo-3,5-dimethoxythiophenol **171.9**. The product is then transformed into the S-benzoyl derivative **171.10**, by reaction with benzoyl chloride in pyridine, and the product is coupled, as described in Scheme **165**, with a dialkyl butenyl phosphonate **171.11**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, to yield the phosphonate **171.12**. Deprotection, for example by treatment with aqueous ammonia at ambient temperature, as described in J. Am. Chem. Soc., 85, 1337, 1963, then afford the thiol **171.13**. The double bond is reduced with diimide to give the saturated analog **171.14**.

Using the above procedures, but employing, in place of the amine **171.8**, different amines **171.1**, and/or different alkenyl phosphonates **171.4**, the corresponding products **171.6** and **171.7** are obtained.

Scheme **172** illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group directly attached to the phenyl ring. In this procedure, a protected bromodimethoxythiophenol **172.1**, prepared, for example, from the corresponding aniline, as described above, is coupled, in the presence of a palladium catalyst, as described in Scheme **165**, with a dialkyl phosphite **172.2**. The product is then deprotected to afford the phosphonate ester **172.4**.

For example, 3-bromo-4,5-dimethoxyaniline **172.5**, prepared as described in DE 2355394, is converted, as described above in Schemes **165** and **171**, into S-benzoyl 3-bromo-4,5-dimethoxythiophenol **172.6**. This compound is then coupled, in toluene solution at reflux, with a dialkyl phosphite **172.2**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to yield the phenyl phosphonate **172.7**. Deprotection, as described in Scheme **171**, then affords the thiol **172.8**.

Using the above procedures, but employing, in place of the protected thiol **172.6**, different thiol **172.1**, the corresponding products **172.4** are obtained.

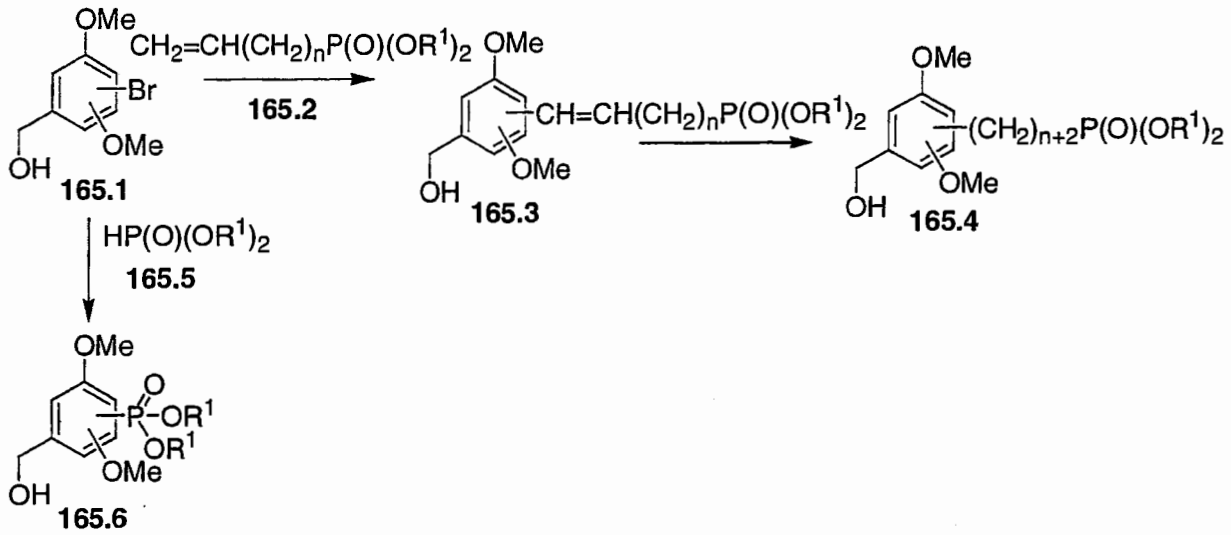
Scheme **173** illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached to the phenyl ring by means of an alkoxy group. In this procedure, a dimethoxy aminophenol **173.1** is converted, via the diazo compound, into the corresponding thiophenol **173.2**. The thiol group is then protected, and the product **173.3** is alkylated, as described in Scheme **168**, with a dialkyl bromoalkyl phosphonate **173.4**. Deprotection of the product **173.5** then affords the thiophenol **173.6**.

For example, 5-amino-2,3-dimethoxyphenol **173.7**, prepared as described in WO 9841512, is converted by diazotization, as described above, into the thiophenol **173.8**, and the product is protected by reaction with one molar equivalent of benzoyl chloride in pyridine, to yield the S-benzoyl product **173.9**. The latter compound is then reacted, in dimethylformamide solution at 80°C, with a dialkyl bromoethyl phosphonate **173.10** (Aldrich) and cesium carbonate, to produce the ethoxyphosphonate **173.11**. Deprotection, as described in Scheme **171**, then yields the thiol **173.12**.

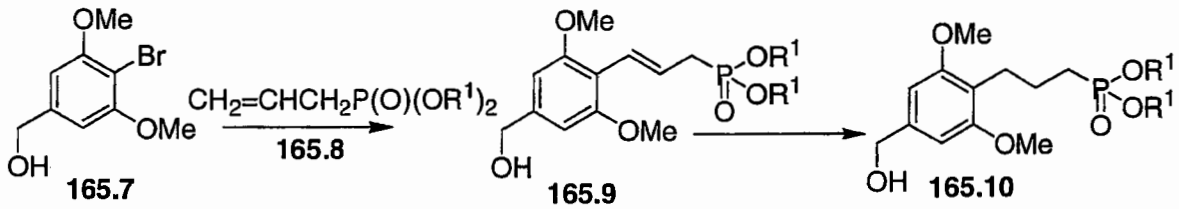
Using the above procedures, but employing, in place of the thiol **173.8**, different thiol **173.2**, and/or different bromoalkyl phosphonates **173.4**, the corresponding products **173.6** are obtained.

Scheme 165

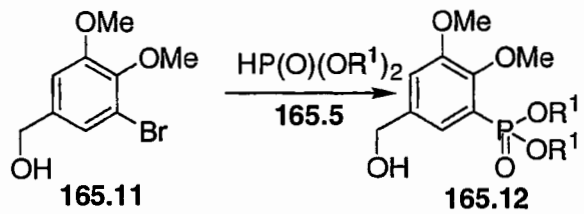
Method



Example 1

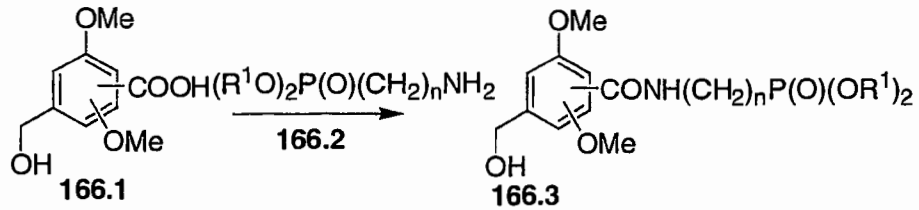


Example 2

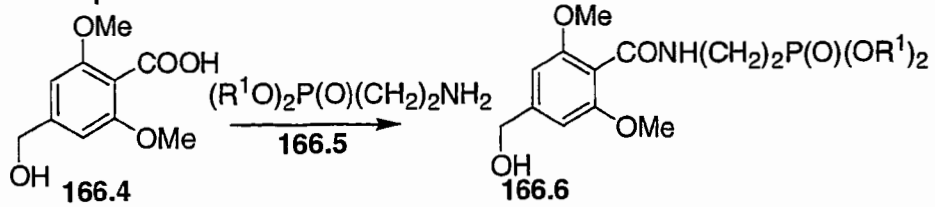


Scheme 166

Method

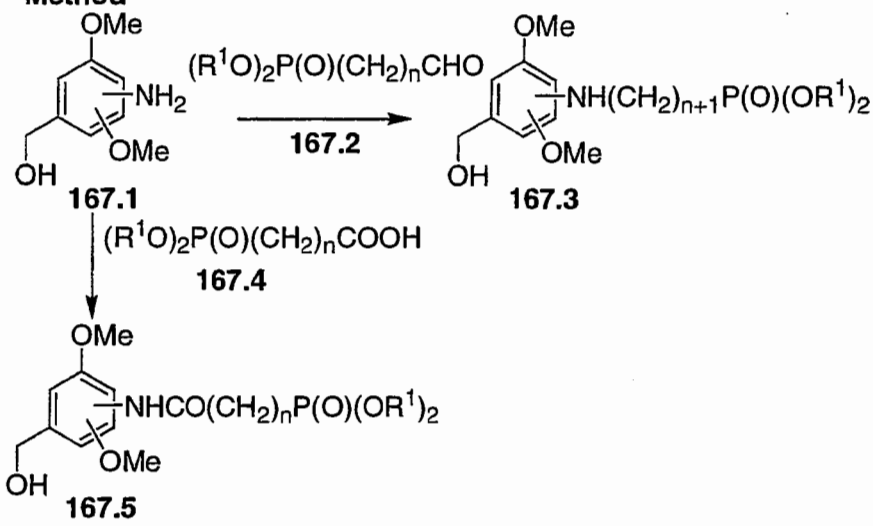


Example

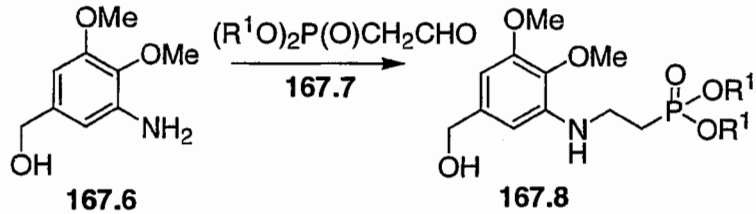


Scheme 167

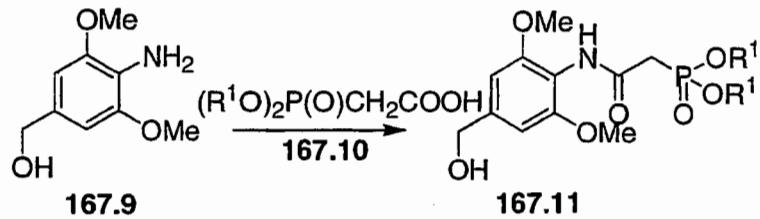
Method



Example 1

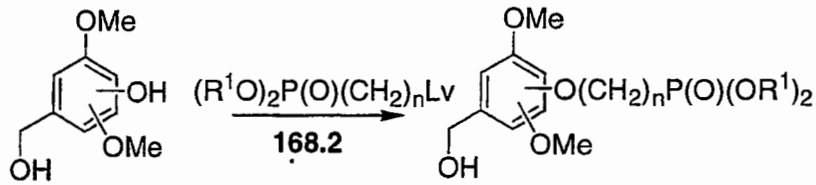


Example 2



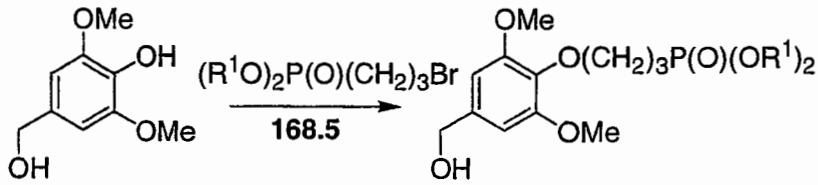
Scheme 168

Method



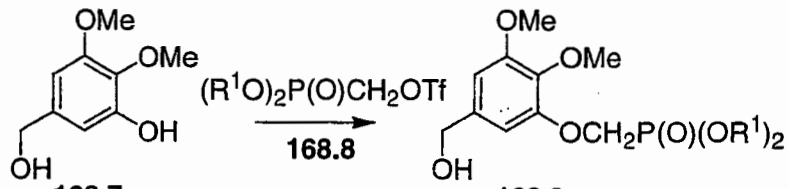
168.1 168.3

Example 1



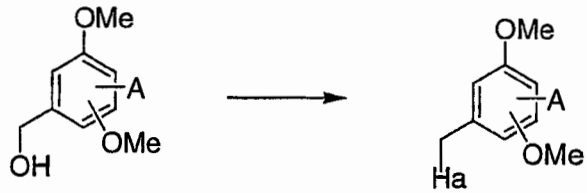
168.4 168.6

Example 2



168.7 168.9

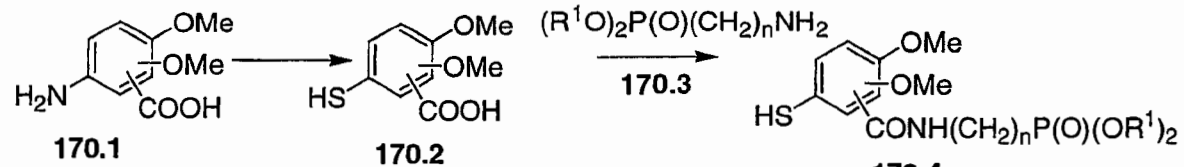
Scheme 169



169.1 49.7

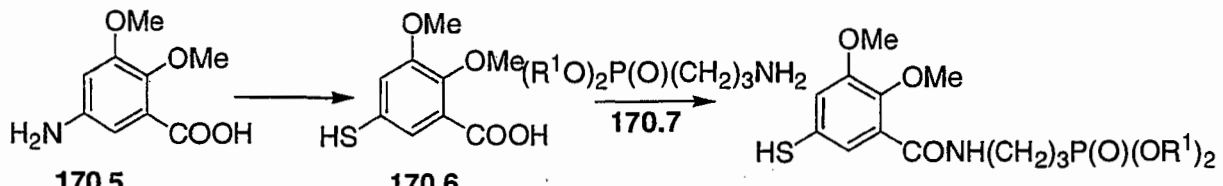
Scheme 170

Method



170.1 170.2 170.4

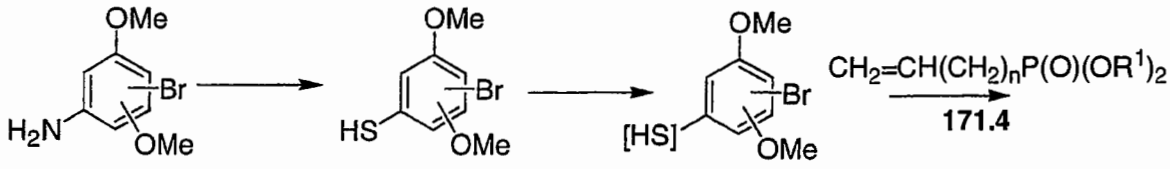
Example 1



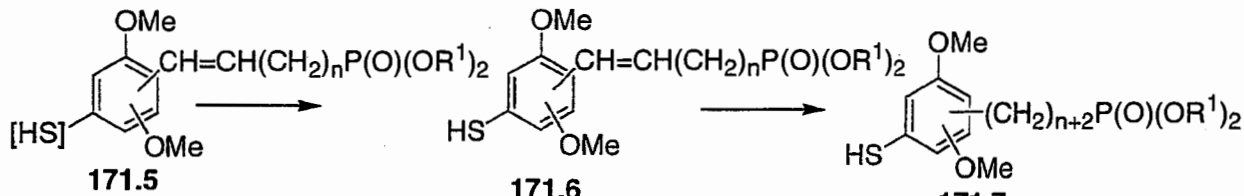
170.5 170.6 170.8

Scheme 171

Method

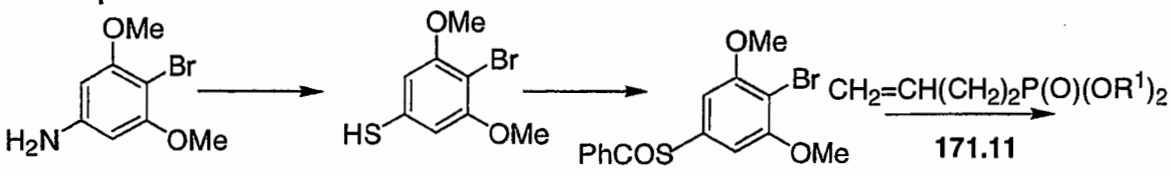


171.1 171.2 171.3

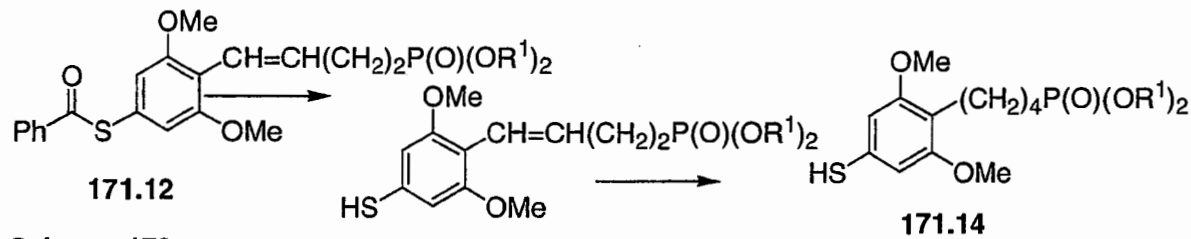


171.5 171.6 171.7

Example



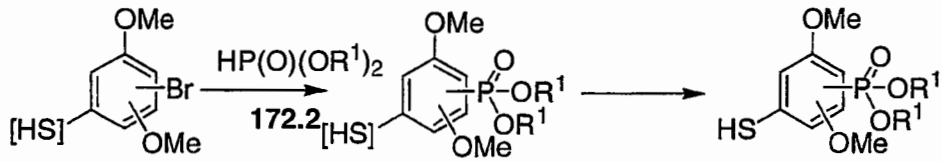
171.8 171.9 171.10



171.12 171.13 171.14

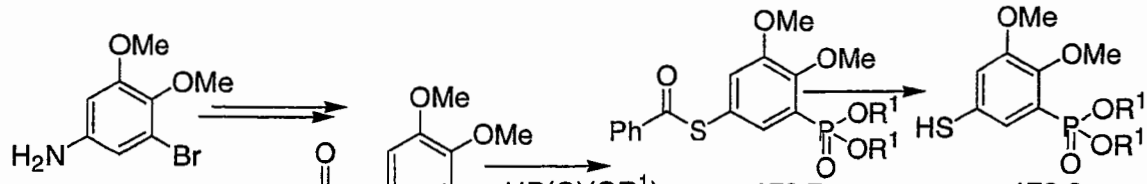
Scheme 172

Method



172.1 172.3 172.4

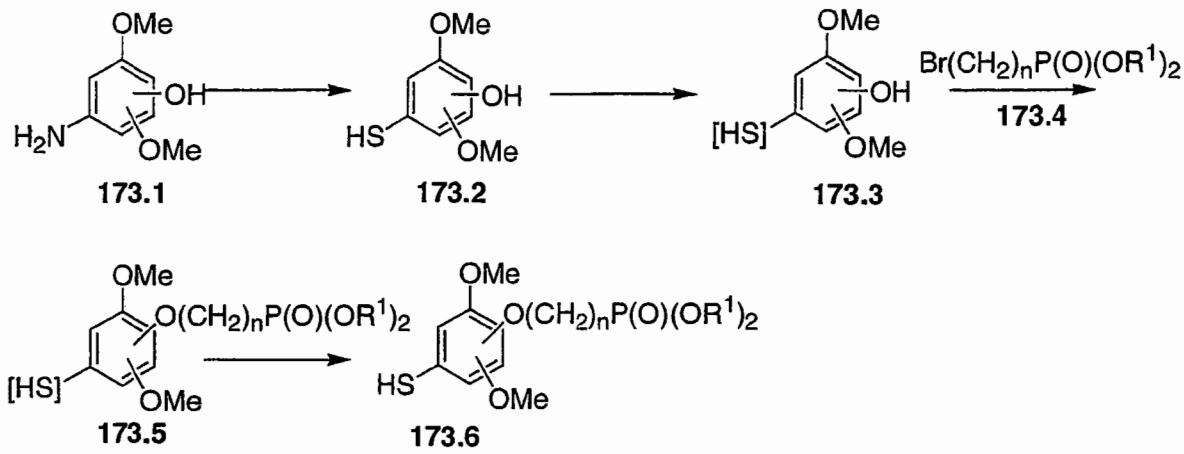
Example



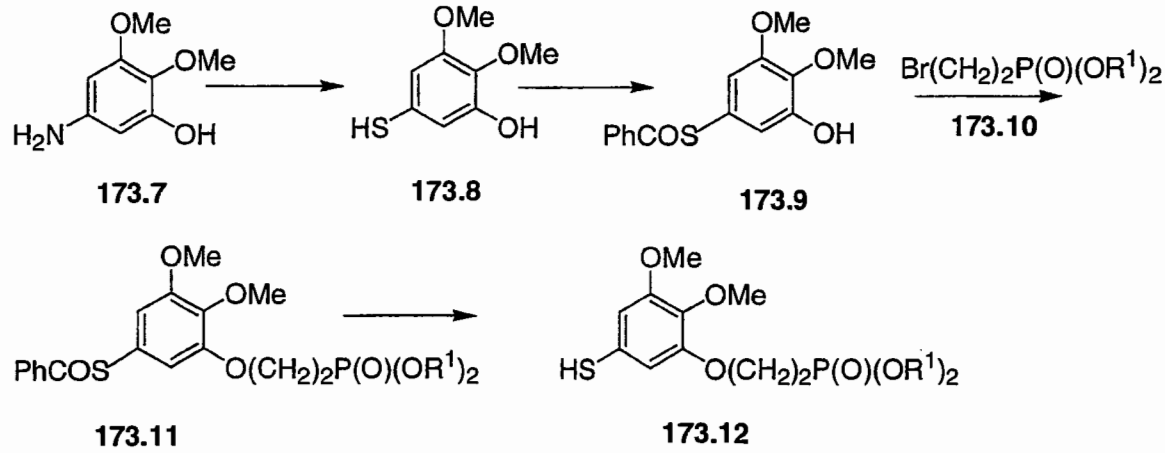
172.5 172.6 172.7 172.8

Scheme 173

Method



Example



Preparation of ethanolamine derivatives 29.1 incorporating phosphonate groups.

Schemes **174** - **178** illustrate the preparation of the ethanolamine derivatives **29.1** which are employed in the preparation of the phosphonate esters **18** and **8.**

Scheme **174** illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkyl chain. In this procedure, ethanolamine **174.1** is protected to give the derivative **174.2.** The product is then reacted with a dialkyl alkyl phosphonate **174.3** in which the alkyl group incorporates a leaving group Lv. The alkylation

reaction is performed in a polar organic solvent such as acetonitrile or dimethylformamide, in the presence of a strong base such as sodium hydride or lithium hexamethyldisilazide, to afford the ether product **174.4**. The protecting group is then removed to yield the amine **174.5**. The protection and deprotection of amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 309. The amino compound **174.5** is then coupled, as described in Scheme **1**, with the aminoacid **174.6**, to give the amide **174.7**.

For example, equimolar amounts of phthalimide and ethanolamine are reacted in toluene at 70°C, as described in J. Org. Chem., 43, 2320, 1978, to prepare the phthalimido derivative **174.8**, in which Phth is phthalimido. The product is then reacted, in tetrahydrofuran, with sodium hydride and an equimolar amount of a dialkyl trifluoromethylsulfonyloxymethyl phosphonate **174.9**, the preparation of which is described in Tet. Lett., 1986, 27, 1497, to afford the ether product **174.10**. The phthalimido group is then removed by treatment of the product **174.10** with ethanolic hydrazine at ambient temperature, as described in J. Org. Chem., 43, 2320, 1978, to yield the amine **174.11**. The product is then coupled, in the presence of dicyclohexylcarbodiimide, with the aminoacid **174.6**, to yield the amide **174.12**. Using the above procedures, but employing, in place of the methylphosphonate **174.9**, different alkylphosphonates **174.3**, the corresponding products **174.7** are obtained.

Scheme **175** illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkylene chain incorporating a nitrogen. In this procedure, ethanolamine **174.1** and the aminoacid **174.6** are coupled, as described in Scheme **1**, to form the amide **175.1**. The product is then alkylated with a bromoalkyl aldehyde **175.2** to yield the ether **175.3**. The alkylation reaction is performed in a polar organic solvent such as acetonitrile or dioxan, in the presence of a strong base such as potassium tert. butoxide or sodium hydride, at about 60°C. The aldehyde product is then reacted, under reductive amination conditions, as described in Scheme **135**, with a dialkyl aminoalkyl phosphonate **175.4**, to produce the amine product **175.5**.

For example, the amide **175.1** is reacted, as described above, with bromoacetaldehyde **175.6**, to afford the ether **175.7**. The product is then reacted in ethanol with a dialkyl aminoethyl phosphonate **175.8**, (Aurora)and sodium triacetoxyborohydride, to yield the amine **175.9**.

Using the above procedures, but employing, in place of the bromoacetaldehyde **175.6**, different bromoalkyl aldehydes **175.2**, and/or different aminoalkyl phosphonates **175.4,** the corresponding products **175.5** are obtained.

Scheme **176** illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of a phenyl ring. In this procedure, bromoethylamine **176.1** and the aminoacid **174.6** are coupled, as described in Scheme **1**, to afford the amide **176.2**. The product is then reacted with the dialkyl hydroxyalkyl-substituted phenylphosphonate **176.3** to prepare the ether **176.4.** The alkylation reaction is performed in a polar organic solvent such as dimethyl sulfoxide or dioxan, in the presence of a base such as lithium bis(trimethylsilyl)amide, sodium hydride or lithium piperidide.
For example, the amide **176.2** is reacted in dimethylformamide with a dialkyl 4-(2-hydroxyethyl)phenyl phosphonate **176.5**, prepared as described in J. Am. Chem. Soc., 1996, 118, 5881, and sodium hydride, to furnish the ether product **176.6**.
Using the above procedures, but employing, in place of the hydroxyethyl phenylphosphonate **176.5**, different phosphonates **176.3,** the corresponding products **176.4** are obtained.

Scheme **177** illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkylene chain. In this procedure, the aminoacid **174.6** is coupled with a bromoalkoxy-substituted ethylamine **177.1** to give the amide **177.2**. The product is then subjected to an Arbuzov reaction with a trialkyl phosphite $P(OR^1)_3$. In this procedure, described in Handb. Organophosphorus Chem., 1992, 115, the reactants are heated together at ca. 100°C to afford the product **177.4**.
For example, the aminoacid **174.6** is coupled, as described in Scheme **1,** in acetonitrile solution containing dicyclohexylcarbodiimide, with 2-bromoethoxyethylamine **177.5**, prepared as described in Vop. Khim. Tekh., 1974, 34, 6, to produce the amide **177.6**. The product is then heated at 120°C with excess trialkyl phosphite **177.3**, to afford the phosphonate **177.7**.
Using the above procedures, but employing, in place of the bromoethoxyethylamine **177.5**, different bromoalkyl ethylamines **177.1,** the corresponding products **177.4** are obtained.

Scheme **178** depicts the preparation of the amines **29.1**. The BOC-protected ethanolamine derivatives **178.1**, in which the group A is either the substituent link-$P(O)(OR^1)_2$, or a

precursor thereto, prepared as described in Schemes **174 - 177**, are deprotected to afford the amines **29.1**. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection is effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride in ethyl acetate, or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preparation of the chroman phosphonate esters 33.1.

Schemes **179 – 181a** illustrate the preparation of the chroman phosphonate esters **33.1** which are employed in the preparation of the phosphonate esters **17** and **9.**

Scheme **179** depicts the preparation of (2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazol-4-yl)-methanol, **179.6**, 2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazole-4-carbaldehyde, **179.7**, and 2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazole-4-carboxylic acid, **179.8**, which are used in the preparation of the phosphonates **33.1**. In this procedure, (2H-chromen-2-yl)-methanol **179.1**, prepared as described in J. Chem. Soc., (D), 344, 1973, is converted, as described above, (Scheme **1**)into the tert. butyldimethylsilyl ether **179.2**. The product is then reacted, as described in J. Het. Chem., 1975, 12, 1179, with silver cyanate and iodine in ether, so as to afford the addition product **179.3**. This compound is then heated on methanol to yield the carbamate derivative **179.4**. The latter compound is heated in xylene at reflux, as described in J. Het. Chem., 1975, 12, 1179, to produce the oxazoline derivative **179.5**. The silyl group is then removed by reaction with tetrabutylammonium fluoride in tetrahydrofuran to yield the carbinol **179.6**. The carbinol is oxidized to produce the aldehyde **179.7**. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. The alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, dimethyl sulfoxide/acetic anhydride or dimethyl sulfoxide-dicyclohexyl carbodiimide. The reaction is conducted in an inert aprotic solvent such as dichloromethane or toluene. The aldehyde **179.7** is oxidized to the carboxylic acid **179.8**. The oxidation of aldehydes to carboxylic acids is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 838ff. The conversion is effected by treatment with oxidizing agents such as potassium permanganate,

ruthenium tetroxide, chromium trioxide in acetic acid, or, preferably, by the use of silver oxide, as described in J. Am. Chem. Soc., 73, 2590, 1951.

Scheme **180** illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of an aminoalkyl chain. In this procedure, the aldehyde **179.7** is reacted, under reductive amination conditions, as described in Scheme **175**, with a dialkyl aminoalkyl phosphonate **180.1**, to give the amine **180.2**. The oxazoline group is then hydrolyzed, for example by reaction with aqueous potassium hydroxide, as described in J. Het. Chem., 1975, 12, 1179, to yield the hydroxyamine **180.3**.

For example, the aldehyde **179.7** is reacted in ethanol with a dialkyl aminomethyl phosphonate **180.4**, (Interchim) and sodium triacetoxyborohydride, to produce the amine **180.5**. The oxazoline is then hydrolyzed, as described above, to afford the hydroxyamine **180.6**.
Using the above procedures, but employing, in place of the aminomethyl phosphonate **180.4**, different phosphonates **180.1**, the corresponding products **180.3** are obtained.

Scheme **181** illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of an amide group. In this procedure, the carboxylic acid **179.8** is coupled, as described in Scheme **1**, with a dialkyl aminoalkyl phosphonate **180.1**, to produce the amide **181.1**. Hydrolysis of the oxazoline group, as described above, then yields the hydroxyamine **181.2**.

For example, the carboxylic acid **179.8** is coupled with a dialkyl aminopropyl phosphonate **181.3**, (Acros) to afford the amide **181.4**, which is then hydrolyzed to give the hydroxyamine **181.5**.
Using the above procedures, but employing, in place of the aminopropyl phosphonate **181.3**, different phosphonates **180.1**, the corresponding products **181.2** are obtained.

Scheme **181a** illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of a thioalkyl group. In this procedure, the carbinol **179.6** is converted into the bromo derivative **181a.1**. The conversion of alcohols into bromides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 356ff. For example, the alcohol is reacted with triphenyl phosphine and carbon tetrabromide, trimethylsilyl bromide, thionyl bromide and the like. The bromo compound is

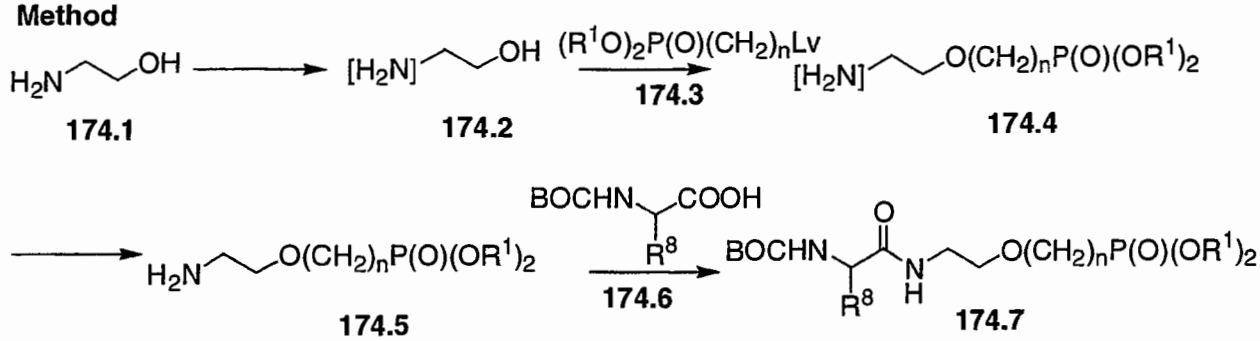
then reacted with a dialkyl thioalkyl phosphonate **181a.2** to effect displacement of the bromide and formation of the thioether **181a.3**. The reaction is performed in a polar organic solvent such as ethanol in the presence of a base such as potassium carbonate. Removal of the isoxazoline group then produces the hydroxyamine **181a.4**.

For example, the bromo compound **181a.1** is reacted in ethanol with a dialkyl thioethyl phosphonate **181a.5**, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, and potassium carbonate, to yield the thioether product **181a.6**. Hydrolysis, as described above, then affords the hydroxyamine **181a.7**.

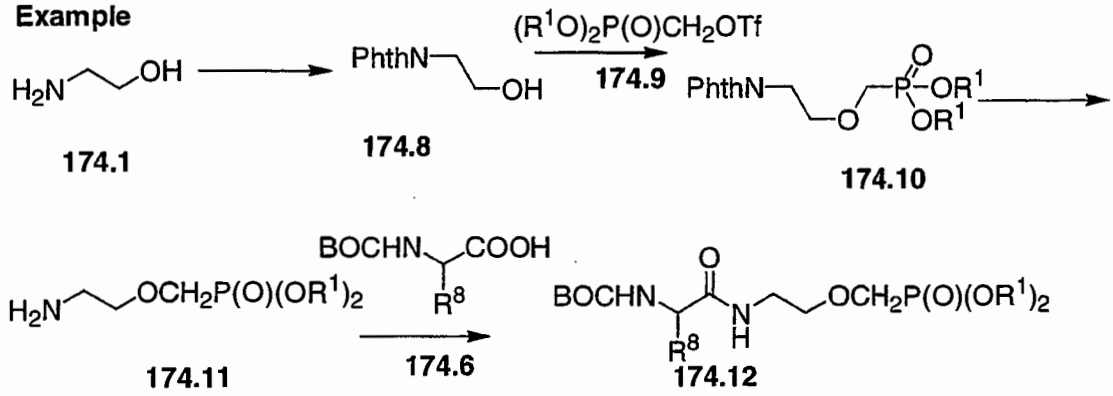
Using the above procedures, but employing, in place of the thioethyl phosphonate **181a.5**, different phosphonates **181a.2**, the corresponding products **181a.4** are obtained.

Scheme 174

Method

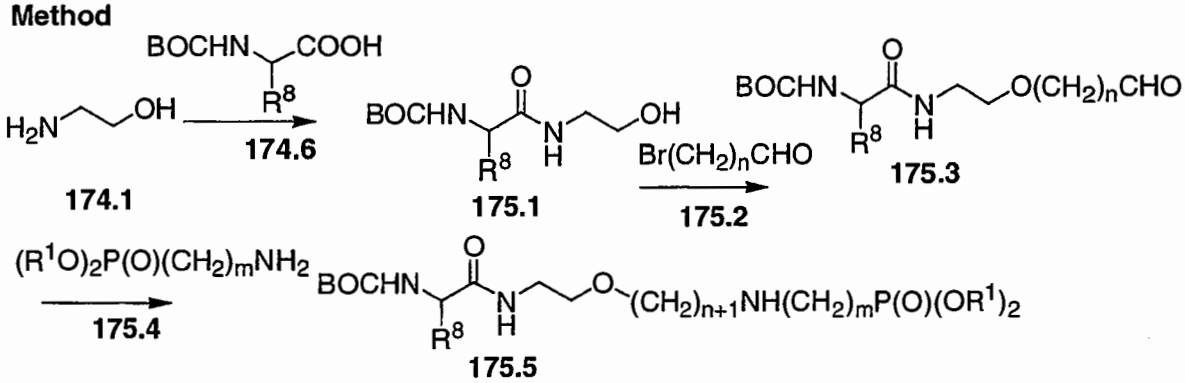


Example

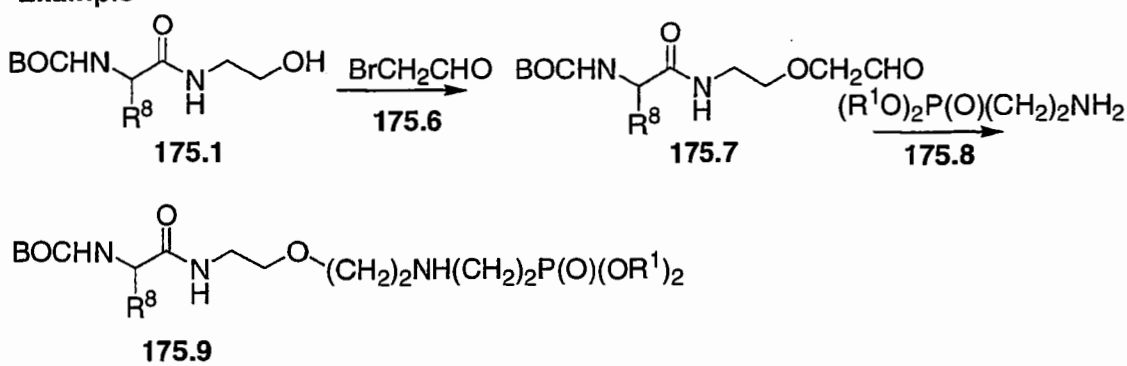


Scheme 175

Method

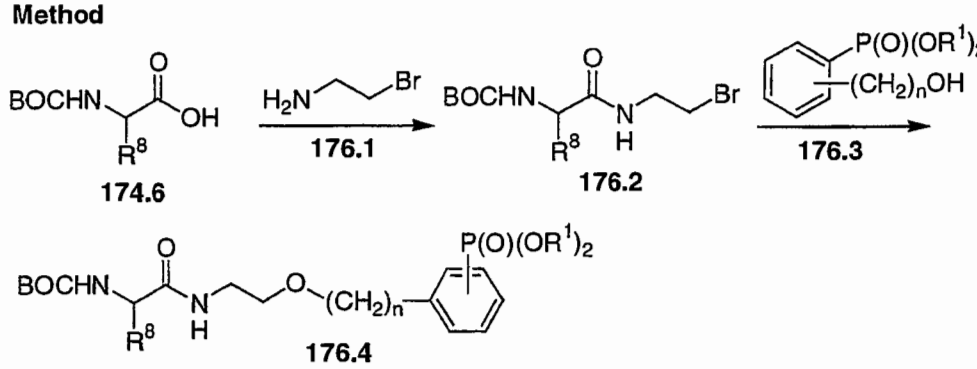


Example

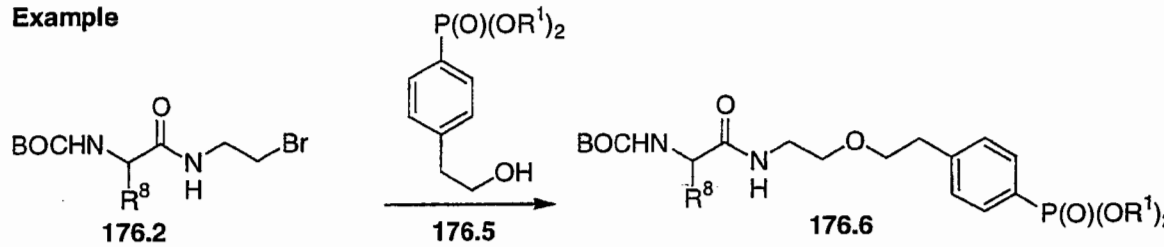


Scheme 176

Method

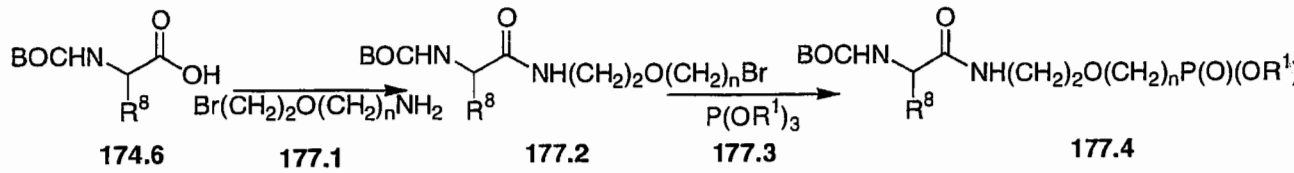


Example

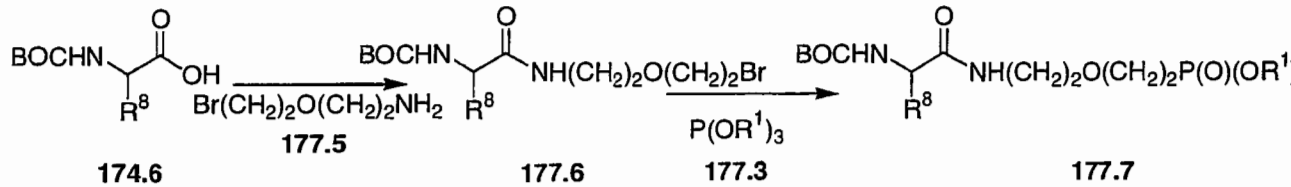


Scheme 177

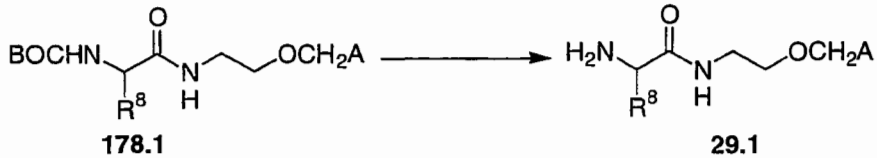
Method



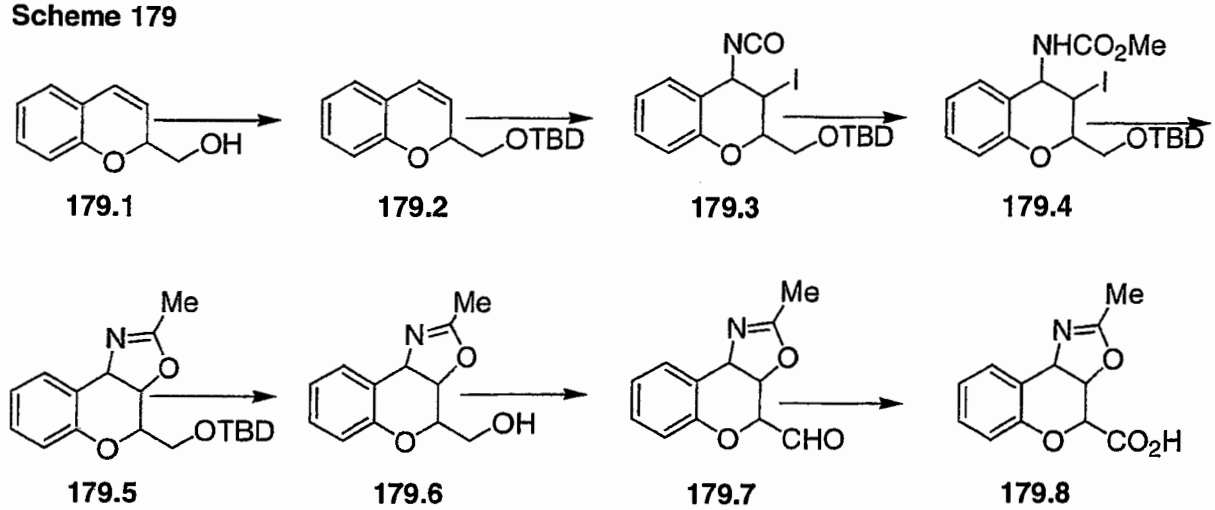
Example



Scheme 178



Scheme 179

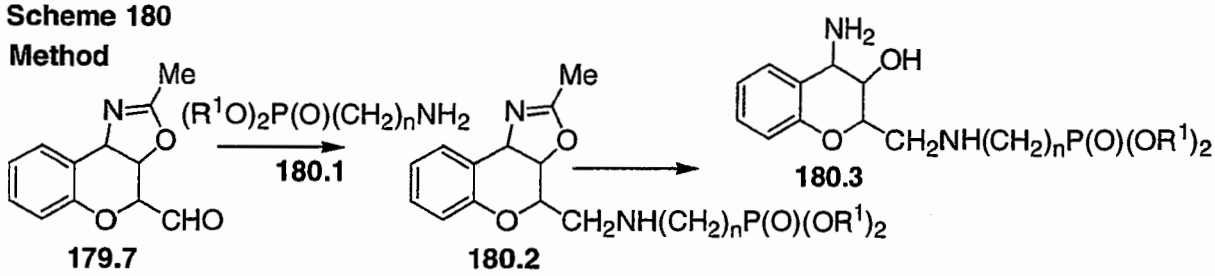


179.1 179.2 179.3 179.4

179.5 179.6 179.7 179.8

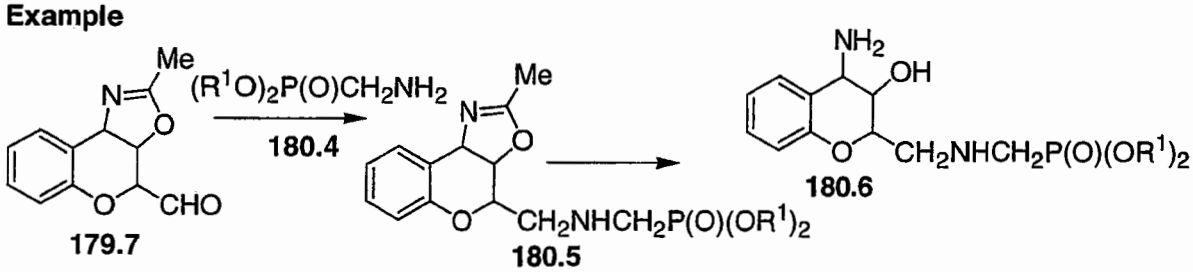
Scheme 180

Method



179.7 180.2 180.3

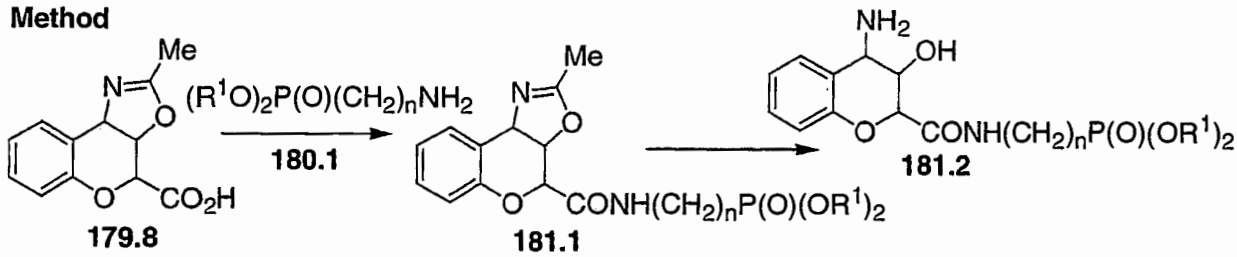
Example



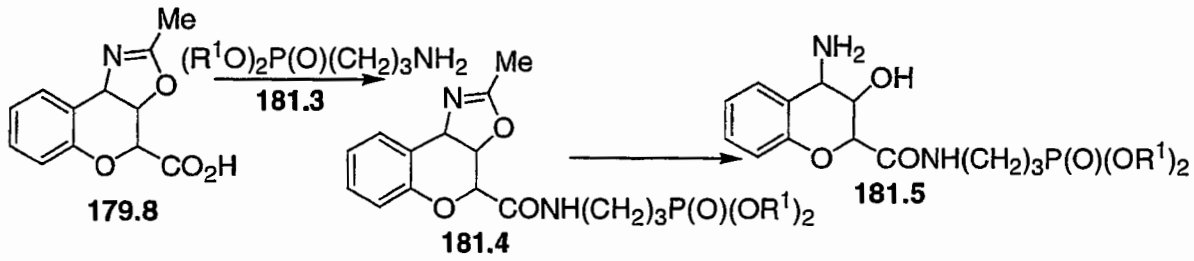
179.7 180.5 180.6

Scheme 181

Method

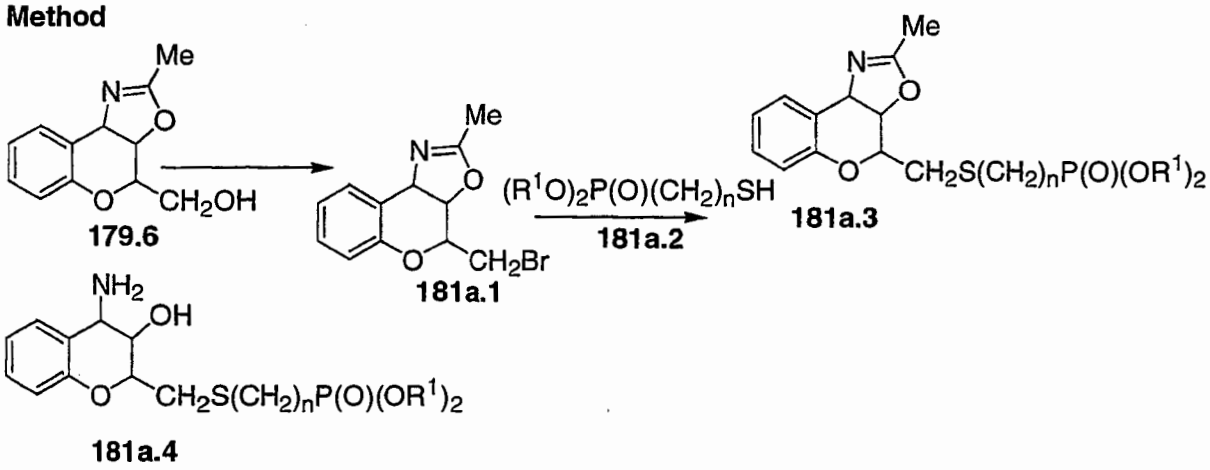


Example

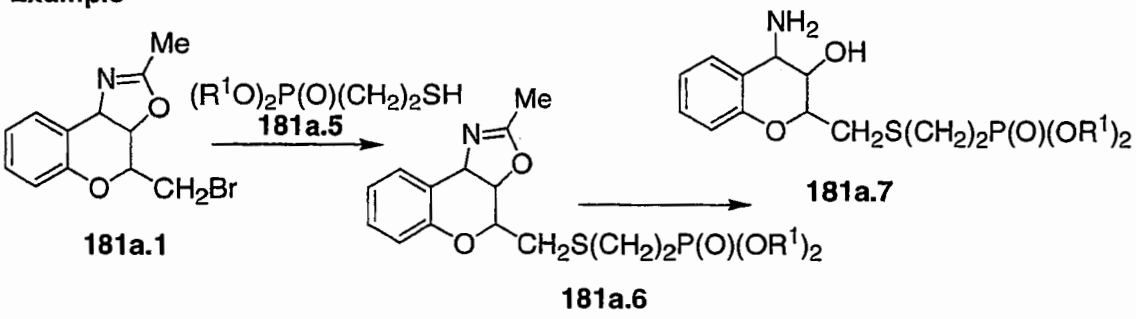


Scheme 181a

Method



Example



Preparation of phenylalanine derivatives 37.1 incorporating phosphonate moieties.

Schemes **182** - **185** illustrate the preparation of phosphonate-containing phenylalanine derivatives **37.1** which are employed in the preparation of the intermediate phosphonate esters **10** and **19**.

Scheme **182** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives **182.1**.

In this procedure, a hydroxy or mercapto-substituted phenylalanine is converted into the benzyl ester **182.2**. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion is effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester **182.2** is then protected. Protection methods for phenols and thiols are described respectively, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, suitable protecting groups for phenols and thiophenols include tert-butyldimethylsilyl or tert-butyldiphenylsilyl. Thiophenols are also protected as S-adamantyl groups, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. The protected hydroxy- or mercapto ester **182.3** is then converted into the BOC derivative **182.4**. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride, in a solvent such as tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972. S-Adamantyl groups are removed by treatment with mercuric trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.

The resultant phenol or thiophenol **182.5** is then reacted under various conditions to provide protected phenylalanine derivatives **182.9**, **182.10** or **182.11**, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

In this step, the phenol or thiophenol **182.5** is reacted with a dialkyl bromoalkyl phosphonate **182.6** to afford the ether or thioether product **182.9**. The alkylation reaction is effected in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate. The reaction is performed at from ambient temperature to ca. 80°C, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product **182.9**. Deprotection of the benzyl ester group, for example by means of catalytic hydrogenation over a palladium catalyst, then yields the carboxylic acid **182.12**. The benzyl esters **182.10** and **182.11**, the preparation of which is described above, are similarly deprotected to produce the corresponding carboxylic acids.

For example, as illustrated in Scheme **182**, Example **1**, a hydroxy-substituted phenylalanine derivative such as tyrosine, **182.13** is converted, as described above, into the benzyl ester **182.14**. The latter compound is then reacted with one molar equivalent of chloro tert-butyldimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether **182.15**. This compound is then converted, as described above, into the BOC derivative **182.16**. The silyl protecting group is removed by treatment of the silyl ether **182.16** with a tetrahydrofuran solution of tetrabutylammonium fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol **182.17**. The latter compound is then reacted in dimethylformamide at ca. 60°C, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **182.18** (Aldrich), in the presence of cesium carbonate, to afford the alkylated product **182.19**. Debenzylation then produces the carboxylic acid **182.20**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **182.13**, different hydroxy or thio-substituted phenylalanine derivatives **182.1**, and/or different bromoalkyl phosphonates **182.6**, the corresponding ether or thioether products **182.12** are obtained.

Alternatively, the hydroxy or mercapto-substituted phenylalanine derivative **182.5** is reacted with a dialkyl hydroxymethyl phosphonate **182.7** under the conditions of the Mitsonobu reaction, to afford the ether or thioether compounds **182.10**. The preparation of aromatic ethers and thioethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic

solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **182.10**.

For example, as shown in Scheme **182**, Example **2**, 3-mercaptophenylalanine **182.21**, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester **182.22**. The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether **182.23**. This compound is then converted into the BOC-protected derivative **182.24**. The 4-methoxybenzyl group is then removed by the reaction of the thioether **182.24** with mercuric trifluoroacetate and anisole in trifluoroacetic acid, as described in J.Org. Chem., 52, 4420, 1987, to afford the thiol **182.25**. The latter compound is reacted, under the conditions of the Mitsonobu reaction, with a dialkyl hydroxymethyl phosphonate **182.7**, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product **182.26**. The benzyl ester protecting group is then removed to afford the carboxylic acid **182.27**.

Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative **182.21**, different hydroxy or mercapto-substituted phenylalanines **182.1**, and/or different dialkyl hydroxymethyl phosphonates **182.7**, the corresponding products **182.10** are obtained.

Alternatively, the hydroxy or mercapto-substituted protected phenylalanine derivative **182.5** is reacted with an activated derivative of a dialkyl hydroxymethylphosphonate **182.8** in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base such as triethylamine or cesium carbonate, to afford the ether or thioether products **182.11**.

For example, as illustrated in Scheme **182**, Example **3**, 3-hydroxyphenylalanine **182.28** (Fluka) is converted, using the procedures described above, into the protected compound **182.29**. The latter compound is reacted, in dimethylformamide at ca. 50°C, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate **182.30**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product **182.31**. Debenzylation then produces the carboxylic acid **182.32**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **182.28**, different hydroxy or mercapto-substituted phenylalanines **182.1**, and/or

different dialkyl trifluoromethanesulfonyloxymethylphosphonates **182.8**, the corresponding products **182.11** are obtained.

Scheme **183** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a formyl-substituted protected phenylalanine derivative **183.3** and a dialkyl aminoalkylphosphonate **183.4**.

In this procedure, a hydroxymethyl-substituted phenylalanine **183.1** is converted, as described above, into the BOC protected benzyl ester **183.2**. The latter compound is then oxidized to afford the corresponding aldehyde **183.3**. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product **183.3**. For example, the carbinol **183.2** is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in J. Org. Chem., 43, 2480, 1978, to yield the aldehyde **183.3**. This compound is reacted with a dialkyl aminoalkylphosphonate **183.4** in the presence of a suitable reducing agent to afford the amine product **183.5**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The benzyl protecting group is then removed to prepare the carboxylic acid **183.6.**

For example, 3-(hydroxymethyl)-phenylalanine **183.7**, prepared as described in Acta Chem. Scand. Ser. B, 1977, B31, 109, is converted, as described above, into the formylated derivative **183.8.** This compound is then reacted with a dialkyl aminoethylphosphonate **183.9**, prepared as described in J. Org. Chem., 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated product **183.10**, which is then deprotected to give the carboxylic acid **183.11**.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine **183.7**, different hydroxymethyl phenylalanines **183.1**, and/or different aminoalkyl phosphonates **183.4**, the corresponding products **183.6** are obtained.

Scheme **184** depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **184.1** is converted, as described above, (Scheme **182**) into the protected derivative **184.2**. The product is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **184.3** to produce the phosphonate ester **184.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The product is then deprotected to afford the carboxylic acid **184.5**.

For example, 3-bromophenylalanine **184.6**, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme **182**) into the protected compound **184.7**. This compound is then reacted, in toluene solution at reflux, with diethyl phosphite **184.8**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product **184.9**. Debenzylation then yields the carboxylic acid **184.10**.

Using the above procedures, but employing, in place of 3-bromophenylalanine **184.6**, different bromophenylalanines **184.1**, and/or different dialkylphosphites **184.3**, the corresponding products **184.5** are obtained.

Scheme **185** depicts the preparation of the aminoacid derivative **37.1** which is employed in the preparation of the phosphonate esters **10** and **19**. In this procedure, the BOC-protected phenylalanine derivatives **185.1**, in which the substituent A is the group link-P(O)$(OR^1)_2$ or a precursor group, the preparation of which is described in Schemes **182 – 184**, is converted into the esters or amides **185.2** in which R^9 is morpholino or alkoxy. The transformation is accomplished by coupling the acid, as described in Scheme **1**, with morpholine or an alkanol in the presence of a carbodiimide. The product **185.2** is then deprotected to afford the free amine **185.3**, for example as described in Scheme **3**. The amine **185.3** is then coupled, as described in Scheme **1**, with the aminoacid **174.6**, to give the amide **185.4**. The BOC group is then removed, as described in Scheme **49**, to produce the amine **37.1**.

Preparation of the dimethoxyphenylpropionic esters 21.1 incorporating phosphonate groups.

Scheme **186** illustrates the preparation of the dimethoxyphenylpropionic acid derivatives **21.1** which are employed in the preparation of the phosphonate esters **6**. In this procedure, the dimethoxybenzyl alcohol derivative **186.1**, in which the substituent A is the group link-$P(O)(OR^1)_2$ or a precursor group, the preparation of which is described in Schemes **165 – 168**, is converted into the corresponding aldehyde **186.2**. The oxidation is effected as described in Scheme **175**. The aldehyde is then subjected to a Wittig reaction with methyl triphenylphosphoranylideneacetate **138.2**, as described in Scheme **138**, to generate the cinnamic ester derivative **186.3**. The double bond is then reduced, as described in Scheme **138**, to afford the phenylpropionic ester **21.1**. Alternatively, the dimethoxybenzyl bromide derivative **186.4**, the preparation of which is described in Scheme **169**, is reacted, as described in Scheme **138**, with dimethyl malonate **186.5** to yield the malonic ester derivative **186.6**, which is then transformed, as described in Scheme **138**, into the ester **21.1**.

Preparation of the phosphonate-containing benzyl iodides 58.1 and benzylcarbamates 125.3.

Schemes **187 - 191** illustrate methods for the preparation of the benzyl iodide derivatives **58.1** which are employed in the synthesis of the phosphonate esters **14**, and of the benzyl carbamates **125.3** which are employed in the preparation of the phosphonate esters **22**.

Scheme **187** illustrates the preparation of benzaldehyde phosphonates **187.3** in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde **187.1** is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate **187.2**, under reductive amination conditions, as describe above in Scheme **135**, to yield the phosphonate product **187.3**.
For example, benzene-1,3-dialdehyde **187.4** is reacted with a dialkyl aminopropyl phosphonate **187.5**, (Acros) and sodium triacetoxyborohydride, to afford the product **187.6**.

Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde **187.4**, different benzene dialdehydes **187.1**, and/or different phosphonates **187.2**, the corresponding products **187.3** are obtained.

Scheme **188** illustrates the preparation of benzaldehyde phosphonates either directly attached to the benzene ring or attached by means of a saturated or unsaturated carbon chain. In this procedure, a bromobenzaldehyde **188.1** is coupled, under palladium catalysis as described in Scheme **150**, with a dialkyl alkenylphosphonate **188.2**, to afford the alkenyl phosphonate **188.3**. Optionally, the product is reduced, as described in Scheme **150**, to afford the saturated phosphonate ester **188.4**. Alternatively, the bromobenzaldehyde is coupled, as described in Scheme **144**, with a dialkyl phosphite **188.5** to afford the formylphenylphosphonate **188.6**. For example, as shown in Example **1**, 3-bromobenzaldehyde **188.7** is coupled with a dialkyl propenylphosphonate **188.8** (Aldrich) to afford the propenyl product **188.9**. Optionally, the product is reduced, as described in Scheme **150**, to yield the propyl phosphonate **188.10**.
Using the above procedures, but employing, in place of 3-bromobenzaldehyde **188.7**, different bromobenzaldehydes **188.1**, and/or different alkenyl phosphonates **188.2**, the corresponding products **188.3** and **188.4** are obtained.
Alternatively, as shown in Example **2**, 4-bromobenzaldehyde **188.11** is coupled, as described in Scheme **144**, with a dialkyl phosphite **188.5** to afford the 4-formylphenyl phosphonate product **188.12**.
Using the above procedures, but employing, in place of 4-bromobenzaldehyde **188.11**, different bromobenzaldehydes **188.1**, the corresponding products **188.6** are obtained.

Scheme **189** illustrates the preparation of formylphenyl phosphonates in which the phosphonate moiety is attached by means of alkylene chains incorporating two heteroatoms O, S or N. In this procedure, a formyl phenoxy, phenylthio or phenylamino alkanol, alkanethiol or alkylamine **189.1** is reacted with a an equimolar amount of a dialkyl haloalkyl phosphonate **189.2**, to afford the phenoxy, phenylthio or phenylamino phosphonate product **189.3**. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile **189.1**. In cases in which Y is O, a strong base such as sodium hydride or lithium

hexamethyldisilazide is employed. In cases in which Y is S or N, a base such as cesium carbonate or dimethylaminopyridine is employed.

For example, 2-(4-formylphenylthio)ethanol **189.4**, prepared as described in Macromolecules, 1991, 24, 1710, is reacted in acetonitrile at 60°C with one molar equivalent of a dialkyl iodomethyl phosphonate **189.5**, (Lancaster) to give the ether product **189.6**.

Using the above procedures, but employing, in place of the carbinol **189.4**, different carbinols, thiols or amines **189.1**, and/or different haloalkyl phosphonates **189.2**, the corresponding products **189.3** are obtained.

Scheme **190** illustrates the preparation of formylphenyl phosphonates in which the phosphonate group is linked to the benzene ring by means of an aromatic or heteroaromatic ring. In this procedure, a formylbenzeneboronic acid **190.1** is coupled, in the presence of a palladium catalyst, with one molar equivalent of a dibromoarene, **190.2**, in which the group Ar is an aromatic or heteroaromatic group. The coupling of aryl boronates with aryl bromides to afford diaryl compounds is described in Palladium Reagents and Catalysts, by J. Tsuji, Wiley 1995, p. 218. The components are reacted in a polar solvent such as dimethylformamide in the presence of a palladium(0) catalyst and sodium bicarbonate. The product **190.3** is then coupled, as described above (Scheme **144**) with a dialkyl phosphite **190.4** to afford the phosphonate **190.5**.

For example, 4-formylbenzeneboronic acid **190.6** is coupled with 2,5-dibromothiophene **190.7** to yield the phenylthiophene product **190.8**. This compound is then coupled with the dialkyl phosphite **190.4** to afford the thienyl phosphonate **190.9**.

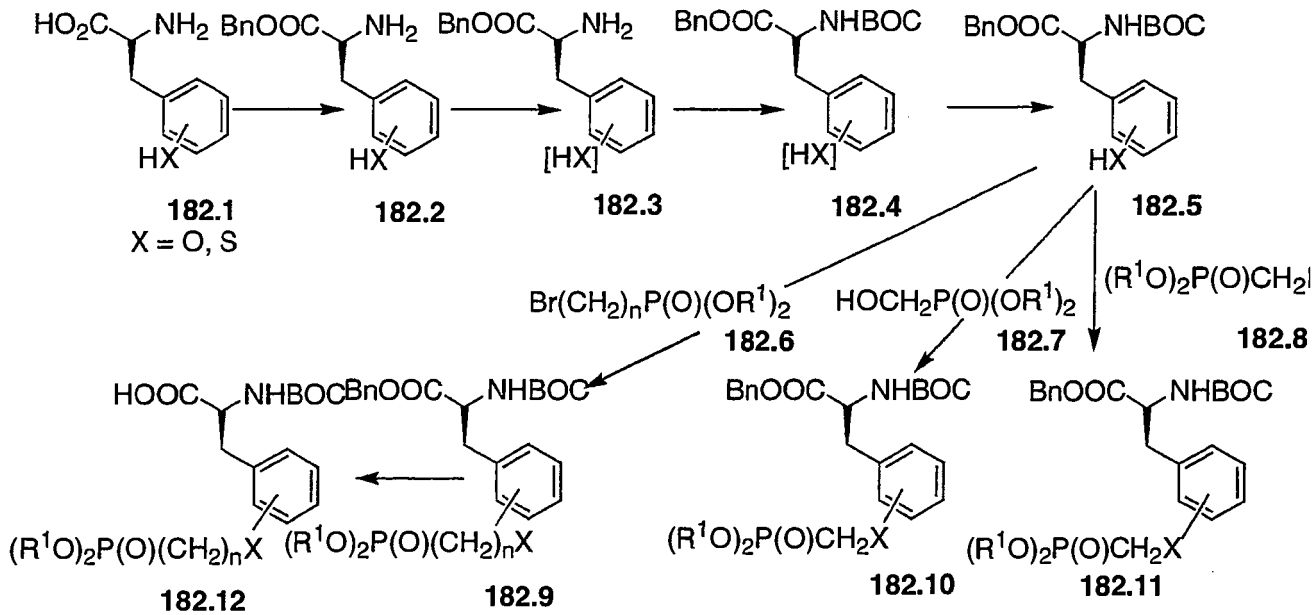
Using the above procedures, but employing, in place of dibromothiophene **190.7**, different dibromoarenes **190.2**, and/or different formylphenyl boronates **190.1**, the corresponding products **190.5** are obtained.

Scheme **191** illustrates the preparation of the benzyl carbamates **125.3** and the benzyl iodides **58.1**, which are employed respectively in the preparation of the phosphonate esters **22** and **4**. In this procedure, the substituted benzaldehydes **191.1**, prepared as shown in Schemes **187** – **190**, are converted into the corresponding benzyl alcohols **191.2**. The reduction of aldehydes to afford alcohols is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 527ff. The transformation is effected by the use of reducing agents such as

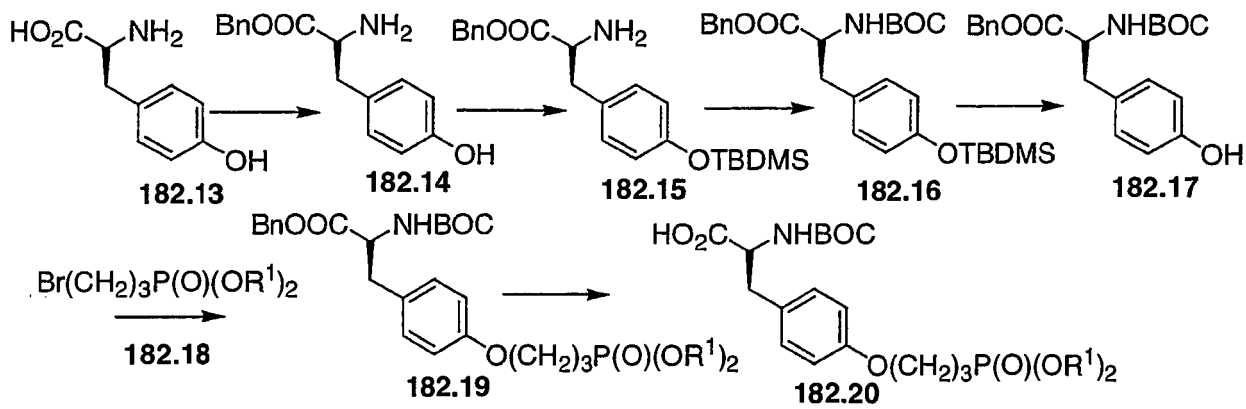
sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride, diisobutyl aluminum hydride and the like. The resultant benzyl alcohol is then reacted with the aminoester **191.3** to afford the carbamate **191.4**. The reaction is performed under the conditions described below, Scheme **198**. For example, the benzyl alcohol is reacted with carbonyldiimidazole to produce an intermediate benzyloxycarbonyl imidazole, and the intermediate is reacted with the aminoester **191.3** to afford the carbamate **191.4**. The methyl ester is then hydrolyzed, as described in Scheme **3**, to yield the carboxylic acid **125.3**. Alternatively, the benzyl alcohol **191.2** is converted, using the procedures of Scheme **169**, into the iodide **58.1**.

Scheme 182

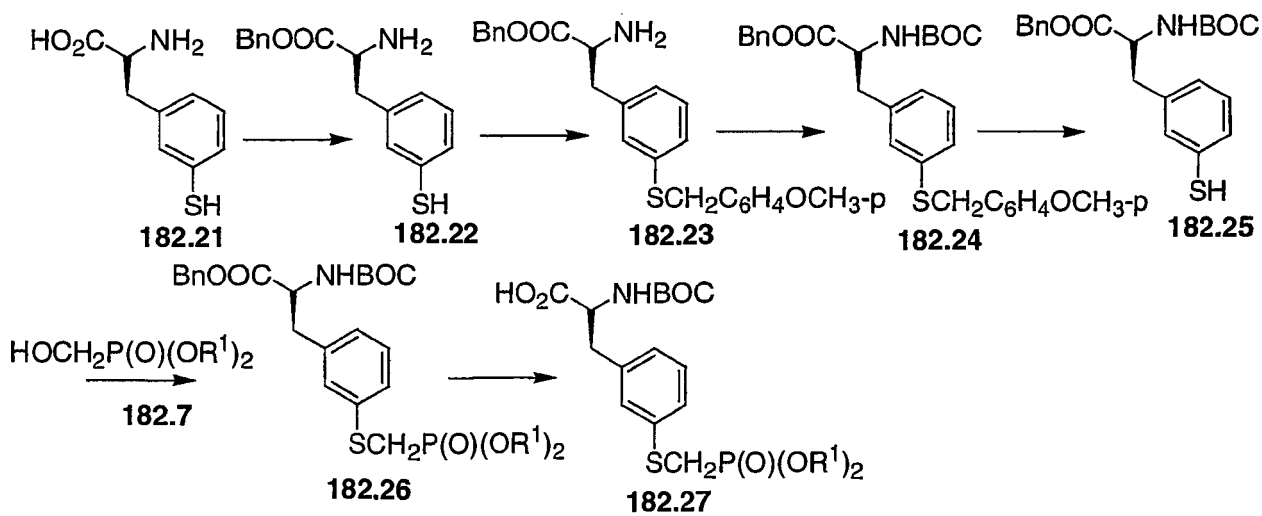
Method



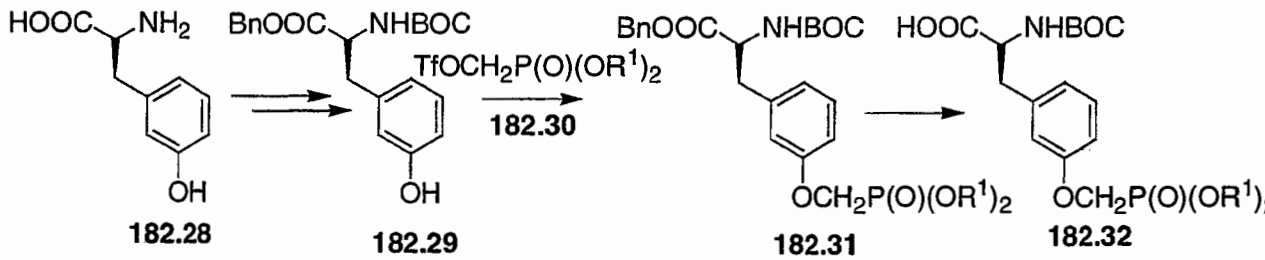
Example1



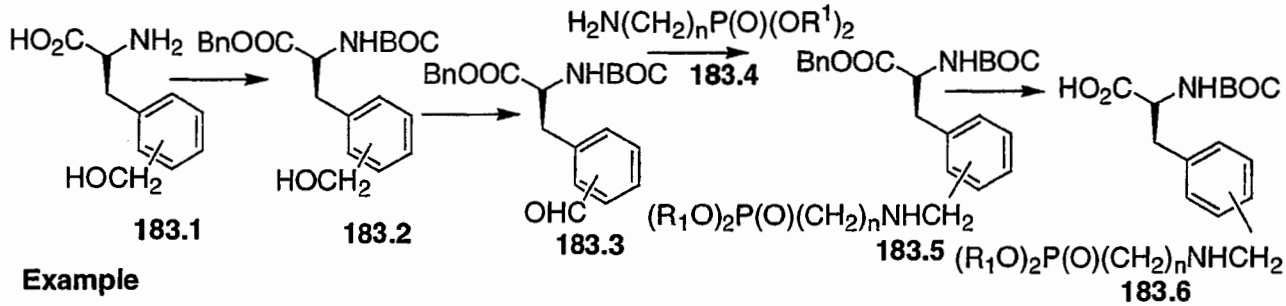
Example 2



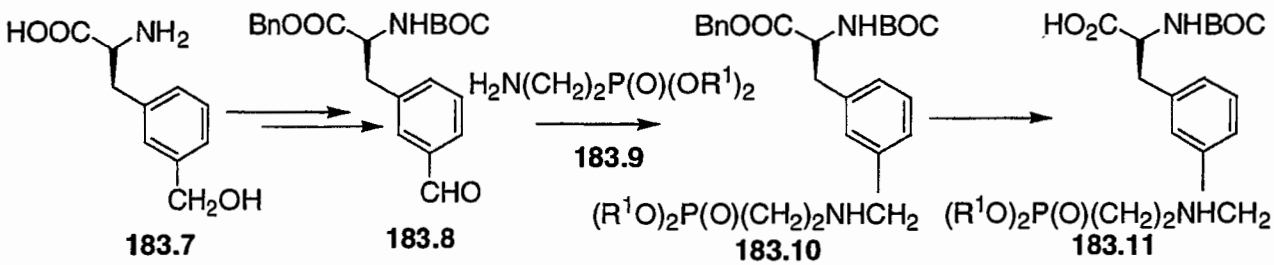
Example 3



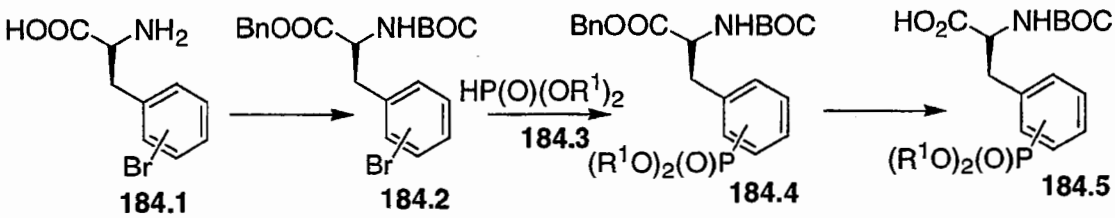
Scheme 183
Method



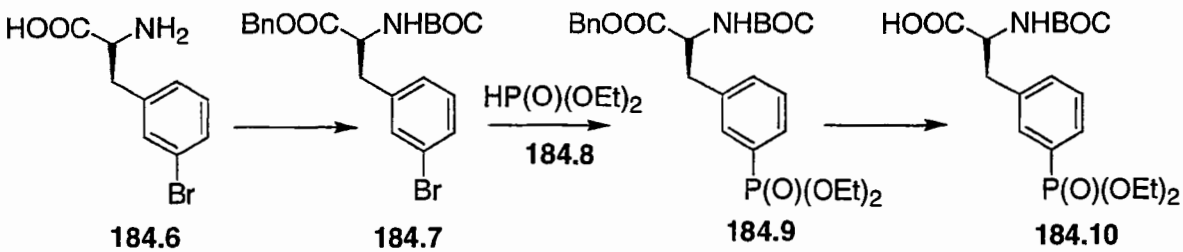
Example



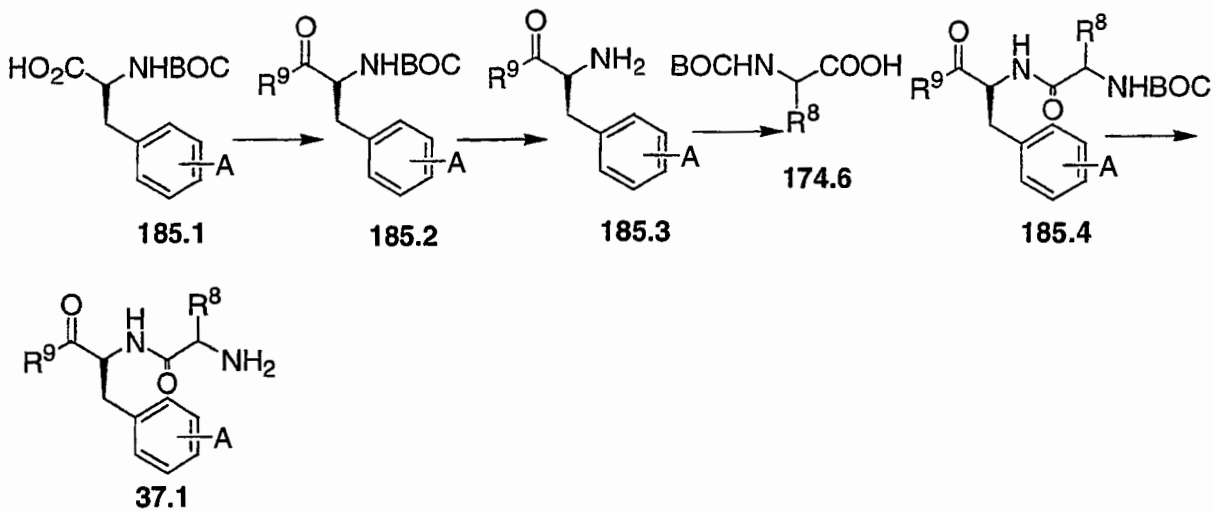
Scheme 184



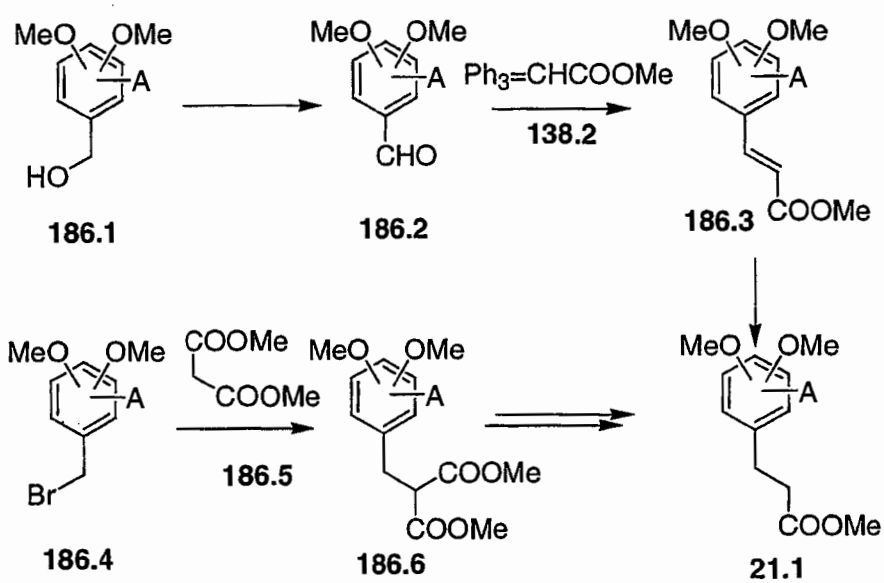
Example



Scheme 185

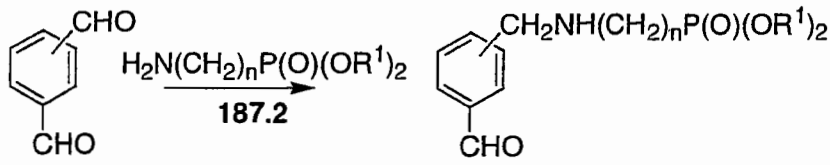


Scheme 186



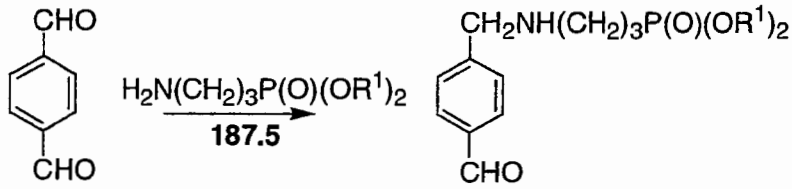
Scheme 187

Method



187.1 **187.3**

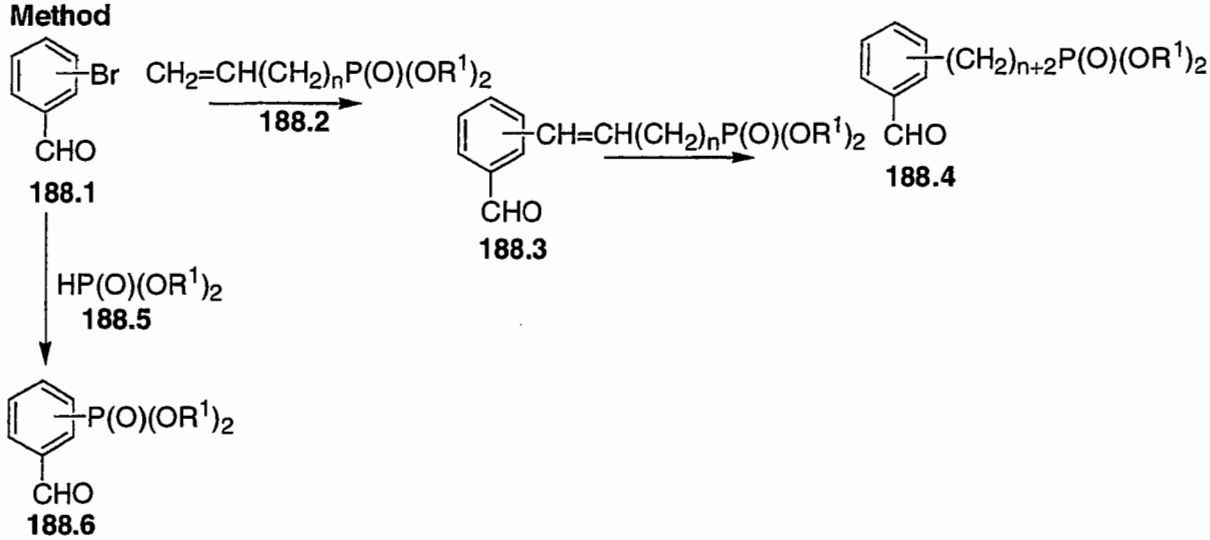
Example



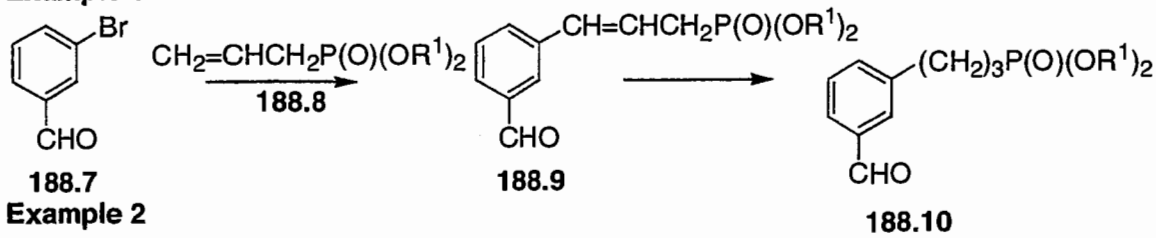
187.4 **187.6**

Scheme 188

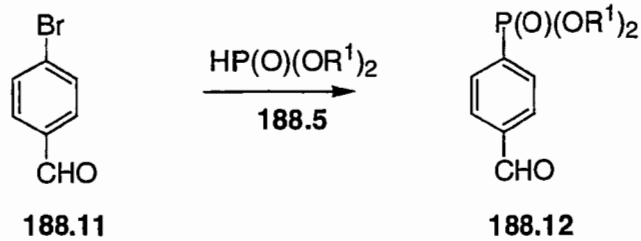
Method



Example 1

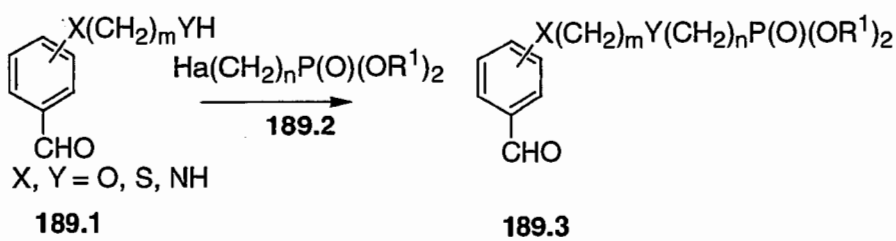


Example 2

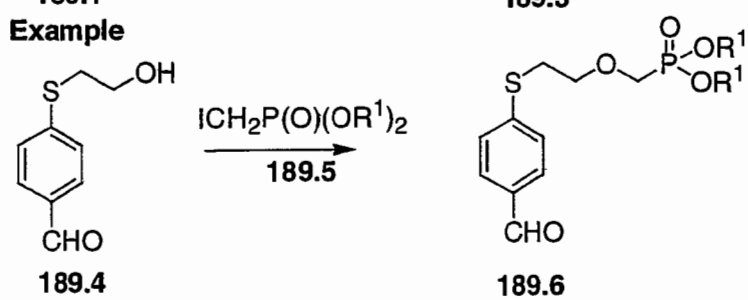


Scheme 189

Method

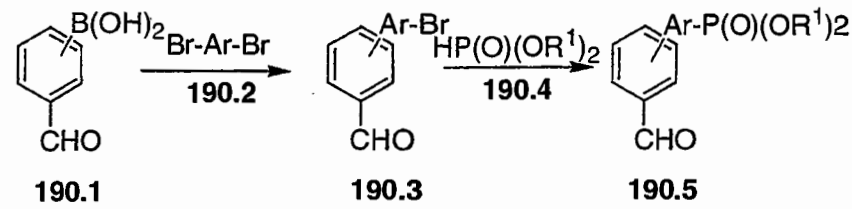


Example

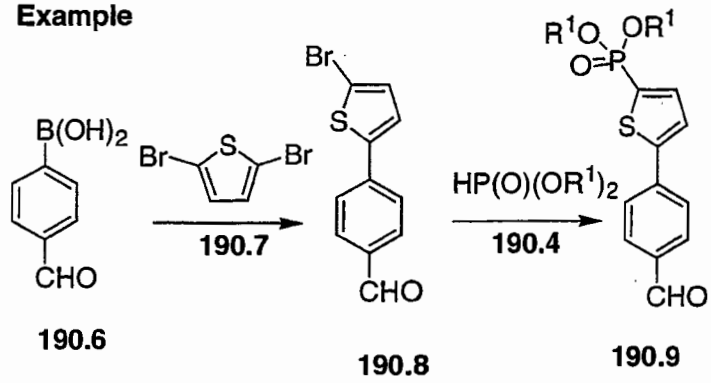


Scheme 190

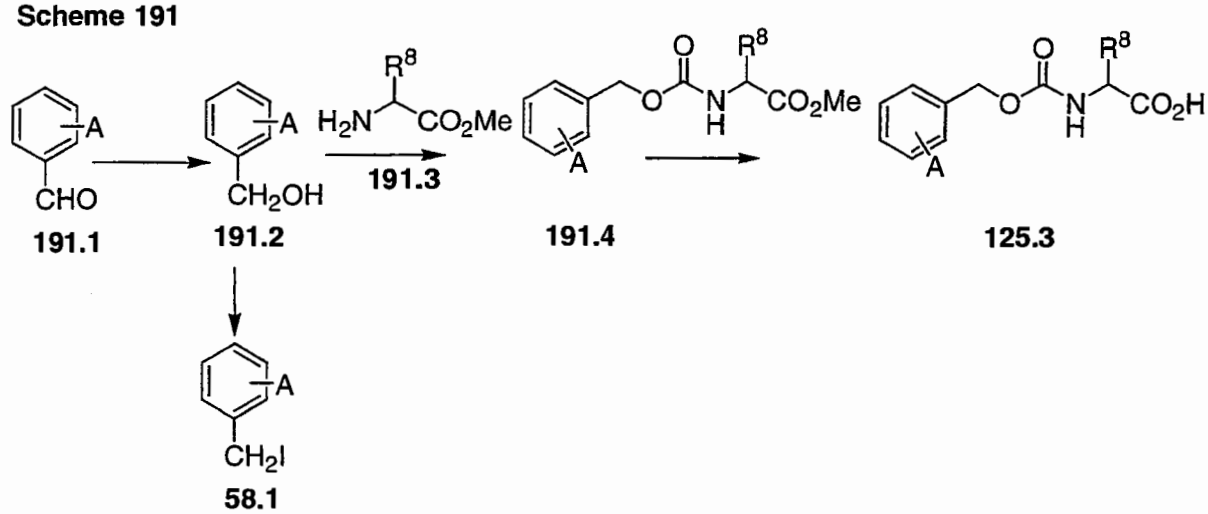
Method



Example



Scheme 191



Preparation of phosphonate-substituted decahydroquinolines 17.1.

Schemes **192 – 97** illustrate the preparation of decahydroisoquinoline derivatives **17.1** in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor, such as [OH], [SH], Br.

The compounds are employed in the preparation of the intermediate phosphonate esters **5**, **12** and **21**.

Scheme **192** illustrates methods for the synthesis of intermediates for the preparation of decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the benzenoid intermediate **192.4** are shown.

In the first route, 2-hydroxy-6-methylphenylalanine **192.1**, the preparation of which is described in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative **192.2**. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product **192.2**, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product **192.3**. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound **192.3** is then treated with acid, for example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline **192.4**, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline **192.4** is obtained from 2-hydroxyphenylalanine **192.5**, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem. Rev., 1995, 95, 1797.

Typically, the substrate **192.5** is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product **192.4**, in which R is H. Catalytic hydrogenation of the latter compound, using, for example, a platinum catalyst, as described in J. Am. Chem. Soc., 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-substituted decahydroisoquinoline **192.6**. The reduction is also performed electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline **192.4** is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at ca 50°C, to afford the decahydroisoquinoline **192.6**.

Protection of the carboxyl and NH groups present in **192.6**, for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH into the N-cbz group, as described above, followed by oxidation, using, for example, pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone **192.9**, in which R is trichloroethyl and R^1 is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in J. Am. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butoxy aluminum hydride, as described in J. Am. Chem. Soc., 80, 5372, 1958, then affords the alcohol **192.10**.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as isopropanol, at ambient temperature, to afford the alcohol **192.10**.

The alcohol **192.6** is converted into the thiol **192.13** and the amine **192.14**, by means of displacement reactions with suitable nucleophiles, with inversion of stereochemistry.

For example, the alcohol **192.6** is converted into an activated ester such as the trifluoromethanesulfonyloxy ester or the methanesulfonate ester **192.7**, by treatment with methanesulfonyl chloride and a base. The mesylate **192.7** is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol **192.13**.

For example, the mesylate **192.7** is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **192.12**, in which R is $COCH_3$. The product then treated with a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol **192.13**.

The mesylate **192.7** is treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p. 399, followed by deprotection as described previously, to afford the amine **192.14**.

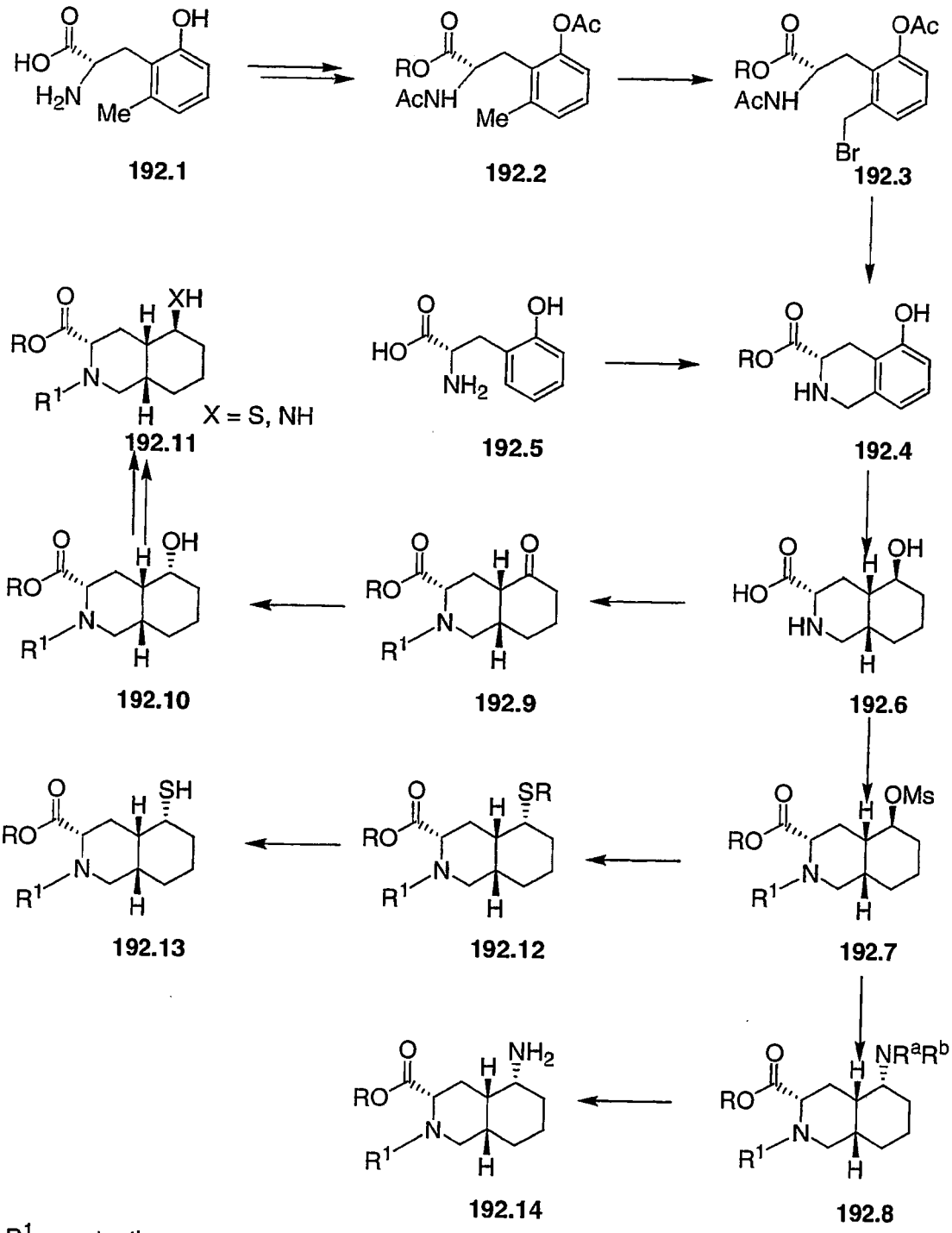
For example, the mesylate **192.7** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such

as, for example, dimethylformamide, at ambient temperature, to afford the displacement product **192.8**, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the amine **192.14**.

The application of the procedures described above for the conversion of the β-carbinol **192.6** to the α-thiol **192.13** and the α-amine **192.14** can also be applied to the α-carbinol **192.10**, so as to afford the β-thiol and β-amine, **192.11**.

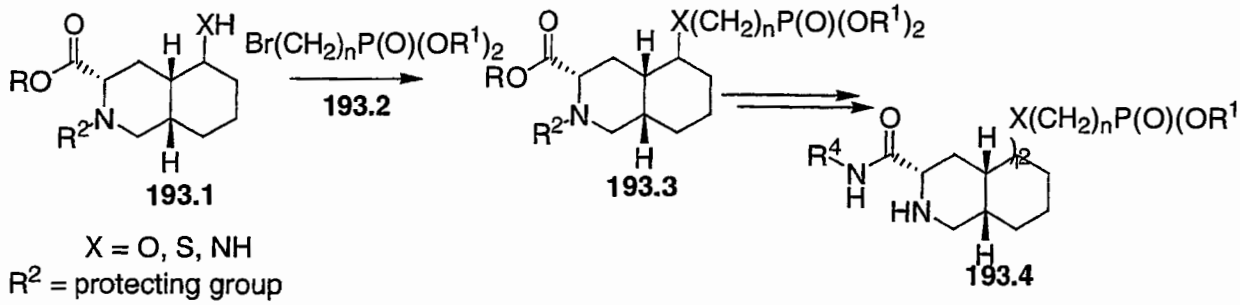
Scheme **193** illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain.
In this procedure, an alcohol, thiol or amine **193.1** is reacted with a bromoalkyl phosphonate **193.2**, under the conditions described above for the preparation of the phosphonate **155.4** (Scheme **155**), to afford the displacement product **193.3**. Removal of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **197**) then yields the amine **193.4**.
For example, the thiol **193.5**, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, **193.6**, the preparation of which is described in J. Am. Chem. Soc., 2000, 122, 1554 to afford the displacement product **193.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **197**) then yields the amine **193.8**.
Using the above procedures, but employing, in place of the α-thiol **193.5**, the alcohols, thiols or amines **192.6, 192.10, 192.11, 192.13, 192.14**, of either α- or β-orientation, there are obtained the corresponding products **193.4**, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme 192

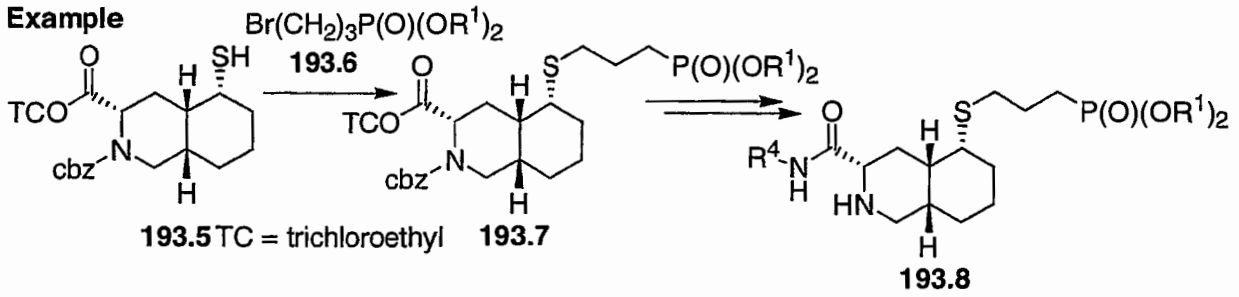

192.1
192.2
192.3
192.4
192.5
192.6
192.7
192.8
192.9
192.10
192.11
X = S, NH
192.12
192.13
192.14
R1 = protecting group

Scheme 193

Method

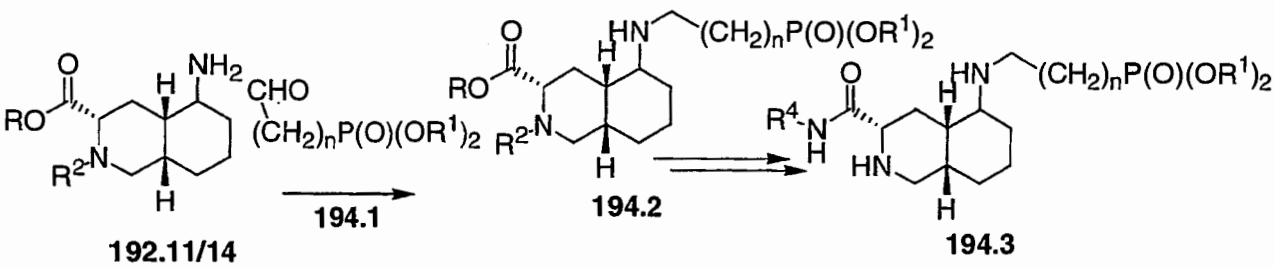


Example

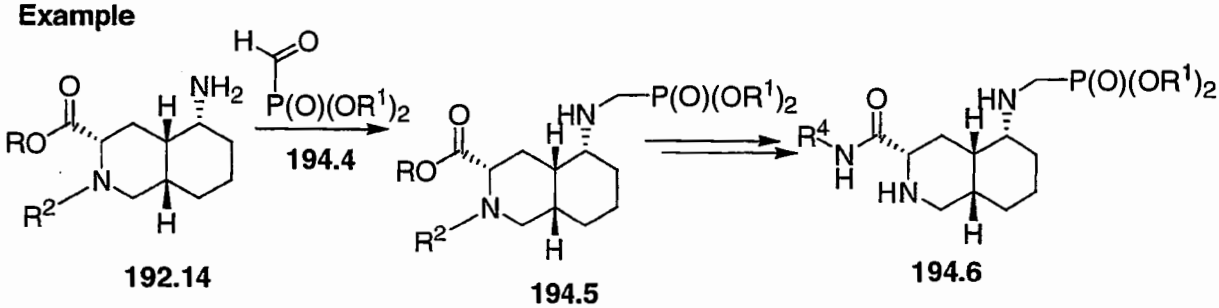


Scheme 194

Method



Example



Scheme **194** illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive Organic Transformations, by R. C. Larock, p. 421.

In this procedure, the amines **192.14** or **192.11** are reacted with a phosphonate aldehyde **194.1**, in the presence of a reducing agent, to afford the alkylated amine **194.2**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **197**) then yields the amine **194.3**.

For example, the protected amino compound **192.14** is reacted with a dialkyl formylphosphonate **194.4**, the preparation of which is described in U.S. Patent 3,784,590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate **194.5**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **194.6**.

Using the above procedures, but employing, instead of the α-amine **192.14**, the β isomer, **192.11** and/or different aldehydes **194.1**, there are obtained the corresponding products **194.3**, in which the orientation of the side chain is the same as that of the amine precursor.

Scheme **195** depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain.

In this procedure, a dialkyl mercaptoalkyl phosphonate **195.2** is reacted with a mesylate **195.1**, to effect displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product **195.3**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **195.4**.

For example, the protected mesylate **195.5** is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate **195.6**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thioether phosphonate **195.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **195.8**

Using the above procedures, but employing, instead of the phosphonate **195.6**, different phosphonates **195.2**, there are obtained the corresponding products **195.4**.

Scheme **196** illustrates the preparation of decahydroisoquinoline phosphonates **196.4** in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The compounds are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates **196.1** and a bromomethyl-substituted arylphosphonate **196.2**. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant **196.1**. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate is employed. If X is O, a strong base such as sodium hydride or lithium hexamethyldisilylazide is employed. The displacement reaction affords the ether, thioether or amine compounds **196.3**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **196.4**.

For example, the alcohol **196.5** is reacted at ambient temperature with a dialkyl 3-bromomethyl benzylphosphonate **196.6**, the preparation of which is described above, (Scheme **143**). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a strong base, such as, for example, lithium hexamethyldisilylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate **196.6**, to afford the product **196.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **196.8**.

Using the above procedures, but employing, instead of the β-carbinol **196.5**, different carbinols, thiols or amines **196.1**, of either α- or β-orientation, and/or different phosphonates **196.2**, in place of the phosphonate **196.6**, there are obtained the corresponding products **196.4** in which the orientation of the side-chain is the same as that of the starting material **196.1**.

Schemes **193** - **196** illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

Scheme **197** illustrates the conversion of the latter group of compounds **197.1** (in which the group A is link-$P(O)(OR^1)_2$ or optionally protected precursor substituents, such as, for example, OH, SH, or NH_2 to the corresponding R^4NH amides **17.1**.

As shown in Scheme **197**, the ester compounds **197.1** are deprotected to form the corresponding carboxylic acids **197.2**. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R^2, and

the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is removed by treatment with zinc in acetic acid, as described in J. Am. Chem. Soc., 88, 852, 1966. Conversion of the carboxylic acid **197.2** to the R^4NH amide **197.4** is then accomplished by reaction, as described in Scheme **1**, of the carboxylic acid, or an activated derivative thereof, with the amine R^4NH_2 (**197.3**) to afford the amide **197.4**. Deprotection of the NR^2 group, as described above, then affords the free amine **17.1**.

Preparation of carbamates.

The phosphonate esters **13 - 20** in which the R^{10} is alkoxy, and the phosphonate esters **22** contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme **198** illustrates various methods by which the carbamate linkage is synthesized. As shown in Scheme **198**, in the general reaction generating carbamates, a carbinol **198.1**, is converted into the activated derivative **198.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **198.2** is then reacted with an amine **198.3**, to afford the carbamate product **198.4**. Examples **1 – 7** in Scheme **198** depict methods by which the general reaction is effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.

Scheme **198**, Example **1** illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **198.1**. In this procedure, the carbinol is reacted with phosgene, in an inert solvent such as toluene, at about 0°C, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **198.6**. The latter compound is then reacted with the amine component **198.3**, in the presence of an organic or inorganic base, to afford the carbamate **198.7**. For example, the chloroformyl compound **198.6** is reacted with the amine **198.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **198.7**. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme **198**, Example **2** depicts the reaction of the chloroformate compound **198.6** with imidazole to produce the imidazolide **198.8**. The imidazolide product is then reacted with the amine **198.3** to yield the carbamate **198.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°C, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme **198** Example **3**, depicts the reaction of the chloroformate **198.6** with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester **198.10**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **198.19** - **198.24** shown in Scheme **198**, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **198.19**, N-hydroxysuccinimide **198.20**, or pentachlorophenol, **198.21**, the mixed carbonate **198.10** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **198.22** or 2-hydroxypyridine **198.23** is performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme **198** Example **4** illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **198.8** is employed. In this procedure, a carbinol **198.5** is reacted with an equimolar amount of carbonyl diimidazole **198.11** to prepare the intermediate **198.8**. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **198.8** is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **198.7**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate **198.7**.

Scheme **198**, Example **5** illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **198.13**. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **198.12**, to afford the alkoxycarbonyl product **198.13**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. The product is then reacted with the amine $R'NH_2$ to afford the

carbamate **198.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80°C as described in Syn., 1977, 704.

Scheme **198**, Example **6** illustrates the preparation of carbamates in which a carbonate $(R"O)_2CO$, **198.14**, is reacted with a carbinol **198.5** to afford the intermediate alkyloxycarbonyl intermediate **198.15**. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate **198.7**. The procedure in which the reagent **198.15** is derived from hydroxybenztriazole **198.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **198.15** is derived from N-hydroxysuccinimide **198.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **198.15** is derived from 2-hydroxypyridine **198.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **198.15** is derived from 4-nitrophenol **198.24** is described in Syn. 1993, **199**. The reaction between equimolar amounts of the carbinol ROH and the carbonate **198.14** is conducted in an inert organic solvent at ambient temperature.

Scheme **198**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides **198.16**. In this procedure, an alkyl chloroformate **198.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **198.16**. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **198.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme **198**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine **198.17**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **198.7**.

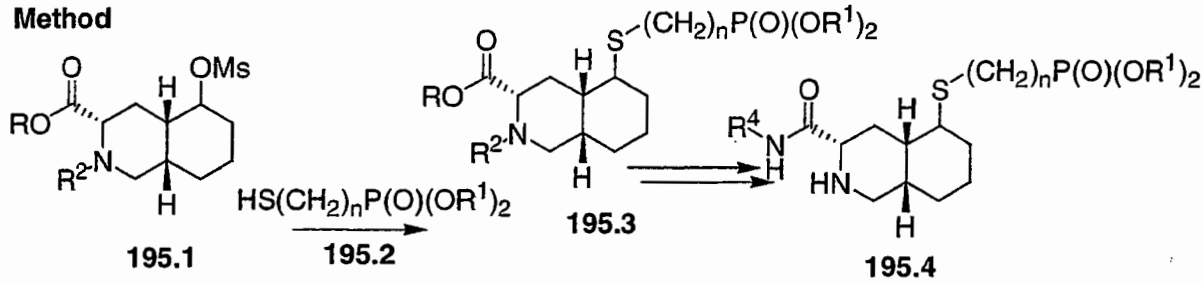
Scheme **198**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **198.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **198.7**.

Scheme **198**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem.

Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **198.7**.

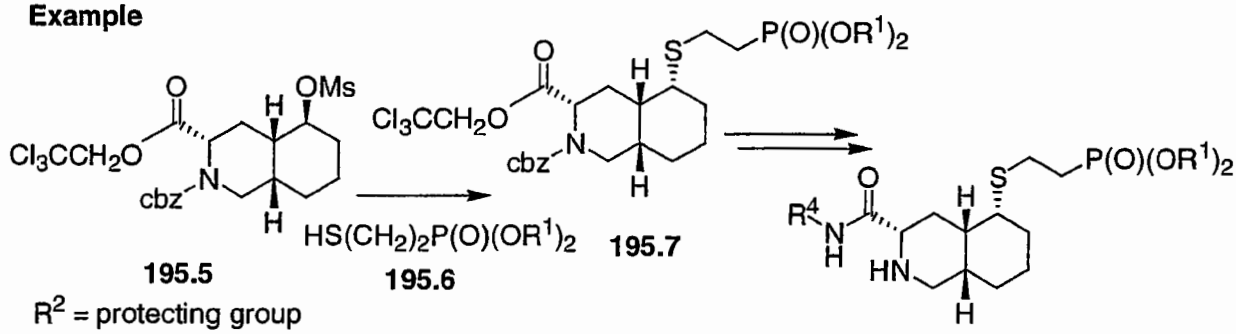
Scheme 195

Method



195.1 **195.2** **195.3** **195.4**

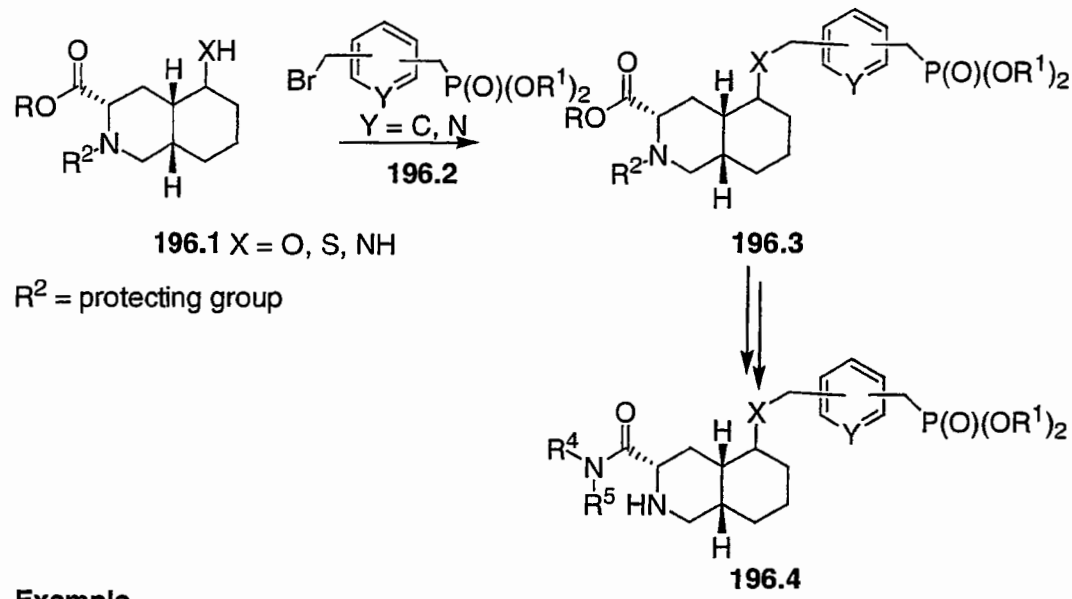
Example



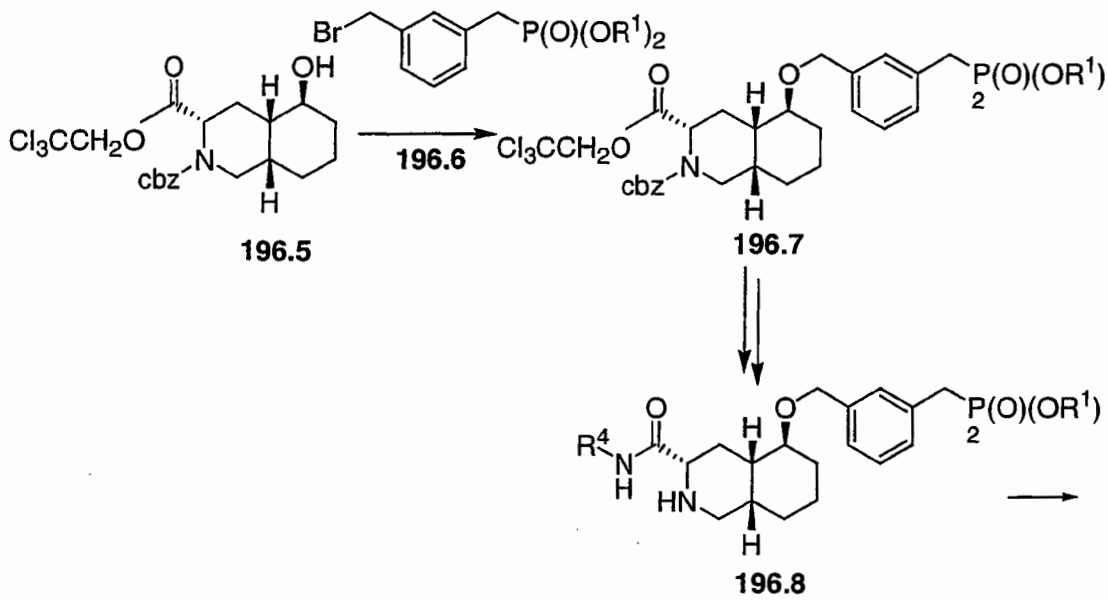
195.5 **195.6** **195.7** **195.8**

R^2 = protecting group

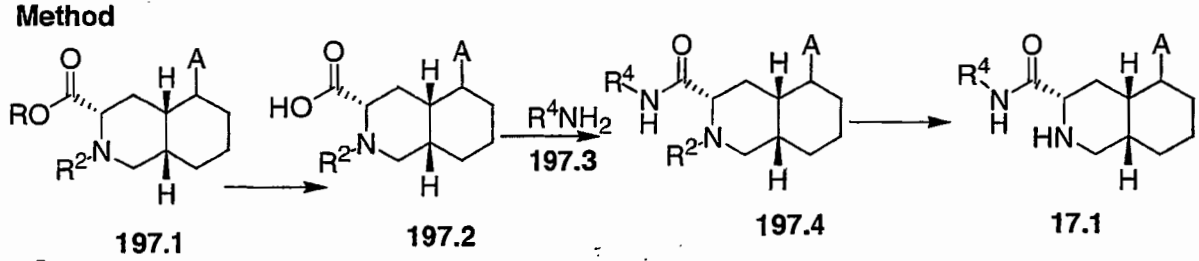
Scheme 196
Method



Example

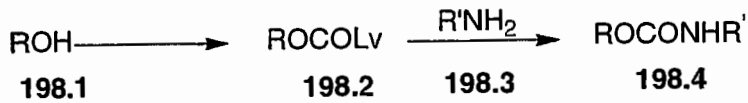


Scheme 197
Method

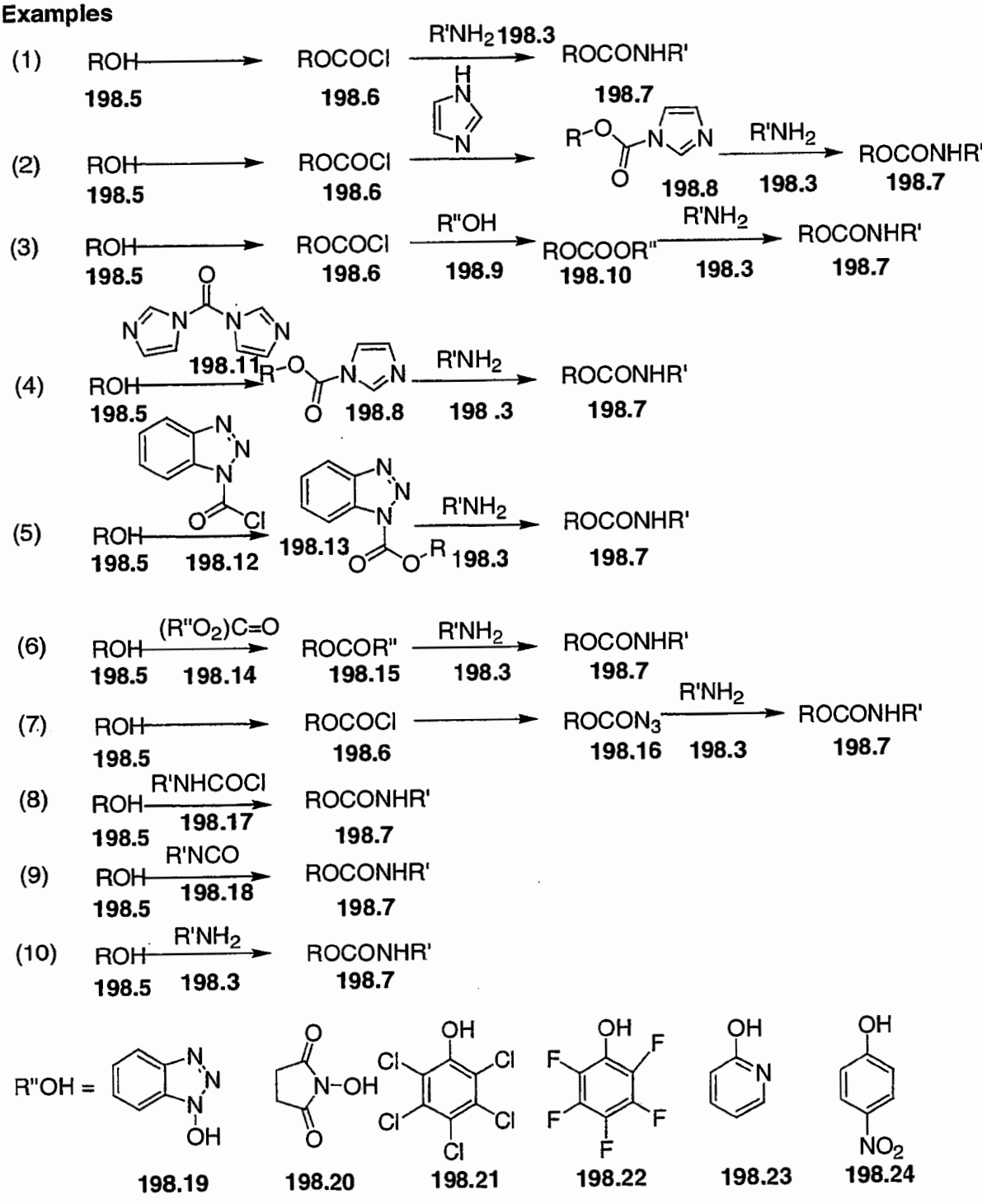


Scheme 198

General reaction



Examples



Interconversions of the phosphonates R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH) and R-link-P(O)(OH)$_2$.

Schemes **1** - **197** described the preparations of phosphonate esters of the general structure R-link-P(O)(OR^1)$_2$, in which the groups R^1, the structures of which are defined in Chart **1**, may be the same or different. The R^1 groups attached to the phosphonate esters **1** - **24**, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme **199**. The group R in Scheme **199** represents the substructure to which the substituent link-P(O)(OR^1)$_2$ is attached, either in the compounds **1** - **24** or in precursors thereto. The R^1 group may be changed, using the procedures described below, either in the precursor compounds, or in the esters **1** - **24**. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **199.1** into the corresponding phosphonate monoester **199.2** (Scheme **199**, Reaction **1**) is accomplished by a number of methods. For example, the ester **199.1** in which R^1 is an aralkyl group such as benzyl, is converted into the monoester compound **199.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester **199.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **199.2** is effected by treatment of the ester **199.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **199.1** in which one of the groups R^1 is aralkyl, such as benzyl, and the other is alkyl, are converted into the monoesters **199.2** in which R^1 is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, are converted into the monoester **199.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **199.1** or a phosphonate monoester **199.2** into the corresponding phosphonic acid **199.3** (Scheme **199**, Reactions **2** and **3**) is effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **199.2** in which R^1 is aralkyl such as benzyl, is converted into the corresponding phosphonic acid **199.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **199.2** in which R^1 is alkenyl such as, for example, allyl, is converted into the phosphonic acid **199.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **199.1** in which R^1 is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **199.1** in which R^1 is phenyl is described in J. Am. Chem. Soc., 78, 2336, 1956.

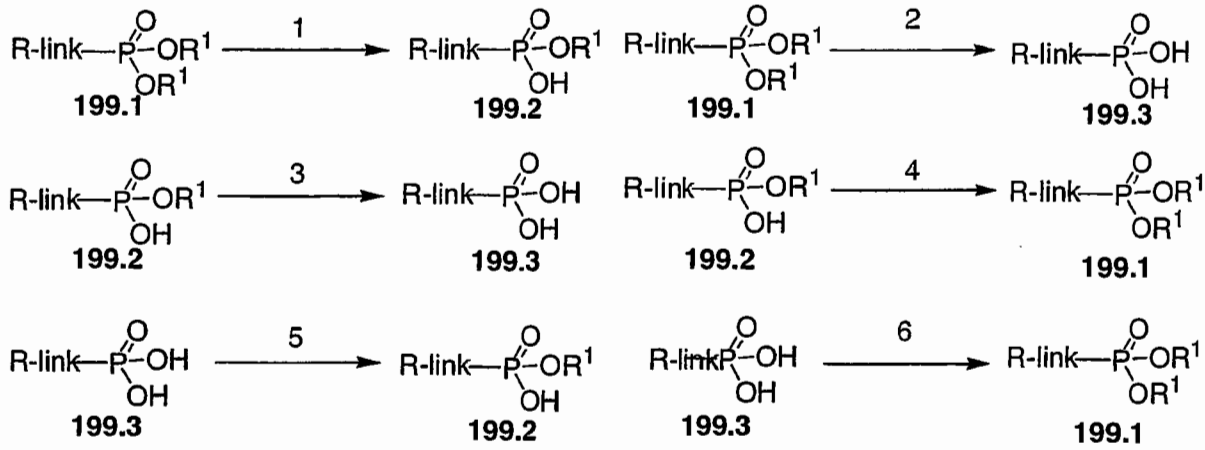
The conversion of a phosphonate monoester **199.2** into a phosphonate diester **199.1** (Scheme **199**, Reaction **4**) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl is effected by a number of reactions in which the substrate **199.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **199.2** to the diester **199.1** is effected by the use of the Mitsonobu reaction, as described above (Scheme **142**). The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **199.2** is transformed into the phosphonate diester **199.1**, in which the

introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester is transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **199.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **199.1**.

A phosphonic acid R-link-$P(O)(OH)_2$ is transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **199**, Reaction **5**) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ **199.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid R-link-$P(O)(OH)_2$ **199.3** is transformed into a phosphonate diester R-link-$P(O)(OR^1)_2$ **199.1** (Scheme **199**, Reaction **6**) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **199.3** are transformed into phosphonic esters **199.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°C. Alternatively, phosphonic acids **199.3** are transformed into phosphonic esters **199.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **199.1**.

Scheme 199



General applicability of methods for introduction of phosphonate substituents.

The procedures described for the introduction of phosphonate moieties (Schemes **133** - **192**) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into indanols (Schemes **133** - **137**) are applicable to the introduction of phosphonate moieties into phenylpropionic acids, thiophenols, tert. butylamines, pyridines, benzyl halides, ethanolamines, aminochromans, phenylalanines and benzyl alcohols, and the methods described for the introduction of phosphonate moieties into the above-named substrates (Schemes **138** - **192**) are applicable to the introduction of phosphonate moieties into indanol substrates.

Preparation of phosphonate intermediates 23 and 24 with phosphonate moieties incorporated into the R^2, R^3, R^5, R^{10} or R^{11} groups.

The chemical transformations described in Schemes **1** - **192** illustrate the preparation of compounds **1** - **22** in which the phosphonate ester moiety is attached to the indanol moiety, (Schemes **1** – **4**, **76** – **84**), the phenyl group (Schemes **5** – **8**, **21** – **24**, **37** – **40**, **49** – **52**, **58** – **61**, **67** – **68**, **74**, **75**, **101** – **108**, **125** – **132**) the tert. butylamine group, (Schemes **9** – **12**, **25** - **28**, **41** – **44**, **109** – **116**), the pyridine group (Schemes **13** – **16**), the decahydroisoquinoline group (Schemes **17** – **20**, **45** – **48**, **117** – **124**), the ethanolamine group (Schemes **29**- **32**, **93** – **100**), the aminochroman group (Schemes **33** – **36**, **85** – **92**), and the thiophenyl group

(Schemes **53 – 57**, **62 – 66**, **69 – 73**). The various chemical methods employed for the introduction of phosphonate ester groups into the above-named moieties can, with appropriate modifications known to those skilled in the art, be applied to the introduction of a phosphonate ester group into the compounds R^2R^3NH, R^5SH, R^5CH_2I, $R^{10}CO$, $R^{11}SH$, and $R^{11}CH_2CH(NH_2)COOH$. The resultant phosphonate-containing analogs, designated as $R^{2a}R^{3a}NH$, $R^{5a}SH$, $R^{5a}CH_2I$, $R^{10a}CO$, $R^{11a}SH$, and $R^{11a}CH_2CH(NH_2)COOH$ are then, using the procedures described above, employed in the preparation of the compounds **23** and **24**. The procedures required for the utilization of the phosphonate-containing analogs are the same as those described above for the utilization of the compounds R^2R^3NH, R^5SH, R^5CH_2I, $R^{10}CO$, $R^{11}SH$, and $R^{11}CH_2CH(NH_2)COOH$.

For example, Schemes **200-204** and Schemes **205-207** depict the introduction of the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as, [OH], [NH_2], [SH] onto the R^2R^3NH amines **A10a** and **A10b** in Chart **4**, to give amines **200.5** and **205.10** respectively. These amine products are then utilized in the generation of compounds **23** where R^2R^3NH is now $R^{2a}R^{3a}NH$ in Chart **3** following the same procedures outlined in Schemes **13** and **15** but replacing the amine **13.1** with **200.5** or **205.10** respectively.

Preparation of piperazine furan compounds 200.5 with phosphonate attachments

Schemes **200** - **204** depict the preparation of the piperazine furan aryl phosphonate compounds **200.5** that are employed in the preparation of the phosphonate esters **23** where R^2R^3NH is now $R^{2a}R^{3a}NH$ as described above.

Scheme **200** depicts the preparation of piperazine biaryl phosphonates in which the terminal aryl ring bears the phosphonate moiety through a linking group. Methods for the preparation of the reagents **200.2** are shown in Schemes **201-204**. Furan **200.1** prepared as described in WO02/096359, is treated with the aryl bromide **200.2** in the presence of palladium catalyst by the method of Gronowitz et al. (J. Heterocyclic Chemistry, 1995, 35, p. 771) to give **200.3**. The product **200.3** is then subjected to the sequence of reactions and conditions described in WO02/096359 to prepare the piperazine **200.5**. The preparation of reagent **200.6** where R^4 = CH_2CF_3 is also described in WO02/096359. Alternatively, deprotection of amines **164.1** by treatment with trifluoroacetic acid at room temperature as described in Int. J. Pept. Protein Res., 12, 258, 1978, followed by treatment with alloc chloro formate and a base such as

pyridine, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 526-527 yields **200.6** where R^4 is as defined in Chart **1**.

Scheme **201** depicts the preparation of phosphonates **200.2** in which the phosphonate moiety is attached to the phenyl ring by means of a heteroatom and an alkyl chain. Many halogenated aromatic compounds are commercially available or can be generated from readily available aromatic compounds through aromatic substitution. Methods for chlorinating or brominating an aryl ring can be found in Comprehensive Organic Transformations, by R. C. Larock, 2nd Edition, 1999 p619. The phenol, thiol or amine **201.1** is reacted with a derivative of a hydroxymethyl dialkylphosphonate **140.2**, in which Lv is a leaving group such as methanesulfonyloxy and the like. The reaction is conducted in a polar aprotic solvent, in the presence of an organic or inorganic base, to afford the displacement product **201.2**. For example, the phenols **201.5** (Aldrich) or **201.9** (Apollo-Chem) are reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **140.6**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether products. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C, to afford the products **201.6** and **201.10** respectively. Alternatively treatment of amine **201.11** (Apollo) or **201.7** (Aldrich) with the dialkyl trifluoromethylsulfonyloxymethyl phosphonate **140.6** in the presence of a base as described above affords **201.12** and **201.8** respectively.

Using the above procedures, but employing, in place of the phenols and amines, different phenols, thiols or amines **201.1**, and /or different dialkyl trifluoromethyl-sulfonyloxymethyl phosphonates **140.2**, the corresponding products **201.2** are obtained.

Scheme **202** illustrates the preparation of compounds in which the phosphonate group is attached by means of an aminoalkyl chain. In this procedure, the aldehyde **202.1** is reacted, under reductive amination conditions, as described in Scheme **135**, with a dialkyl aminoalkyl phosphonate **202.2**, to give the amine **202.3**.

For example, the aldehyde **202.4** (Aldrich) is reacted in ethanol with a dialkyl aminoethyl phosphonate **166.5**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, and sodium triacetoxyborohydride, to produce the amine **202.5**.

Using the above procedures, but employing, in place of the aldehyde, **202.4** different aldehydes **202.1** and different phosphonates **202.2**, the corresponding products **202.3** are obtained.

Scheme **203** illustrates the preparation of aryl halides incorporating phosphonate groups attached by means of an amide group. In this procedure, a carboxy-substituted aryl halide **203.1** is coupled, as described in Scheme **1**, with a dialkyl aminoalkyl phosphonate **202.2** to prepare the amide **203.2**.

For example, 2-chloro-4-bromobenzoic acid **203.4**, the preparation of which is described in Bioorg. Med. Chem. Lett. 2001, 11, 10, p. 1257, is coupled in dimethylformamide solution, in the presence of dicyclohexylcarbodiimide, with a dialkyl aminoethyl phosphonate **166.5**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, to afford the amide **203.5**. Using the above procedures, but employing, in place of the benzoic acid **203.4**, different benzoic acids **203.1**, and/or different aminoalkyl phosphonates **202.2**, the corresponding products **203.2** are obtained.

Scheme **204** illustrates the preparation of phosphonate-substituted aryl halides in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a benzoic acid **203.1** is first methylated to give methyl ester **204.1** and then reduced with a reducing agent, as described in J. Org Chem 1987, 52, p. 5419 to give alcohol **204.2**. The alcohol **204.2** is then reacted with hexabromoethane in the presence of triphenyl phosphine as described in Syn. 1983, p. 139 to give the bromide **204.3**. The bromide **204.3** is reacted with a sodium dialkyl phosphite **204.5** or a trialkyl phosphite, to give the product **204.4**

For example, acid **204.6** (Lancaster) is converted to the methyl ester **204.7** by refluxing in methanol and concentrated sulfuric acid and then reduced with lithium aluminum hydride in THF to give **204.8** as described above. The product **204.8** is reacted with hexabromoethane in the presence of triphenyl phosphine as described in Syn. 1983, p. 139 to give the bromide **204.9.** This material is reacted with a sodium dialkyl phosphite **204.5**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **204.10**. Alternatively, the bromomethyl compound **204.9** is converted into the phosphonate **204.10** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure,

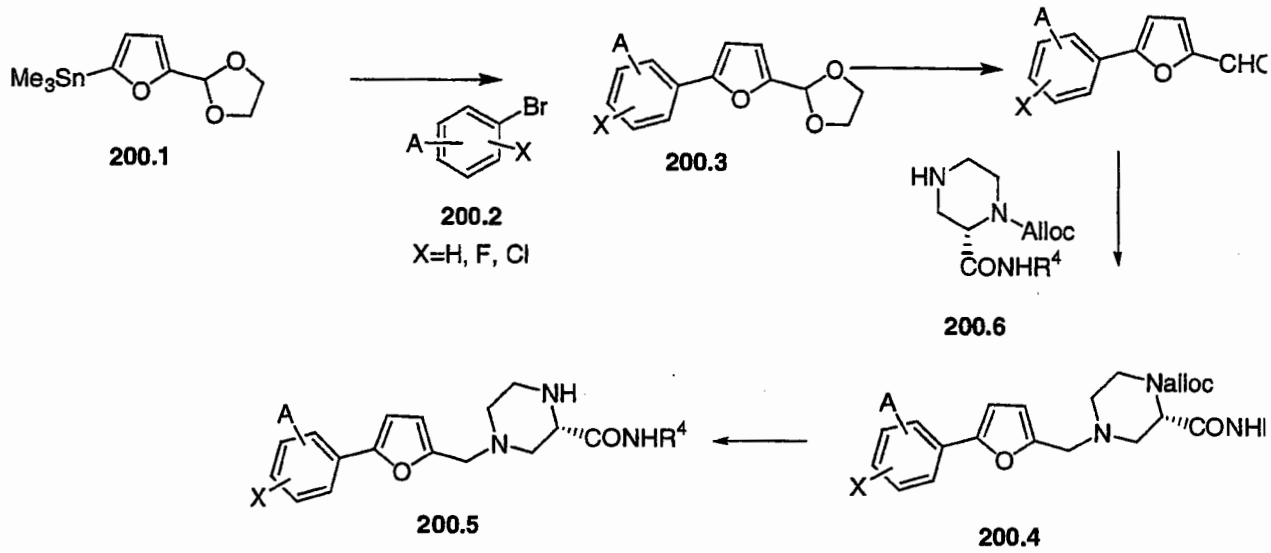
the bromomethyl compound **204.9** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100°C to produce the phosphonate **204.10.**

Using the above procedures, but employing, in place of the acid **204.6**, different acids **203.1**, and different phosphites **204.5** there are obtained the corresponding aryl halides **204.4**.

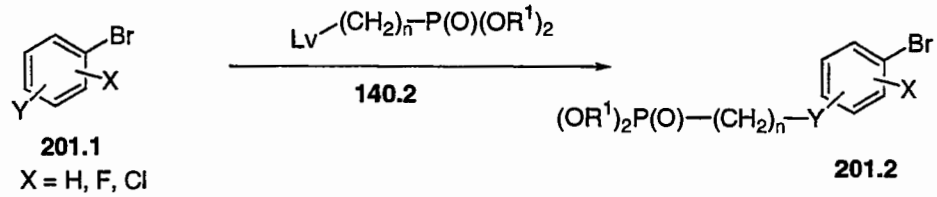
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The phosphonate-containing bromobenzene derivatives prepared as described in Schemes **201** - **204** are then transformed, as described in Scheme **200**, into the phenylfuran piperazine derivatives **200.5**.

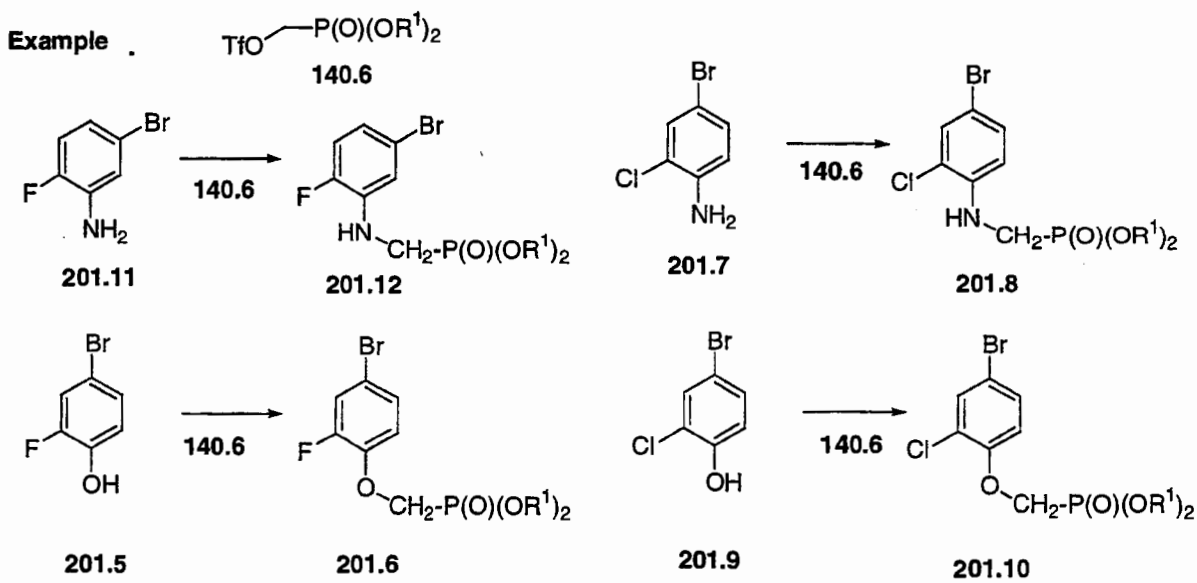
Scheme 200



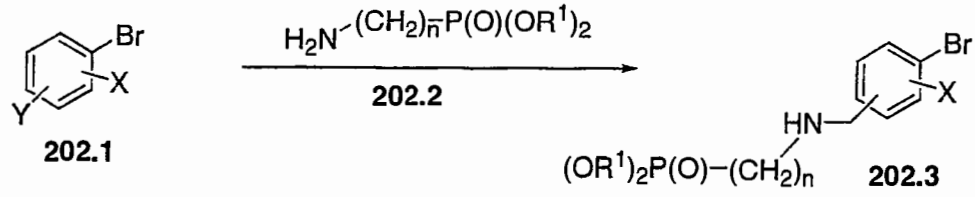
Scheme 201



Example



Scheme 202



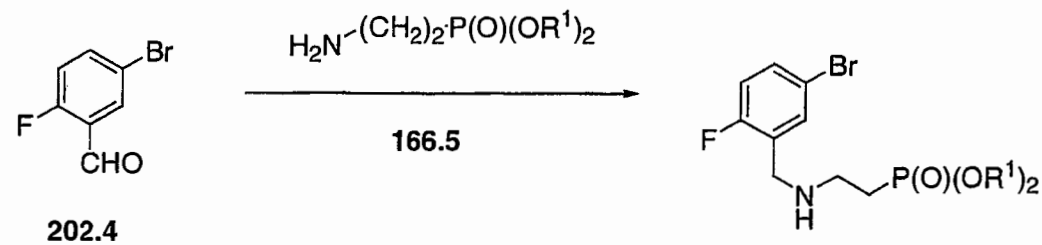
202.1

X = H, F, Cl

Y = CHO

202.3

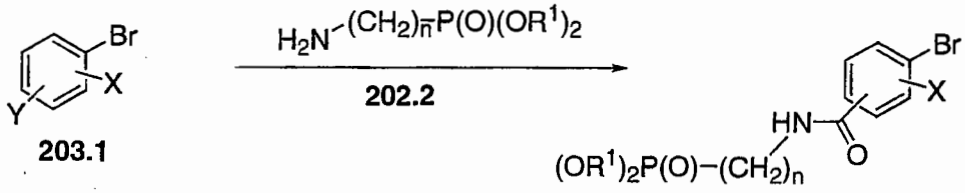
Example



202.4

202.5

Scheme 203



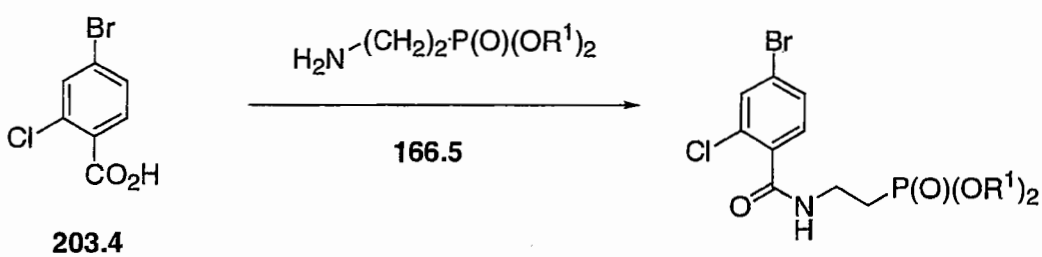
203.1

X = H, F, Cl

Y = CO_2H

203.2

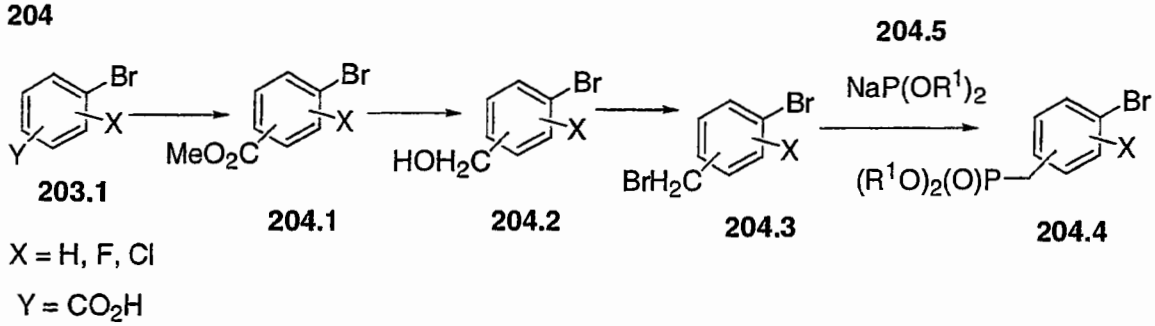
Example



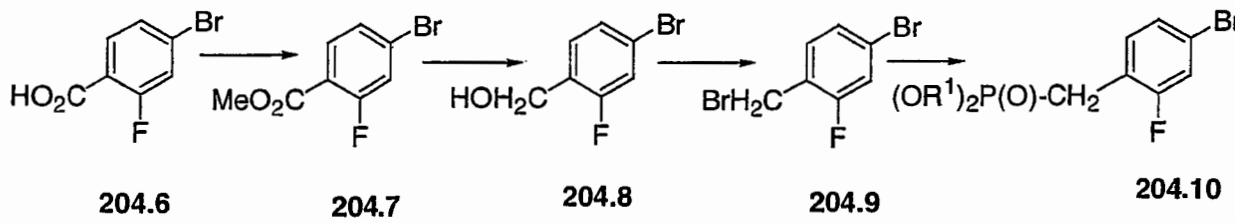
203.4

203.5

Scheme 204



Example



Preparation of piperazine ozaxole compounds 205.10 bearing phosphonate attachments

Schemes **205** - **207** depict the preparation of the piperazine oxazole phosphonate compounds **205.10** that are employed in the preparation of the phosphonate esters **23** where R^2R^3NH is now $R^{2a}R^{3a}NH$ as described above.

Scheme **205** depicts the preparation of piperazine oxazole phosphonates **205.10** in which the terminal aryl ring bears the phosphonate moiety. The acid **205.1** is converted to the Weinreb amide, for example ,as described in J. Med. Chem., 1994, 37, 2918, and then reacted with a methyl Grignard reagent e.g. MeMgBr. Examples of this procedure are reviewed in Org prep Proc Intl 1993, 25, 15. Ketone **205.3** is then brominated using conditions described in Comprehensive Organic Transformations, by R. C. Larock, 2nd Edition, 1999, p. 710-711. For example, treatment of **205.3** with bromine in acetic acid yields **205.4**. Conversion of the bromomethyl compound **205.4** into the piperazine derivative **205.10**, via the intermediates **205.5** - **205.9**, is effected by means of the reactions and procedures described in WO02/096359 for related compounds in which R^4 is CH_2CF_3 and A is H.

Scheme **206** illustrates the preparation of benzoic acid phosphonates in which the phosphonate moiety is attached by means of alkylene chains and a heteroatom O, S or N. In this procedure, a benzoic acid **206.1** is protected with a suitable protecting group (see Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 ch5 and then reacted with a an equimolar amount of a dialkyl phosphonate **206.3**, in which Ha is a leaving group e.g. halogen, to afford the alkyl phosphonate product **206.4**. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile **206.2**. In cases in which Y is O, a strong base such as sodium hydride or lithium hexamethyldisilazide is employed. In cases in which Y is S or N, a base such as cesium carbonate or dimethylaminopyridine is employed. Following this reaction the product **206.4** is hydrolyzed by treatment with base to give the acid **206.5**

For example, benzoic acid **206.6**, (Aldrich) is reacted with diazomethane in ether at 0°C to give the methyl ester **206.7** or simply refluxed in acidic methanol. The ester in acetonitrile at 60°C is treated with one molar equivalent of a dialkyl iodomethyl phosphonate **206.8**, (Lancaster) to give the ether product **206.9**. This product **206.9** is then hydrolyzed by treatment with lithium hydroxide in aqueous THF to give the acid **206.10.**

Using the above procedures, but employing, in place of the benzoic acid **206.6**, different acids **206.1**, and/or different haloalkyl phosphonates **206.3**, the corresponding products **206.5** are obtained.

Scheme **207** depicts the preparation of phosphonate esters linked to a benzoic acid nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **207.3** is coupled with an aromatic bromo compound **207.2**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **207.4**. Deprotection, or hydrogenation of the double bond

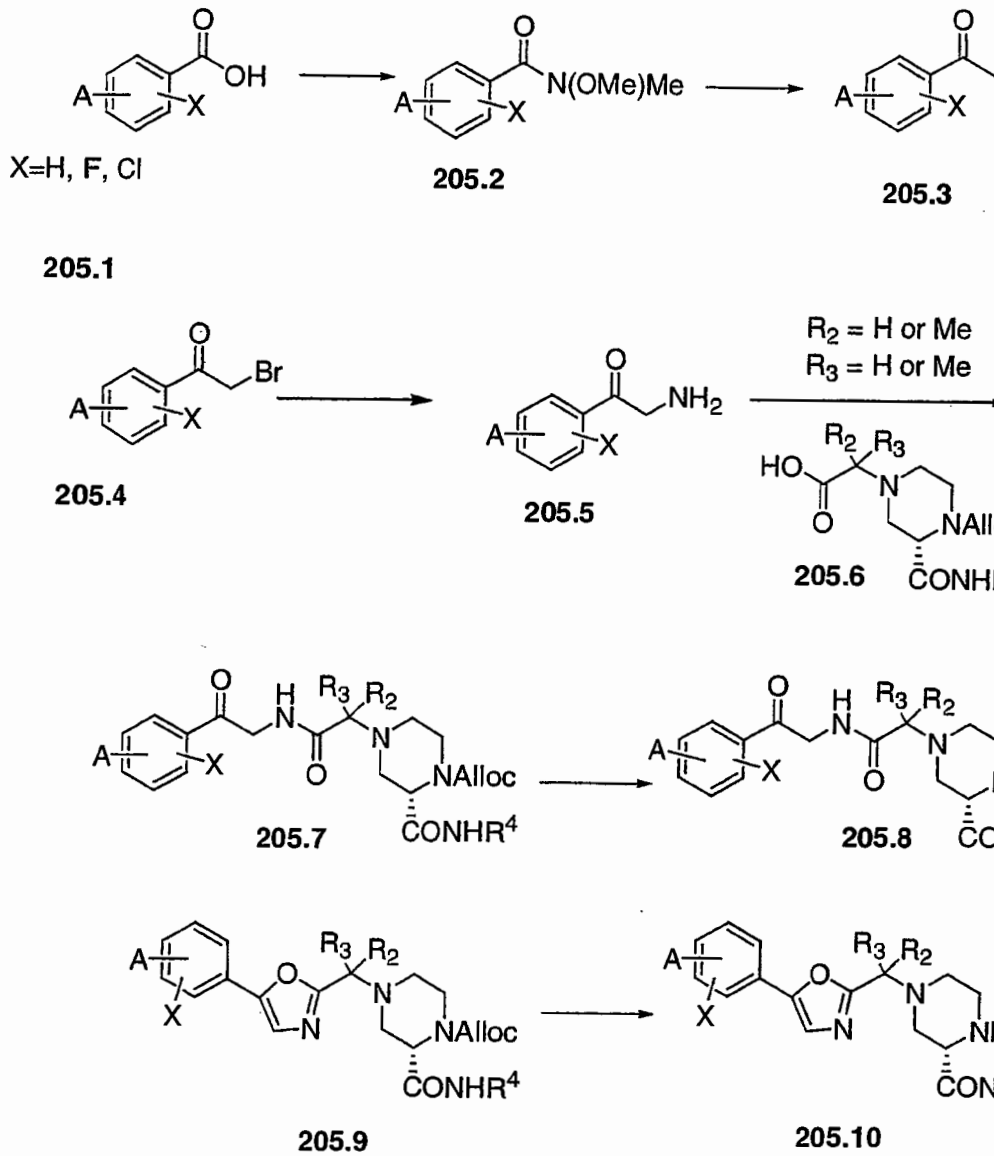
followed by deprotection, affords respectively the unsaturated phosphonate acid **207.5**, or the saturated analog **207.6** respectively.

For example, 4-bromo-3-fluorobenzoic acid **207.7** (Apollo) is converted to the tert butyl ester **207.8** by treatment with t-butanol and DCC in the presence of dimethylaminopyridine. The ester **207.8** is then reacted with a dialkyl 1-propenyl phosphonate **150.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **207.10**. Deprotection as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 406-408, then affords the acid **207.11**. Optionally, the acid **207.11** is subjected to catalytic or chemical reduction, for example using diimide, as described in Scheme **138**, to yield the saturated product **207.12.**

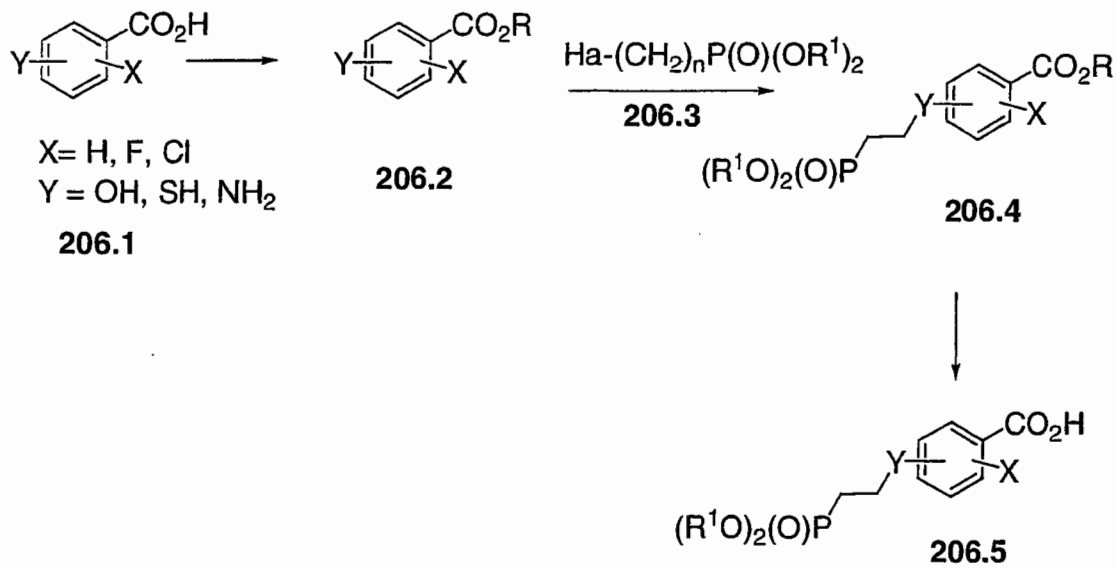
Using the above procedures, but employing, in place of the acid compound **207.7**, different acid compounds **207.1**, and/or different phosphonates **207.3**, there are obtained the corresponding products **207.5** and **207.6**.

The phosphonate-containing benzoic acids, prepared as described in Schemes **206** and **207**, are then transformed, using the procedures shown in Scheme **205**, into the phenyloxazole piperazine derivatives **205.10**.

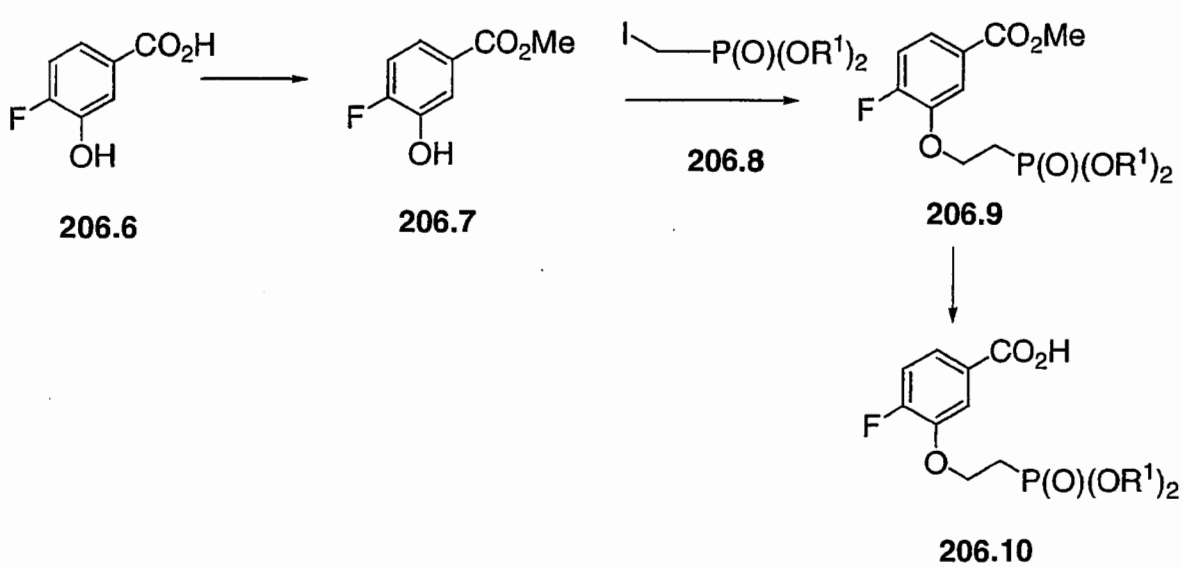
Scheme 205


X=H, F, Cl
205.1
205.2
205.3
205.4
205.5
R_2 = H or Me
R_3 = H or Me
205.6
205.7
205.8
205.9
205.10

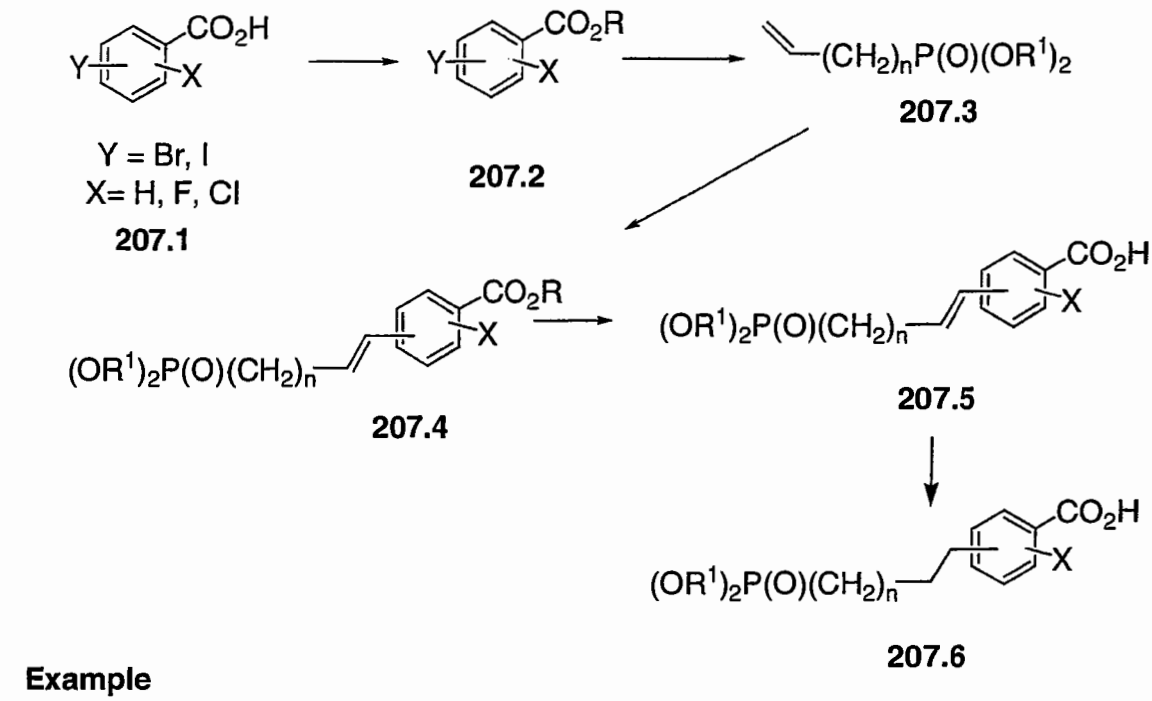
Scheme 206



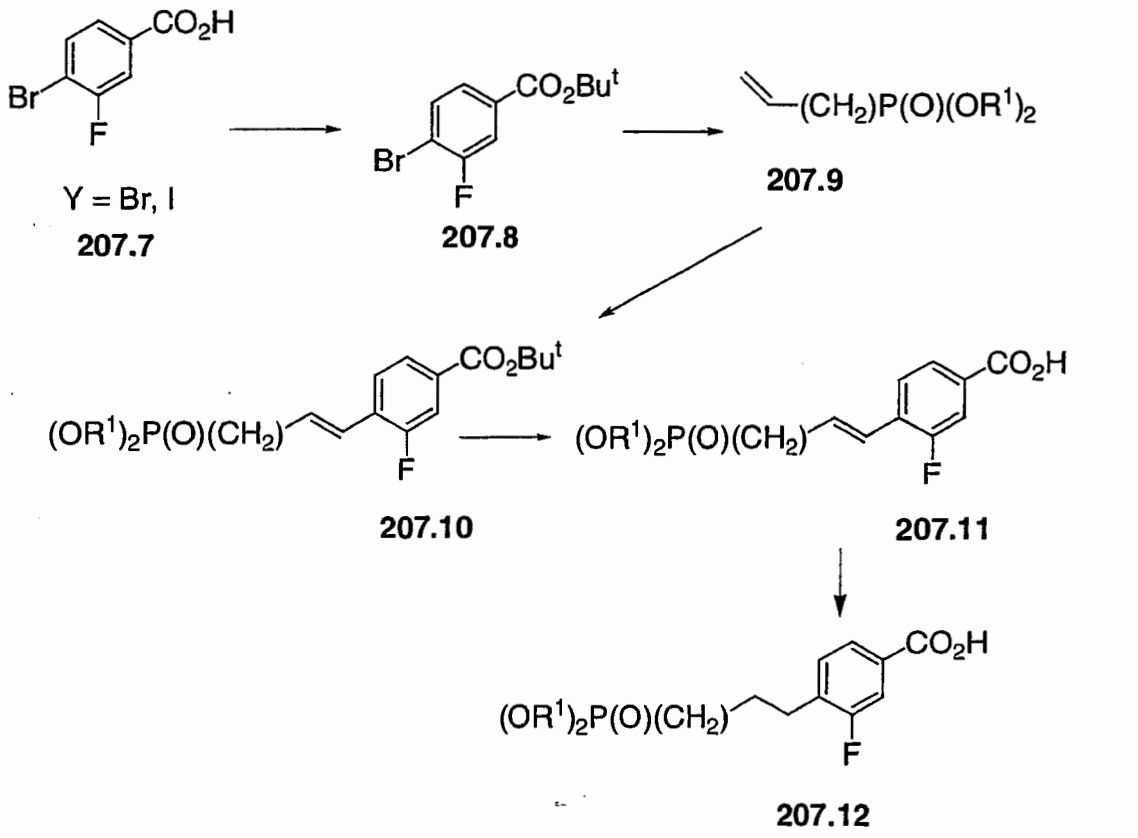
Example



Scheme 207



Example



Nelfinavir-like phosphonate protease inhibitors - (NLPPI)

Preparation of the intermediate phosphonate esters.

The intermediate phosphonate esters **1** to **4a** of this invention are shown in Chart **1**. Subsequent chemical modifications, as described herein, permit the synthesis of the final compounds of this invention.

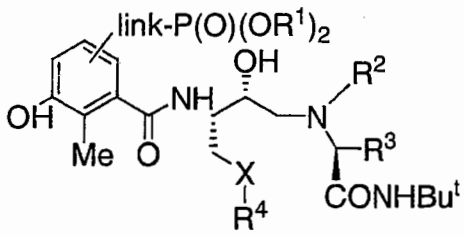
The structures of the amine components $R^2NHCH(R^3)CONHBu^t$ **6-20e** are shown in Chart **2**. Although specific stereoisomers of some of the amines are shown, all stereoisomers of the amine components are utilized. Chart **2** also illustrates that, in addition to the tert. butyl amines **5**, the corresponding 2,2,2-trifluororoethyl and 2-methylbenzyl amides are utilized in the synthesis of the phosphonate intermediate compounds of this invention.

Chart **3** depicts the structures of the R^4 components **21-26**. Charts **4a-4c** illustrate the structures of the carboxylic acid components R^5COOH, **C1-C49**.

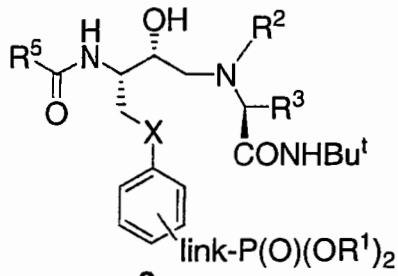
The intermediate compounds **1** to **4a** incorporate a phosphonate moiety connected to the a nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **5** and **5a** illustrate examples of the linking groups **38-59** present in the structures **1-4a,** and in which "etc" refers to the scaffold, e.g., nelfinavir.

Schemes **1** - **50** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1-4a**, and of the intermediate compounds necessary for their synthesis.

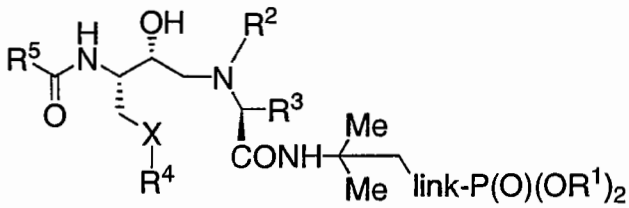
Chart 1. Structures of phosphonate ester intermediate compounds



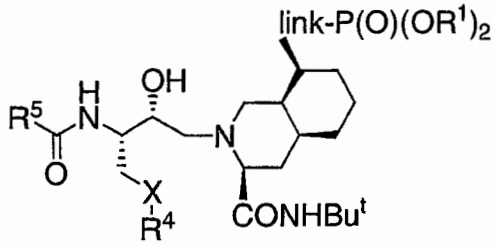
1



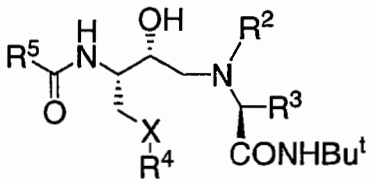
2



3



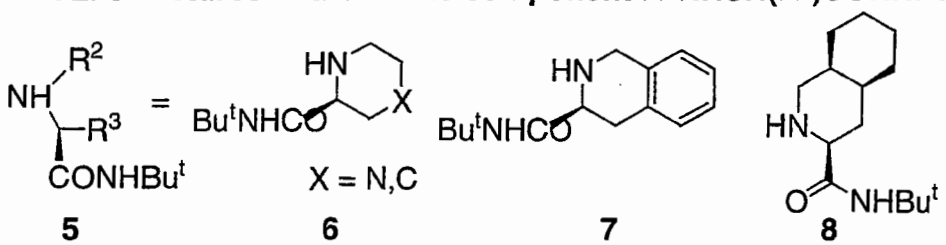
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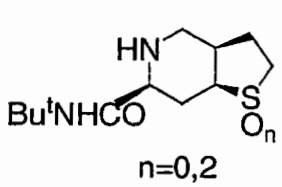
4a

R^1 = H, alkyl, alkenyl, aryl, aralkyl

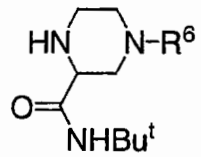
Chart 2. Structures of the amine component $R^2NHCH(R^3)CONHBu^t$



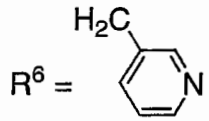
5 6 7 8



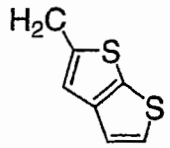
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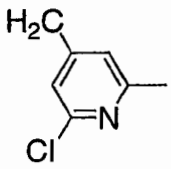
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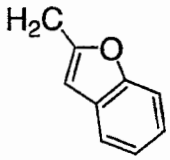
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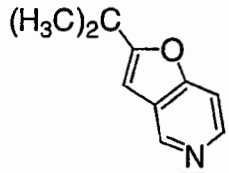
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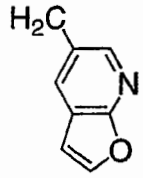
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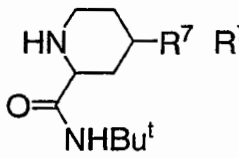
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15

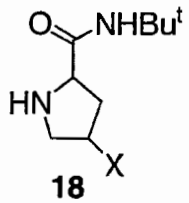


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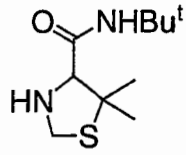
17

R^7=OCH_2Ph
S-3-pyridyl
S-4-pyridyl
OCH_2-4-pyridyl

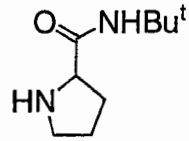


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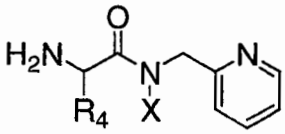
X = Cl, OMe



19

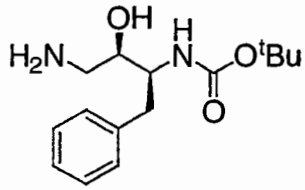


20

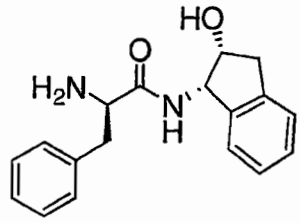


X=H or Me

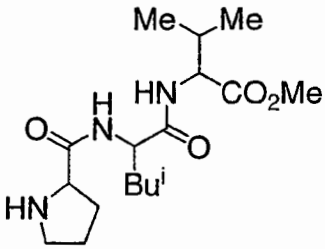
20a



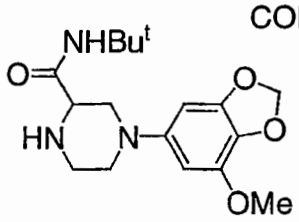
20b



20c



20d

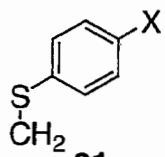


20e

$CONHBu^t$ = $CONHC(CH_3)_3$
$CONHCH_2CF_3$
$CONHCH_2C_6H_4(CH_3)$-2

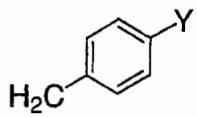
Chart 3. Structures of the R^4 components

CH_2XR^4 =



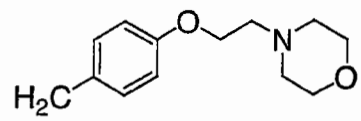
21

X = H, F

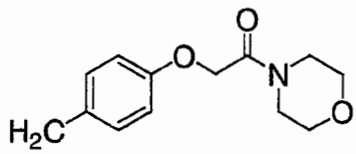


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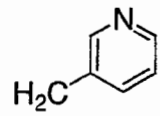
Y = H, OC_2H_5, $OCH_2C_6H_5$



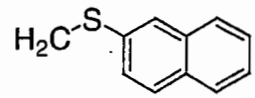
23



24

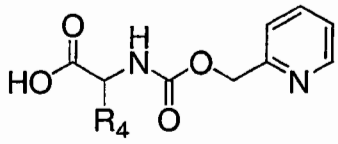


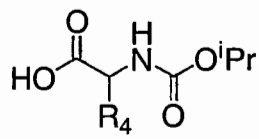
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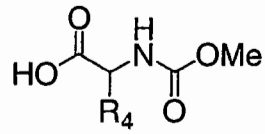


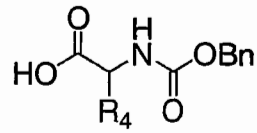
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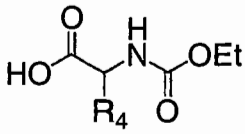
Chart 4a Structures of the R^5COOH components

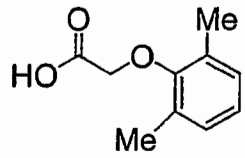

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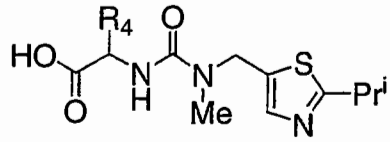

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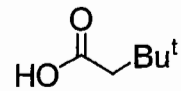

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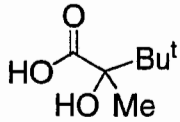

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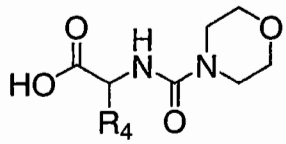

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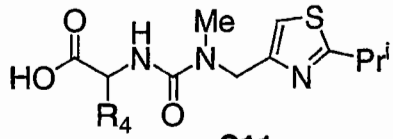

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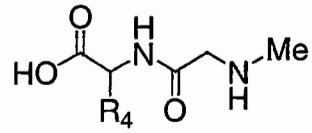

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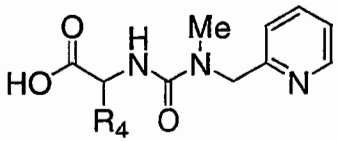

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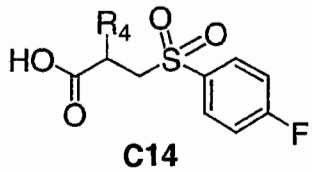

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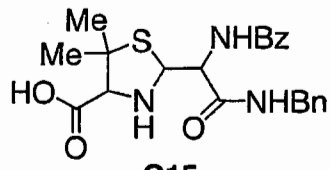

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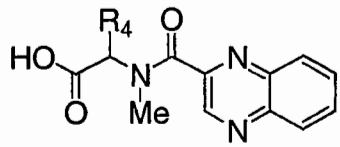

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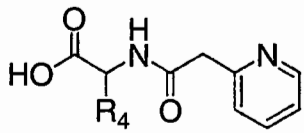

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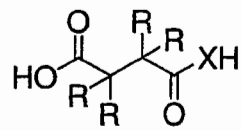

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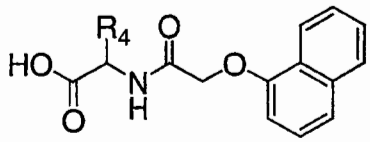

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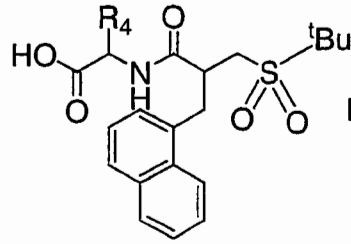

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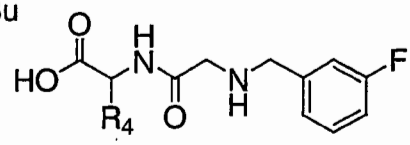

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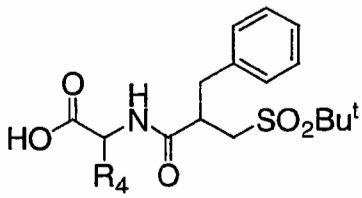

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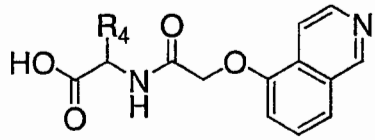

X = O, NH
R = H, alkyl
C18

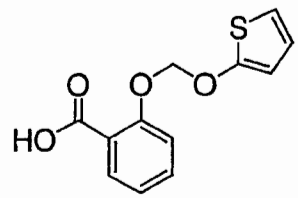

C19


C20


C21

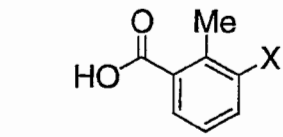

C22


C23


C24

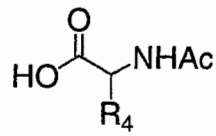
R^4 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

Chart 4b Structures of the R^5COOH components

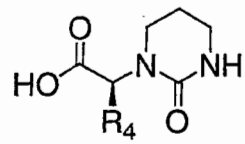


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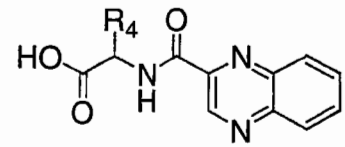
X = OH, NH_2



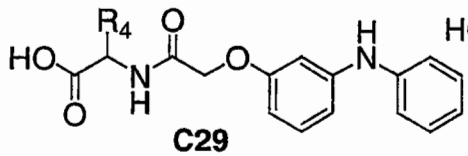
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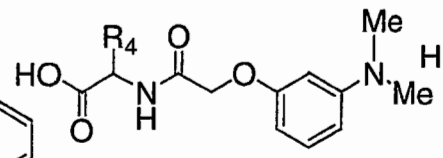
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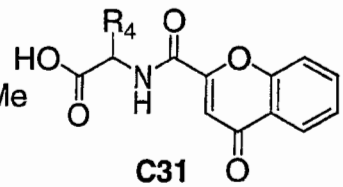
C28



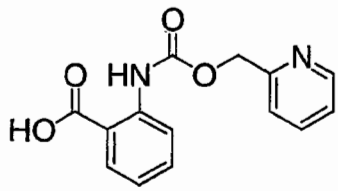
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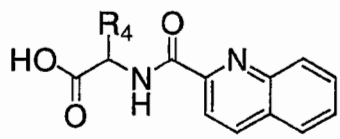
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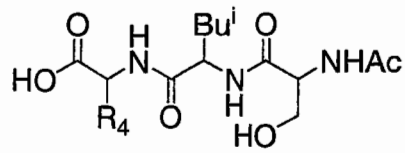
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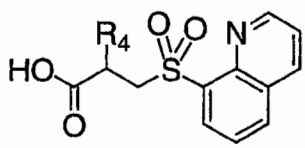
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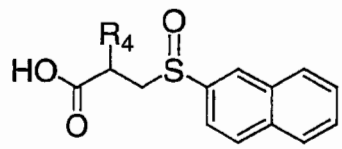
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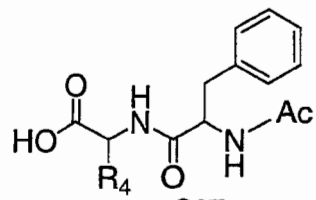
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C35



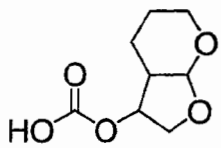
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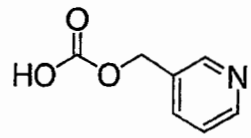
C37

R^4 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

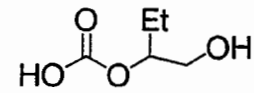
Chart 4c Structures of the R^5COOH components



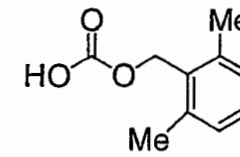
C38



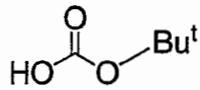
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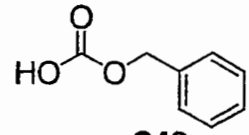
C40



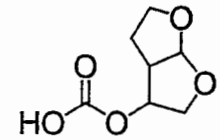
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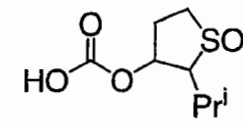
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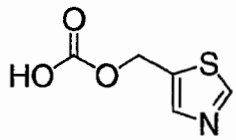
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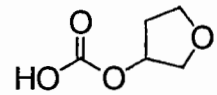
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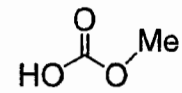
C45



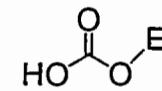
C46



C47



C48



C49

Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.

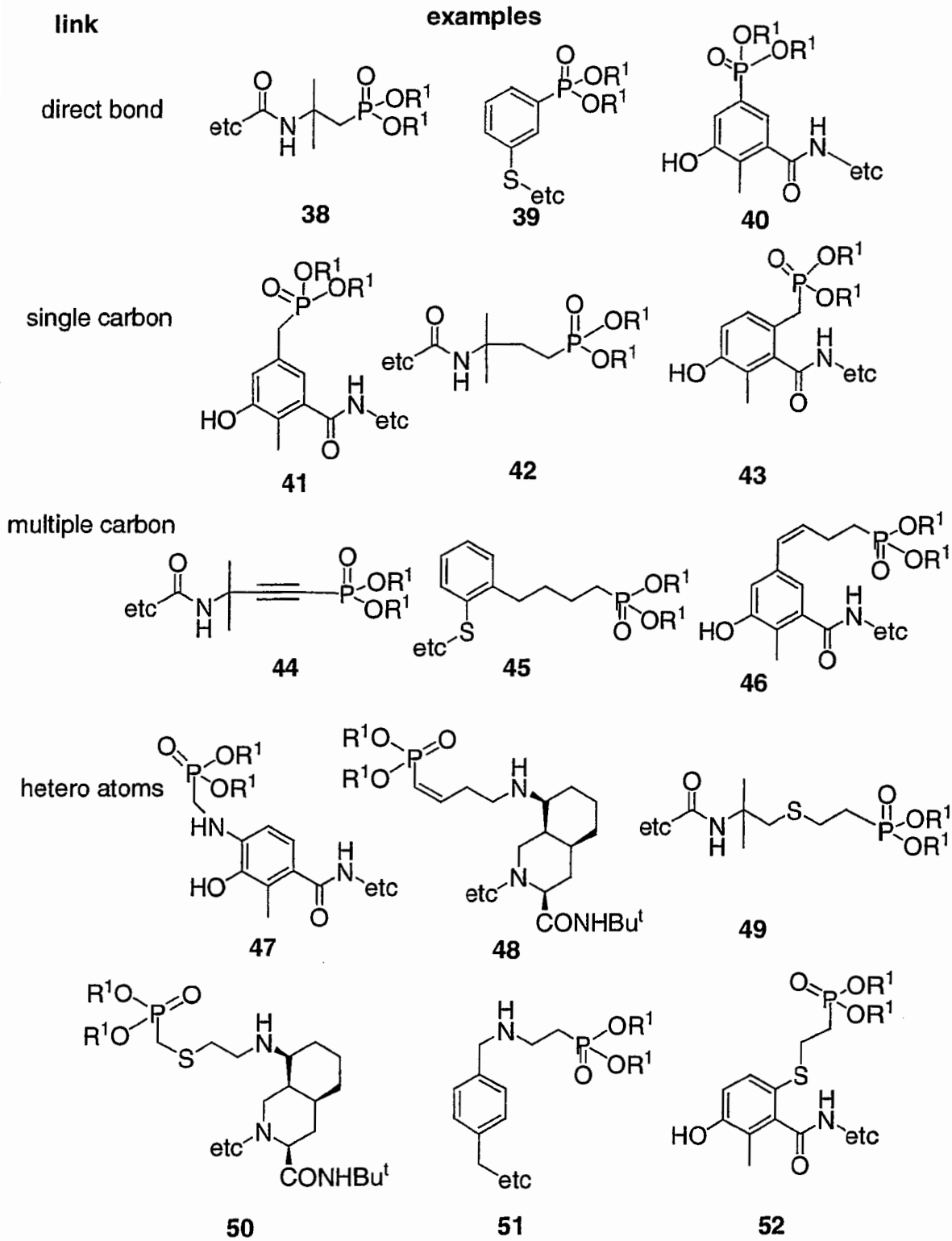
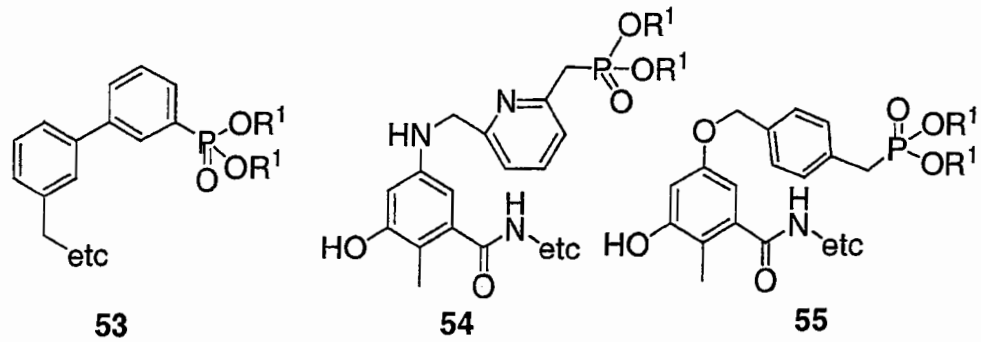
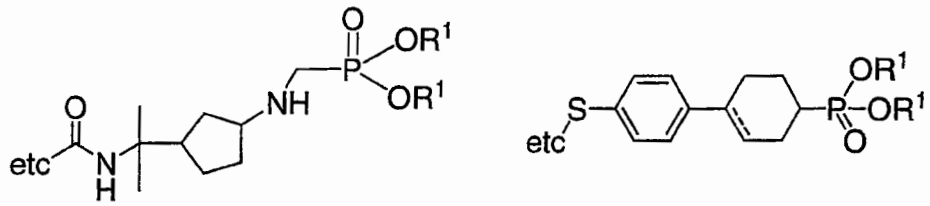
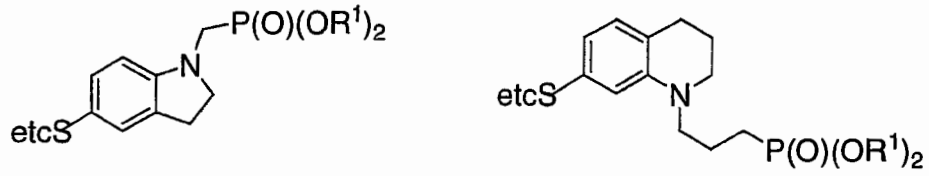


Chart 5a Examples of the linking group between the scaffold and the phosphonate moiety.

link	examples
aryl, heteroaryl	
	53 54 55
cycloalkyl	
	56 57
cyclized	
	58 59

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M Wuts, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate intermediates 1, in which X=S.

The syntheses of the phosphonates **1** in which X=S, and in which the group link-P(O)$(OR^1)_2$ is attached to the benzoic acid moiety, are shown in Schemes **1- 3.**

Scheme **1** illustrates the preparation of the phosphonate intermediate compounds **1**, or precursors thereto. 4-Amino-tetrahydro-furan-3-ol **60,** the preparation of which is described in Tet. Lett., 2000, 41, 7017, is reacted with the carboxylic acid **61**, or an activated derivative thereof, the preparations of which are described below, to form the amide **62.**

The preparation of amides by reaction of carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p 274. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride or anhydride, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

Preferably, the carboxylic acid is first converted into the acid chloride by reaction with, for example, thionyl chloride, oxalyl chloride and the like. The acid chloride **61**, in which X is Cl, is then reacted with an equimolar amount of the amine **60**, in the presence of a weak inorganic base such as sodium bicarbonate, in an aprotic solvent such as dichloromethane, at ambient temperature, to afford the amide **62.**

The hydroxyl group on the tetrahydrofuran moiety so obtained is converted into a leaving group such as p-toluenesulfonyl or the like, by reaction with a sulfonyl chloride in an aprotic solvent such as pyridine or dichloromethane.

Preferably, the hydroxy amide **62** is reacted with an equimolar amount of methanesulfonyl chloride in pyridine, at ambient temperature, to afford the methanesulfonyl ester **63.**

The product **63**, bearing a suitable sulfonyl ester leaving group, is then subjected to acid-catalyzed rearrangement to afford the isoxazoline **64**. The rearrangement reaction is conducted in the presence of an acylating agent such as a carboxylic anhydride, in the presence of a strong acid catalyst.

Preferably, the mesylate **63** is dissolved in an acylating agent such as acetic anhydride at about 0°, in the presence of about 5 mole % of a strong acid such as sulfuric acid, to afford the isoxazoline mesylate **64**.

The leaving group, for example a mesylate group, is next subjected to a displacement reaction with an amine.

The compound **64** is reacted with an amine **5**, as defined in Chart **2**, in a protic solvent such as an alcohol, in the presence of an organic or inorganic base, to yield the displacement product **65**.

Preferably, the mesylate compound **64** is reacted with an equimolar amount of the amine **5**, in the presence of an excess of an inorganic base such as potassium carbonate, at ambient temperature, to afford the product **65**.

The isoxazoline compound **65** is then reacted with a thiol R^4SH **66**, in which R^4 is phenyl, 4-fluorophenyl or 2-naphthyl, as shown in Chart **3**, to afford the thioether **1**. The reaction is conducted in a polar solvent such as DMF, pyridine or an alcohol, in the presence of a weak organic or inorganic base, to afford the product **1**.

Preferably, the isoxazoline **65** is reacted, in methanol, with an equimolar amount of the thiol R^4SH **66**, in the presence of an excess of a base such as potassium bicarbonate, at ambient temperature, to afford the thioether **1**.

Alternatively, the compounds **1** can be obtained by means of the reactions shown in Scheme **2**. In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, **67**, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol R^4SH **66**, as defined above, to afford the thioether **68**.

The reaction is conducted in a suitable solvent such as, for example, pyridine, DMF and the like, in the presence of an inorganic or organic base, at from 0° to 80°, for from 1-12 hours, to afford **68**.

Preferably the mesylate **67** is reacted with an equimolar amount of the thiol R^4SH **66**, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°, to give the product **68**.

The 1,3-dioxolane protecting group present in the compound **68** is removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol **69**. Methods

for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M Wuts, Second Edition 1990, p. 191.

For example, the 1,3-dioxolane compound **68** is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture.

Preferably, the 1,3-dioxolane **68** is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°, to yield the product **69**.

The primary hydroxyl group of the diol **69** is then selectively acylated by reaction with an electron-withdrawing acyl halide such as, for example, pentafluorobenzoyl chloride or mono- or di-nitrobenzoyl chlorides. The reaction is conducted in an inert solvent such as dichloromethane and the like, in the presence of an inorganic or organic base.

Preferably, equimolar amounts of the diol **69** and 4-nitrobenzoyl chloride are reacted in a solvent such as ethyl acetate, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, to afford the ester **70**.

The hydroxy ester **70** is next reacted with a sulfonyl chloride such as methanesulfonyl chloride, 4-toluenesulfonyl chloride and the like, in the presence of a base, in an aprotic polar solvent at low temperature, to afford the corresponding sulfonyl ester **71**.

Preferably, equimolar amounts of the carbinol **70** and methanesulfonyl chloride are reacted together in ethyl acetate containing triethylamine, at about 10°C, to yield the mesylate **71**.

The compound **71** is then subjected to a hydrolysis-cyclization reaction to afford the oxirane **72**.

The mesylate or analogous leaving group present in **71** is displaced by hydroxide ion, and the carbinol thus produced, without isolation, spontaneously transforms into the oxirane **72** with elimination of 4-nitrobenzoate. To effect this transformation, the sulfonyl ester **71** is reacted with an alkali metal hydroxide or tetraalkylammonium hydroxide in an aqueous organic solvent.

Preferably, the mesylate **71** is reacted with potassium hydroxide in aqueous dioxan at ambient temperature for about 1 hour, to afford the oxirane **72**.

The oxirane compound **72** is then subjected to regiospecific ring-opening reaction by treatment with an amine **5**, to give the aminoalcohol **73**.

The amine and the oxirane are reacted in a protic organic solvent, optionally in the additional presence of water, at 0° to 100°, and in the presence of an inorganic base, for 1 to12 hours, to give the product **73**.

Preferably, equimolar amounts of the reactants **5** and **72** are reacted in aqueous methanol at about 60° in the presence of potassium carbonate, for about 6 hours, to afford **73**.

The carbobenzyloxy (cbz) protecting group in the product **73** is removed to afford the free amine **74**. Methods for removal of cbz groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M. Wuts, Second Edition, p. 335. The methods include catalytic hydrogenation and acidic or basic hydrolysis.

For example, the cbz-protected amine **73** is reacted with an alkali metal or alkaline earth hydroxide in an aqueous organic or alcoholic solvent, to yield the free amine **74**.

Preferably, the cbz group is removed by the reaction of **73** with potassium hydroxide in an alcohol such as isopropanol at ca. 60° to afford the amine **74**.

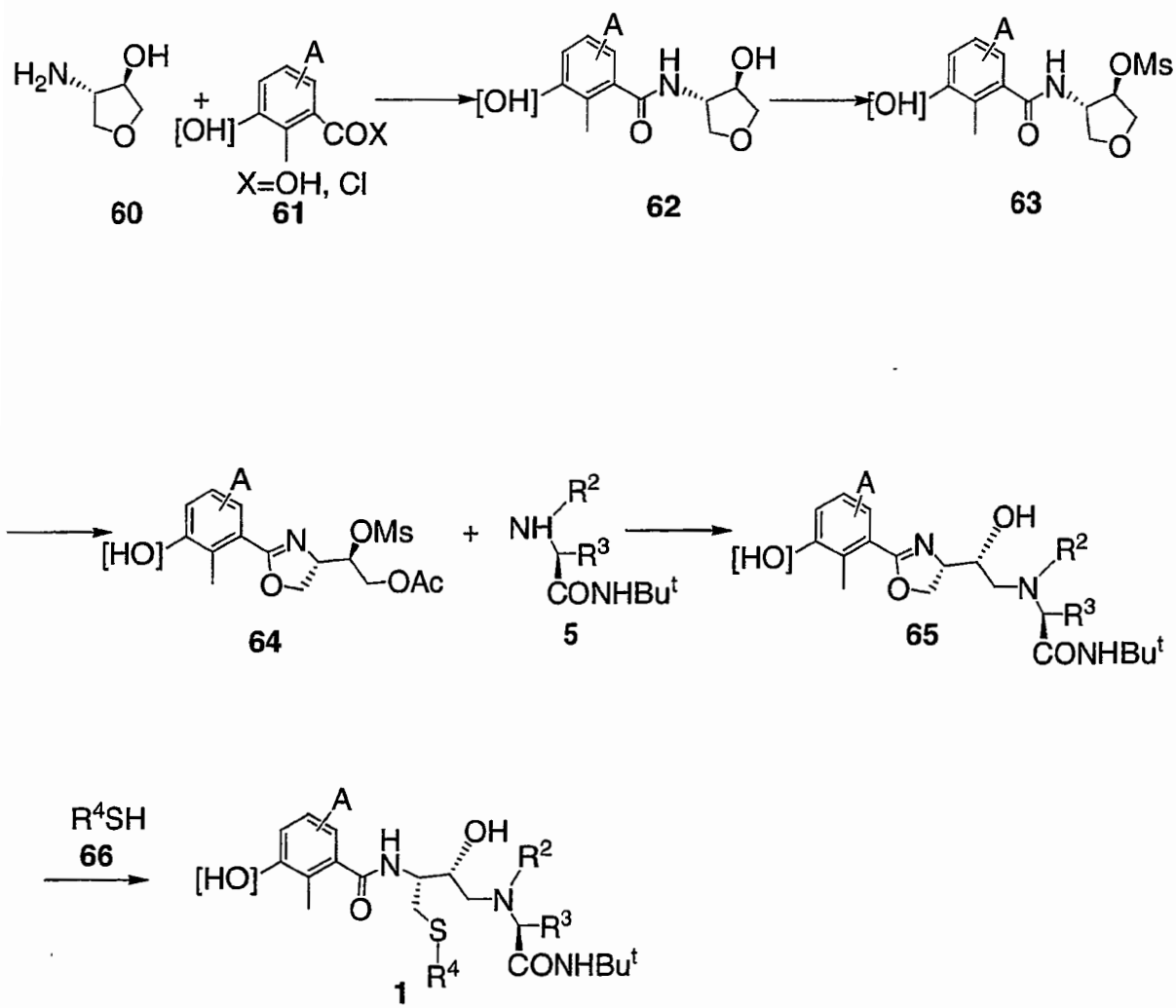
The amine **74** so obtained is next acylated with a carboxylic acid or activated derivative **61**, using the conditions described above for the conversion of **60** to **62**, to yield the final amide product **75**.

The reactions shown in the above-described Schemes **1** and **2** depict the preparation of intermediates **1** in which A is either link-P(O)$(OR^1)_2$ or precursor groups to link-P(O)$(OR^1)_2$ such as OH, SH, NH, as described herein.

Scheme **3** shows the conversion of the compounds **75** in which A is OH, SH, NH, to the compounds **1** in which A is link-P(O)$(OR^1)_2$.

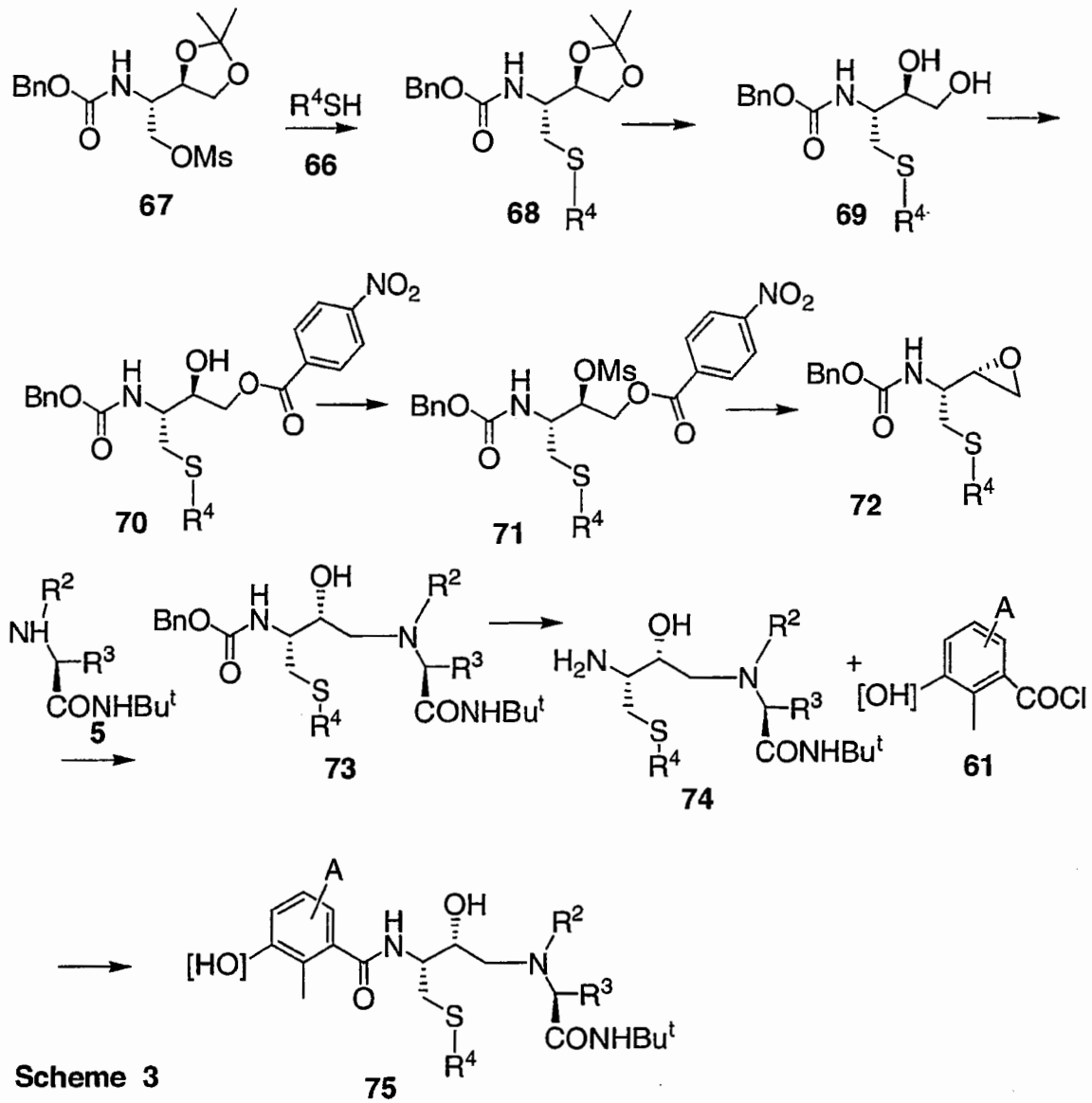
Methods for these transformations are described below, Schemes **20-48**, in the descriptions of the preparations of the phosphonate-containing reactants.

Scheme 1

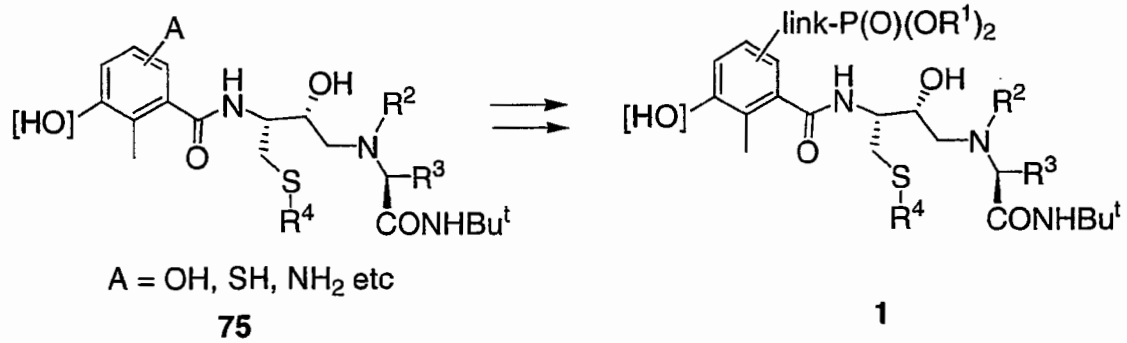


A = link-(P)$(OR^1)_2$ or A = OH, SH, NH, etc

Scheme 2



Scheme 3



Preparation of the phosphonate intermediates 2, in which X = S.

The synthesis of the phosphonate compounds **2** in which the link-P(O)$(OR^1)_2$ group is attached to the phenylthio moiety, is shown in Scheme **4**.

In this sequence, 4-amino-tetrahydro-furan-3-ol, **60**, the preparation of which is described in Tet. Lett., 2000, 41, 7017, is reacted with a carboxylic acid or activated derivative thereof, R^5COX, **76**, using the conditions described above for the preparation of the amide **62**, Scheme **1**, to afford the amide **77**. The compounds **77**, and analogous acylation products described below, in which the carboxylic acid R^5COOH is one of the carbonic acid derivatives **C36-C49**, as defined in Chart **4c**, are carbamates. Methods for the preparation of carbamates are described below, (Scheme **50**).

The amide product **77** is then transformed, using the sequence of reactions shown in Scheme **4**, into the isoxazoline compound **80**. The conditions for this sequence of transformations are the same as those described for the preparation of the isoxazoline **65** in Scheme **1**.

The isoxazoline compound **80** is then reacted with a thiol compound **66**, in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor thereto, such as OH, SH, NH, as described herein, to afford the thioether **81**.

The conditions for this reaction are the same as those described above for the preparation of the thioether **1**, (Scheme **1**).

Alternatively, the thioether **81** can be prepared by the sequence of reactions shown in Scheme **5**. In this sequence, the previously described 1,3-dioxolane mesylate compound **67** is reacted with a thiol compound **66** in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor thereto, such as OH, SH, NH, as described herein, to afford the thioether **82**. The conditions for this reaction are the same as those described above for the preparation of the thiether **68**, (Scheme **2**).

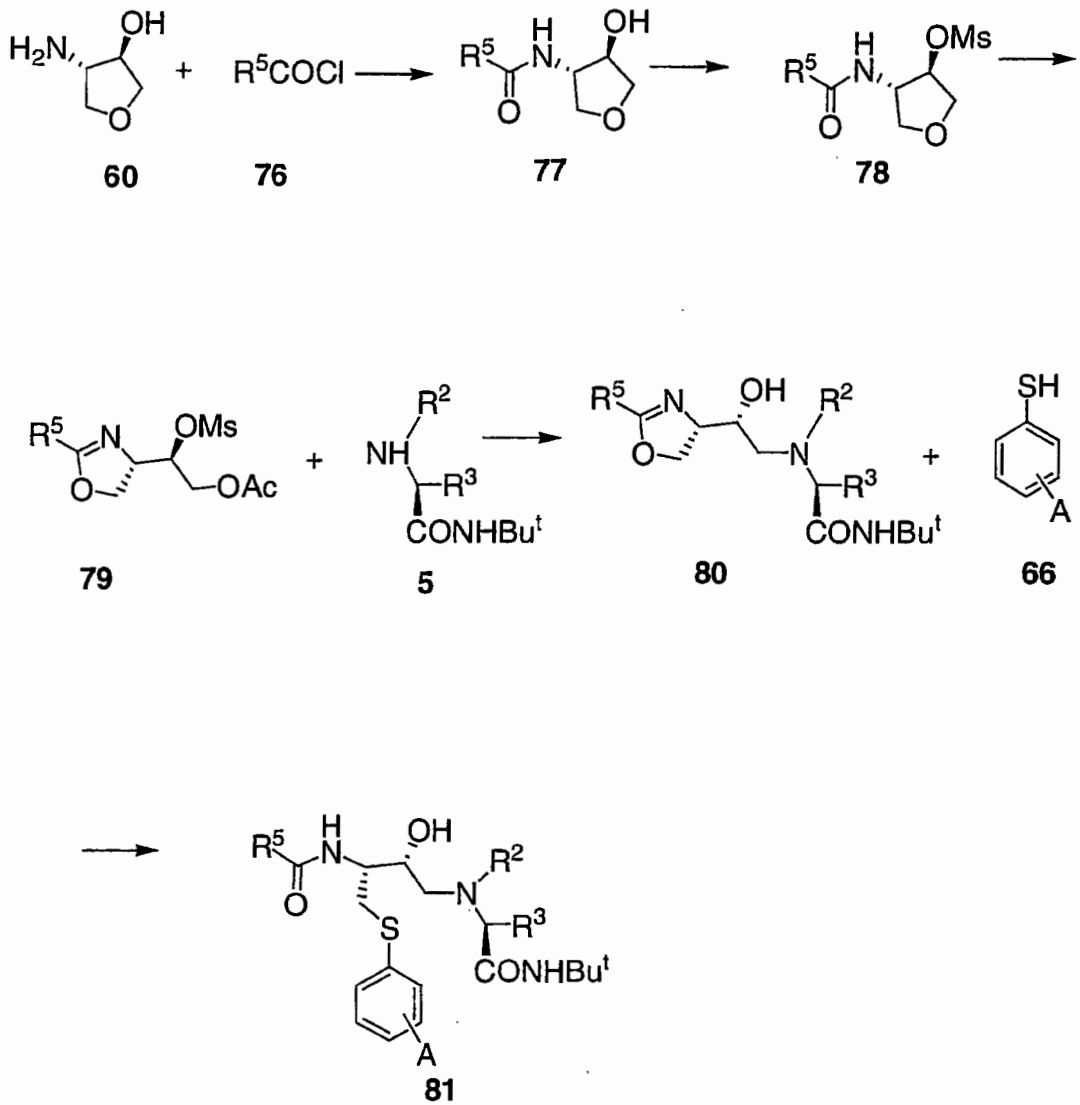
The thus-obtained thioether **82** is then transformed, using the sequence of reactions shown in Scheme **2** into the compound **81**.

The reactions shown in the above-described Schemes **4** and **5** depict the preparation of intermediates **81** in which A is either link-P(O)$(OR^1)_2$ or precursor groups to link-P(O)$(OR^1)_2$ such as OH, SH, NH, as described herein.

Scheme **6** shows the conversion of the compounds **81** in which A is OH, SH, NH, into the compounds **2** in which A is link-P(O)$(OR^1)_2$.

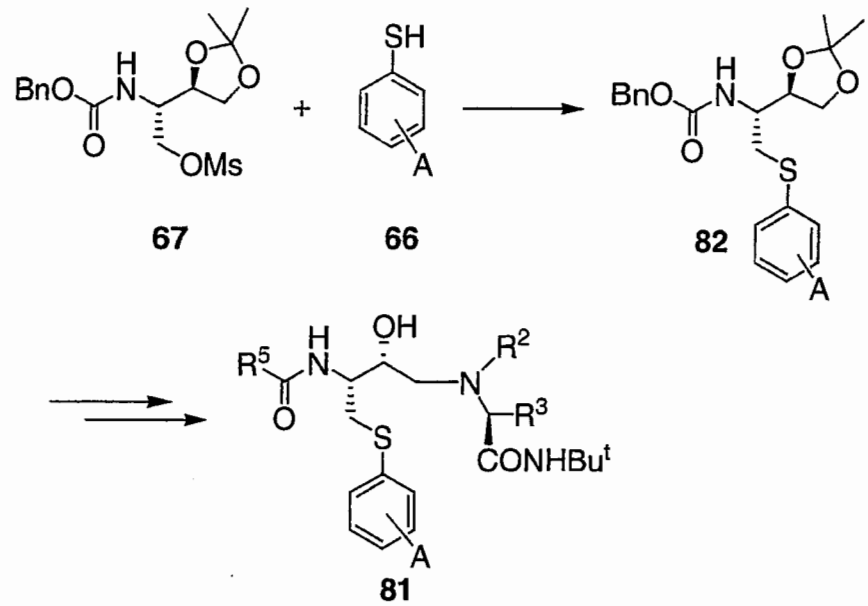
Methods for these transformations are shown in Schemes **20-48** and are discussed in the descriptions of the preparations of the phosphonate-containing reactants.

Scheme 4



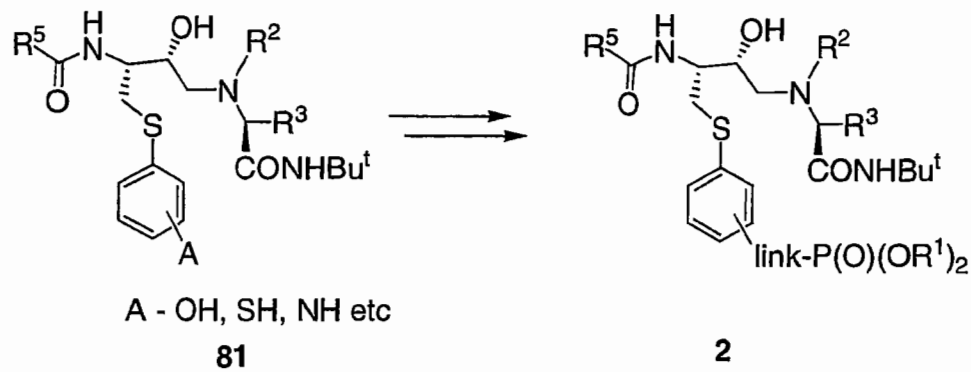
A = link-(P)(OR^1)$_2$ or A = OH, SH, NH, etc.

Scheme 5



A = link-(P)$(OR^1)_2$ or A = OH, SH, NH, etc

Scheme 6



A - OH, SH, NH etc

81 **2**

Preparation of the phosphonate intermediates 3, in which X = S.

The phosphonate intermediates **3** in which X = S, and in which the link-P(O)$(OR^1)_2$ group is attached to the tert. butyl moiety, are prepared as shown in Schemes **7** and **8.**

As shown in Scheme 7, the isoxazolines **79**, the preparation of which are described above, are reacted with the amines **83**, using the conditions described above for the conversion of **64** to **65**, (Scheme **1**) to afford the product **84**.

This compound is then converted, using the methods described above, (Scheme **1**) into the compound **85**, in which B is either link-P(O)$(OR^1)_2$ or precursor groups to link-P(O)$(OR^1)_2$ such as OH, SH, NH, as described herein.

Alternatively, the compounds **85** can be prepared by the reactions shown in Scheme **8**.

In this method, the oxirane **72**, the preparation of which is described above, (Scheme **2**) is reacted with the amine **83**, using the reaction conditions described above for the conversion of **72** to **73** (Scheme **2**), to afford the hydroxyamine **86**. This compound is then converted, using the procedures described above, into the compound **85**, in which B is either link-P(O)$(OR^1)_2$ or precursor groups to link-P(O)$(OR^1)_2$ such as OH, SH, NH, as described herein.

The reactions shown in the above-described Schemes **7** and **8** depict the preparation of intermediates **85** in which A is either link-P(O)$(OR^1)_2$ or precursor groups to link-P(O)$(OR^1)_2$ such as OH, SH, NH, as described herein.

Scheme **9** shows the conversion of the compounds **85** in which A is OH, SH, NH, into the compounds **3** in which A is link-P(O)$(OR^1)_2$.

Methods for these transformations are described below in Schemes **20** to **48** in which the preparations of the phosphonate-containing reactants are depicted.

Preparation of the phosphonate intermediates 4 in which X = S.

The preparations of the phosphonate intermediates **4**, in which the link-P(O)$(OR^1)_2$ group is attached to the decahydroisoquinoline moiety, are shown in Schemes **10** to **12**.

As shown in Scheme **10**, the isoxazoline mesylate **79**, the preparation of which is described above, (Scheme **4**) is reacted with the amine **88**, the preparation of which is described below. The reaction is preformed using the procedures described above for the preparation of **65** (Scheme **1**).

The reaction product **89** is then transformed, using the procedures described above, (Scheme **1**) into the compound **90**, in which B is either link-P(O)$(OR^1)_2$ or precursor groups to link-P(O)$(OR^1)_2$ such as OH, SH, NH, as described herein.

Alternatively, the compound **90** can be prepared by the reactions shown in Scheme **11**.

In this reaction scheme, the oxirane **72**, the preparation of which is described above, (Scheme **2**) is reacted with the amine **88**, using the conditions described above for the preparation of **73** (Scheme **2**) to afford the hydroxyamine **91**. This compound is then converted, using the reaction schemes and conditions described above for the preparation of **1**, (Scheme **2**) into the compound **90**, in which B is either link-$P(O)(OR^1)_2$ or precursor groups to link-$P(O)(OR^1)_2$ such as OH, SH, NH, as described herein.

The reactions shown in the above-described Schemes **10** and **11** depict the preparation of intermediates **90** in which B is either link-$P(O)(OR^1)_2$ or precursor groups to link-$P(O)(OR^1)_2$ such as OH, SH, NH, as described herein.

Scheme **12** shows the conversion of the compounds **90** in which B is OH, SH, NH, to the compounds **4** in which A is link-$P(O)(OR^1)_2$.

Methods for these transformations are described below in Schemes **20-48** in which the preparations of the phosphonate-containing reactants are depicted.

Preparation of the phosphonate intermediates 1, in which X is a direct bond

As shown in Scheme **13,** the oxirane **92**, in which X is H, the preparation of which is described in J. Med. Chem., 1997, 40, 1995, and in Bioorg. Med. Chem. Lett., 5, 2885, 1995, is reacted with the amine **5**. The compounds are reacted together using the conditions described above for the preparation of **73**, (Scheme **2**) to afford the hydroxyamine **93**. This compound is then transformed, using the procedures described above for the preparation of **1**, (Scheme **2**) into the compound **94**, in which A is either link-$P(O)(OR^1)_2$ or precursor groups to link-$P(O)(OR^1)_2$ such as OH, SH, NH, as described herein.

Scheme **14** shows the conversion of the compounds **94** in which A is OH, SH, NH, to the compounds **1** in which A is link-$P(O)(OR^1)_2$.

Methods for these transformations are described below in Schemes **20-43** in which the preparations of the phosphonate-containing reactants are depicted.

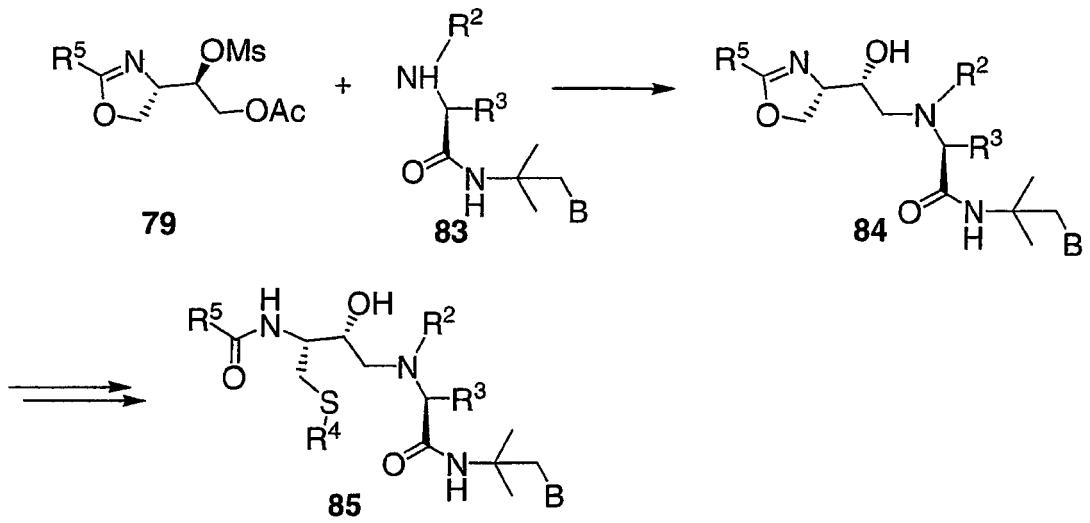
Preparation of the phosphonate intermediates 2, in which X is a direct bond.

The preparation of the compounds **2**, in which X is a direct bond, and the group link-$P(O)(OR^1)_2$ is attached to the phenyl ring, is illustrated in Schemes **14a** and **14b.**

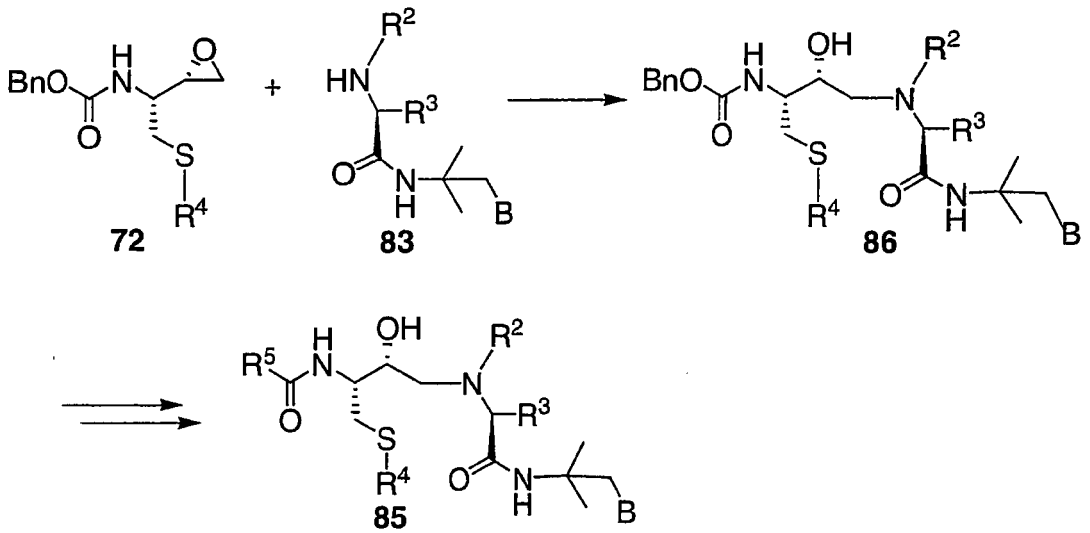
In the procedure shown in Scheme **14a**, the epoxide **14a-1**, prepared as described below (Scheme **45**) is reacted with an amine **5**, using the conditions described above for the preparation of the hydroxyamine **73** (Scheme **2**), to afford the hydroxyamine **14a-2**. The latter compound, after removal of the BOC protecting group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M. Wuts, Third Edition 1999, p. 520-522, is then converted, by reaction with the carboxylic acid R^5COOH, or an activated derivative thereof, into the amide **14a-3**. The conditions for this reaction are the same as those described above for the preparation of the amide **62**, (Scheme **1**).

The reactions shown in Scheme **14a** illustrate the preparation of the compounds **14a-3** in which A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto such as OH, SH, NH_2. Scheme **14b** illustrates the conversion of the compounds **14a-3**, in which A is OH, SH, NH_2, into the compounds **2** in which A is the group link-$P(O)(OR^1)_2$. The methods for this transformation are described below in Schemes **20-48**, in which the preparation of the phosphonate-containing reactants are described.

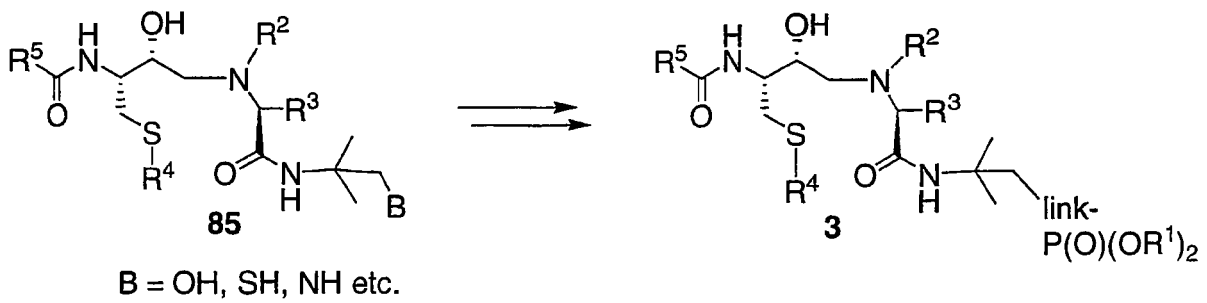
Scheme 7



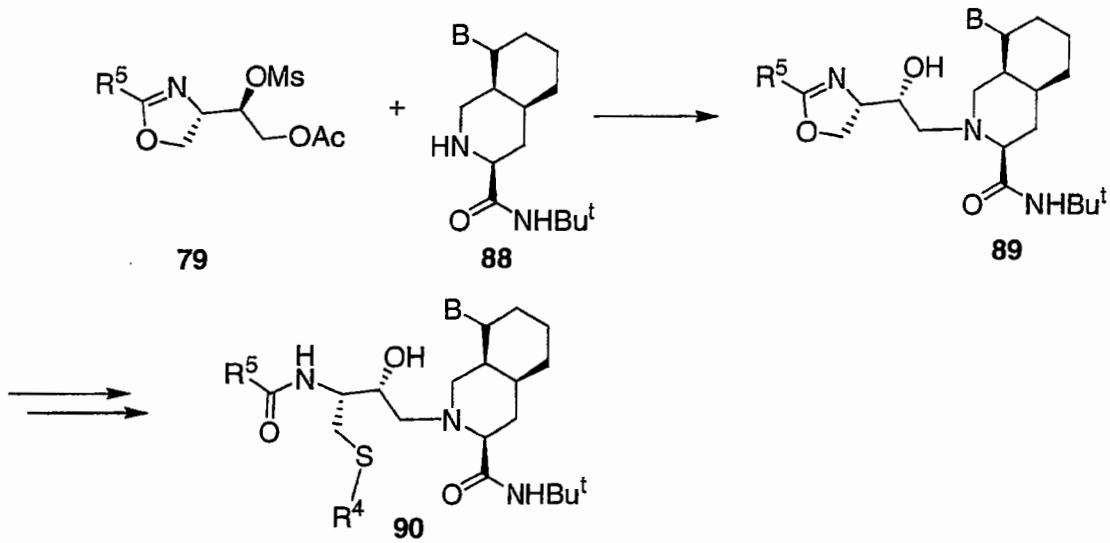
Scheme 8



Scheme 9

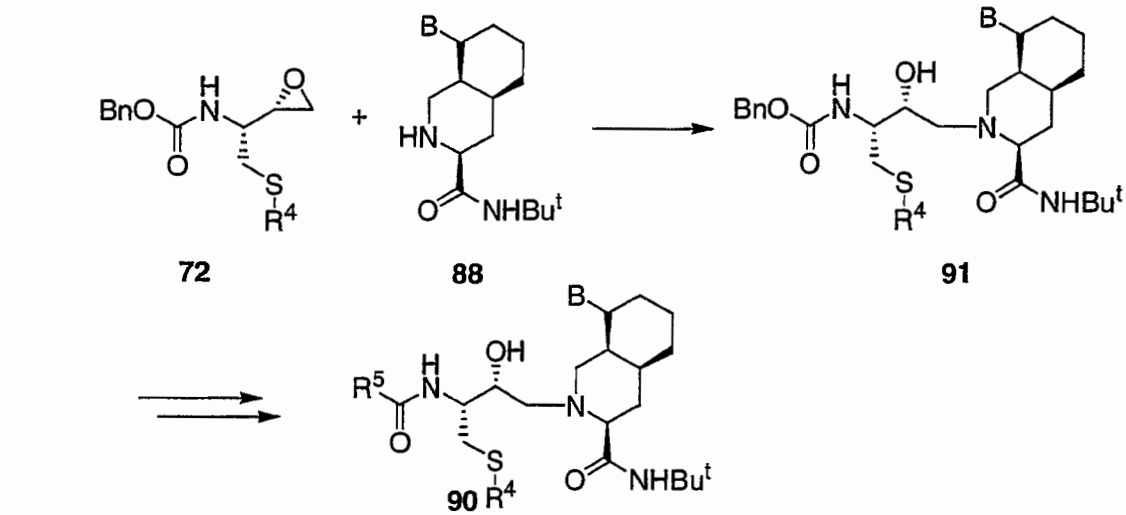


Scheme 10



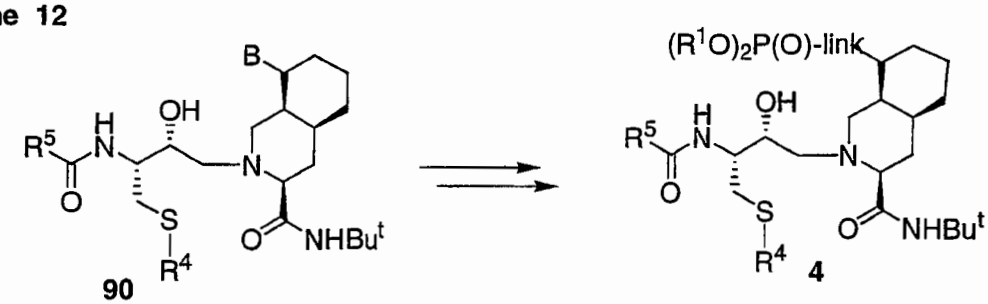
B = link-(P)$(OR^1)_2$ or B = OH, SH, NH etc

Scheme 11



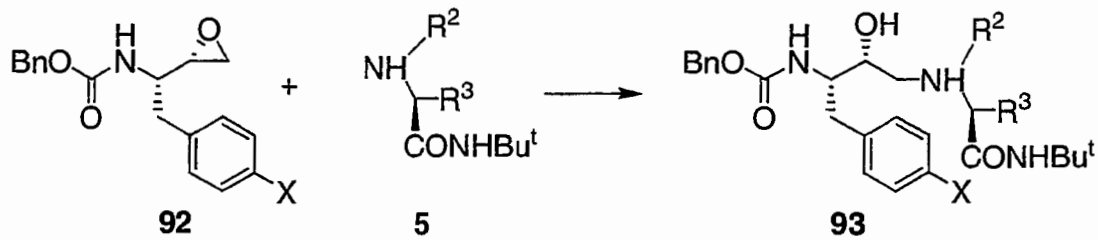
B = link-(P)$(OR^1)_2$ or B = OH, SH, NH etc

Scheme 12

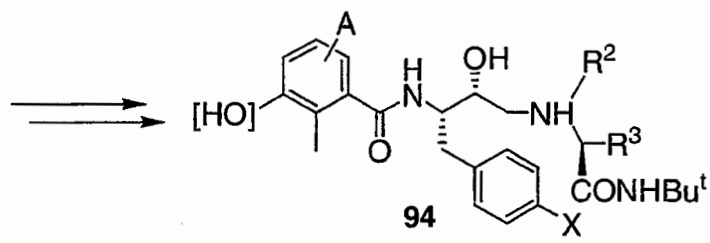


B = OH, SH, NH etc

Scheme 13

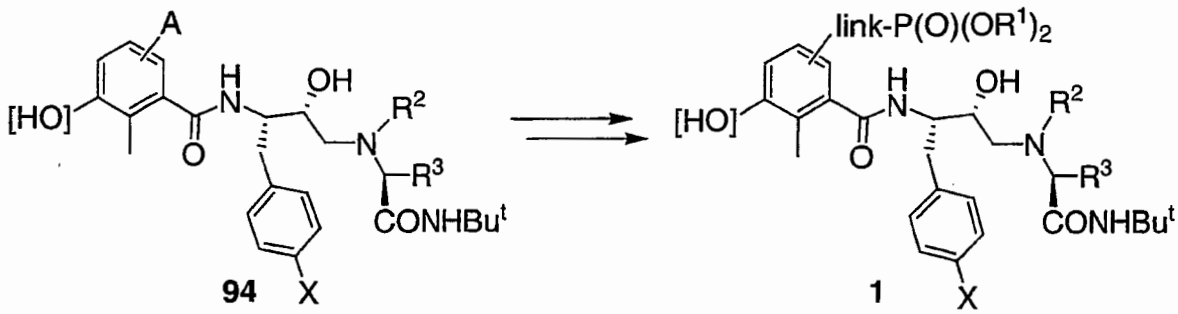


X = H, [OH]



A = link-(P)$(OR^1)_2$ or A = OH, SH, NH etc

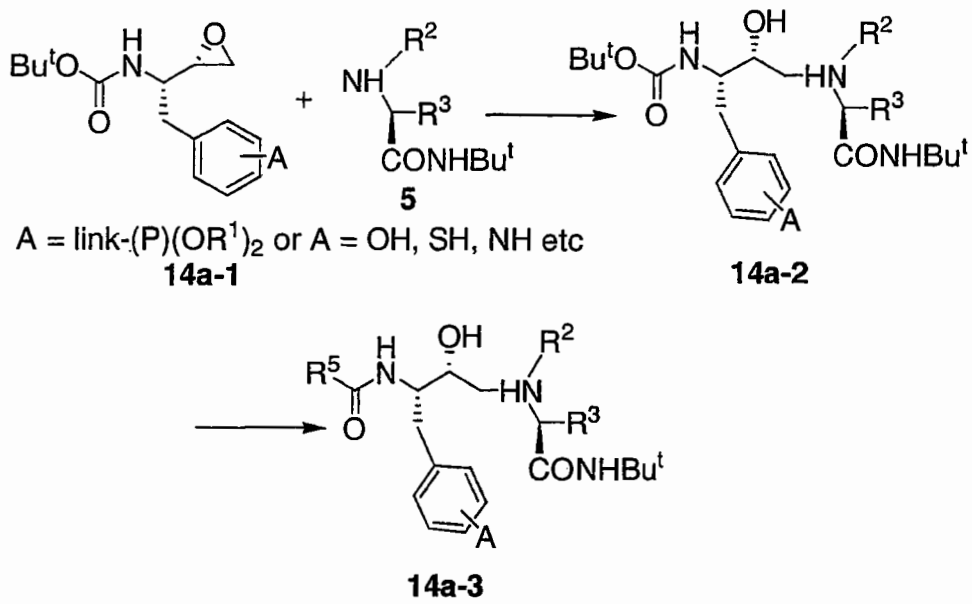
Scheme 14



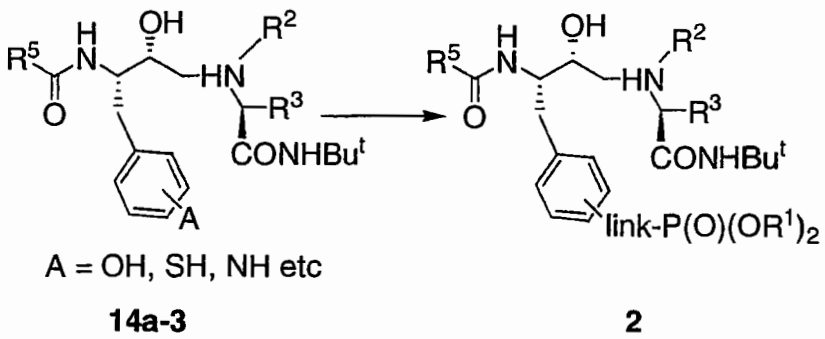
X = H, [OH]A = OH, SH, NH_2 etc

25 OCT 2006

Scheme 14a



Scheme 14b



Preparation of the phosphonate intermediates 3, in which X is a direct bond.

As shown in Scheme **15**, the oxirane **92**, in which X is H, is reacted with the amine **83**, in which the phosphonate or precursor group is attached to the tert. butyl group, to afford the product **95**. The conditions for this reaction are the same as described above for the preparation of **73** (Scheme **2**). This compound is then transformed, using the procedures described above for the preparation of **1**, (Scheme **2**) into the compound **96**, in which B is either link-$P(O)(OR^1)_2$ or precursor groups to link-$P(O)(OR^1)_2$ such as OH, SH, NH, as described herein.

Scheme **16** shows the conversion of the compounds **96** in which B is OH, SH, NH, to the compounds **3** in which B is link-$P(O)(OR^1)_2$.

Methods for these transformations are described below in Schemes **20-48** in which the preparations of the phosphonate-containing reactants are depicted.

Preparation of the phosphonate intermediates 4, in which X is a direct bond.

As shown in Scheme **17**, the oxirane **92** is reacted with the amine **88**, in which the phosphonate or precursor group is attached to the decahydroisoquinoline moiety, to afford the product **97**. The conditions for this reaction are the same as described above for the preparation of **73** (Scheme **2**). This compound is then transformed, using the procedures described above for the preparation of **1**, (Scheme **2**) into the compound **98**, in which B is either link-$P(O)(OR^1)_2$ or precursor groups to link-$P(O)(OR^1)_2$ such as OH, SH, NH, as described herein.

Scheme **18** shows the conversion of the compounds **98** in which B is OH, SH, NH, into the compounds **4** in which B is link-$P(O)(OR^1)_2$.

Methods for these transformations are described below in Schemes **20-48** in which the preparations of the phosphonate-containing reactants are depicted.

Schemes **13-18** illustrate the preparations of the compounds **1**, **3** and **4**, in which X is a direct bond, and in which the phenyl ring is either unsubstituted or incorporates a protected hydroxyl group at the 4-position.

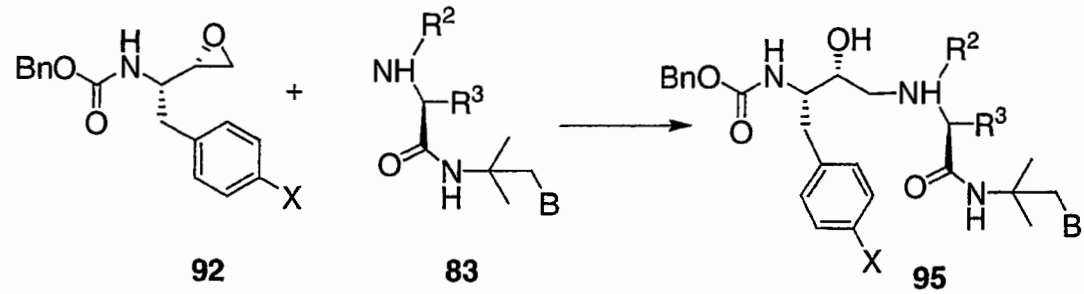
Scheme **19** depicts the synthesis of compounds **1**, **3** and **4**, in which X is a direct bond, and in which the phenyl ring incorporates different substituents, as described above (Chart **3**) in the 4-position.

In this procedure, [2-(4-hydroxy-phenyl)-1-oxiranyl-ethyl]-carbamic acid tert-butyl ester **99**, the preparation of which is described in U.S. Patent 5,492,910, is reacted with an appropriate alkylating agent, such as, for example, ethyl iodide, benzyl chloride, bromoethyl morpholine or bromoacetyl morpholine. The reaction is conducted in an aprotic solvent, such as, for example, dichloromethane or dimethylformamide, in the presence of an organic or inorganic base.

Preferably the hydroxy compound **99** is reacted with an equimolar amount of the alkylating agent in dichloromethane, in the presence of diisopropylethylamine, at ambient temperature, so as to afford the ether products **100**. The compounds **100** are then transformed, using the

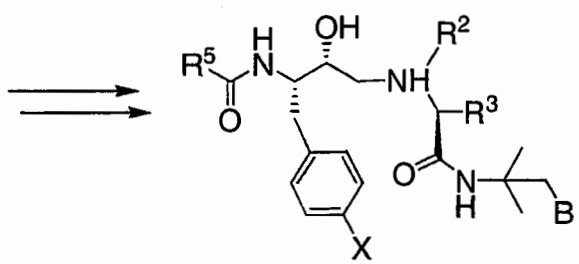
conditions described above for the reactions depicted in Schemes **13-18**, into the products **1**, **3** and **4**, in which X is a direct bond, and in which R is as defined in Scheme **19**.

Scheme 15



92 **83** **95**

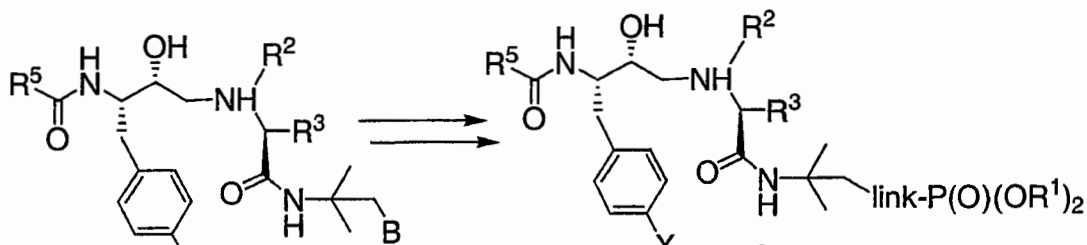
X = H, [OH]



96

B = link-(P)(OR^1)$_2$ or B = OH, SH, NH etc

Scheme 16

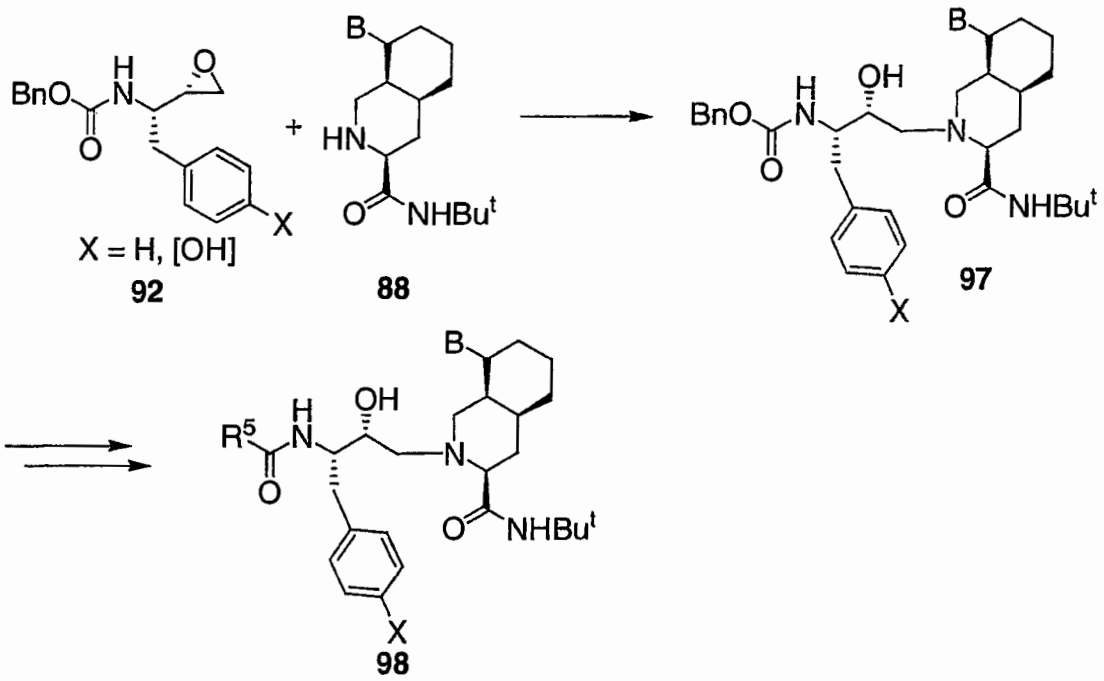


96 **3**

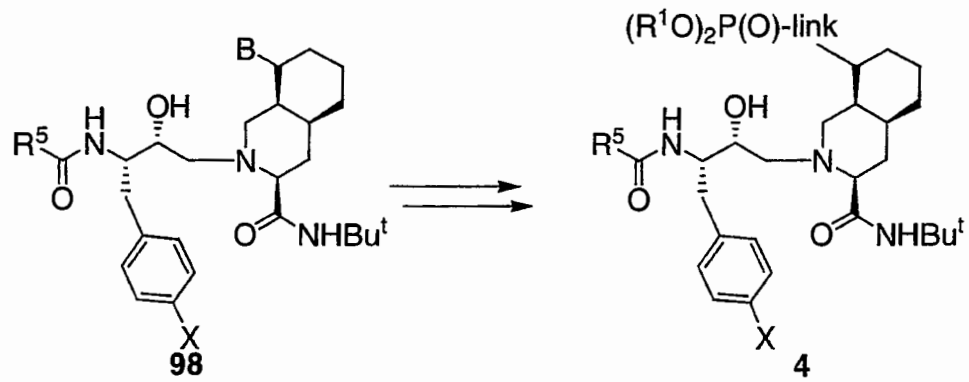
X =H, [OH]B = OH, SH, NH etc

5

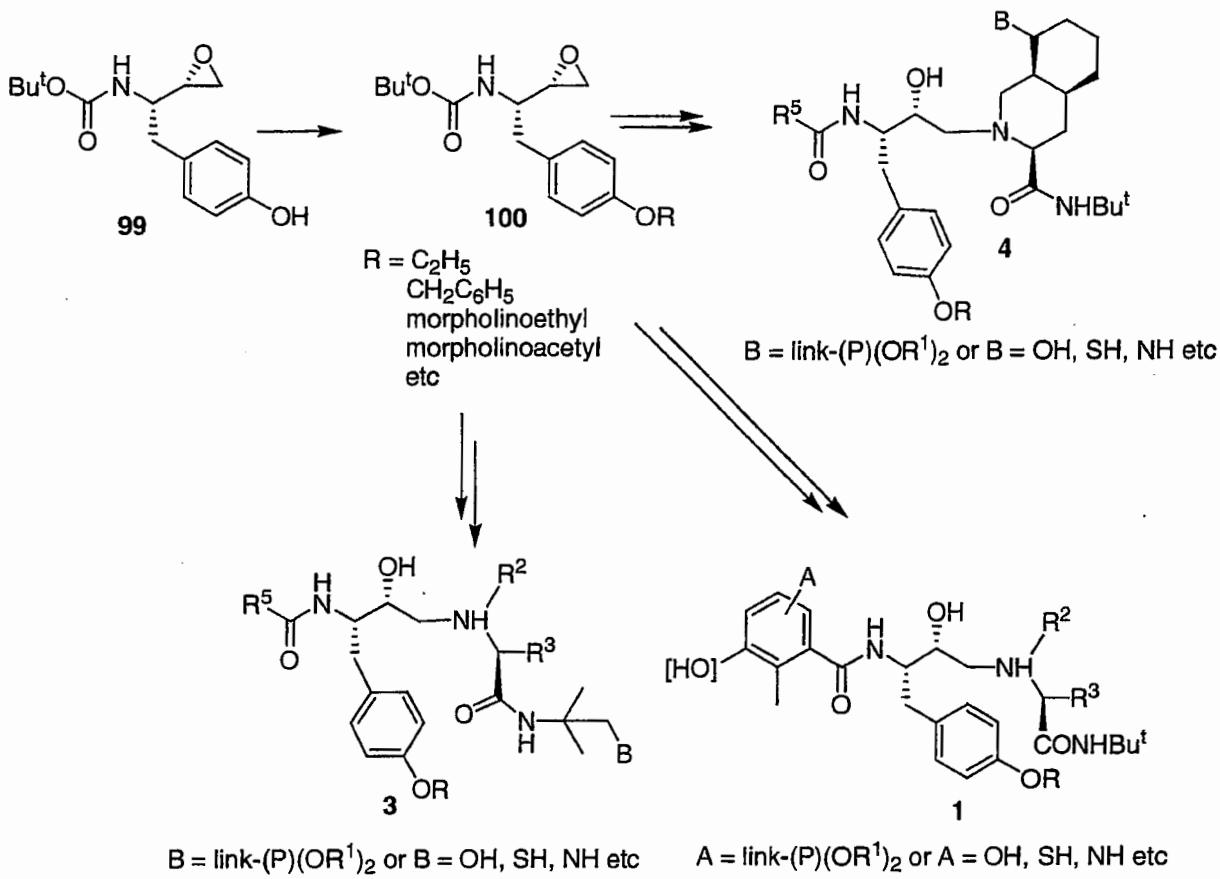
Scheme 17



Scheme 18



Scheme 19



Nel10b.cdx Schemes 19a, 19b

Preparation of thiophenol derivatives R^4SH incorporating phosphonate substituents

Various methods for the preparation of thiols are described in The Chemistry of the Thiol Group, S. Patai, Ed., Wiley, 1974, Vol. 14, Part 3, p 42.

Protection/deprotection of SH groups.

The preparations of thiophenols incorporating phosphonate moieties are shown in Schemes **20 -30**. In order to avoid unwanted reactions, it may be necessary to protect the SH group, and to deprotect it after the transformations shown. Protected SH groups are shown in the Schemes as [SH]. The protection and deprotection of SH groups is described in a number of publications. For example, in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 277-308, are described the introduction and removal of a

number of SH protecting groups. The selection of a SH protecting group for a given series of reactions requires that it be stable to the reaction conditions employed, and that the protecting group can be removed at the end of the reaction sequence without the occurrence of undesired reactions. In the following descriptions, appropriate protection and deprotection methods are indicated.

Scheme **20** illustrates the preparation of thiophenols in which a phosphonate moiety is attached directly to the aromatic ring.

In this procedure, a halo-substituted thiophenol is subjected to a suitable protection procedure. The protected compound **101** is then coupled, under the influence of a transition metal catalyst, with a dialkyl phosphite **102**, to afford the product **103**. The product is then deprotected to afford the free thiophenol **104.**

Suitable protecting groups for this procedure include alkyl groups such as triphenylmethyl and the like. Palladium (0) catalysts are employed, and the reaction is conducted in an inert solvent such as benzene, toluene and the like, as described in J. Med. Chem., 35, 1371, 1992.

Preferably, the 3-bromothiophenol **105** is protected by conversion to the 9-fluorenylmethyl derivative, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 284, and the product **106** is reacted in toluene with a dialkyl phosphite in the presence of tetrakis(triphenylphosphine)palladium (0) and triethylamine, to yield the product **108**. Deprotection, for example by treatment with aqueous ammonia in the presence of an organic co-solvent, as described in J. Chem. Soc. Chem. Comm. 1501, 1986, then gives the thiol **109**.

Using the above procedures, but employing, in place of the bromo compound **105**, different bromo compounds **101**, there are obtained the corresponding thiols **104**.

Scheme **21** illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol **101** is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative **110**. The latter compound is reacted with a halodialkyl phosphate **111** to afford the product **103**.

Preferably, the 4-bromothiophenol **112** is converted into the S-triphenylmethyl (trityl) derivative **113**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and

P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **114** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorodiethyl phosphite **115** to afford the phosphonate **116**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **117**.
Using the above procedures, but employing, in place of the halo compound **112**, different halo compounds **101**, there are obtained the corresponding thiols **104**.

Scheme **22** illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link.
In this procedure, a suitably protected methyl-substituted thiophenol is subjected to free-radical bromination to afford a bromomethyl product **118**. This compound is reacted with a sodium dialkyl phosphite **119** or a trialkyl phosphite, to give the displacement or rearrangement product **120**, which upon deprotection affords the thiophenols **121**.
Preferably, 2-methylthiophenol **123** is protected by conversion to the benzoyl derivative **124**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **125.** This material is reacted with a sodium dialkyl phosphite **119**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **126**. Alternatively, the bromomethyl compound **125** can be converted into the phosphonate **126** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **125** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100^0 to produce the phosphonate **126**. Deprotection of **126**, for example by treatment with aqueous ammonia, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiol **127**.
Using the above procedures, but employing, in place of the bromomethyl compound **125**, different bromomethyl compounds **118**, there are obtained the corresponding thiols **121**.

Scheme **23** illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **128** is reacted with a dialkyl hydroxyalkylphosphonate **129** under the conditions of the Mitsonobu reaction, for example as described in Org. React., 1992, 42,

335, to afford the coupled product **130**. Deprotection then yields the O- or S-linked products **131**.

Preferably, the substrate, for example 3-hydroxythiophenol, **132**, is converted into the monotrityl ether **133**, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **134** in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound **135**. Removal of the trityl protecting group, as described above, then affords the thiophenol **136**.

Using the above procedures, but employing, in place of the phenol **132**, different phenols or thiophenols **128**, there are obtained the corresponding thiols **131**.

Scheme **24** illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **137** is reacted with an activated ester, for example the trifluoromethanesulfonate, of a dialkyl hydroxyalkyl phosphonate **138**, to afford the coupled product **139**. Deprotection then affords the thiol **140**.

For example, the substrate, 4-methylaminothiophenol **141**, is reacted with one equivalent of acetyl chloride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the product **142**. This material is then reacted with, for example, diethyl trifluoromethanesulfonylmethyl phosphonate **143**, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product **144**.

Preferably, equimolar amounts of the phosphonate **143** and the amine **142** are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product **144**. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiophenol **145**.

Using the above procedures, but employing, in place of the thioamine **142**, different phenols, thiophenols or amines **137**, and/or different phosphonates **138**, there are obtained the corresponding products **140**.

Scheme **25** illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate **146**.

In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol **137** is reacted with a dialkyl bromoalkyl phosphonate **146** to afford the product **147**. Deprotection then affords the free thiophenol **148**.

For example, 3-hydroxythiophenol **149** is converted into the S-trityl compound **150**, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate **151**, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°, to yield the ether product **152**. Deprotection, as described above, then affords the thiol **153**.

Using the above procedures, but employing, in place of the phenol **149**, different phenols, thiophenols or amines **137**, and/or different phosphonates **146**, there are obtained the corresponding products **148**.

Scheme **26** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **155** is coupled with an aromatic bromo compound **154**. In this procedure, a suitably protected bromo-substituted thiophenol **154** is reacted with a terminally unsaturated phosphonate **155**, to afford the coupled product **156**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **157**, or the saturated analog **159**.

For example, 3-bromothiophenol is converted into the S-Fm derivative **160**, as described above, and this compound is reacted with diethyl 1-butenyl phosphonate **161**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for

example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product **162**. Deprotection, as described above, then affords the thiol **163**. Optionally, the initially formed unsaturated phosphonate **162** can be subjected to catalytic hydrogenation, using, for example, palladium on carbon as catalyst, to yield the saturated product **164**, which upon deprotection affords the thiol **165**.

Using the above procedures, but employing, in place of the bromo compound **160**, different bromo compounds **154**, and/or different phosphonates **155**, there are obtained the corresponding products **157** and **159**.

Scheme **28** illustrates the preparation of an aryl-linked phosphonate ester **169** by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57.

The sulfur-substituted phenylboronic acid **166** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product **168** which is deprotected to yield the thiol **169**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **170**. This material is reacted with diethyl 4-bromophenylphosphonate **171**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **172**. Deprotection, for example by the use of tetrabutyl ammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **173**.

Using the above procedures, but employing, in place of the boronate **170**, different boronates **166**, and/or different phosphonates **167**, there are obtained the corresponding products **169**.

Scheme **29** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring.

In this procedure, a suitably protected O, S or N-substituted thiophenol **137** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **174**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **175** is then deprotected to afford the thiol **176**. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **177** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **177** is then reacted with, for example diethyl 4-(bromomethyl)phenylphosphonate, **178**, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The thioether product **179** thus obtained is deprotected, as described above, to afford the thiol **180**.

Using the above procedures, but employing, in place of the thiophenol **177**, different phenols, thiophenols or amines **137**, and/or different phosphonates **174**, there are obtained the corresponding products **176**.

Scheme **30** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

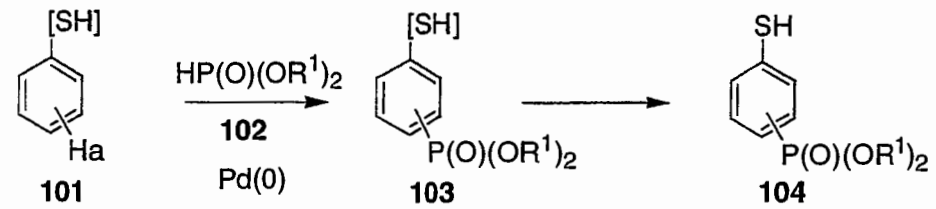
In this procedure, a suitably protected thiophenol **181**, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **138**, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **182**. Deprotection, as described above, then affords the thiol **183**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in

J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al., eds., Pergamon, 1995, Vol. 2, p. 707. For example, 2,3-dihydro-1H-indole-5-thiol, **184**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **185**, as described above, and the ester is then reacted with the triflate **143**, using the conditions described above for the preparation of **144**, (Scheme **24**), to yield the phosphonate **186**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **187**.

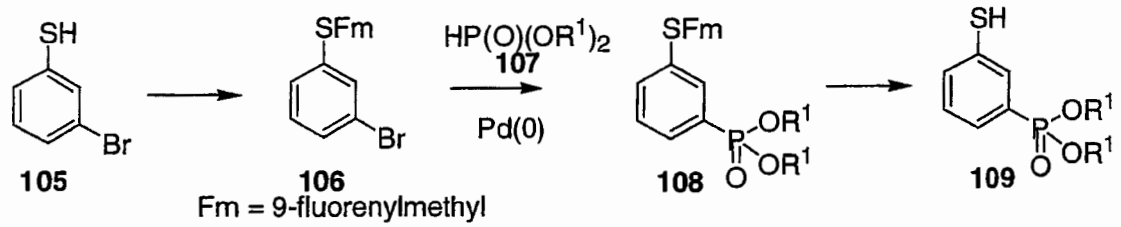
Using the above procedures, but employing, in place of the thiol **184**, different thiols **181**, and/or different triflates **138**, there are obtained the corresponding products **183**.

Scheme 20

Method



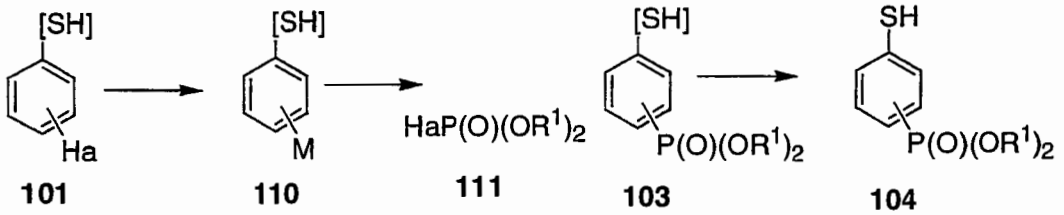
Example



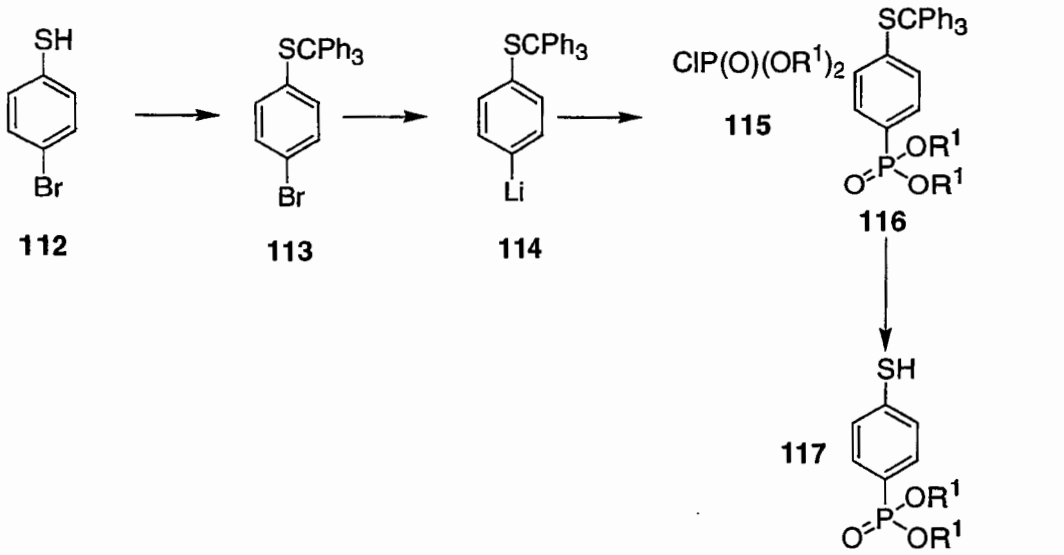
Fm = 9-fluorenylmethyl

Scheme 21

Method

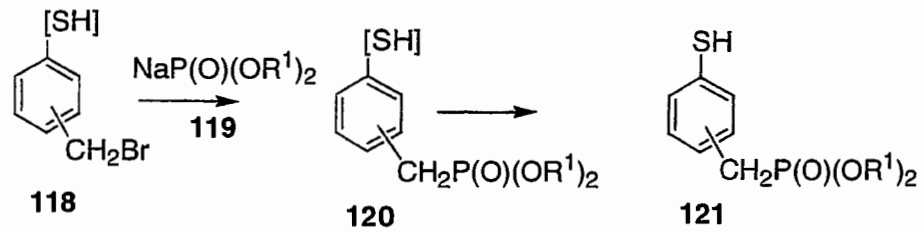


Example

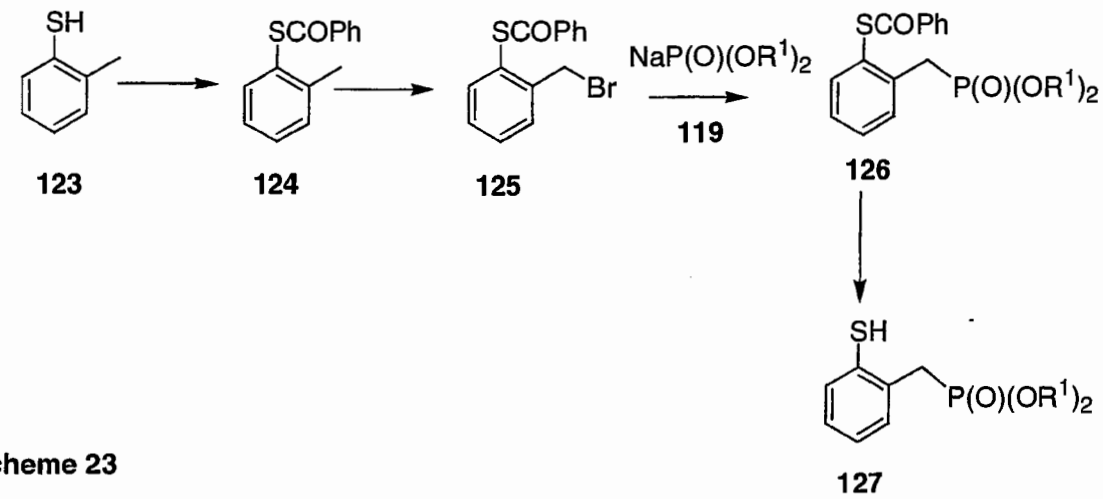


Scheme 22

Method

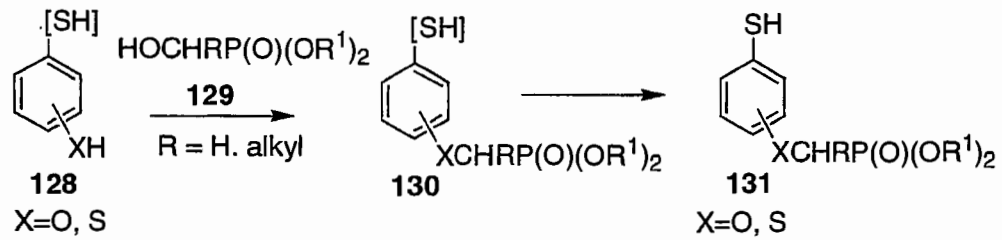


Example

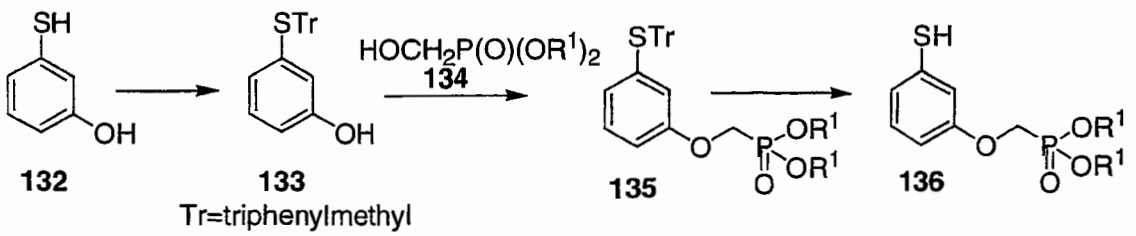


Scheme 23

Method

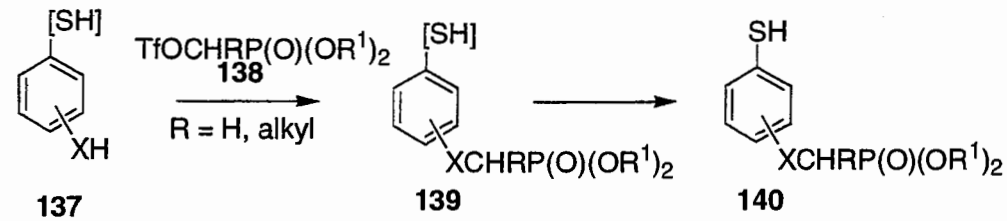


Example



Scheme 24

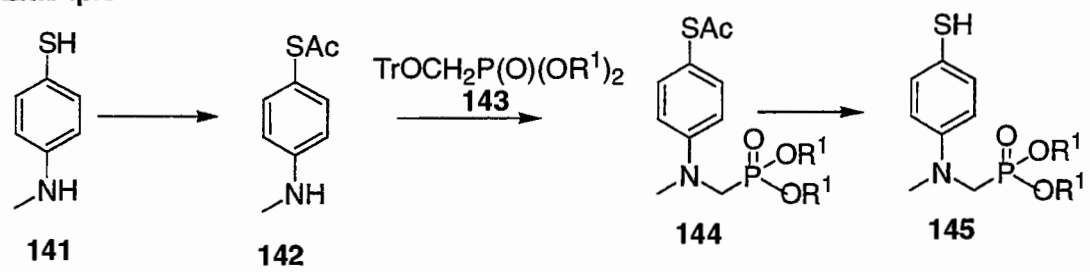
Method



137 **139** **140**

X=O,S, NH, Nalkyl

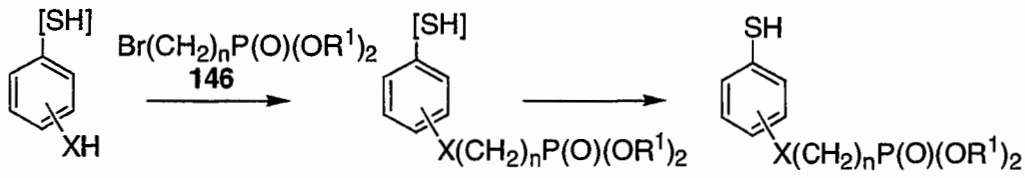
Example



141 **142** **144** **145**

Scheme 25

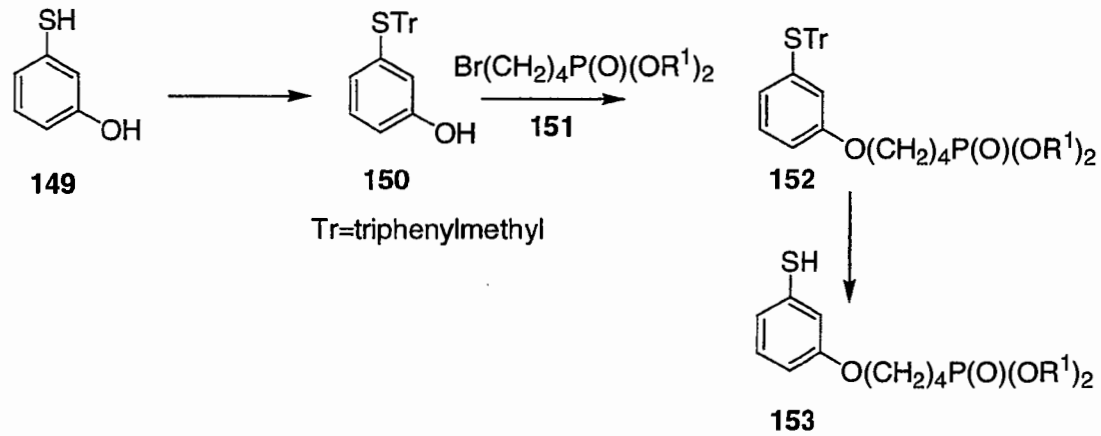
Method



137 **147** **148**

X=O,S,NH, Nalkyl

Example

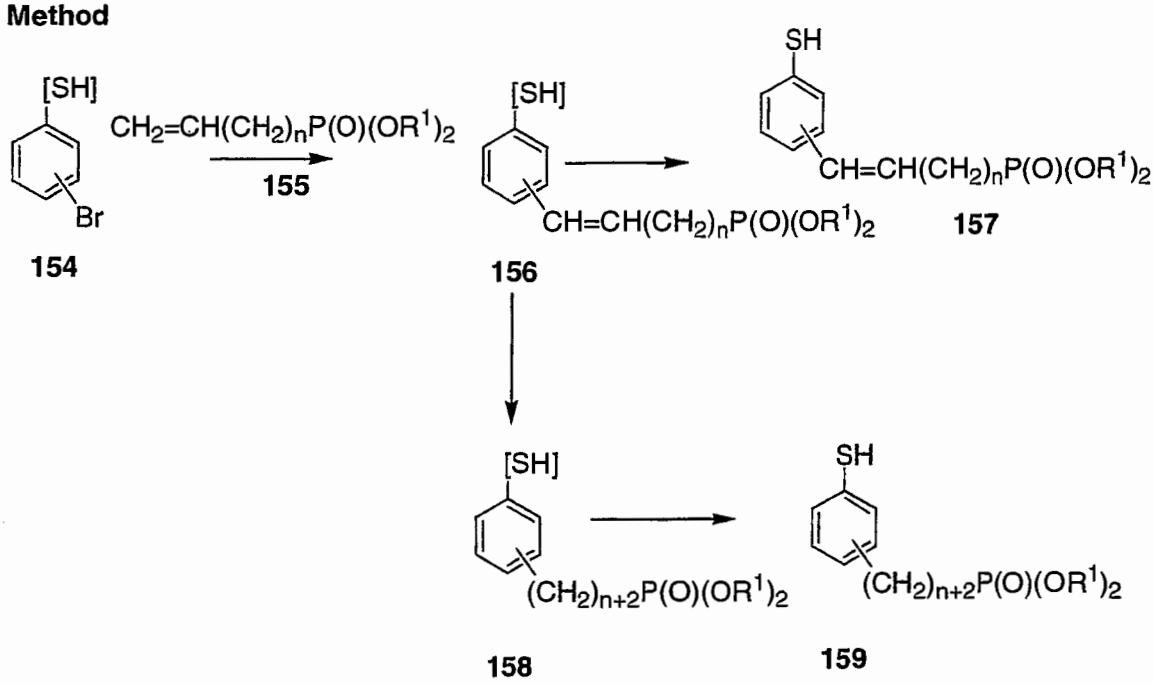


149 **150** **152** **153**

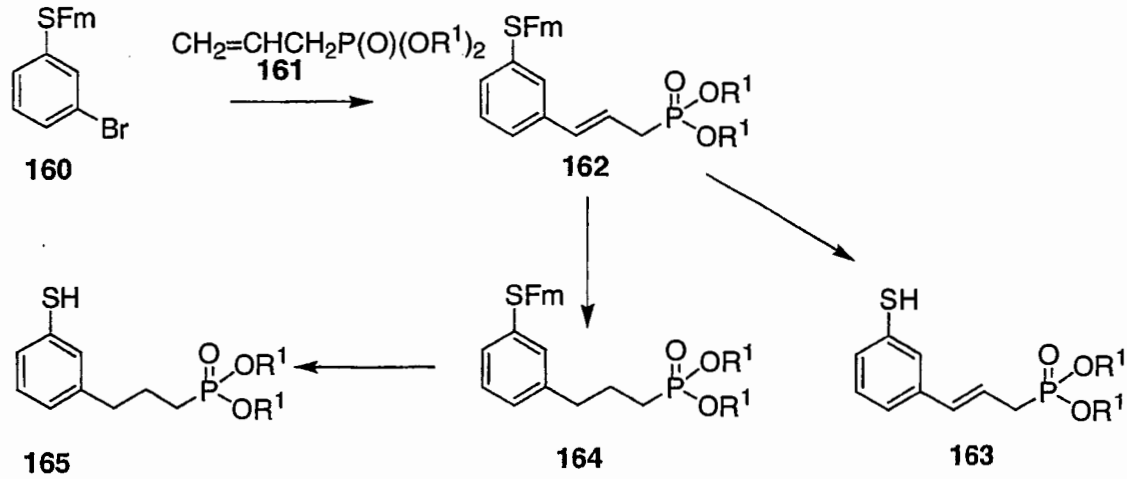
Tr=triphenylmethyl

Scheme 26

Method

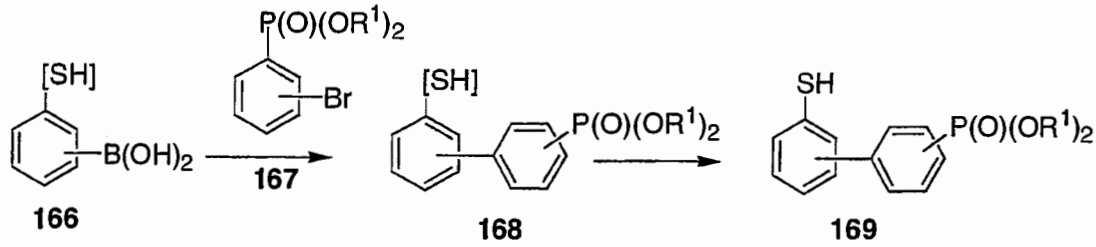


Example

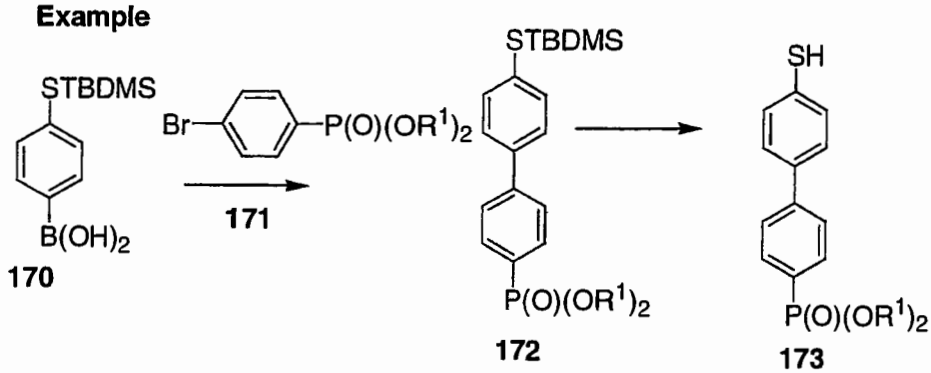


Scheme 28

Method

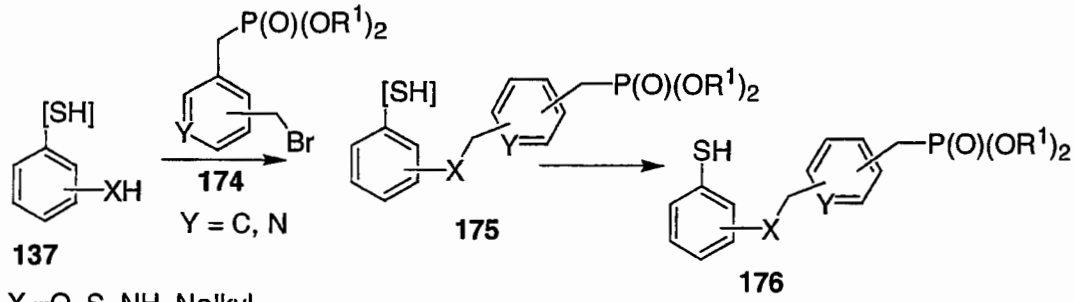


Example

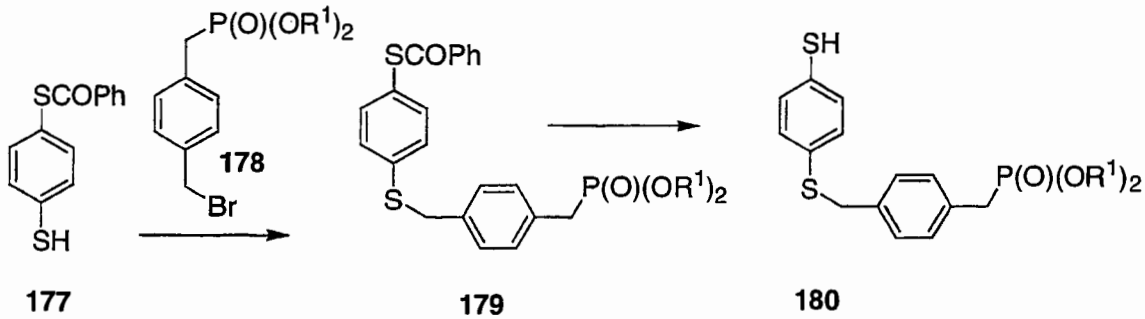


Scheme 29

Method

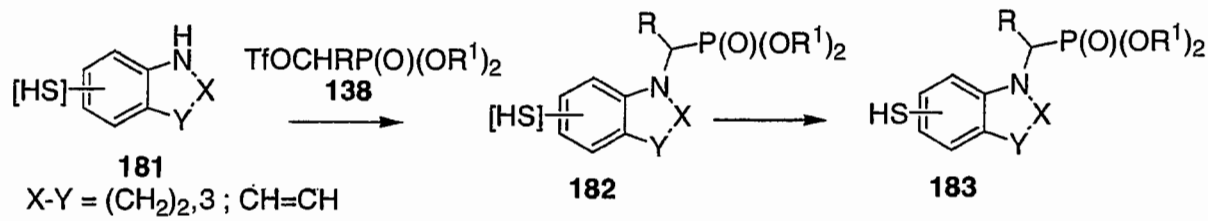


Example

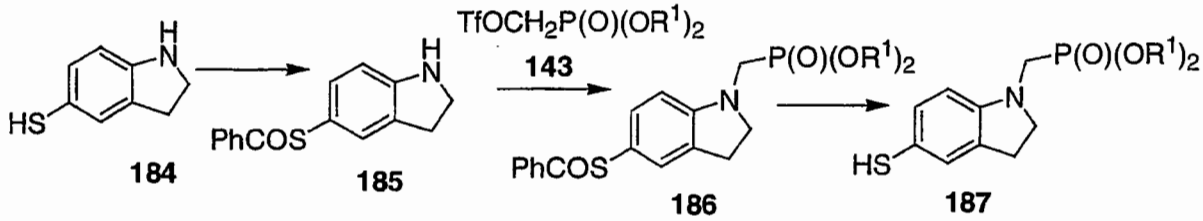


Scheme 30

Method



Example



Preparation of benzoic acid derivatives incorporating phosphonate moieties.

Scheme **31** illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid **188** is subjected to halogen-methyl exchange to afford the organometallic intermediate **189**. This compound is reacted with a chlorodialkyl phosphite **115** to yield the phenylphosphonate ester **190**, which upon deprotection affords the carboxylic acid **191**.

For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, **192**, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Amer. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane **193**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester **194**. This compound is treated with boron trifluoride at 0° to effect rearrangement to the orthoester **195**, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether **196**. Halogen-metal exchange is performed by the reaction of **196** with butyllithium, and the lithiated intermediate is then coupled with a

chlorodialkyl phosphite **115**, to produce the phosphonate **197**. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid **198**.

Using the above procedures, but employing, in place of the bromo compound **192**, different bromo compounds **188**, there are obtained the corresponding products **191**.

Scheme **32** illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

In this method, a suitably protected dimethyl hydroxybenzoic acid, **199**, is reacted with a brominating agent, so as to effect benzylic bromination. The product **200** is reacted with a sodium dialkyl phosphite, **119**, to effect displacement of the benzylic bromide to afford the phosphonate **201**.

For example, 2,5-dimethyl-3-hydroxybenzoic acid, **203**, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p. 17, to afford the ether ester **204**. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or diisopropylethylamine. The product **204** is then reacted with a brominating agent, for example N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product **205**. This compound is then reacted with a sodium dialkyl phosphite **119**, using the conditions described above for the preparation of **120**, (Scheme **22**) to afford the phosphonate **206**. Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields the carboxylic acid **207**.

Using the above procedures, but employing, in place of the methyl compound **203**, different methyl compounds **199**, there are obtained the corresponding products **202**.

Scheme **33** illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom.

In this method, a suitably protected hydroxy- or mercapto-substituted hydroxymethyl benzoic acid **208** is reacted, under the conditions of the Mitsonobu reaction, with a dialkyl

hydroxymethyl phosphonate **134**, to afford the coupled product **209**, which upon deprotection affords the carboxylic acid **210**.

For example, 3,6-dihydroxy-2-methylbenzoic acid, **211**, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester **212**, by treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, using the conditions described above for the preparation of **170**, to afford the mono-silyl ether **213**. This compound is then reacted with a dialkyl hydroxymethylphosphonate **134**, under the conditions of the Mitsonobu reaction, as described above for the preparation of **130**, (Scheme **23**) to afford the coupled product **214**. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic carboxylic acid **215**.

Using the above procedures, but employing, in place of the phenol **211**, different phenols or thiophenols **208**, there are obtained the corresponding products **210**.

Scheme **34** depicts the preparation of phosphonate esters attached to the hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains.

In this method, a dialkyl alkenylphosphonate **216** is coupled, by means of a palladium catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid **217**. The product **218** can be deprotected to afford the phosphonate **219**, or subjected to catalytic hydrogenation to afford the saturated compound, which upon deprotection affords the corresponding carboxylic acid **220**.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid **221,** prepared as described in WO 9218490, is converted as described above, into the silyl ether OBO ester **222**. This compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate **223**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above for the preparation of **156**, (Scheme **26**) to afford the product **224**. Deprotection, or hydrogenation/deprotection, of this compound, as described above, then affords respectively the unsaturated and saturated products **225** and **227**.

Using the above procedures, but employing, in place of the bromo compound **221**, different bromo compounds **217**, and/or different phosphonates **216**, there are obtained the corresponding products **219** and **220**.

Scheme **35** illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

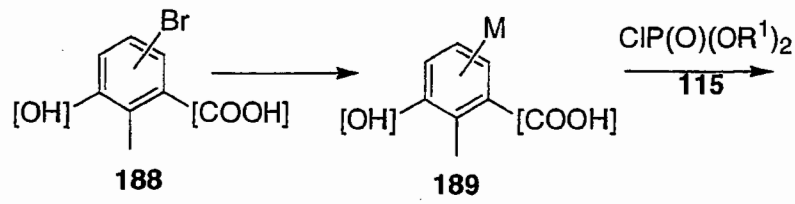
In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid **217** is converted to the corresponding boronic acid, as described above, (Scheme **28**). The product is subjected to a Suzuki coupling reaction, as described above, with a dialkyl bromophenyl phosphonate **229**. The product **230** is then deprotected to afford the diaryl phosphonate product **231**.

For example, the silylated OBO ester **232**, prepared as described above, (Scheme **31**), is converted into the boronic acid **233**, as described above. This material is coupled with a dialkyl 4-bromophenyl phosphonate **234**, prepared as described in J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, as described above for the preparation of **172**, (Scheme **28**) to afford the diaryl phosphonate **235**. Deprotection, as described above, then affords the benzoic acid **236**.

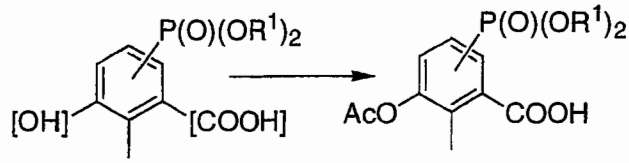
Using the above procedures, but employing, in place of the bromo compound **232**, different bromo compounds **217**, and/or different phosphonates **229**, there are obtained the corresponding carboxylic acid products **231**.

Scheme 31

Method

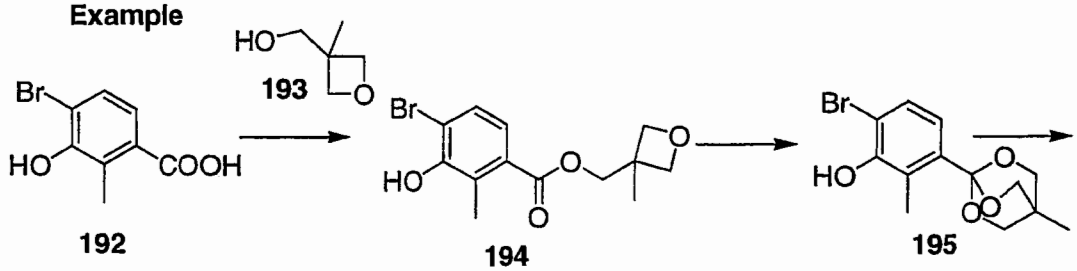


188 189

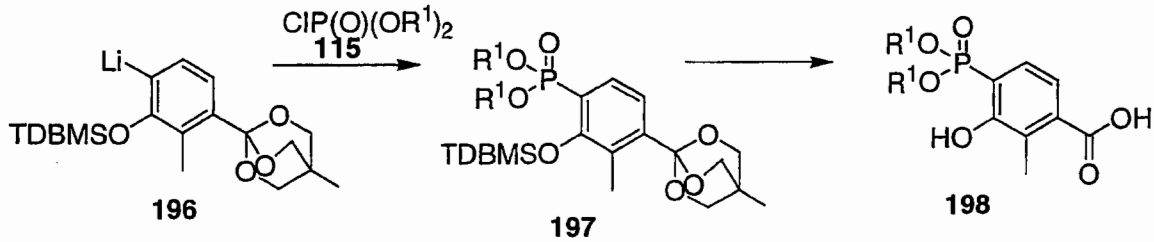


190 191

Example



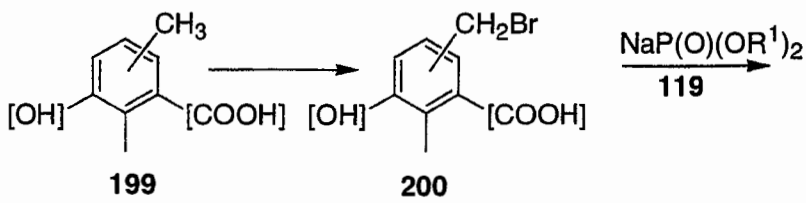
192 194 195



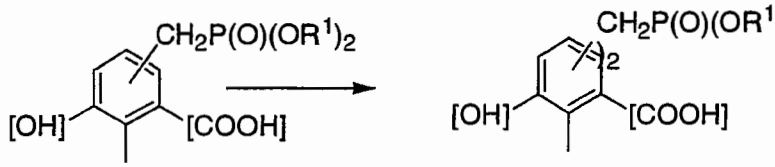
196 197 198

Scheme 32

Method

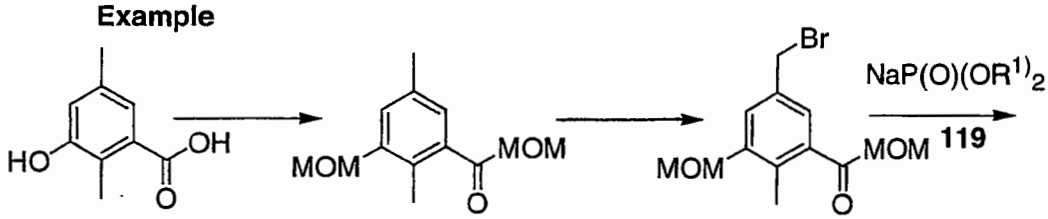


199 **200**

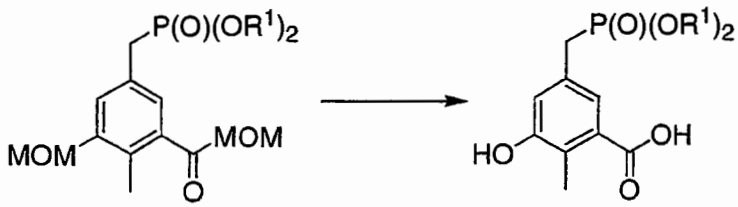


201 **202**

Example



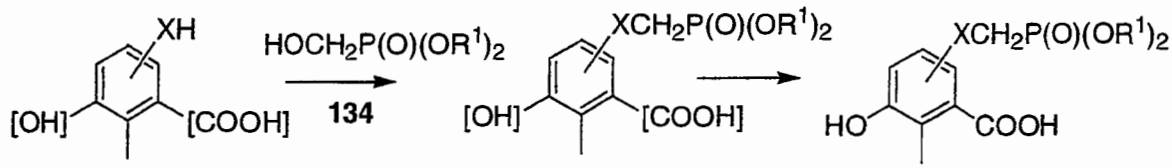
203 **204** MOM = CH_3OCH_2O **205**



206 **207**

Scheme 33

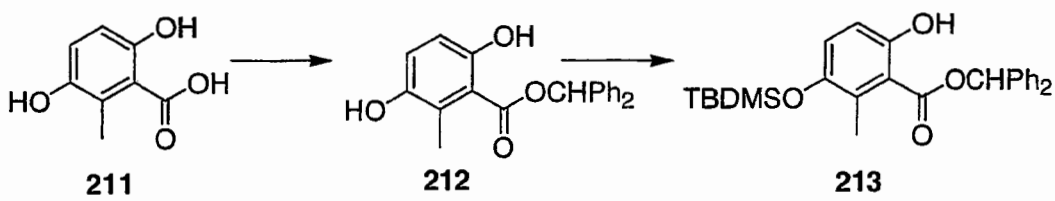
Method



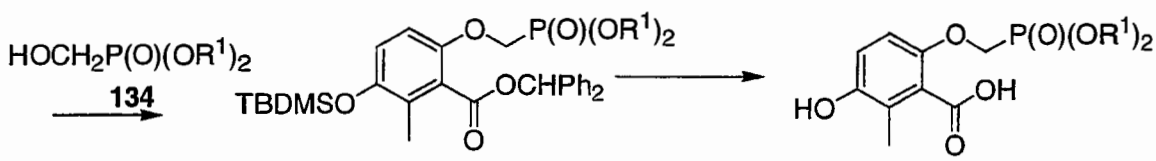
208 **209** **210**

X = O, S

Example

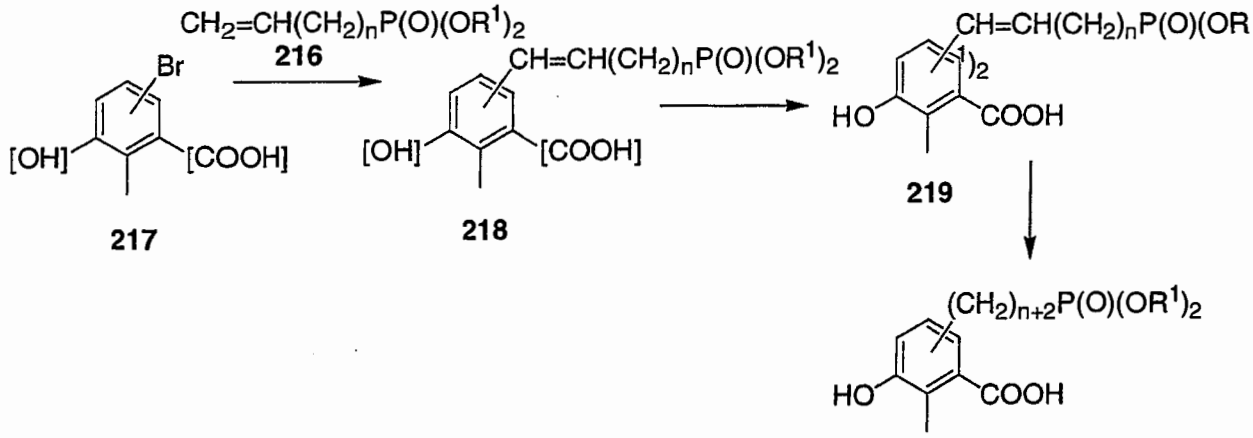


211 **212** **213**

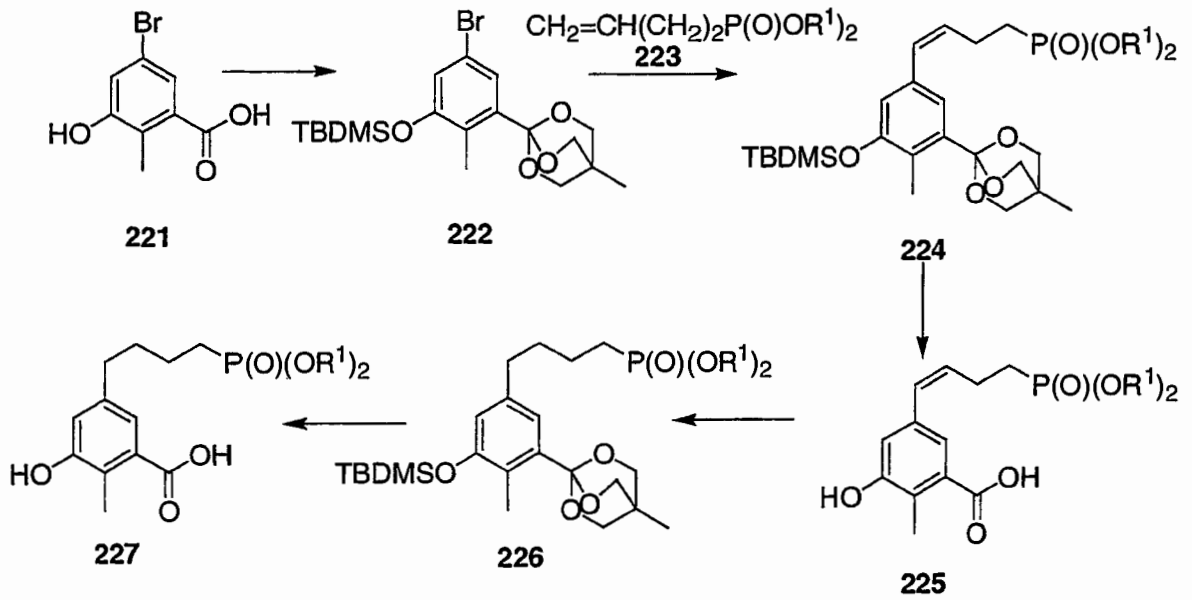


214 **215**

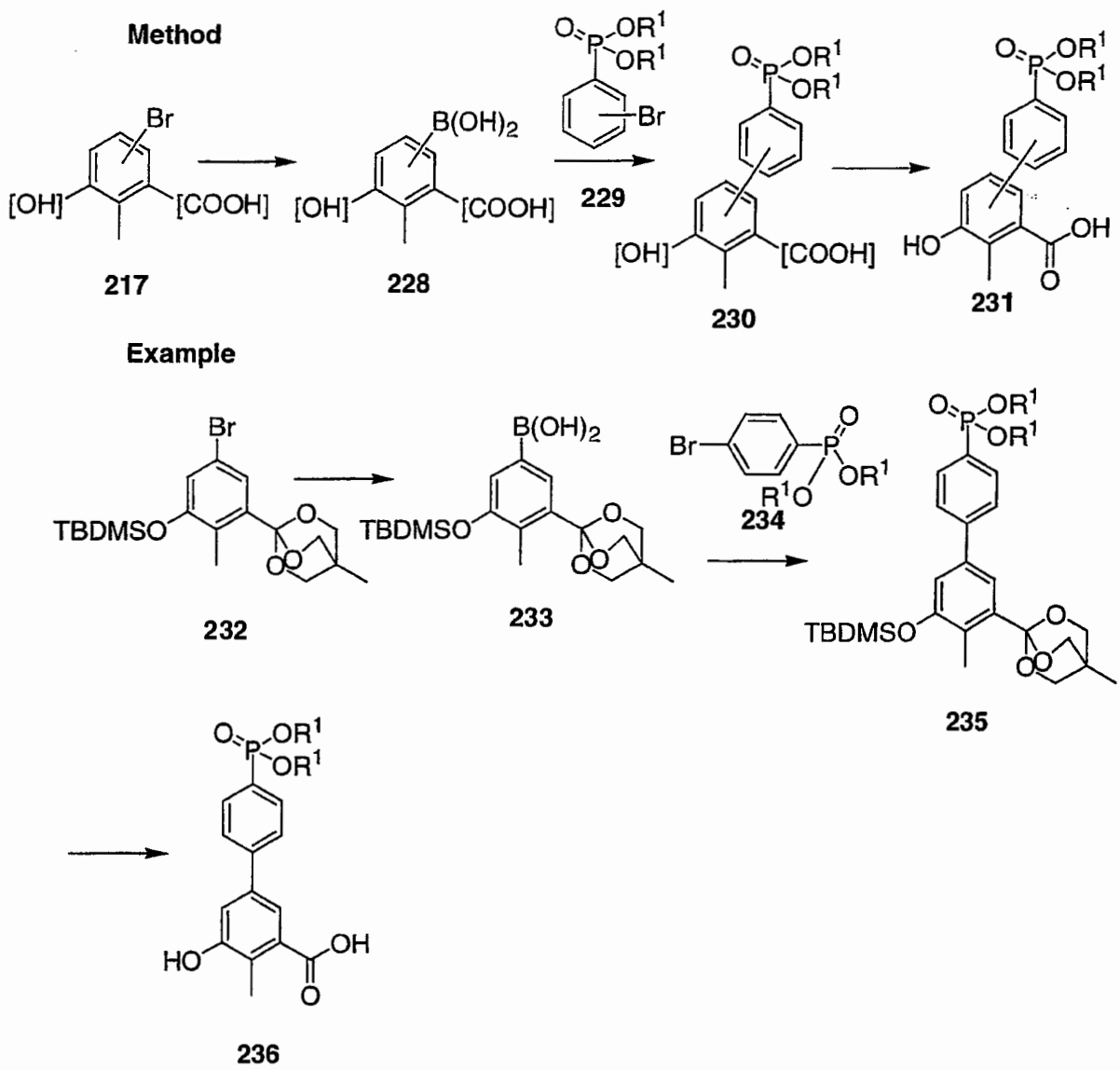
Scheme 34
Method



Example



Scheme 35



Preparation of tert-butylamine derivatives incorporating phosphonate moieties.

Scheme **36** describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2.2-dimethyl-2-aminoethylbromide **237** is reacted with a trialkyl phosphite, under the conditions of the Arbuzov reaction, as described above, to afford the phosphonate **238**.

For example, the cbz derivative of 2.2-dimethyl-2-aminoethylbromide **240**, is heated with a trialkyl phosphite at ca 150° to afford the product **241**. Deprotection, as previously described, then affords the free amine **242**.

Using the above procedures, but employing different trisubstituted phosphites, there are obtained the corresponding amines **239**.

Scheme **37** illustrates the preparation of phosphonate esters attached to the tert butylamine by means of a heteroatom and a carbon chain.

An optionally protected alcohol or thiol **243** is reacted with a bromoalkylphosphonate **146,** to afford the displacement product **244**. Deprotection, if needed, then yields the amine **245**.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol **246** is reacted with a dialkyl 4-bromobutyl phosphonate **247**, prepared as described in Synthesis, 1994, 9, 909, in dimethylformamide containing potassium carbonate and potassium iodide, at ca 60° to afford the phosphonate **248**. Deprotection then affords the free amine **249**.

Using the above procedures, but employing different alcohols or thiols **243**, and/or different bromoalkylphosphonates **146**, there are obtained the corresponding products **245**.

Scheme **38** describes the preparation of carbon-linked phosphonate tert butylamine derivatives, in which the carbon chain can be unsaturated or saturated.

In the procedure, a terminal acetylenic derivative of tert-butylamine **250** is reacted, under basic conditions, with a dialkyl chlorophosphite **115**, as described above in the preparation of **104**, (Scheme **21**). The coupled product **251** is deprotected to afford the amine **252.** Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products **253** and **254** respectively.

For example, 2-amino-2-methylprop-1-yne **255**, the preparation of which is described in WO 9320804, is converted into the N-phthalimido derivative **256**, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide in tetrahydrofuran at -78°. The resultant anion is then reacted with a dialkyl chlorophosphite **115** to afford the phosphonate **257**. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine **258**. Partial catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for

Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p. 566, produces the olefinic phosphonate **259**, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate **260**.

Using the above procedures, but employing different acetylenic amines **250**, there are obtained the corresponding products **252**, **253** and **254**.

Scheme **39** illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.

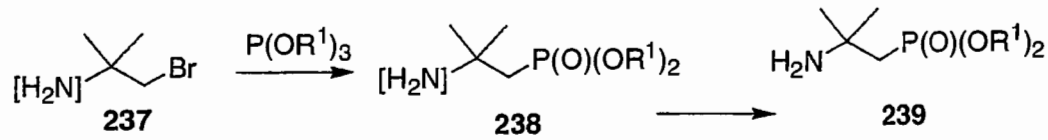
In this method, an aminoethyl-substituted cyclic amine **261** is reacted with a limited amount of a bromoalkyl phosphonate **146**, using, for example, the conditions described above for the preparation of **147**, (Scheme **25**) to afford the displacement product **262**.

For example, 3-(1-amino-1-methyl)ethylpyrrolidine **263**, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with a dialkyl 4-bromobutyl phosphonate **151**, prepared as described in Synthesis, 1994, 9, 909, to afford the displacement product **264**.

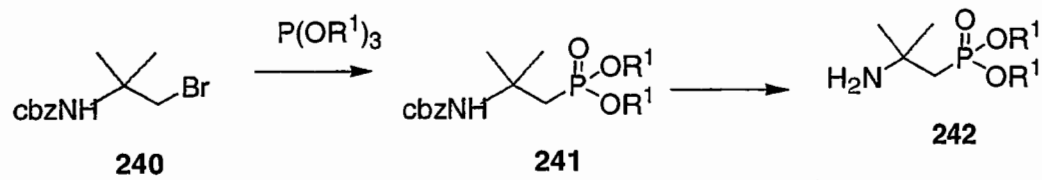
Using the above procedures, but employing different cyclic amines **261**, and/or different bromoalkylphosphonates **146**, there are obtained the corresponding products **262**.

Scheme 36

Method

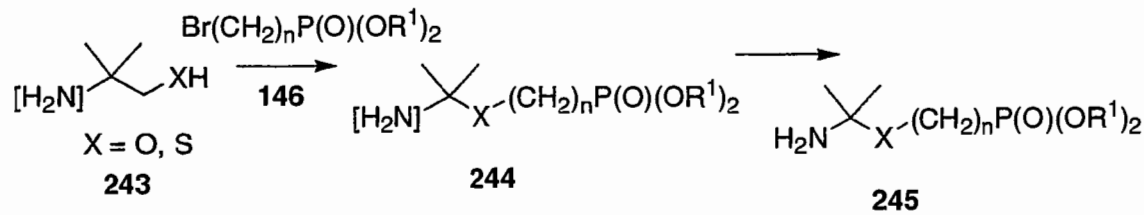


Example

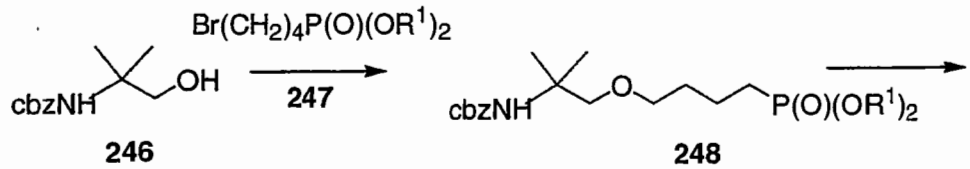


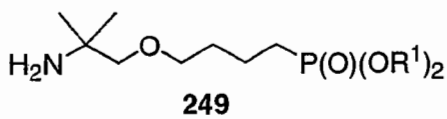
Scheme 37

Method



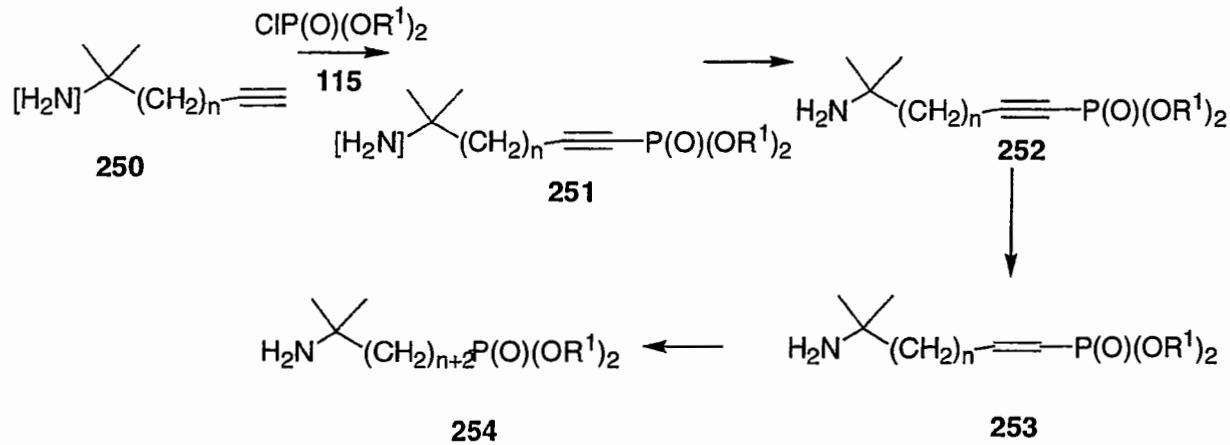
Example



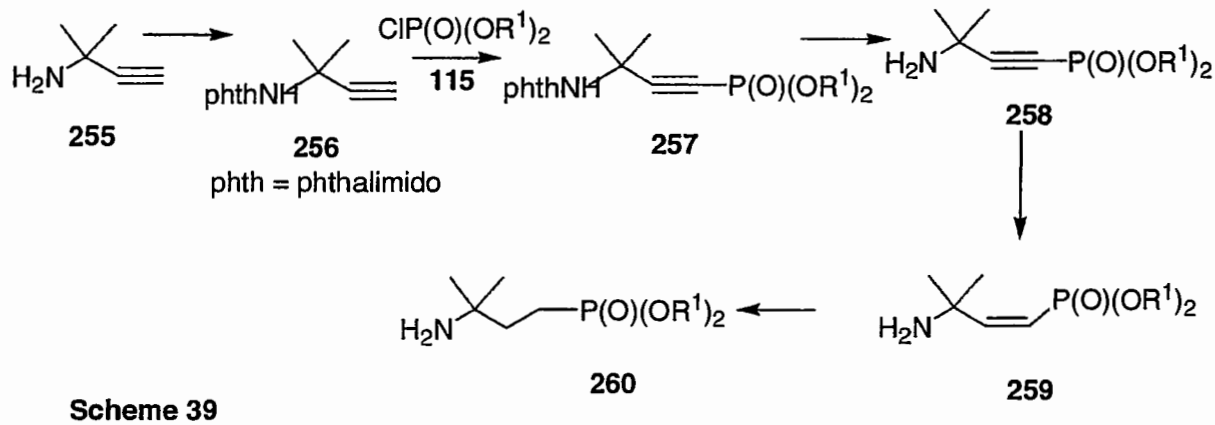


Scheme 38

Method

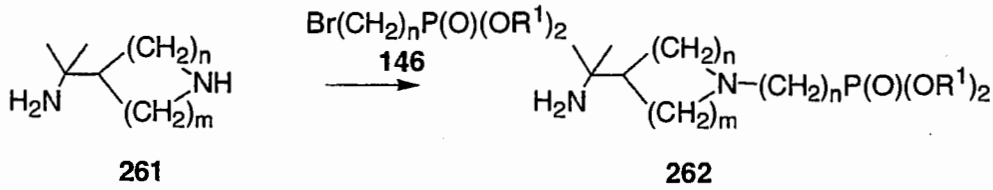


Example

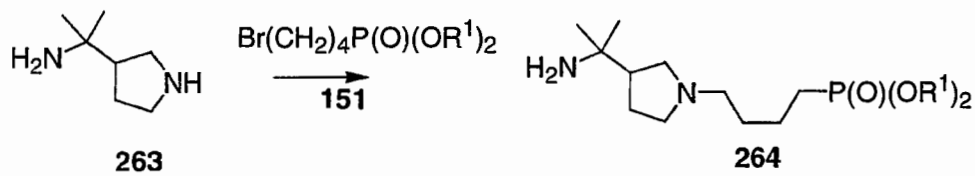


Scheme 39

Method



Example



Preparation of decahydroquinolines with phosphonate moieties at the 6-position.

Chart **6** illustrates methods for the synthesis of intermediates for the preparation of decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the intermediate **265** are shown.

In the first route, 2-hydroxy-6-methylphenylalanine **266**, the preparation of which is described in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative **267**. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product **267**, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product **268**. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound **268** is then treated with acid, for example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline **265**, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline **265** can be obtained from 2-hydroxyphenylalanine **269**, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem. Rev., 1995, 95, 1797.

Typically, the substrate **269** is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product **265**, in which R is H.

Catalytic hydrogenation of the latter compound, using, for example, platinum as catalyst, as described in J. Amer. Chem. Soc., 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-substituted decahydroisoquinoline **270**. The reduction can also be performed electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline **265** is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at ca 50°, to afford the decahydroisoquinoline **270**.

Protection of the carboxyl and NH groups present in **270** for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic

Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH into the N-cbz group, as described above, followed by oxidation, using, for example, pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone **276**, in which R is trichloroethyl and R_1 is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in J. Amer. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butyl aluminum hydride, as described in J. Amer. Chem. Soc., 80, 5372, 1958, then affords the alcohol **277**.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as, for example, isopropanol, at ambient temperature, to afford the alcohol **277**. The alcohol **270** carboxyl and NH groups can be protected, for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and by conversion of the NH into the N-cbz group, as described above. The protected alcohol **270** can then be converted into the thiol **271** and the amine **272**, by means of displacement reactions with suitable nucleophiles, with inversion of stereochemistry. For example, the alcohol **270** can be converted into an activated ester, for example trifluoromethanesulfonyl ester or the methanesulfonate ester **273**, by treatment with methanesulfonyl chloride, as described above for the preparation of **63**, (Scheme **1**). The mesylate **273** is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol **271**.

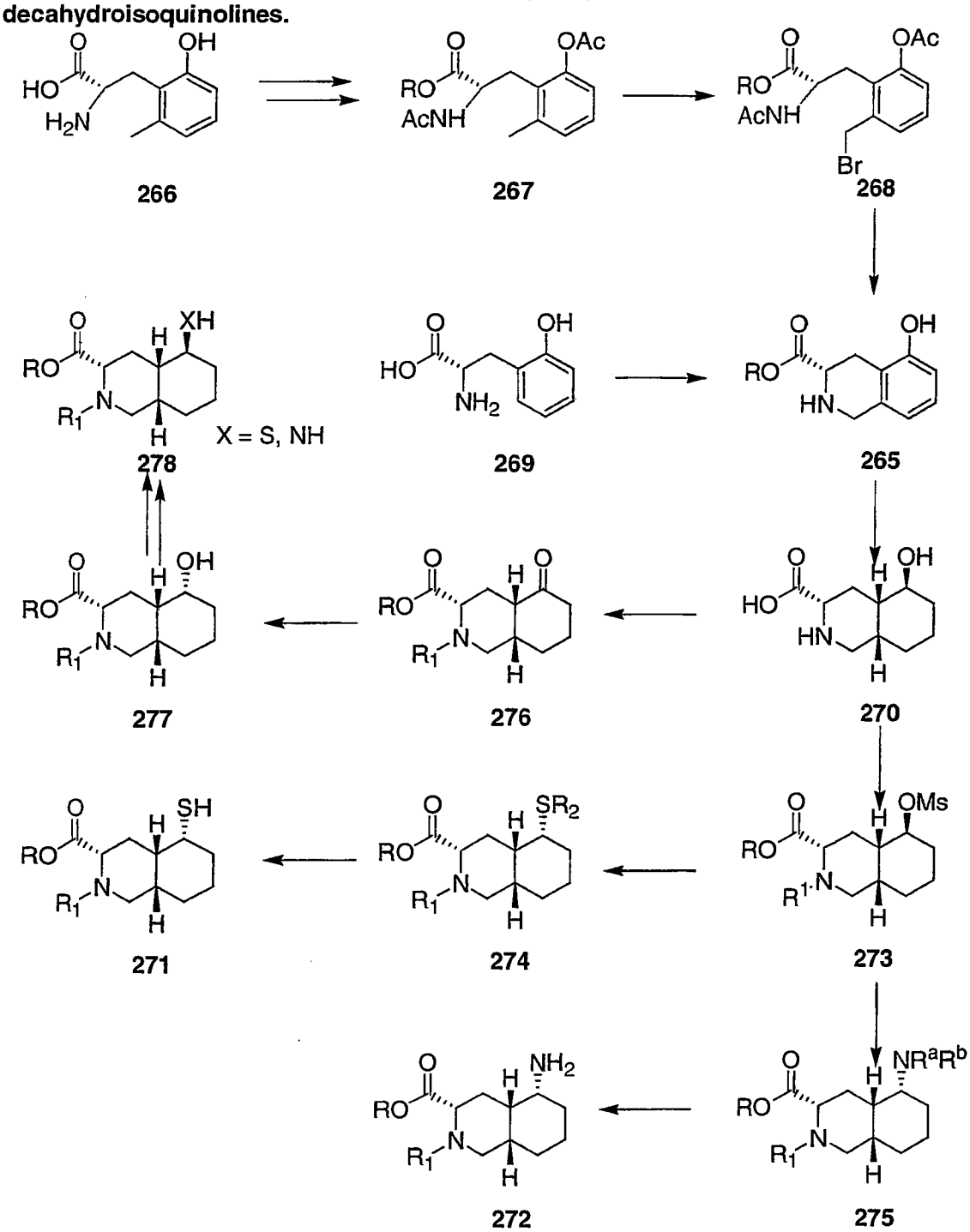
For example, the mesylate **273** is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **274**, in which R2 is $COCH_3$. The product then treated with, a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol **271**.

The mesylate **273** can be treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p. 399, to afford the amine **272**.

For example, the mesylate **273** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such as, for example, dimethylformamide, at ambient temperature, to afford the displacement product **275**, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the amine **272**.

The application of the procedures described above for the conversion of the β-carbinol **270** to the α-thiol **271** and the α-amine **272** can also be applied to the α-carbinol **277**, so as to afford the β-thiol and β-amine, **278**.

Chart 6. Intermediates for the preparation of phosphonate-containing decahydroisoquinolines.



Scheme **40** illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain. In this procedure, an alcohol, thiol or amine **279** is reacted with a bromoalkyl phosphonate **146**, under the conditions described above for the preparation of **147** (Scheme **25**), to afford

the displacement product **280**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme **44**) then yields the amine **281**.

For example, the compound **282**, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, **283**, the preparation of which is described in J. Amer. Chem. Soc., 2000, 122, 1554 to afford the displacement product **284**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme **44**) then yields the amine **285**.

Using the above procedures, but employing, in place of the α-thiol **282**, the alcohols, thiols or amines **270**, **272**, **277**, and **278**, of either α- or β-orientation, there are obtained the corresponding products **281**, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme **41** illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive Organic Transformations, by R. C. Larock, p. 421.

In this procedure, the amines **272** or **278** are reacted with a phosphonate aldehyde **286**, in the presence of a reducing agent, to afford the alkylated amine **287**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme **44**) then yields the amine **288**.

For example, the protected amino compound **272** is reacted with a dialkyl formylphosphonate **289**, the preparation of which is described in U.S. Patent 3,784,590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate **290**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme **44**) then yields the amine **291**.

Using the above procedures, but employing, instead of the α-amine **272**, the β isomer, **278** and/or different aldehydes **286**, there are obtained the corresponding products **288**, in which the orientation of the side chain is the same as that of the amine precursor.

Scheme **42** depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain.

In this procedure, a thiol phosphonate **292** is reacted with a mesylate **293**, to effect displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product **294**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme **44**) then yields the amine **295**. For example, the protected mesylate **273** is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate **296**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thio ether phosphonate **297**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme **44**) then yields the amine **298**.

Using the above procedures, but employing, instead of the phosphonate **296**, different phosphonates **292**, there are obtained the corresponding products **295**.

Scheme **43** illustrates the preparation of decahydroisoquinoline phosphonates **299** in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The compounds are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates **300** and a bromomethyl substituted phosphonate **301**. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant **300**. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate can be employed. If X is O, a strong base such as sodium hydride or lithium hexamethyldisilylazide is required. The displacement reaction affords the ether, thioether or amine compounds **302**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme **44**) then yields the amine **299**.

For example, the protected alcohol **303** is reacted at ambient temperature with a dialkyl 3-bromomethyl phenylmethylphosphonate **304**, the preparation of which is described above, (Scheme **29**). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a

strong base, such as, for example, lithium hexamethyldisylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate **304**, to afford the product **305**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme **44**) then yields the amine **306**.

Using the above procedures, but employing, instead of the β-carbinol **303**, different carbinols, thiols or amines **300**, of either α- or β-orientation, and/or different phosphonates **301**, in place of the phosphonate **304**, there are obtained the corresponding products **299**, in which the orientation of the side-chain is the same as that of the starting material **300**.

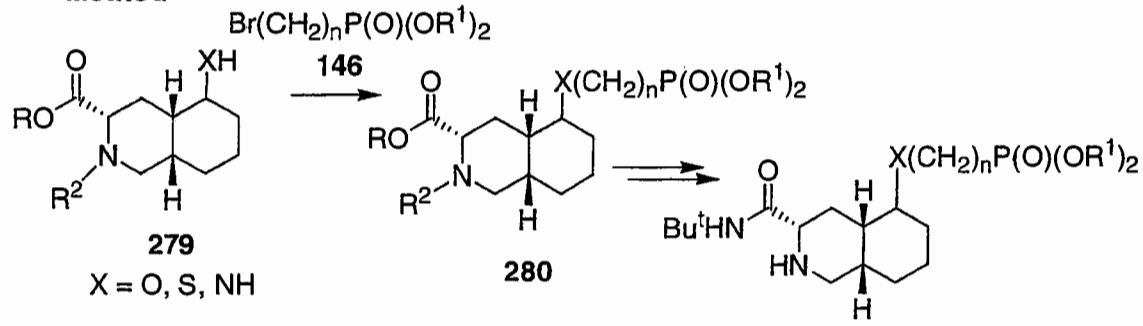
Schemes **43-43** illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

Scheme **44** illustrates the conversion of the latter group of compounds **307** (in which the group B is link-$P(O)(OR^1)_2$ and precursor compounds thereto (in which B is an optionally protected precursor to the group link-$P(O)(OR^1)_2$ such as, for example, OH, SH, NH_2) to the corresponding tert butyl amides **88**.

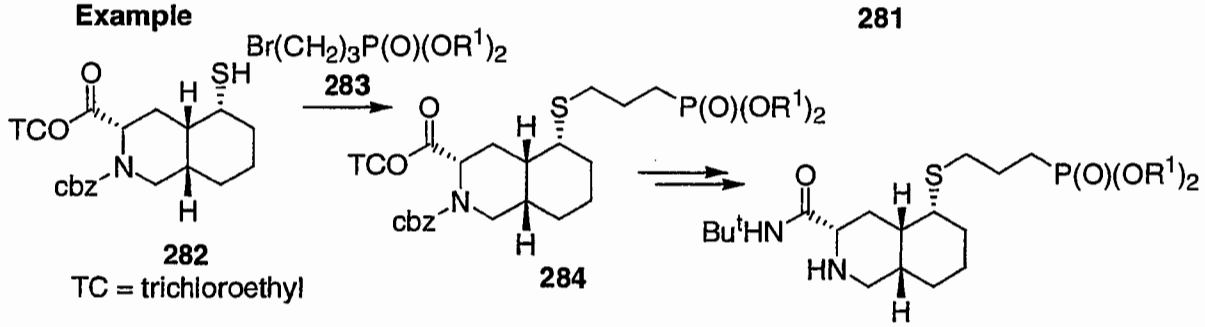
As shown in Scheme **44**, the ester compounds **307** are deprotected to form the corresponding carboxylic acids **308**. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R^2, and the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is removed by treatment with zinc in acetic acid, as described in J. Amer. Chem. Soc., 88, 852, 1966. Conversion of the carboxylic acid **308** to the tert. butyl amide **309** is then accomplished by reaction of the carboxylic acid, or an activated derivative thereof, with tert. butylamine, as described above for the preparation of **62** (Scheme **1**). Deprotection of the NR^2 group, as described above, then affords the free amine **88**.

Scheme 40

Method

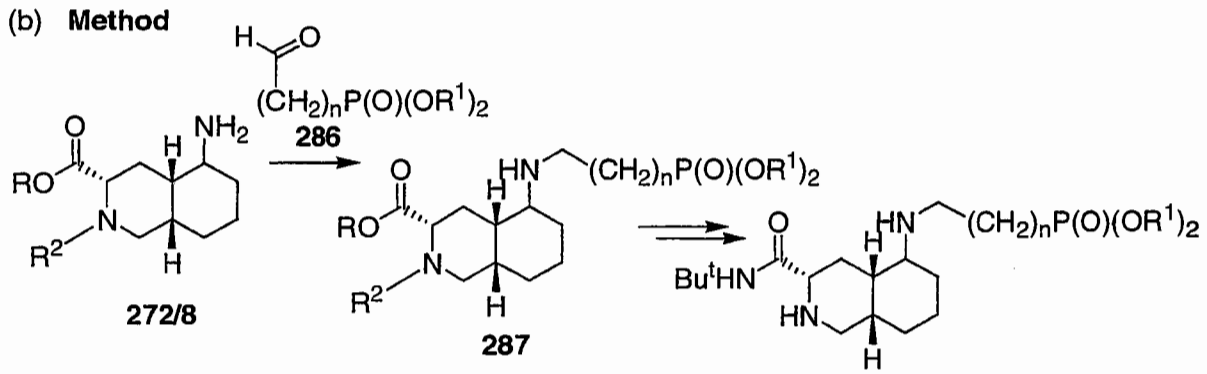


Example

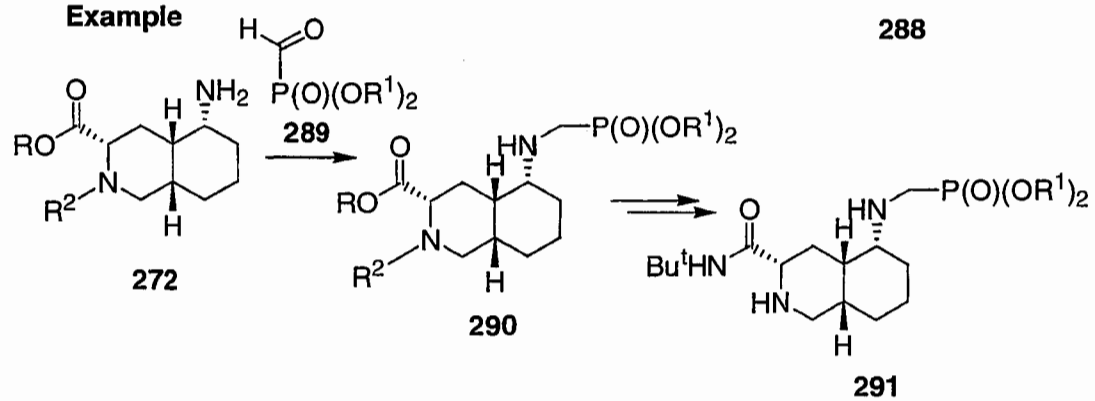


Scheme 41

(b) **Method**

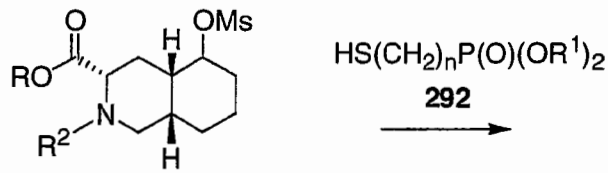


Example

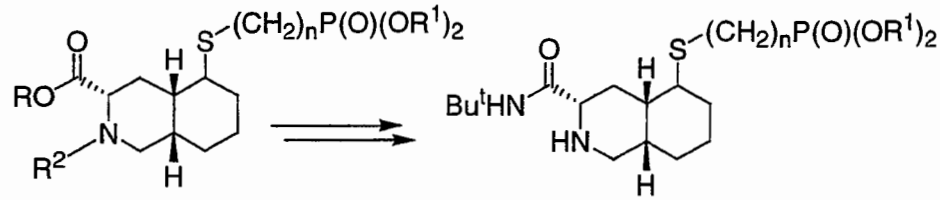


Scheme 42

Method

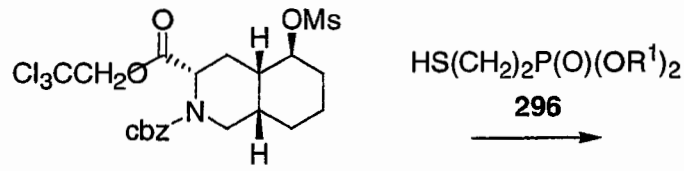


293

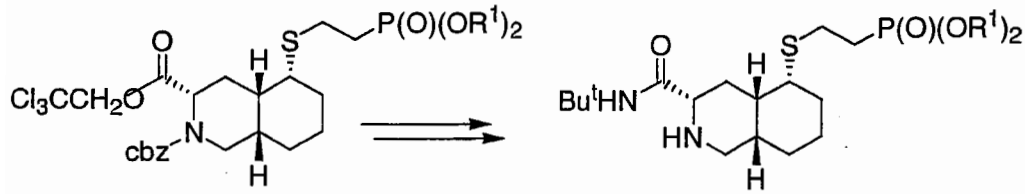


294 **295**

Example



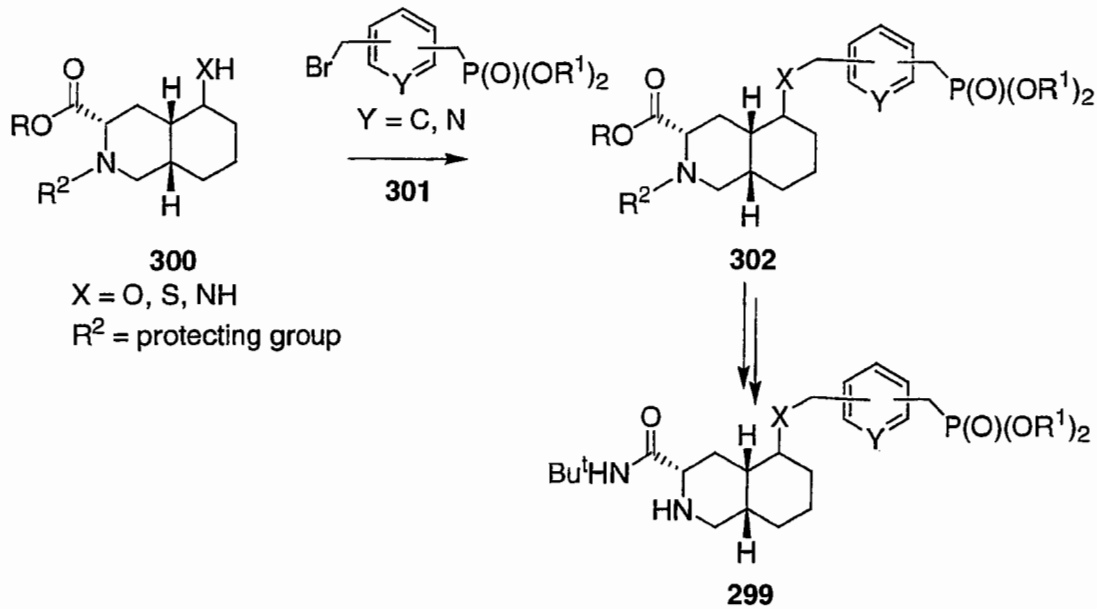
273



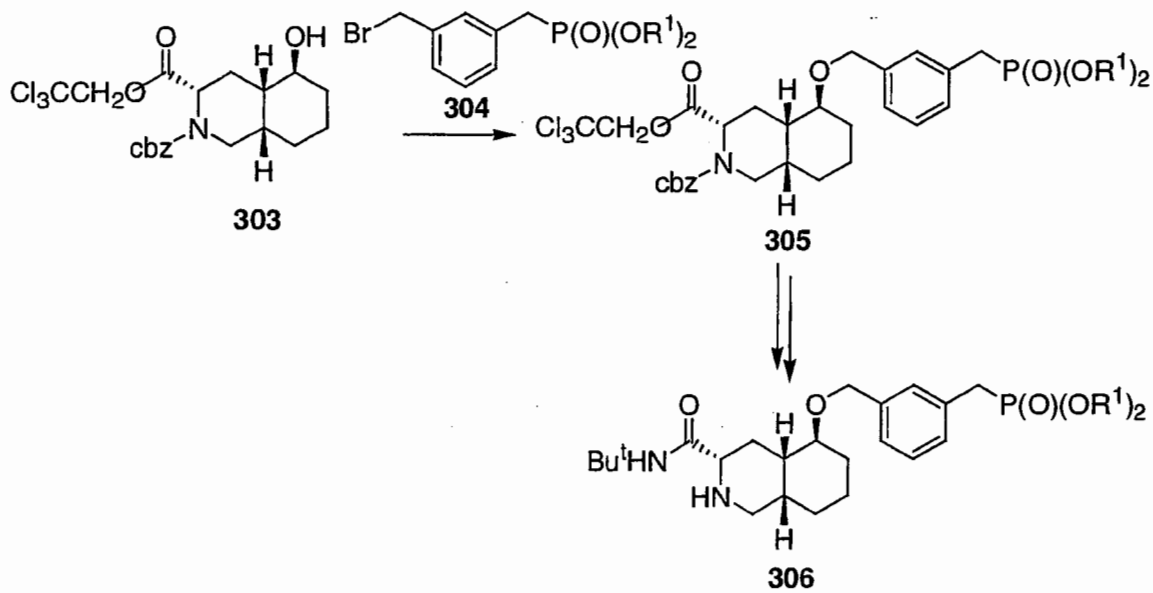
297 **298**

Scheme 43

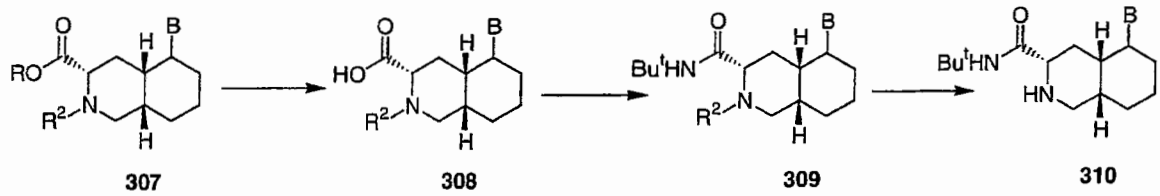
Method



Example



Scheme 44



Preparation of phenylalanine derivatives incorporating phosphonate moieties.

Scheme **45** illustrates the conversion of variously substituted phenylalanine derivatives **311** into epoxides **14a-1**, the incorporation of which into the compounds **2** is depicted in Scheme **14a**.

A number of compounds **311** or **312**, for example those in which X is 2, 3, or 4-OH, or X is 4-NH_2 are commercially available. The preparations of different compounds **311** or **312** are described in the literature. For example, the preparation of compounds **311** or **312** in which X is 3-SH, 4-SH, 3-NH_2, 3-CH_2OH or 4-CH_2OH, are described respectively in WO0036136, J. Amer. Chem. Soc., 1997, 119, 7173, Helv. Chim. Acta, 1978, 58, 1465, Acta Chem. Scand., 1977, B31, 109 and Syn. Com., 1998, 28, 4279. Resolution of compounds **311**, if required, can be accomplished by conventional methods, for example as described in Recent Dev. Synth. Org. Chem., 1992, 2, 35.

The variously substituted aminoacids **312** are protected, for example by conversion to the BOC derivative **313**, by treatment with BOC anhydride, as described in J. Med. Chem., 1998, 41, 1034. The product **313** is then converted into the methyl ester **314**, for example by treatment with ethereal diazomethane. The substituent X in **314** is then transformed, using the methods described below, Schemes **46-48**, into the group A. The products **315** are then converted, via the intermediates **316-319**, into the epoxides **14a-1**. The methyl ester **315** is first hydrolyzed, for example by treatment with one molar equivalent of aqueous methanolic lithium hydroxide, or by enzymatic hydrolysis, using, for example, porcine liver esterase, to afford the carboxylic acid **316**. The conversion of the carboxylic acid **316** into the epoxide **14a-1**, for example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, is then effected. The carboxylic acid is first converted into the acid chloride, for example by treatment with oxalyl chloride, or into a mixed anhydride, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone **317**. The diazoketone is converted into

the chloroketone **318** by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether. The latter compound is then reduced, for example by the use of sodium borohydride, to produce a mixture of chlorohydrins from which the desired 2S, 3S diastereomer **319** is separated by chromatography. This material is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide **14a-1**. Optionally, the above described series of reactions can be performed on the methyl ester **314**, so as to yield the epoxide **14a-1** in which A is OH, SH, NH, Nalkyl or CH_2OH.

Methods for the transformation of the compounds **314**, in which X is a precursor group to the substituent link-$P(O)(OR^1)_2$, are illustrated in Schemes **46-48**.

Scheme **46** depicts the preparation of epoxides **322** incorporating a phosphonate group linked to the phenyl ring by means of a heteroatom O, S or N. In this procedure, the phenol, thiol, amine or carbinol **314** is reacted with a derivative of a dialkyl hydroxymethyl phosphonate **320**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is OH, SH, NH_2 or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is CH_2OH, a base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **321**, which, employing the sequence of reactions shown in Scheme **45**, is transformed into the epoxide **322**.

For example, 2-tert.-butoxycarbonylamino-3-(4-hydroxy-phenyl)-propionic acid methyl ester, **323** (Fluka) is reacted with a dialkyl trifluoromethanesulfonyloxy phosphonate **138**, prepared as described in Tet. Lett., 1986, 27, 1477, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the ether product **324**. The latter compound is then converted, using the sequence of reactions shown in Scheme **45**, into the epoxide **325**.

Using the above procedures, but employing different phenols, thiols, amines and carbinols **314** in place of **323**, and/or different phosphonates **320**, the corresponding products **322** are obtained.

Scheme **47** illustrates the preparation of a phosphonate moiety is attached to the phenylalanine scaffold by means of a heteroatom and a multi-carbon chain.

In this procedure, a substituted phenylalanine derivative **314** is reacted with a dialkyl bromoalkyl phosphonate **146** to afford the product **326**. The conditions employed for this reaction are the same as those described above for the preparation of **148**, (Scheme **25**) The product **326** is then transformed, using the sequence of reactions shown in Scheme **45**, into the epoxide **327**.

For example, the protected aminoacid **328**, prepared as described above (Scheme **45**) from 3-mercaptophenylalanine, the preparation of which is described in WO 0036136, is reacted with a dialkyl 2-bromoethyl phosphonate **329**, prepared as described in Synthesis, 1994, 9, 909, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the thioether product **330**. The latter compound is then converted, using the sequence of reactions shown in Scheme **45**, into the epoxide **331**.

Using the above procedures, but employing different phenols, thiols, and amines **314** in place of **328**, and/or different phosphonates **146**, the corresponding products **327** are obtained.

Scheme **48** depicts the preparation of phosphonate-substituted phenylalanine derivatives in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom.

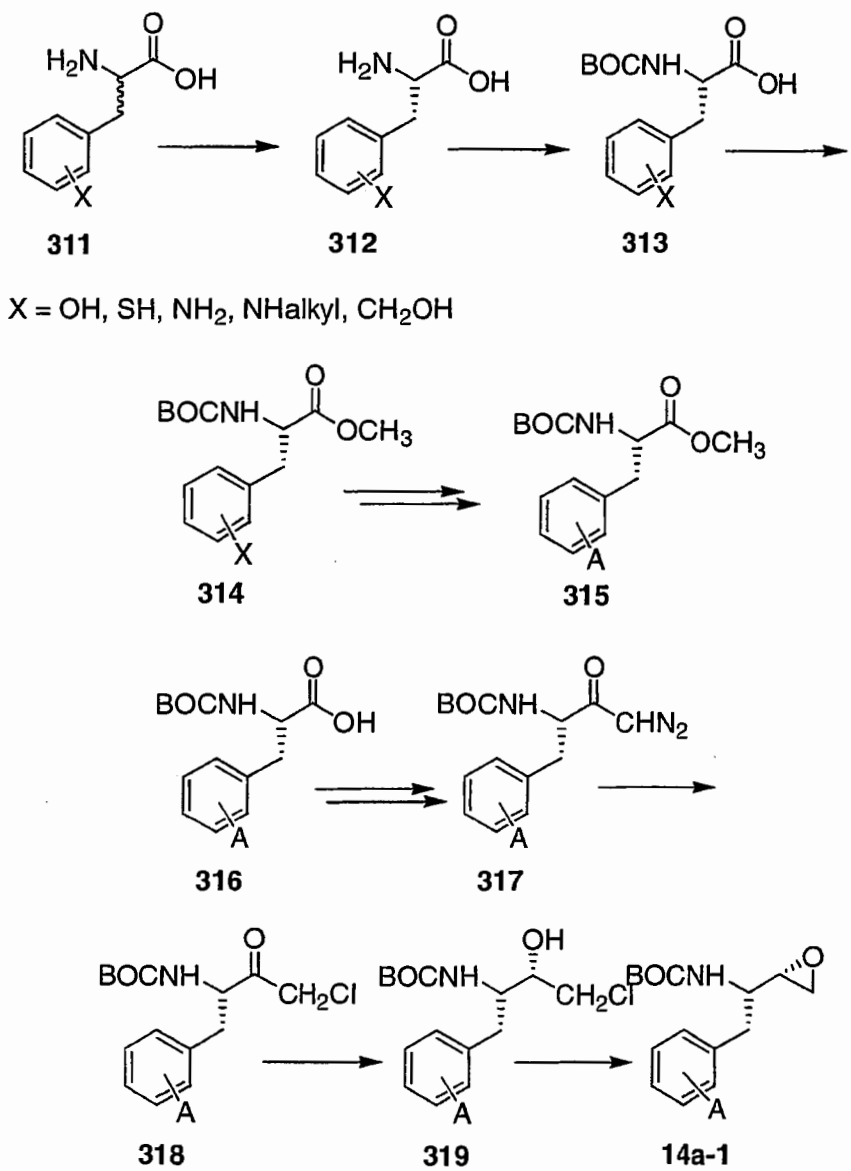
In this procedure, a protected hydroxymethyl-substituted phenylalanine **332** is converted into the halomethyl-substituted compound **333**. For example, the carbinol **332** is treated with triphenylphosphine and carbon tetrabromide, as described in J. Amer. Chem. Soc., 108, 1035, 1986 to afford the product **333** in which Z is Br. The bromo compound is then reacted with a dialkyl terminally hetero-substituted alkylphosphonate **334**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is SH, NH_2 or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is OH, a strong base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **335**, which, employing the sequence of reactions shown in Scheme **45**, is transformed into the epoxide **336**.

For example, the protected 4-hydroxymethyl-substituted phenylalanine derivative **337**, obtained from the 4-hydroxymethyl phenylalanine, the preparation of which is described in Syn. Comm., 1998, 28, 4279, is converted into the bromo derivative **338**, as described above. The product is then reacted with a dialkyl 2-aminoethyl phosphonate **339**, the preparation of

which is described in J. Org. Chem., 2000, 65, 676, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the amine product **340**. The latter compound is then converted, using the sequence of reactions shown in Scheme **45**, into the epoxide **341**.

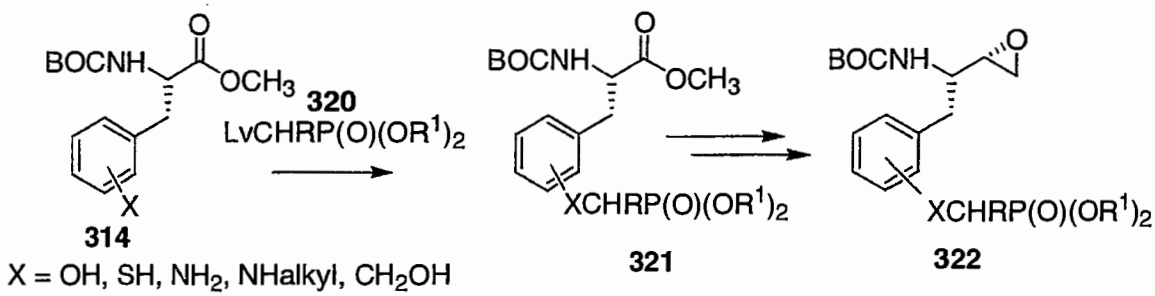
Using the above procedures, but employing different carbinols **332** in place of **337**, and/or different phosphonates **334**, the corresponding products **336** are obtained.

Scheme 45

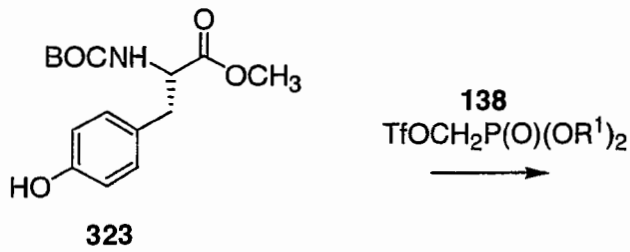


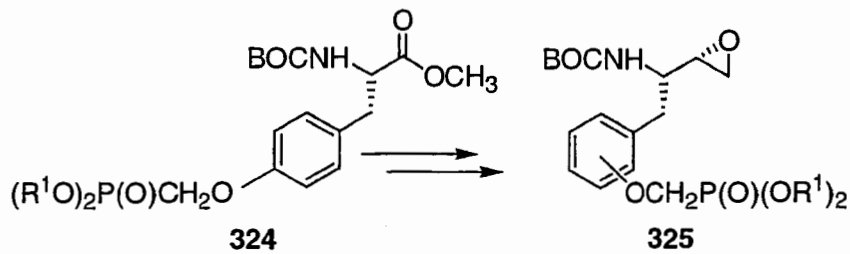
Scheme 46

Method



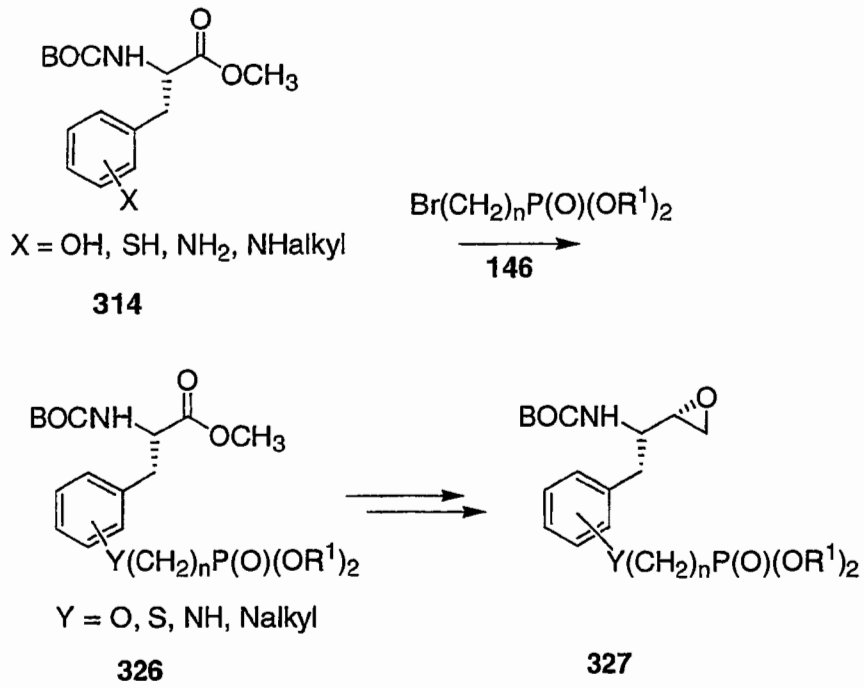
Example



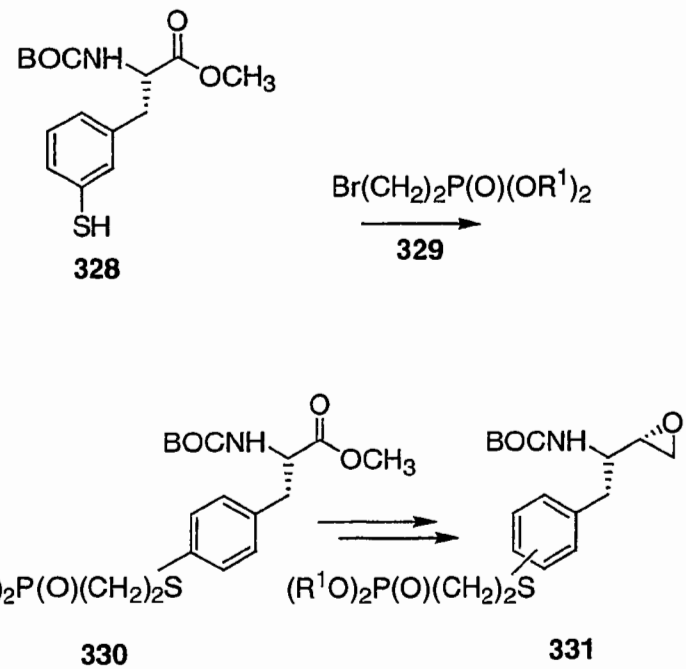


Scheme 47

Method

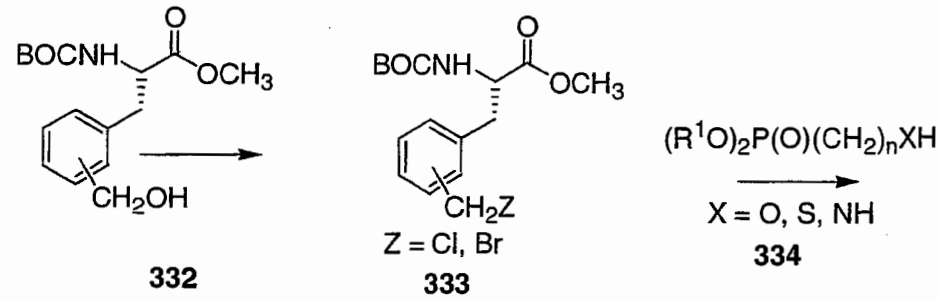


Example

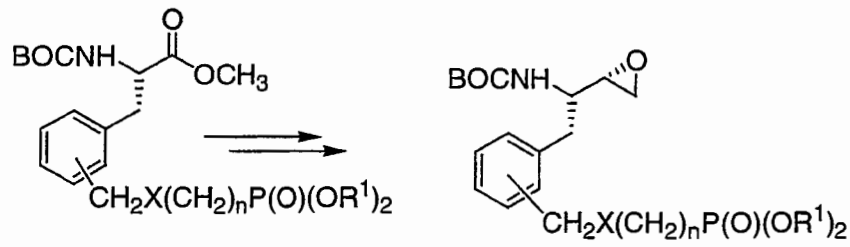


Scheme 48

Method

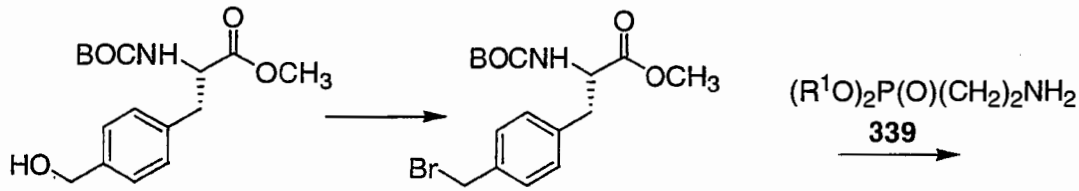


332 **333** **334**

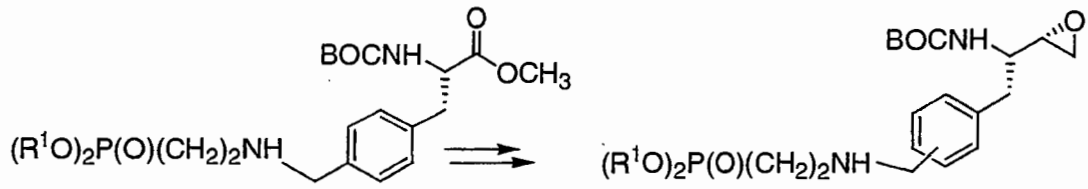


335 **336**

Example



337 **338**



340 **341**

Interconversions of the phosphonates R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH) and R-link-P(O)(OH)$_2$.

Schemes **1-48** describe the preparations of phosphonate esters of the general structure R-link-P(O)(OR^1)$_2$, in which the groups R^1, the structures of which are defined in Chart **1**, may be the same or different. The R^{1}groups attached to phosphonate esters **1-4a**, or to precursors thereto,

may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme **49**. The group R in Scheme **49** represents the substructure to which the substituent link-$P(O)(OR^1)_2$ is attached, either in the compounds **1-4a** or in precursors thereto. The R^1 group may be changed, using the procedures described below, either in the precursor compounds, or in the esters **1-4a**. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **342** into the corresponding phosphonate monoester **343** (Scheme **49**, Reaction 1) can be accomplished by a number of methods. For example, the ester **342** in which $R^1$is an aralkyl group such as benzyl, can be converted into the monoester compound **343** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester **342** in which $R^1$is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **343** can be effected by treatment of the ester **342** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **343** in which one of the groups $R^1$is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **343** in which $R^1$is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups $R^1$are alkenyl, such as allyl, can be converted into the monoester **343** in which $R^1$is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **342** or a phosphonate monoester **343** into the corresponding phosphonic acid **344** (Scheme **49**, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **343**

in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **344** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **343** in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **344** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **342** in which R^1 is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **342** in which R^1 is phenyl is described in J. Amer. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester **343** into a phosphonate diester **342** (Scheme **49**, Reaction 4) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **343** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **342** to the diester **342** can be effected by the use of the Mitsonobu reaction, as described above (Scheme **16**). The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **343** can be transformed into the phosphonate diester **342**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **343** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M.

Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **342**.

A phosphonic acid R-link-$P(O)(OH)_2$ can be transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **49**, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ **342**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid R-link-$P(O)(OH)_2$ **344** can be transformed into a phosphonate diester R-link-$P(O)(OR^1)_2$ **342** (Scheme **49**, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **344** can be transformed into phosphonic esters **342** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°. Alternatively, phosphonic acids **344** can be transformed into phosphonic esters **342** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **342**.

Preparation of carbamates.

The phosphonate ester compounds **2-4a** in which the R^5 CO group is derived from the carbonic acid derivatives **C38-C49**, the structures of which are shown in Chart **4c**, are carbamates. The compounds have the general structure ROCONHR', wherein the substructure ROCO represents the group R^5CO, as defined in Chart **4c**, and the substituent R' represents the substructure to which the amine group is attached. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme **50** illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme **50**, in the general reaction generating carbamates, a carbinol **345** is

converted into the activated derivative **346** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **346** is then reacted with an amine **347**, to afford the carbamate product **348**. Examples **1 – 7** in Scheme **50** depict methods by which the general reaction can be effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.

Scheme **50**, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **349**. In this procedure, the carbinol **349** is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **350**. The latter compound is then reacted with the amine component **347**, in the presence of an organic or inorganic base, to afford the carbamate **351**. For example, the chloroformyl compound **350** is reacted with the amine **347** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **351**. Alternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine..

Scheme **50**, Example **2** depicts the reaction of the chloroformate compound **350** with imidazole, **351**, to produce the imidazolide **352**. The imidazolide product is then reacted with the amine **347** to yield the carbamate **351**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme **50** Example **3**, depicts the reaction of the chloroformate **350** with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester **354**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **363** - **368** shown in Scheme **50**, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **363**, N-hydroxysuccinimide **364**, or pentachlorophenol, **365**, the mixed carbonate **354** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **366** or 2-hydroxypyridine **367** can be performed in

an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme **50** Example **4** illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **352** is employed. In this procedure, a carbinol **349** is reacted with an equimolar amount of carbonyl diimidazole **355** to prepare the intermediate **352**. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **352** is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **351**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate **351**.

Scheme **50**, Example **5** illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **357**. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **356**, to afford the alkoxycarbonyl product **357**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine $R'NH_2$ to afford the carbamate **351**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80° as described in Syn., 1977, 704.

Scheme **50**, Example **6** illustrates the preparation of carbamates in which a carbonate $(R''O)_2CO$, **358**, is reacted with a carbinol **349** to afford the intermediate alkyloxycarbonyl intermediate **359**. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate **351**. The procedure in which the reagent **359** is derived from hydroxybenztriazole **363** is described in Synthesis, 1993, 908; the procedure in which the reagent **359** is derived from N-hydroxysuccinimide **364** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **359** is derived from 2-hydroxypyridine **367** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **359** is derived from 4-nitrophenol **368** is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate **358** is conducted in an inert organic solvent at ambient temperature.

Scheme **50**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides **360**. In this procedure, an alkyl chloroformate **350** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **360**. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **351**. The reaction is

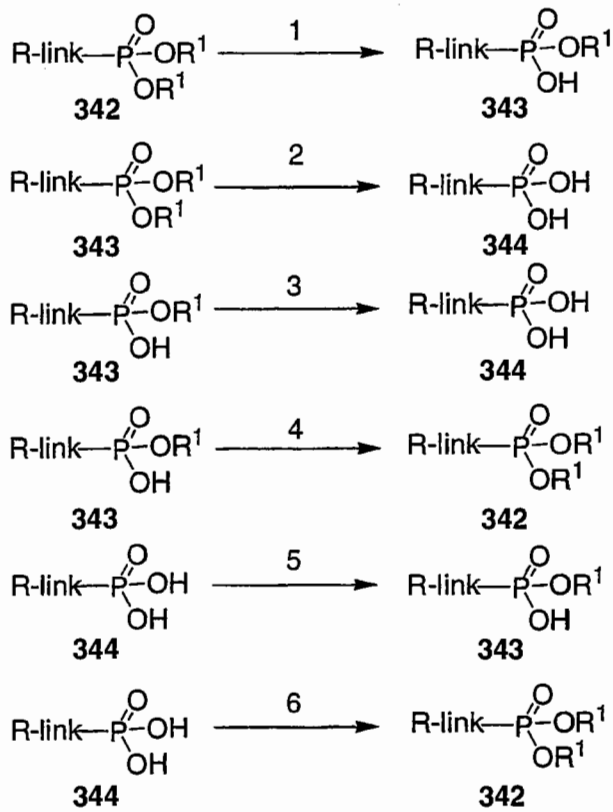
conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme **50**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **351**.

Scheme **50**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **362**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **351**.

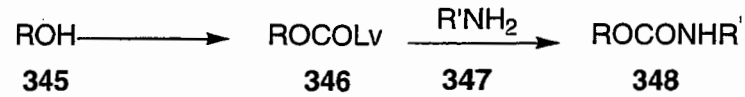
Scheme **50**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **351**.

Scheme 49

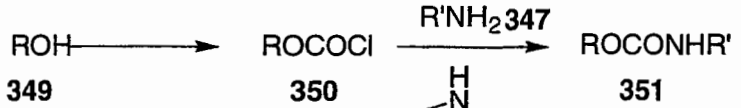

R-link—P(=O)(OR1)(OR1)
342
1
R-link—P(=O)(OR1)(OH)
343
R-link—P(=O)(OR1)(OR1)
343
2
R-link—P(=O)(OH)(OH)
344
R-link—P(=O)(OR1)(OH)
343
3
R-link—P(=O)(OH)(OH)
344
R-link—P(=O)(OR1)(OH)
343
4
R-link—P(=O)(OR1)(OR1)
342
R-link—P(=O)(OH)(OH)
344
5
R-link—P(=O)(OR1)(OH)
343
R-link—P(=O)(OH)(OH)
344
6
R-link—P(=O)(OR1)(OR1)
342

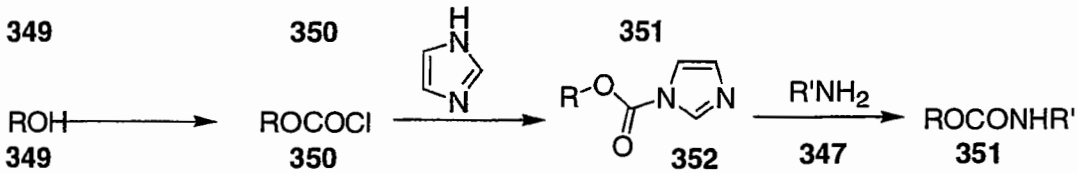
Scheme 50

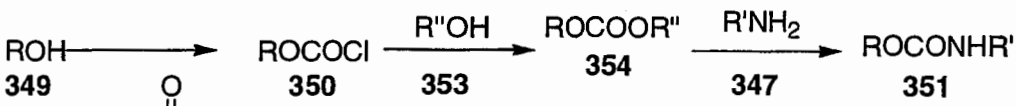
General reaction

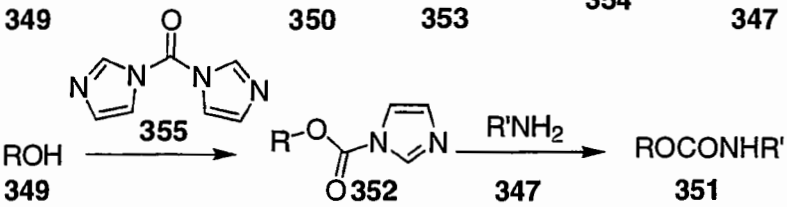


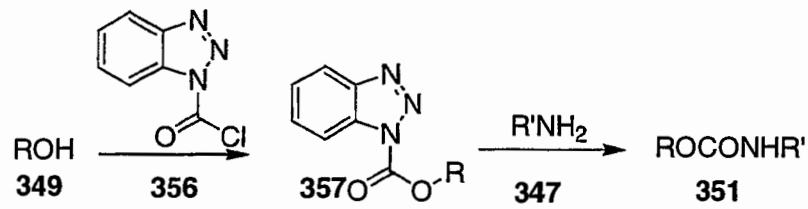
Examples

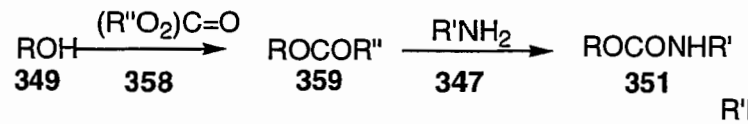
(1)


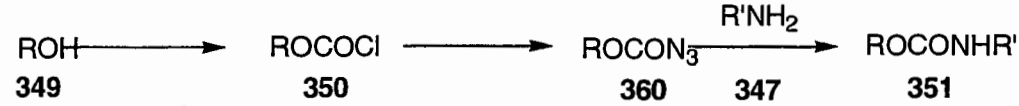
(2)


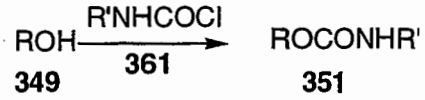
(3)


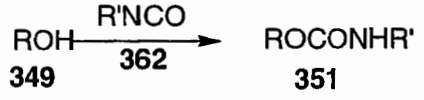
(4)


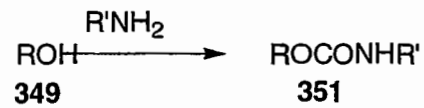
(5)


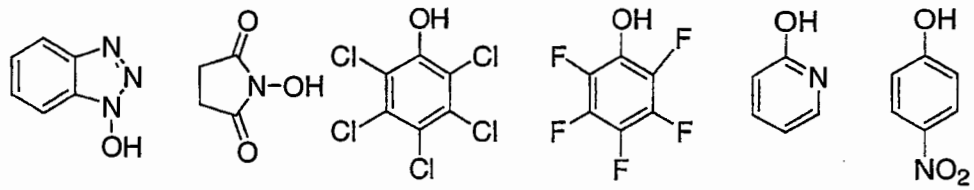
(6)


(7)


(8)


(9)


(10)


R''OH =


363 364 365 366 367 368

General applicability of methods for introduction of phosphonate substituents.

The above-described methods for the preparation of phosphonate-substituted thiols, Schemes **20** to **30**, can, with appropriate modifications according to the knowledge of one skilled in the art, be applied to the preparation of phosphonate-substituted benzoic acids, tert-butylamines, decahydroisoquinolines and phenylalanines.

Similarly, preparative methods described above for phosphonate-substituted benzoic acids, tert-butylamines, decahydroisoquinolines and phenylalanines, Schemes **31** to **48**, can, with appropriate modifications according to the knowledge of one skilled in the art, be applied to the preparation of phosphonate-substituted thiophenols.

Preparation of compounds 1-4a with phosphonate moieties attached to any substructural component.

The chemical transformations described in Schemes **1-50** illustrate the preparation of compounds **1-4** in which the phosphonate ester moiety is attached to the hydroxymethyl benzoic acid group (Schemes **1-3**), the phenylthio moiety (Schemes **4-6**), the amine moiety (Schemes **7-9**), the decahydroisoquinoline moiety (Schemes **10-12**) and the phenyl moiety (Schemes **10-14b**).

Charts **2 - 4** illustrate various chemical substructures that may be substituted for the phosphonate-containing moieties. For example, in Chart **2**, substructures **6**, **7** and **8-20e** may be substituted for the decahydroisoquinoline moiety, and in Chart **3**, substructures **21-26** may be substituted for the group CH_2XR^4 in compounds **1-4**. Charts **4a-c** illustrate the structures of the compounds R^5COOH which may be incorporated into the phosphonate esters **2-4**.

By utilization of the methods described herein for the preparation of, and incorporation of phosphonate-containing moieties, and by the application of the knowledge of one skilled in the art, the phosphonate ester moieties described herein may be incorporated into the amines **6**, **7**, and **8-20**, into the R^4 groups **21-26**, and into the carboxylic acids, or functional equivalents thereof, with the structures **C1-C49**. Subsequently, the thus-obtained phosphonate-ester containing moieties may, utilizing the procedures described above in Schemes **1-14b**, be incorporated into the compounds represented by the formula **4a** (Chart 1) in which one of the

groups R^2NHCR^3, R^4, R^5 or Bu^t contains a phosphonate group of the general formula link-$P(O)(OR^1)_2$.

Lopinavir-like phosphonate protease inhibitors (LLPPI)

Preparation of the intermediate phosphonate esters.

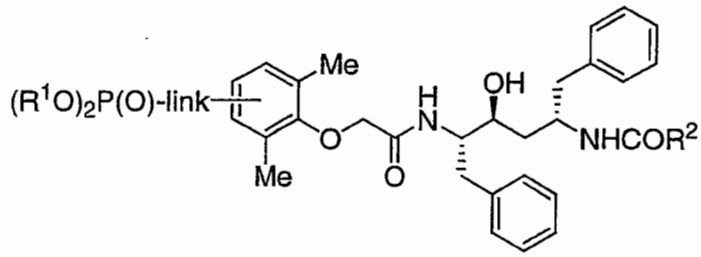
The structures of the intermediate phosphonate esters **1** to **5** and the structures for the component groups $R^1$of this invention are shown in Chart 1.

The structures of the R^2COOH and R^3OOH components **C1- C49** are shown in Charts **2a**, **2b** and **2c**. Specific stereoisomers of some of the structures are shown in Charts **1**, and **2**; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **5**. Subsequent chemical modifications to the compounds **1** to **5**, as described herein, permit the synthesis of the final compounds of this invention.

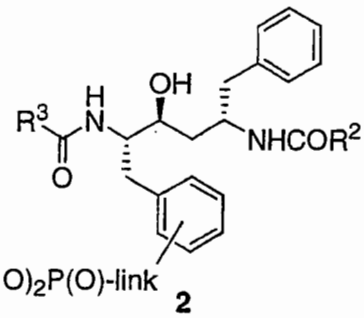
The intermediate compounds **1** to **5** incorporate a phosphonate moiety connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **4** and **5** illustrate examples of the linking groups present in the structures **1 – 5**, and in which "etc" refers to the scaffold, e.g., lopinavir.

Schemes **1 - 33** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1- 3**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **4** and **5**, in which the phosphonate moiety is incorporated into different members of the groups R^2COOH and R^3COOH, is also described below.

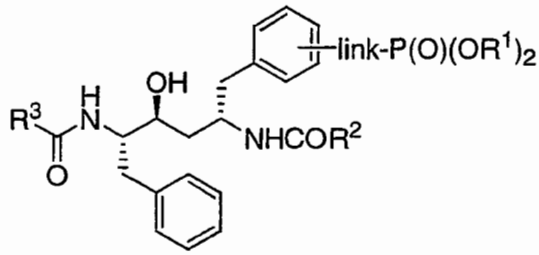
Chart 1 Intermediate phosphonate esters



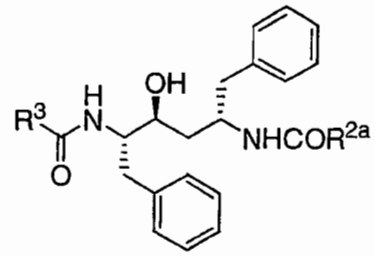
1



2

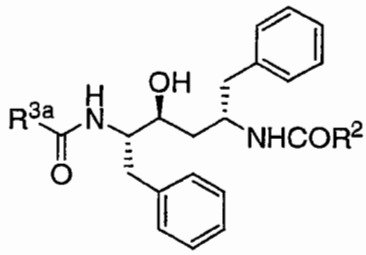


3



4

R^{2a}= phosphonate-containing R^2

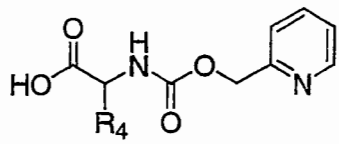


5

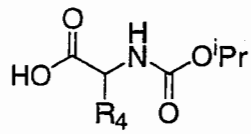
R^{3a}= phosphonate-containing R^3

R^1 = H, alkyl, haloalkyl,alkenyl, aralkyl, aryl

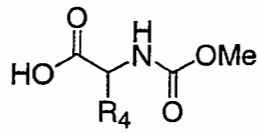
Chart 2a Structures of the R^2COOH and R^3COOH components



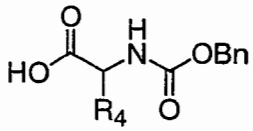
C1



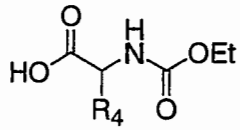
C2



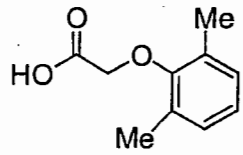
C3



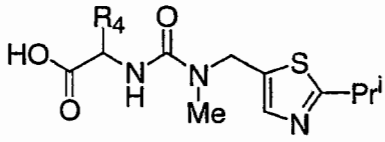
C4



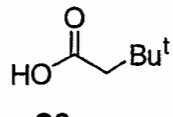
C5



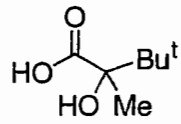
C6



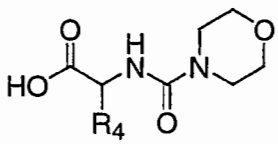
C7



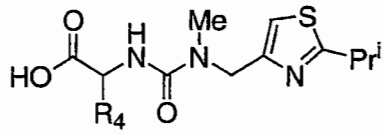
C8



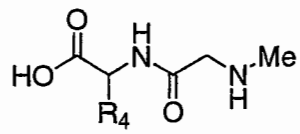
C9



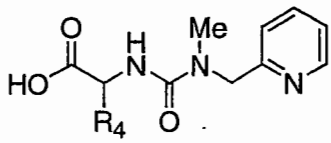
C10



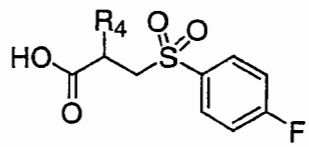
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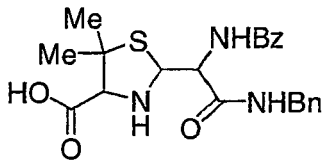
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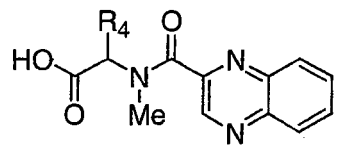
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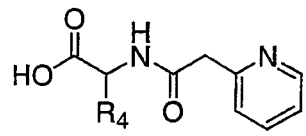
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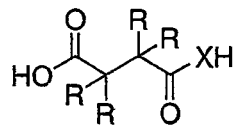
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C16

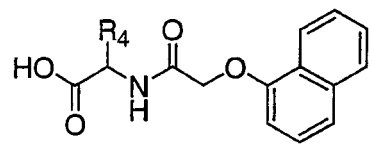


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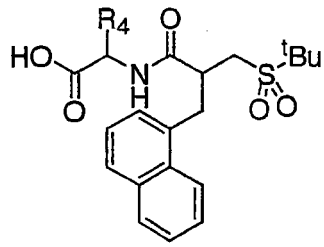


X = O, NH
R = H, alkyl

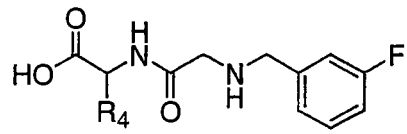
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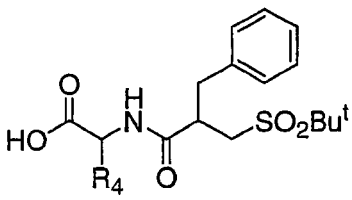
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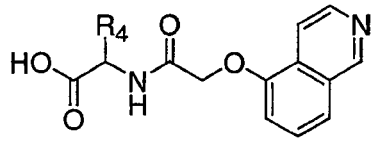
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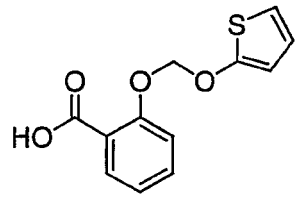
C21



C22



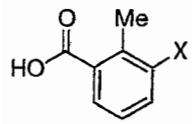
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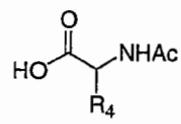
C24

R^4 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

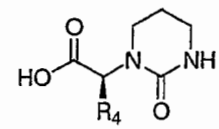
Chart 2b Structures of the R^2COOH and R^3COOH components



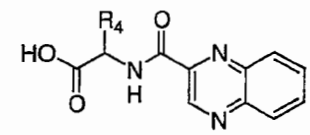
C25
X = OH, NH_2



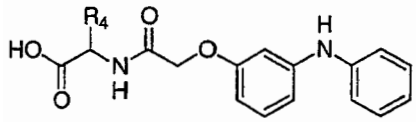
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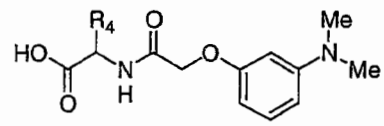
C27



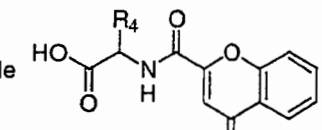
C28



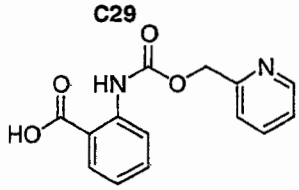
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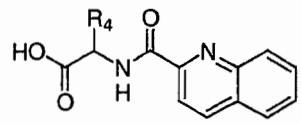
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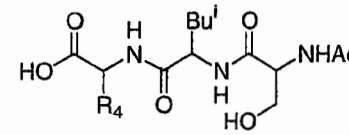
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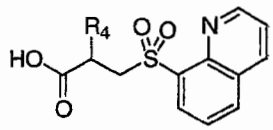
C32



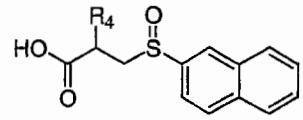
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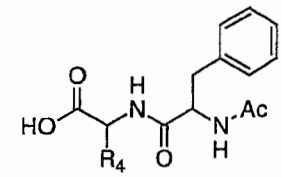
C34



C35



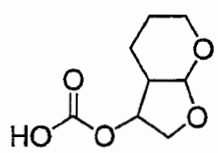
C36



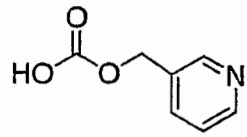
C37

R^4 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

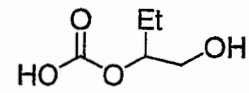
Chart 2c Structures of the R^2COOH and R^3COOH components



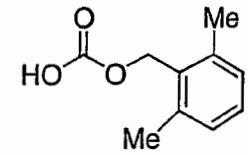
C38



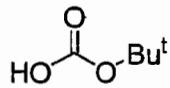
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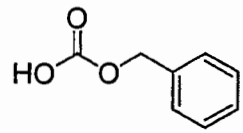
C40



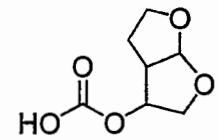
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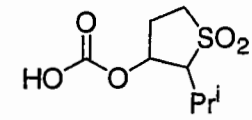
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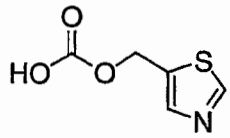
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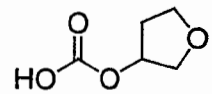
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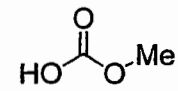
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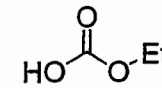
C46



C47



C48



C49

Chart 4 Examples of the linking group between the scaffold and the phosphonate moiety.

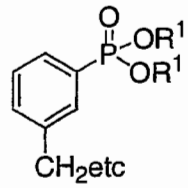
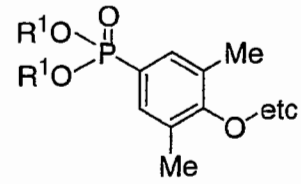
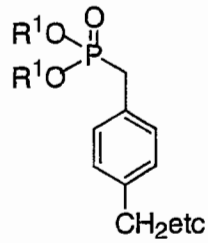
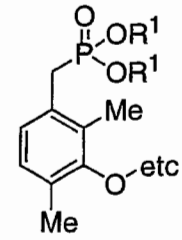
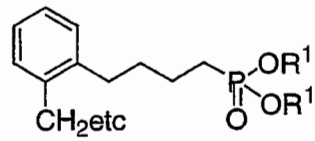
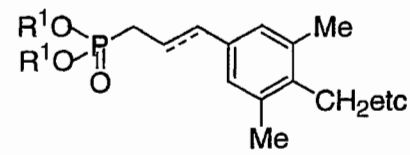
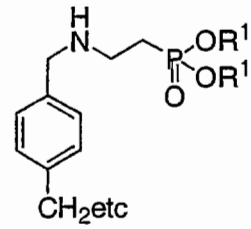
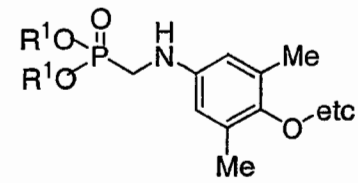
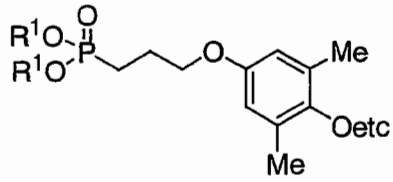
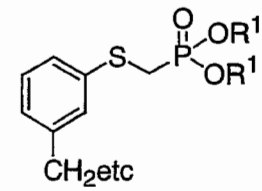
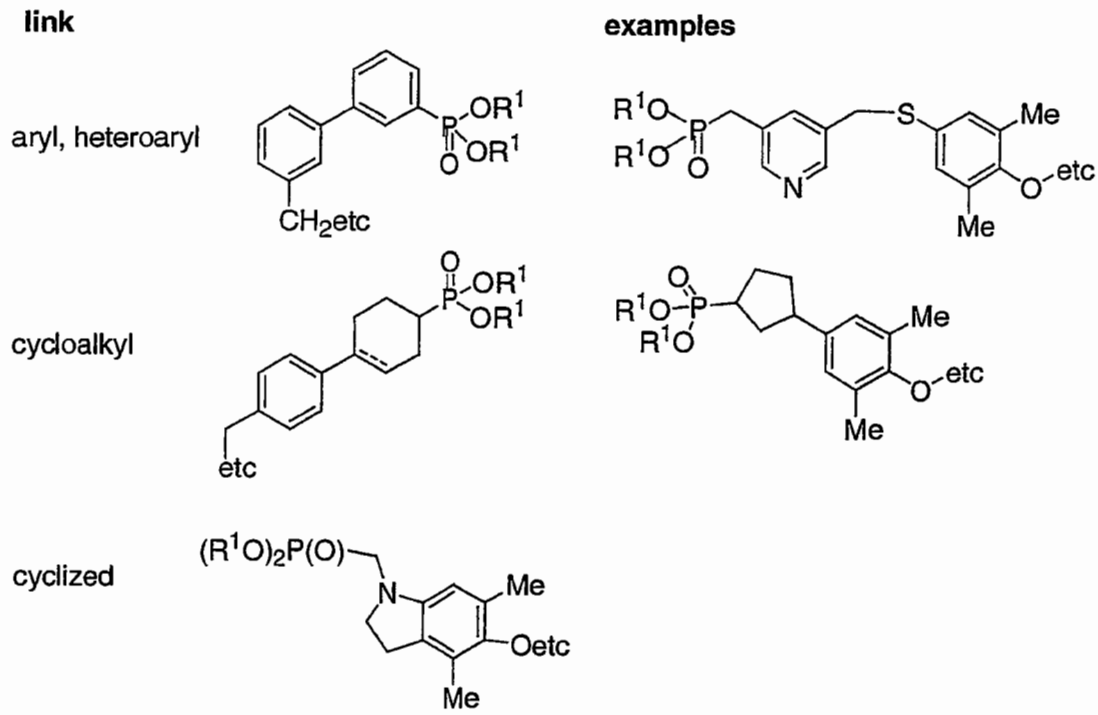
link	examples	
direct bond		
single carbon		
multiple carbon		
hetero atoms		
		

Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.



Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate intermediates 1.

Two methods for the preparation of the phosphonate intermediate compounds **1** are shown in Schemes **1** and **2**. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As shown in Scheme **1**, 5-amino-2-dibenzylamino-1,6-diphenyl-hexan-3-ol, **1.1**, the preparation of which is described in Org. Process Res. Dev., 1994, 3, 94, is reacted with a carboxylic acid R^2COOH, or an activated derivative **1.2** thereof, to produce the amide **1.3**. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid is converted into the acid chloride **1.2**, X = Cl, and the latter compound is reacted with an equimolar amount of the amine **1.1**, in an aprotic solvent such as, for example, tetrahydrofuran, at ambient temperature. The reaction is conducted in the presence of an organic base such as triethylamine, so as to afford the amide product **1.3**.

The N, N-dibenzylamino amide product **1.3** is then transformed into the free amine compound **1.4** by means of a debenzylation procedure. The deprotection of N-benzyl amines is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 365. The transformation can be effected under reductive conditions, for example by the use of hydrogen or a hydrogen transfer agent, in the presence of a palladium catalyst, or by treatment of the N-benzyl amine with sodium in liquid ammonia, or under oxidative conditions, for example by treatment with 3-chloroperoxybenzoic acid and ferrous chloride.

Preferably, the N, N-dibenzyl compound **1.3** is converted into the amine **1.4** by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic

ammonium formate and 5% palladium on carbon catalyst, at ca. 75° for ca. 6 hours, for example as described in U.S. Patent 5,914,332.

The thus-obtained amine **1.4** is then transformed into the amide **1.5** by reaction with the carboxylic acid **1.6**, or an activated derivative thereof, in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH], [NH], [CHO], Br, as described below. Preparations of the carboxylic acids **1.6** are described below, Schemes **9-14**. The amide-forming reaction is conducted under similar conditions to those described above for the preparation of the amide **1.3**.

Preferably, the carboxylic acid **1.6** is converted into the acid chloride, and the acid chloride is reacted with the amine **1.4** in a solvent mixture composed of an organic solvent such as ethyl acetate, and water, in the presence of a base such as sodium bicarbonate, for example as described in Org. Process Res. Dev., 2000, 4, 264, to afford the amide product **1.5**.

Alternatively, the amide **1.5** can be obtained by the procedure shown in Scheme **2**. In this method, 2-tert-butoxycarbonylamino-5-methyl-1,6-diphenyl-hexan-3-ol, **2.1**, the preparation of which is described in U.S. Patent 5,4912,53, is reacted with the carboxylic acid **1.6**, or an activated derivative thereof, in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto. The reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.5**.

Preferably, equimolar amounts of the amine **2.1** and the carboxylic acid **1.6** are reacted in dimethylformamide in the presence of a carbodiimide, such as, for example, 1-dimethylaminopropyl-3-ethylcarbodiimide, as described, for example, in U.S. Patent 5,914,332, to yield the amide **2.2**.

The tert-butoxycarbonyl (BOC) protecting group is then removed from the product **2.2** to afford the free amine **2.3**. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preferably, the BOC group is removed by treatment of the substrate **2.2** with trifluoroacetic acid in dichloromethane at ambient temperature, for example as described in U.S. Patent 5,9142,32, to afford the free amine product **2.3**.

The amine product **2.3** is then reacted with the acid R^2COOH **2.4**, or an activated derivative thereof, to produce the amide **2.5**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.5**.
Preferably, equimolar amounts of the amine **2.3** and the carboxylic acid **2.4** are reacted in dimethylformamide in the presence of a carbodiimide, such as, for example, 1-dimethylaminopropyl-3-ethylcarbodiimide, as described, for example, in U.S. Patent 5,914,332, to yield the amide **1.5**.

The reactions illustrated in Schemes **1** and **2** illustrate the preparation of the compounds **1.5** in which A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as, for example, optionally protected OH, SH, NH , as described below. Scheme **3** depicts the conversion of the compounds **1.5** in which A is OH, SH, NH , as described below, into the compounds **1** in which A is the group link-$P(O)(OR^1)_2$. In this procedure, the compounds **1.5** are converted, using the procedures described below, Schemes **9-33**, into the compounds **1**.

Preparation of the phosphonate intermediates 2.

Two methods for the preparation of the phosphonate intermediate compounds **2** are shown in Schemes **4** and **5**. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.
As depicted in Scheme **4**, the tribenzylated phenylalanine derivative **4.1**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, as described below, is reacted with the anion **4.2** derived from acetonitrile, to afford the ketonitrile **4.3**. Preparations of the tribenzylated phenylalanine derivatives **4.1** are described below, Schemes **15-17**.
The anion of acetonitrile is prepared by the treatment of acetonitrile with a strong base, such as, for example, lithium hexamethyldisilylazide or sodium hydride, in an inert organic solvent such as tetrahydrofuran or dimethoxyethane, as described, for example, in U.S. Patent 5,491,253. The solution of the acetonitrile anion **4.2**, in an aprotic solvent such as tetrahydrofuran, dimethoxyethane and the like, is then added to a solution of the ester **4.1** at low temperature, to afford the coupled product **4.3**.

Preferably, a solution of ca. two molar equivalent of acetonitrile, prepared by the addition of ca. two molar equivalent of sodium amide to a solution of acetonitrile in tetrahydrofuran at -40°, is added to a solution of one molar equivalent of the ester **4.1** in tetrahydrofuran at -40°, as described in J. Org. Chem., 1994, 59, 4040, to produce the ketonitrile **4.3**.

The above-described ketonitrile compound **4.3** is then reacted with an organometallic benzyl reagent, such as a benzyl Grignard reagent or benzyllithium, to afford the ketoenamine **4.5**. The reaction is conducted in an inert aprotic organic solvent such as diethyl ether, tetrahydrofuran or the like, at from -80° to ambient temperature, to yield the benzylated product **4.5**.

Preferably, the ketonitrile **4.3** is reacted with three molar equivalents of benzylmagnesium chloride in tetrahydrofuran at ambient temperature, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59, 4040, the ketoenamine **4.5**.

The ketoenamine **4.5** is then reduced, in two stages, via the ketoamine **4.6**, to produce the amino alcohol **4.7**. The transformation of the compound **4.5** to the aminoalcohol **4.7** can be effected in one step, or in two steps, with or without isolation of the intermediate ketoamine **4.6**, as described in U.S. Patent 5,491,253.

For example, the ketoenamine **4.5** is reduced with a boron-containing reducing agent such as sodium borohydride, sodium cyanoborohydride and the like, in the presence of an acid such as methanesulfonic acid, as described in J. Org. Chem., 1994, 59, 4040, to afford the ketoamine **4.6**. The reaction is performed in an ethereal solvent such as, for example, tetrahydrofuran or methyl tert-butyl ether. The product **4.6** is then reduced with sodium borohydride-trifluoroacetic acid, as described in U.S. Patent 5,491,253, to afford the aminoalcohol **4.7**.

Alternatively, the ketoenamine **4.5** can be reduced to the aminoalcohol **4.7** without isolation of the intermediate ketoamine **4.6**. In this procedure, as described in U.S. Patent 5,491,253, the ketoenamine **4.5** is reacted with sodium borohydride-methanesulfonic acid, in an ethereal solvent such as dimethoxyethane and the like. The reaction mixture is then treated with a quenching agent such as triethanolamine, and the procedure is continued by the addition of sodium borohydride and a solvent such as dimethylformamide or dimethylacetamide or the like, to afford the aminoalcohol **4.7**.

The aminoalcohol **4.7** is converted into the amide **4.8** by reaction with the acid R^2COOH **2.4** or an activated derivative thereof, to produce the amide **4.8**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.5**.

The dibenzylated amide product **4.8** is then deprotected to afford the free amine **4.9**. The conditions for the debenzylation reaction are the same as those described above for the deprotection of the dibenzyl amine **1.3** to yield the amine **1.4**, (Scheme **1**).

The amine **4.9** is then reacted with the carboxylic acid R^3COOH (**4.10**) as defined in Charts **2a –2c** , or an activated derivative thereof, to produce the amide **4.11**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.5**.

Alternatively, the amide **4.11** can be prepared by means of the sequence of reactions illustrated in Scheme **5**.

In this sequence, the tribenzylated amino acid derivative **4.1** is converted, by means of the reaction sequence shown in Scheme **4**, into the dibenzylated amine **4.7**. This compound is then converted into a protected derivative, for example the tert-butoxycarbonyl (BOC) derivative **5.1**. Methods for the conversion of amines into the BOC derivative are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 327. For example, the amine can be reacted with di-tert-butoxycarbonylanhydride (BOC anhydride) and a base, or with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), and the like.

Preferably, the amine **4.7** is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in US Patent 59143332, to yield the BOC-protected product **5.1**.

The N-benzyl protecting groups are then removed from the amide product **5.1** to afford the free amine **5.2**. The conditions for this transformation are similar to those described above for the preparation of the amine **1.4**, (Scheme **1**).

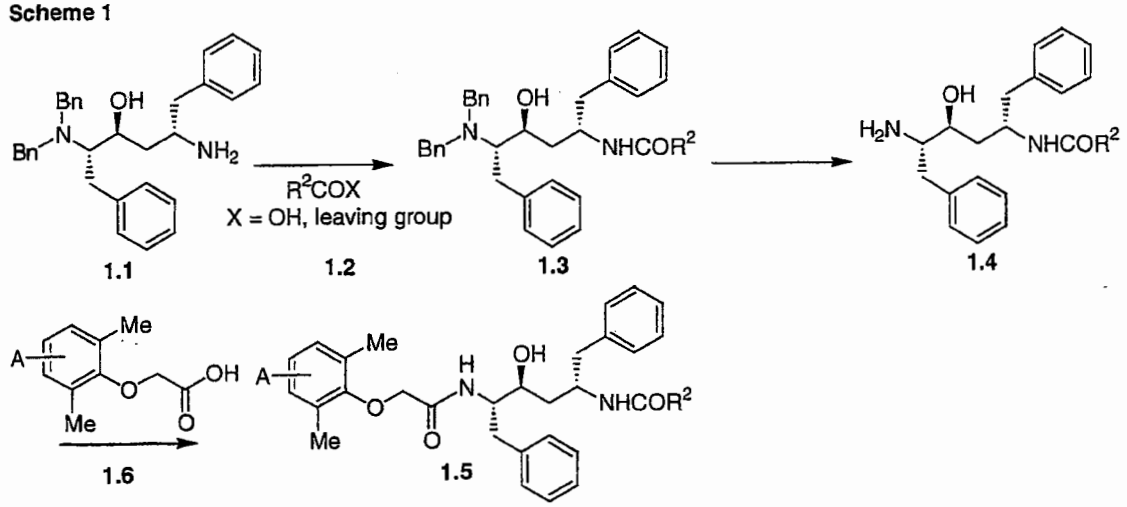
Preferably, the N, N-dibenzyl compound **5.1** is converted into the amine **5.2** by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic ammonium formate and 5% palladium on carbon catalyst, at ca. 75° for ca. 6 hours, for example as described in US Patent 5914332

The amine compound **5.2** is then reacted with the carboxylic acid R^3COOH, or an activated derivative thereof, to produce the amide **5.3**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.5**, (Scheme **1**). The BOC-protected amide **5.3** is then converted into the amine **5.4** by removal of the BOC protecting group. The conditions for this transformation are similar to those described above for the preparation of the amine **2.3** (Scheme **2**). The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC group is removed by treatment of the substrate **5.3** with trifluoroacetic acid in dichloromethane at ambient temperature, for example as described in US Patent 5914232, to afford the free amine product **5.4**.

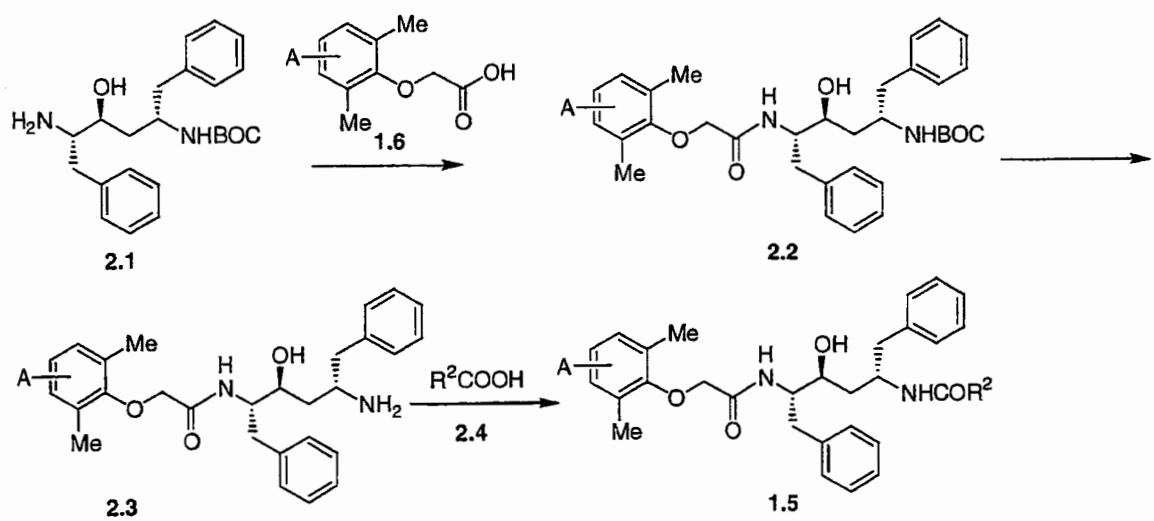
The free amine thus obtained is then reacted with the carboxylic acid R^2COOH **2.4**, or an activated derivative thereof, to produce the amide **4.11**. This reaction is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.5**.

The reactions shown in Schemes **4** and **5** illustrate the preparation of the compounds **4.11** in which A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as, for example, optionally protected OH, SH, NH , as described below. Scheme **6** depicts the conversion of the compounds **4.11** in which A is OH, SH, NH , as described below, into the compounds **2**. In this procedure, the compounds **4.11** are converted, using the procedures described below, Schemes **9-33**, into the compounds **2**.

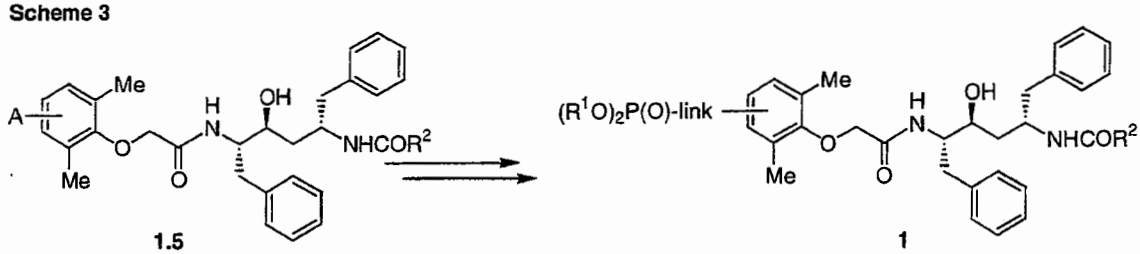
Scheme 1



Scheme 2

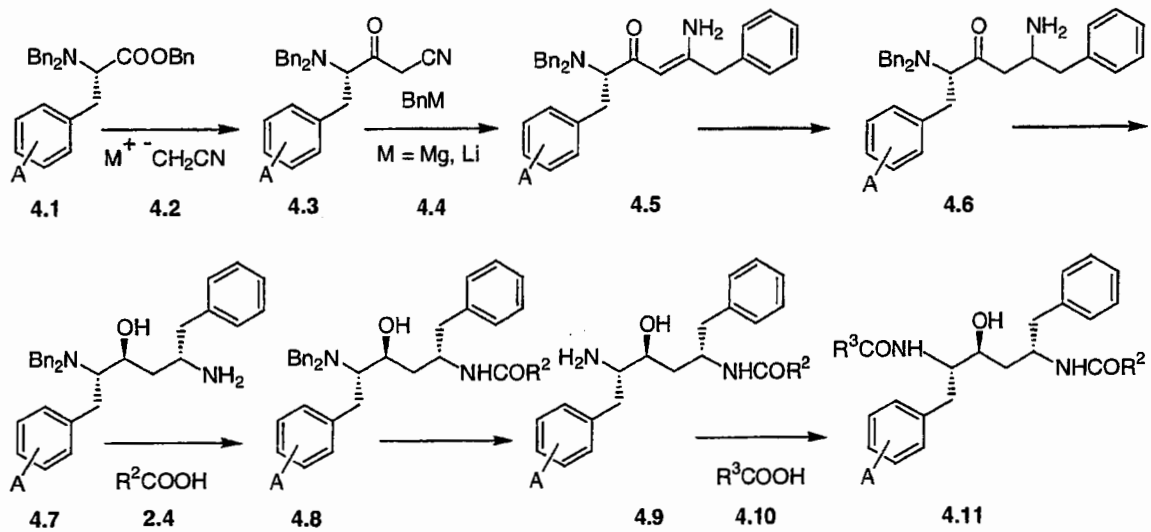


Scheme 3

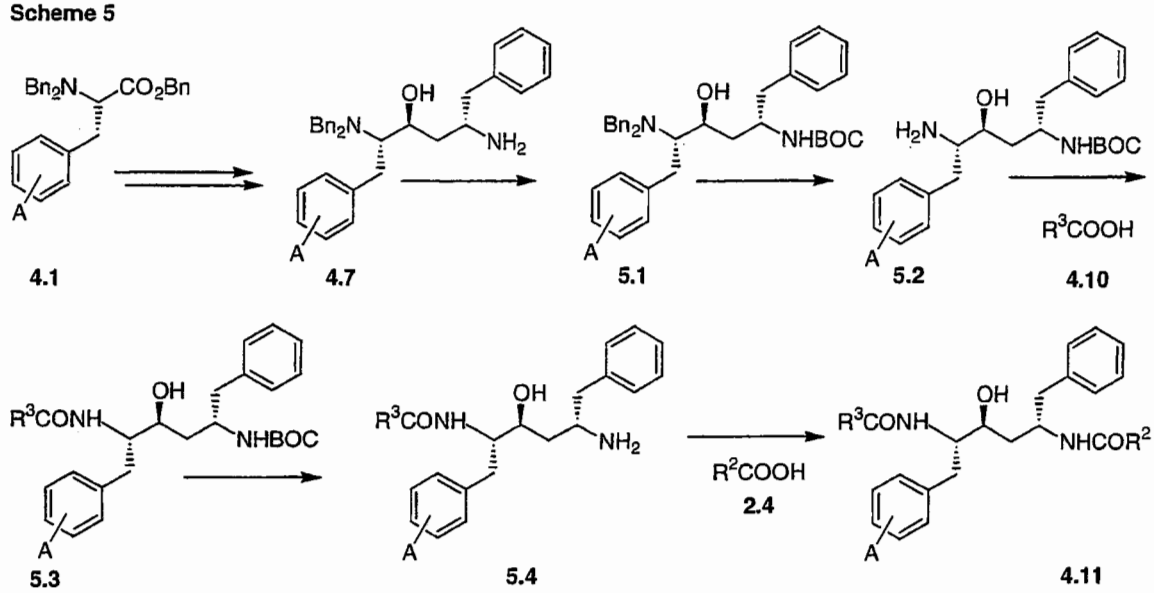


A = [OH], [SH], [NH_2] etc

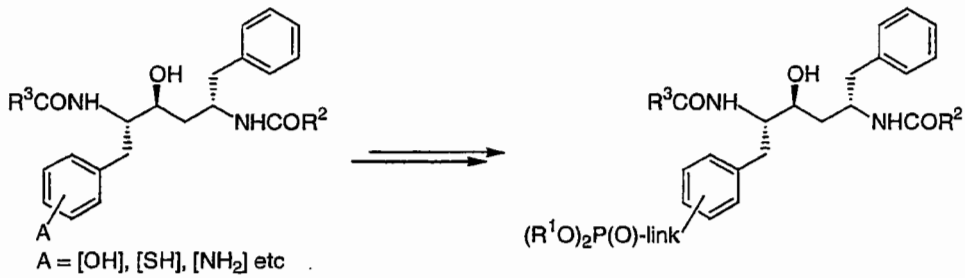
Scheme 4



Scheme 5



Scheme 6



Preparation of the phosphonate intermediates 3.

The phosphonate ester intermediate compounds **3** can be prepared by two alternative methods, illustrated in Schemes **7** and **8**. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As shown in Scheme **7**, 4-dibenzylamino-3-oxo-5-phenyl-pentanenitrile **7.1**, the preparation of which is described in J. Org. Chem., 1994, 59, 4040, is reacted with a substituted benzylmagnesium halide reagent **7.2**, in which the group B is a substituent, protected if appropriate, which can be converted, after the sequence of reactions shown in Scheme **7**, into the substituent link-P(O)(OR^1)$_2$. Examples of the substituent B are Br, [OH], [SH], [NH_2]

[CHO] and the like; procedures for the transformation of these groups into the phosphonate moiety are shown below in Schemes **9-33**.

The conditions for the reaction between the benzylmagnesium halide **7.2** and the ketonitrile **7.1** are similar to those described above for the preparation of the ketoenamine **4.5** (Scheme **4**). Preferably, the ketonitrile **7.1** is reacted with three molar equivalents of the substituted benzylmagnesium chloride **7.2** in tetrahydrofuran at ca. 0°, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59, 4040, the ketoenamine **7.3**.

The thus-obtained ketoenamine **7.3** is then transformed, via the intermediate compounds **7.4**, **7.5**, **7.6** and **7.7** into the diacylated carbinol **7.8**. The conditions for each step in the conversion of the ketoenamine **7.3** to the diacylated carbinol **7.8** are the same as those described above (Scheme **4**) for the transformation of the ketoenamine **4.5** into the diacylated carbinol **4.11**.

The diacylated carbinol **7.8** is then converted into the phosphonate ester **3**, using procedures illustrated below in Schemes **9-33**.

Alternatively, the phosphonate esters **3** can be obtained by means of the reactions illustrated in Scheme **8**. In this procedure, the amine **7.4**, the preparation of which is described above, (Scheme **7**) is converted into the BOC derivative **8.1**. The conditions for the introduction of the BOC group are similar to those described above for the conversion of the amine **4.7** into the BOC-protected product **5.1**, (Scheme **5**).

Preferably, the amine **7.4** is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in US Patent 5914332, to yield the BOC-protected product **8.1**.

The BOC-protected amine **8.1** is then converted, via the intermediates **8.2**, **8.3** and **8.4** into the diacylated carbinol **7.8**. The reaction conditions for this sequence of reactions are similar to those described above for the transformation of the BOC-protected amine **5.1** into the diacylated carbinol **4.11** (Scheme **5**).

The diacylated carbinol **7.8** is then converted into the phosphonate ester **3**, using procedures illustrated below in Schemes **18-20**.

Preparation of dimethylphenoxyacetic acids incorporating phosphonate moieties.

Scheme **9** illustrates two alternative methods by means of which 2,6-dimethylphenoxyacetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the 2,6-dimethylphenol moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed 2,6-dimethylphenoxyacetic acid intermediate. In the first sequence, a substituted 2,6-dimethylphenol **9.1**, in which the substituent B is a precursor to the group link-$P(O)(OR^1)_2$, and in which the phenolic hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound **9.2**. Methods for the conversion of the substituent B into the group link-$P(O)(OR^1)_2$ are described below in Schemes **9 - 33**.

The protected phenolic hydroxyl group present in the phosphonate-containing product **9.2** is then deprotected, using methods described below, to afford the phenol **9.3**.

The phenolic product **9.3** is then transformed into the corresponding phenoxyacetic acid **9.4**, in a two step procedure. In the first step, the phenol **9.3** is reacted with an ester of bromoacetic acid **9.5**, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of phenols to afford phenolic ethers is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the phenol and the alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol **9.3** and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described in US Patent 5914332, to afford the ester **9.6**.

The thus-obtained ester **9.6** is then hydrolyzed to afford the carboxylic acid **9.4**. The methods used for this reaction depend on the nature of the group R. If R is an alkyl group such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group, methods for hydrolysis are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

Preferably, the ester product **9.6** which R is ethyl is hydrolyzed to the carboxylic acid **9.4** by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in US Patent 5914332.

Alternatively, an appropriately substituted 2,6-dimethylphenol **9.7**, in which the substituent B is a precursor to the group link-$P(O)(OR^1)_2$, is transformed into the corresponding phenoxyacetic ester **9.8**. The conditions employed for the alkylation reaction are similar to those described above for the conversion of the phenol **9.3** into the ester **9.6**.

The phenolic ester **9.8** is then converted, by transformation of the group B into the group link-$P(O)(OR^1)_2$ followed by ester hydrolysis, into the carboxylic acid **9.4**. The group B which is present in the ester **9.4** may be transformed into the group link-$P(O)(OR^1)_2$ either before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes **9-14** illustrate the preparation of 2,6-dimethylphenoxyacetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of phenoxyacetic esters acids **9.8**, with, if appropriate, modifications made according to the knowledge of one skilled in the art..

Scheme **10** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester which is attached to the phenolic group by means of a carbon chain incorporating a nitrogen atom. The compounds **10.4** are obtained by means of a reductive alkylation reaction between a 2,6-dimethylphenol aldehyde **10.1** and an aminoalkyl phosphonate ester **10.2**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component **10.2** and the aldehyde component **10.1** are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product **10.3**. The amination product **10.3** is then converted into the phenoxyacetic acid compound **10.4**, using the alkylation and ester hydrolysis procedures described above, (Scheme **9**)

For example, equimolar amounts of 4-hydroxy-3,5-dimethylbenzaldehyde **10.5** (Aldrich) and a dialkyl aminoethyl phosphonate **10.6**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic

acid, as described, for example, in J. Amer. Chem. Soc., 91, 3996, 1969, to afford the amine product **10.3**. The product is then converted into the acetic acid **10.8**, as described above. Using the above procedures, but employing, in place of the aldehyde **10.5**, different aldehydes **10.1**, and/or different aminoalkyl phosphonates **10.2**, the corresponding products **10.4** are obtained.

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme **21**)

Scheme **11** depicts the preparation of 2,6-dimethylphenols incorporating a phosphonate group linked to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, an optionally protected bromo-substituted 2,6-dimethylphenol **11.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **11.2**. The coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst. Following the coupling reaction, the product **11.3** is converted, using the procedures described above, (Scheme **9**) into the corresponding phenoxyacetic acid **11.4**. Alternatively, the olefinic product **11.3** is reduced to afford the saturated 2,6-dimethylphenol derivative **11.5**. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or diimide. Following the reduction reaction, the product **11.5** is converted, as described above, (Scheme **9**) into the corresponding phenoxyacetic acid **11.6**.

For example, 3-bromo-2,6-dimethylphenol **11.7**, prepared as described in Can. J. Chem., 1983, 61, 1045, is converted into the tert-butyldimethylsilyl ether **11.8**, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 p. 77. The product **11.8** is reacted with an equimolar amount of a dialkyl allyl phosphonate **11.9**, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of

bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°, to produce the coupled product **11.10**. The silyl group is removed, for example by the treatment of the ether **11.10** with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Am. Chem., Soc., 94, 6190, 1972, to afford the phenol **11.11**. This compound is converted, employing the procedures described above, (Scheme **9**) into the corresponding phenoxyacetic acid **11.12**. Alternatively, the unsaturated compound **11.11** is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog **11.13**. This compound is converted, employing the procedures described above, (Scheme **9**) into the corresponding phenoxyacetic acid **11.14**.

Using the above procedures, but employing, in place of 3-bromo-2,6-dimethylphenol **11.7**, different bromophenols **11.1**, and/or different dialkyl alkenyl phosphonates **11.2**, the corresponding products **11.4** and **11.6** are obtained.

Scheme **12** illustrates the preparation of phosphonate-containing 2,6-dimethylphenoxyacetic acids **12.1** in which the phosphonate group is attached to the 2,6-dimethylphenoxy moiety by means of a carbocyclic ring. In this procedure, a bromo-substituted 2,6-dimethylphenol **12.2** is converted, using the procedures illustrated in Scheme **9**, into the corresponding 2,6-dimethylphenoxyacetic ester **12.3**. The latter compound is then reacted, by means of a palladium-catalyzed Heck reaction, with a cycloalkenone **12.4**, in which n is 1 or 2. The coupling reaction is conducted under the same conditions as those described above for the preparation of **11.3**. (Scheme **11**). The product **12.5** is then reduced catalytically, as described above for the reduction of **11.3**, (Scheme **11**), to afford the substituted cycloalkanone **12.6**. The ketone is then subjected to a reductive amination procedure, by reaction with a dialkyl 2-aminoethylphosphonate **12.7** and sodium triacetoxyborohydride, as described in J. Org. Chem., 61, 3849, 1996, to yield the amine phosphonate **12.8**. The reductive amination reaction is conducted under the same conditions as those described above for the preparation of the amine **10.3** (Scheme **10**). The resultant ester **12.8** is then hydrolyzed, as described above, to afford the phenoxyacetic acid **12.1**.

For example, 4-bromo-2,6-dimethylphenol **12.9** (Aldrich) is converted, as described above, into the phenoxy ester **12.10**. The latter compound is then coupled, in dimethylformamide

solution at ca. 60°, with cyclohexenone **12.11**, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to yield the cyclohexenone **12.12**. The enone is then reduced to the saturated ketone **12.13**, by means of catalytic hydrogenation employing 5% palladium on carbon as catalyst. The saturated ketone is then reacted with an equimolar amount of a dialkyl aminoethylphosphonate **12.14**, prepared as described in J. Org. Chem., 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the amine **12.15**. Hydrolysis, employing lithium hydroxide in aqueous methanol at ambient temperature, then yields the acetic acid **12.16**.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylphenol **12.9**, different bromo-substituted 2,6-dimethylphenols **12.2**, and/or different cycloalkenones **12.4**, and/or different dialkyl aminoalkylphosphonates **12.7**, the corresponding products **12.1** are obtained.

Scheme **13** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate group attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an optionally protected hydroxy, thio or amino-substituted 2,6-dimethylphenol **13.1** is reacted, in the presence of a base such as, for example, potassium carbonate, and optionally in the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl phosphonate **13.2**. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°. The product of the alkylation reaction, **13.3** is then converted, as described above (Scheme **9**) into the phenoxyacetic acid **13.4**.

For example, 2,6-dimethyl-4-mercaptophenol **13.5**, prepared as described in EP 482342, is reacted in dimethylformamide at ca. 60° with an equimolar amount of a dialkyl bromobutyl phosphonate **13.6**, the preparation of which is described in Synthesis, 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the thioether product **13.7**. This compound is converted, employing the procedures described above, (Scheme **9**) into the corresponding phenoxyacetic acid **13.8**.

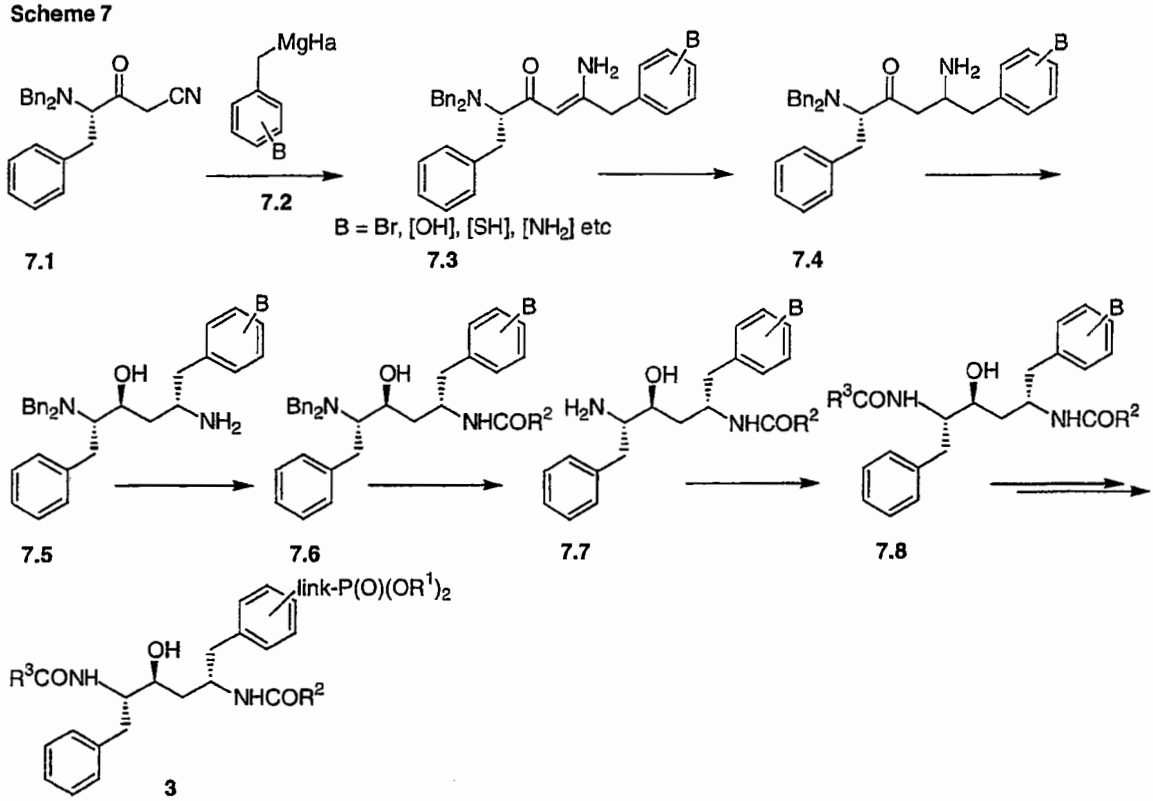
Using the above procedures, but employing, in place of 2,6-dimethyl-4-mercaptophenol **13.5**, different hydroxy, thio or aminophenols **13.1**, and/or different dialkyl bromoalkyl phosphonates **13.2**, the corresponding products **13.4** are obtained.

Scheme **14** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester group attached by means of an aromatic or heteroaromatic group. In this procedure, an optionally protected hydroxy, mercapto or amino-substituted 2.6-dimethylphenol **14.1** is reacted, under basic conditions, with a bis(halomethyl)aryl or heteroaryl compound **14.2**. Equimolar amounts of the phenol and the halomethyl compound are reacted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium or cesium carbonate, or dimethylaminopyridine, to afford the ether, thioether or amino product **14.3**. The product **14.3** is then converted, using the procedures described above, (Scheme **9**) into the phenoxyacetic ester **14.4**. The latter compound is then subjected to an Arbuzov reaction by reaction with a trialkylphosphite **14.5** at ca. 100° to afford the phosphonate ester **14.6**. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in Handb. Organophosphorus Chem., 1992, 115. The resultant product **14.6** is then converted into the acetic acid **14.7** by hydrolysis of the ester moiety, using the procedures described above, (Scheme **9**).

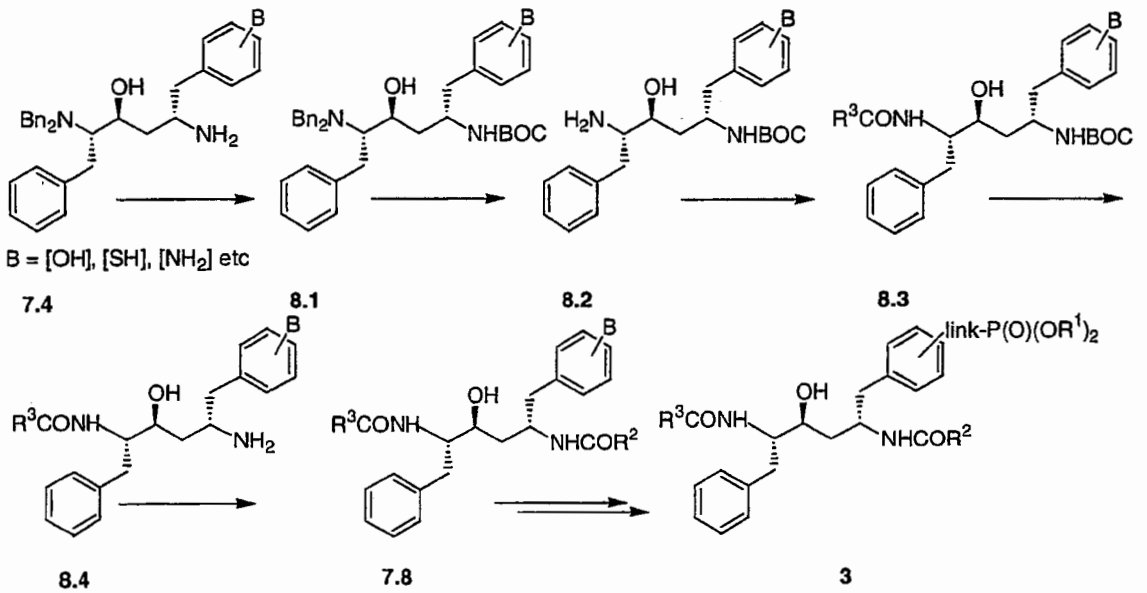
For example, 4-hydroxy-2,6-dimethylphenol **14.8** (Aldrich) is reacted with one molar equivalent of 3,5-bis(chloromethyl)pyridine, the preparation of which is described in Eur. J. Inorg. Chem., 1998, 2, 163, to afford the ether **14.10**. The reaction is conducted in acetonitrile at ambient temperature in the presence of five molar equivalents of potassium carbonate. The product **14.10** is then reacted with ethyl bromoacetate, using the procedures described above, (Scheme **9**) to afford the phenoxyacetic ester **14.11**. This product is heated at 100° for 3 hours with three molar equivalents of triethyl phosphite **14.12**, to afford the phosphonate ester **14.13**. Hydrolysis of the acetic ester moiety, as described above, for example by reaction with lithium hydroxide in aqueous ethanol, then affords the phenoxyacetic acid **14.14**.

Using the above procedures, but employing, in place of the bis(chloromethyl) pyridine **14.9**, different bis(halomethyl) aromatic or heteroaromatic compounds **14.2**, and/or different hydroxy, mercapto or amino-substituted 2,6-dimethylphenols **14.1** and/or different trialkyl phosphites **14.5**, the corresponding products **14.7** are obtained.

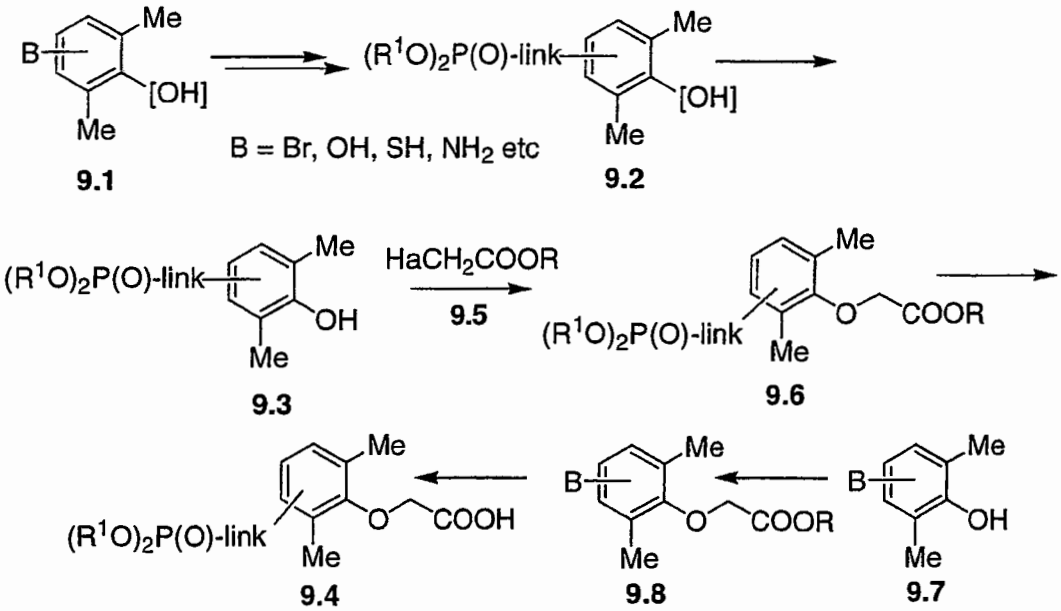
Scheme 7



Scheme 8

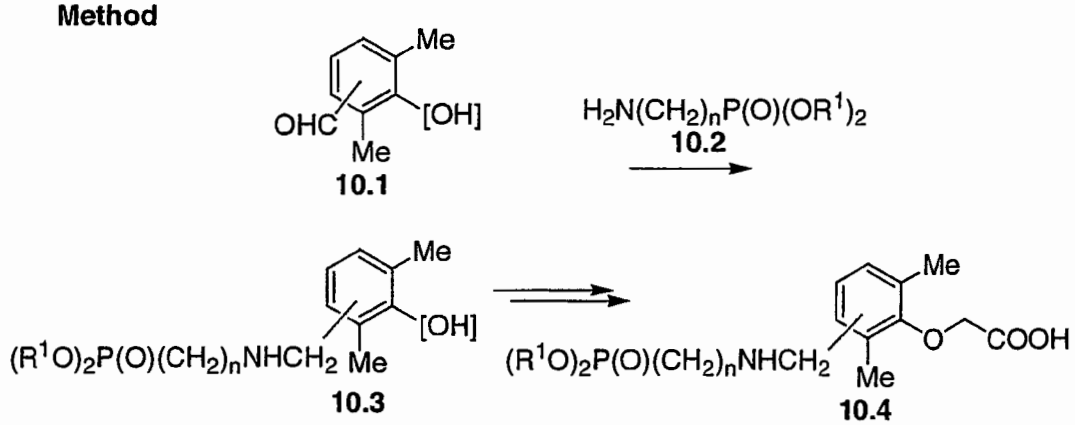


Scheme 9

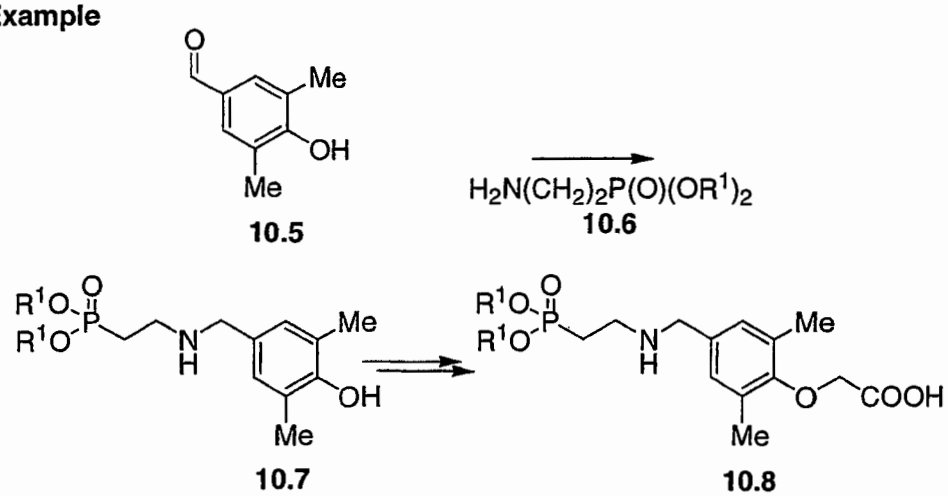


Scheme 10

Method

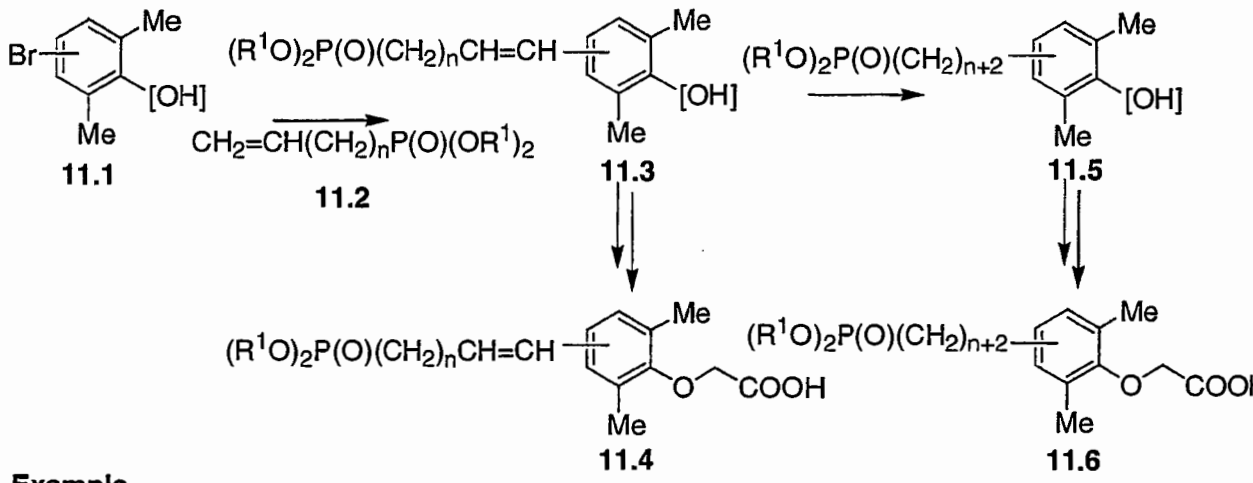


Example

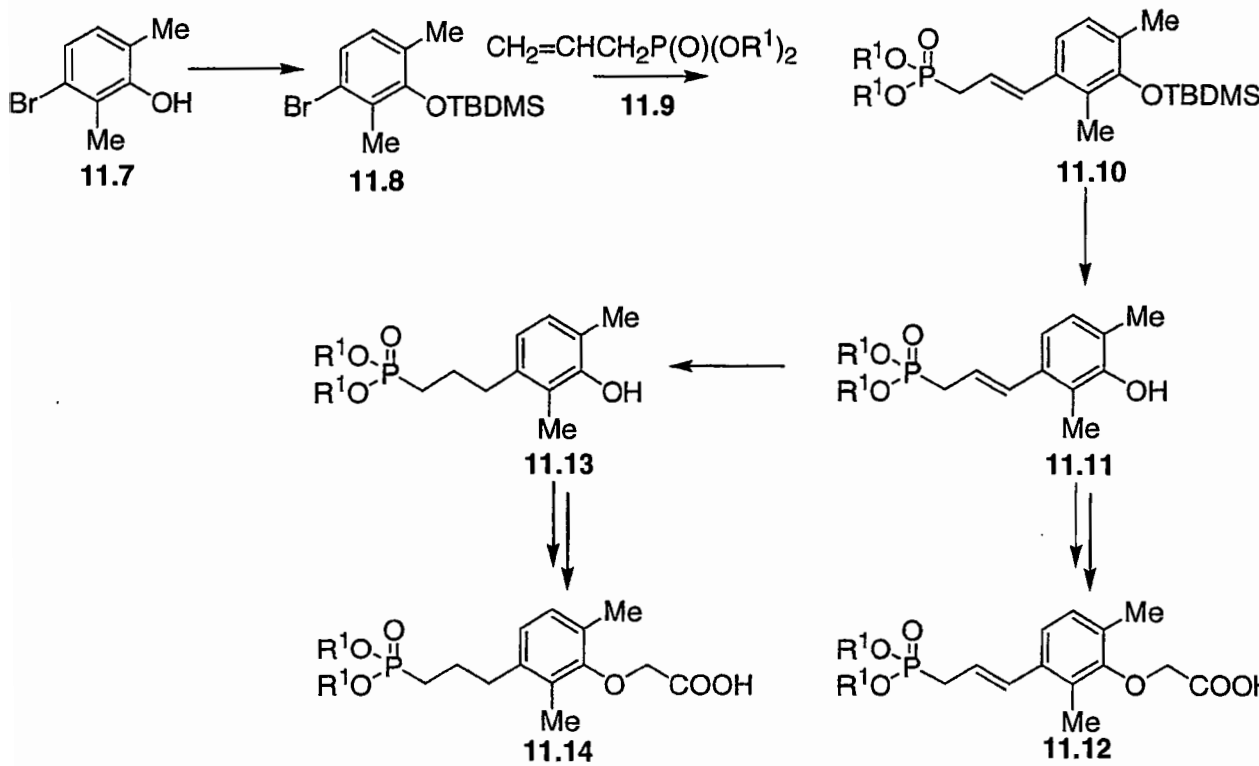


Scheme 11

Method

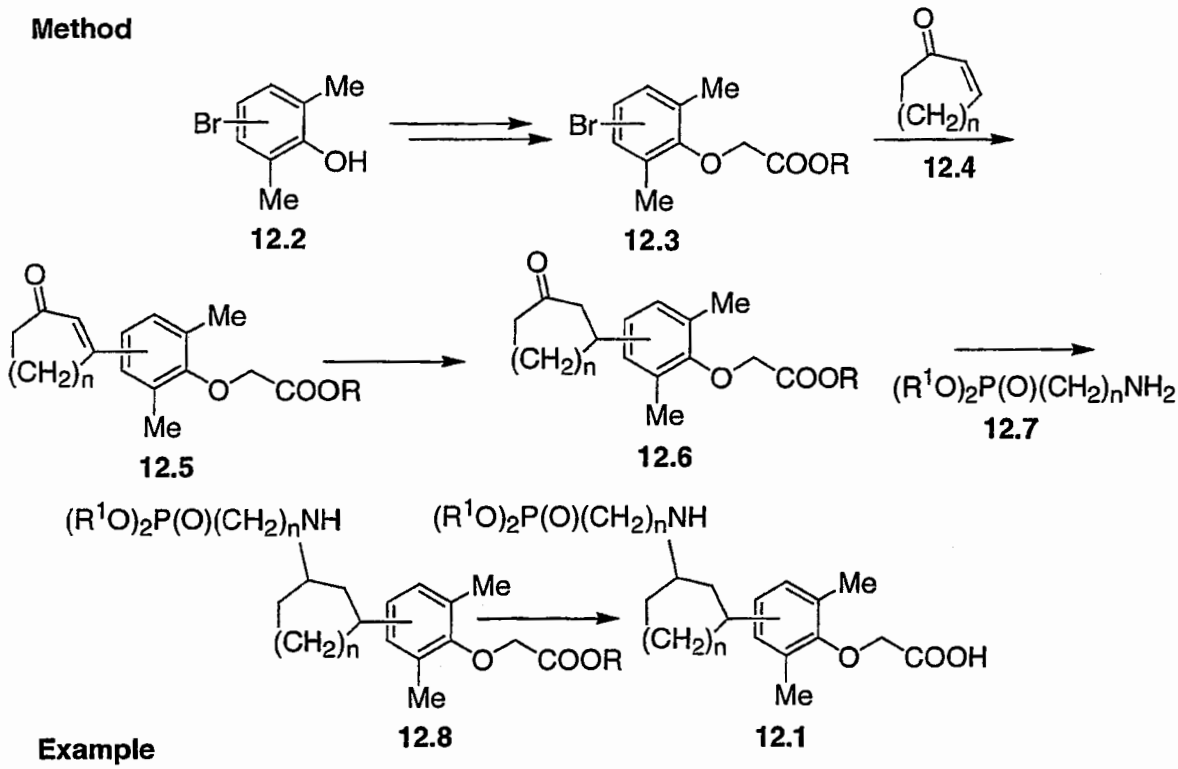


Example

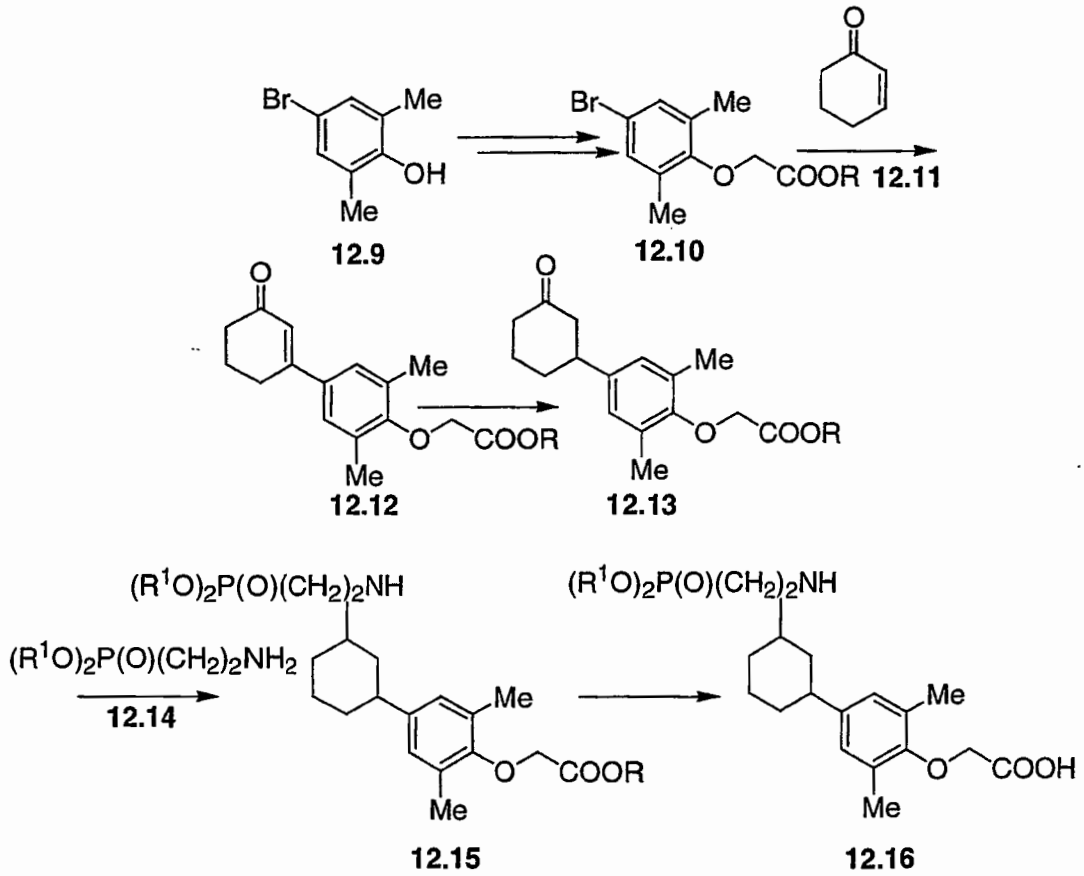


Scheme 12

Method

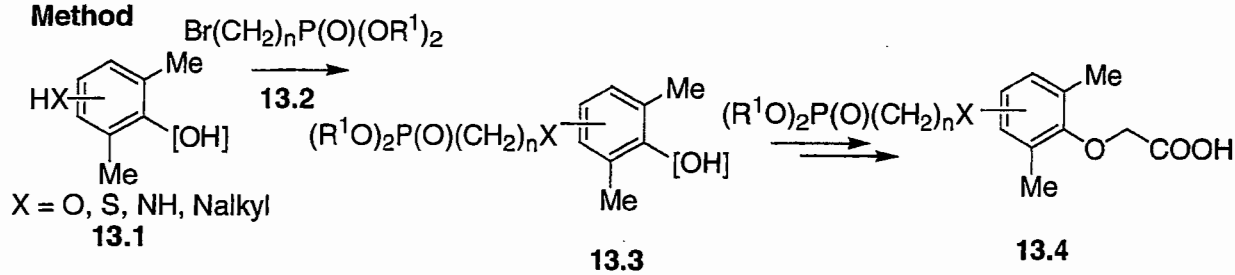


Example

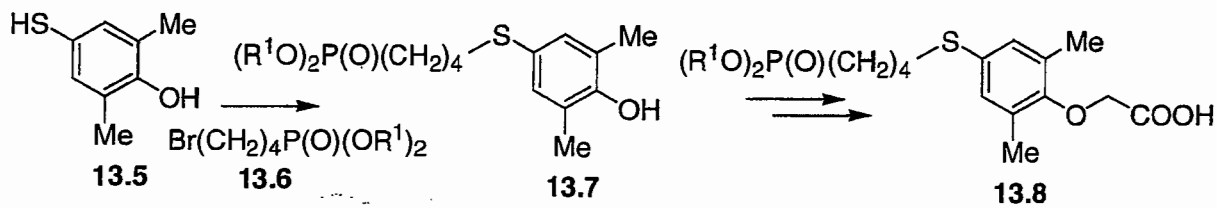


Scheme 13

Method

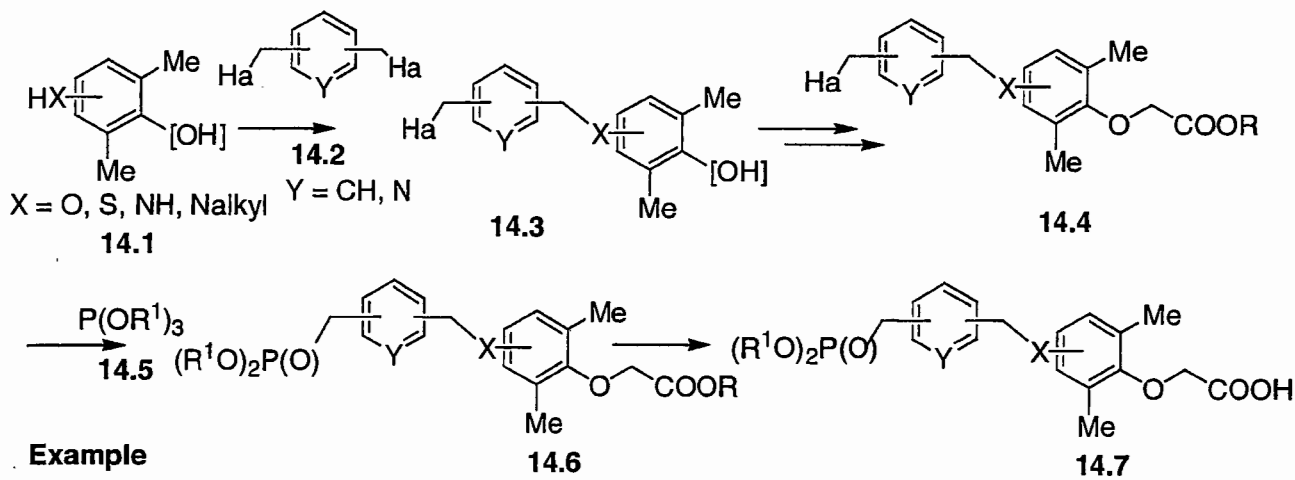


Example

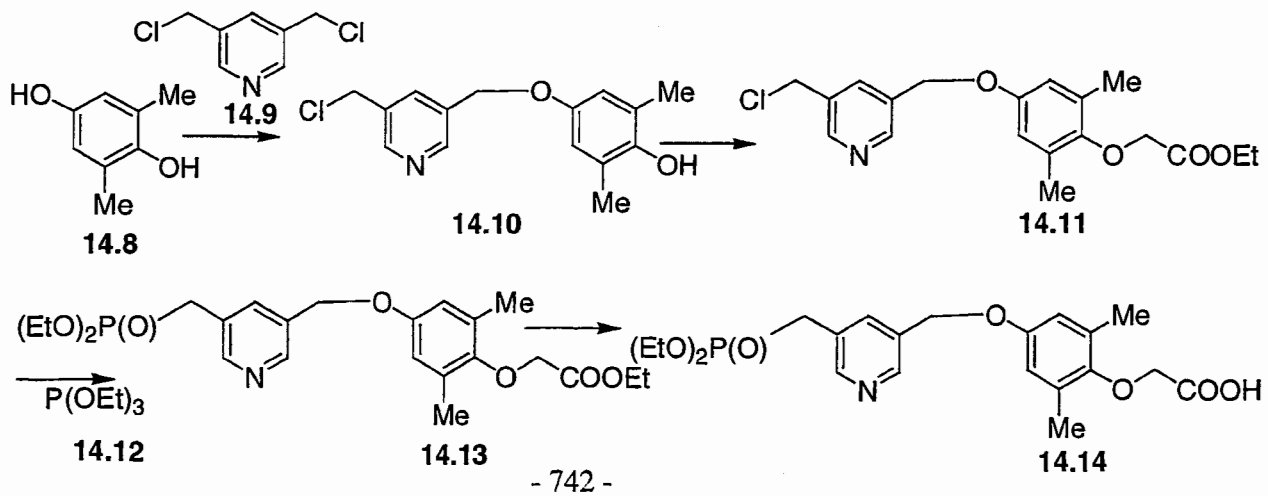


Scheme 14

Method



Example



Preparation of phenylalanine derivatives 4.1 incorporating phosphonate moieties, or precursors thereto.

Schemes **15-17** describe various methods for the preparation of phosphonate-containing analogs of phenylalanine. The compounds are then employed, as described above, (Schemes **4 and 5**) in the preparation of the compounds **2.**

Scheme **15** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives **15.5**.

In this procedure, a hydroxy or mercapto-substituted phenylalanine **15.1** is converted into the benzyl ester **15.2**. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester **15.2** is then protected. Protection methods for phenols and thiols are described respectively, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, suitable OH and SH protecting groups include tert-butyldimethylsilyl or tert-butyldiphenylsilyl. Alternative SH protecting groups include 4-methoxybenzyl and S-adamantyl. The protected hydroxy- or mercapto ester **15.3** is then reacted with a benzyl or substituted benzyl halide and a base, for example as described in U.S. Patent 5,491,253, to afford the N, N-dibenzyl product **15.4**. For example, the amine **15.3** is reacted at ca. 90° with two molar equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, to afford the tribenzylated product **15.4**, as described in U.S. Patent 5,491,253. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p10, p. 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride and the like, in a solvent such as tetrahydrofuran at ambient

temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972. S-Adamantyl protecting groups are removed by treatment with mercuric trifluoroacetate in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.

The resultant phenol or thiophenol **15.5** is then reacted under various conditions to provide protected phenylalanine derivatives **15.6**, **15.7** or **15.8**, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

As one option, the phenol or thiophenol **15.5** is reacted with a dialkyl bromoalkyl phosphonate **15.9** to afford the product **15.6**. The alkylation reaction between **15.5** and **15.9** is effected in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate. The reaction is performed at from ambient temperature to ca. 80°, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product **15.6**.

For example, as illustrated in Scheme **15** Example **1**, a hydroxy-substituted phenylalanine derivative such as tyrosine, **15.12** is converted, as described above, into the benzyl ester **15.13**. The latter compound is then reacted with one molar equivalent of chloro tert-butyldimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether **15.14**. This compound is then converted, as described above, into the tribenzylated derivative **15.15**. The silyl protecting group is removed by treatment of **15.15** with a tetrahydrofuran solution of tetrabutylammonium fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol **15.16**. The latter compound is then reacted in dimethylformamide at ca. 60°, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **15.17** (Aldrich), in the presence of cesium carbonate, to afford the alkylated product **15.18**.

Using the above procedures, but employing, in place of the 4-hydroxy phenylalanine **15.12**, different hydroxy or thio-substituted phenylalanine derivatives **15.1**, and/or different bromoalkyl phosphonates **15.9**, the corresponding ether or thioether products **15.6** are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **15.5** is reacted with a dialkyl hydroxymethyl phosphonate **15.10** under the conditions of the Mitsonobu reaction, to afford the ether or thioether compounds **15.7**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in

Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine.

For example, as shown in Scheme **15**, Example **2**, 3-mercaptophenylalanine **15.19**, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester **15.20**. The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether **15.21**. This compound is then converted, as described above for the preparation of the tribenzylated phenylalanine derivative **15.4**, into the tribenzyl derivative **15.22**. The 4-methoxybenzyl group is then removed by the reaction of the thioether **15.22** with mercuric trifluoroacetate and anisole in trifluoroacetic acid, as described in J.Org. Chem., 52, 4420, 1987, to afford the thiol **15.23**. The latter compound is reacted, under the conditions of the Mitsonobu reaction, with a dialkyl hydroxymethyl phosphonate **15.24**, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product **15.25**.

Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative **15.19**, different hydroxy or mercapto-substituted phenylalanines **15.1**, and/or different dialkylhydroxymethyl phosphonates **15.10**, the corresponding products **15.7** are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **15.5** is reacted with an activated derivative of a dialkyl hydroxymethylphosphonate **15.11** in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base such as triethylamine or cesium carbonate, to afford the ether or thioether products **15.8**.

For example, as illustrated in Scheme **15**, Example **3**, 3-hydroxyphenylalanine **15.26** (Fluka) is converted, using the procedures described above, into the tribenzylated compound **15.27**. The latter compound is reacted, in dimethylformamide at ca. 50°, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate **15.28**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product **15.29**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **15.26**, different hydroxy or mercapto-substituted phenylalanines **15.1**, and/or

different dialkyl trifluoromethanesulfonyloxymethylphosphonates **15.11**, the corresponding products **15.8** are obtained.

Scheme **16** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a formyl-substituted tribenzylated phenylalanine derivative **16.1** and a dialkyl aminoalkylphosphonate **16.2**.

In this procedure, a hydroxymethyl-substituted phenylalanine **16.3** is converted into the tribenzylated derivative **16.4** by reaction with three equivalents of a benzyl halide, for example, benzyl chloride, in the presence of an organic or inorganic base such as diazabicyclononene or potassium carbonate. The reaction is conducted in a polar solvent optionally in the additional presence of water. For example, the aminoacid **16.3** is reacted with three equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, as described in U.S. Patent 5,491,253, to afford the product **16.4**. The latter compound is then oxidized to afford the corresponding aldehyde **16.1**. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product **16.1**. For example, the carbinol **16.4** is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in J. Org. Chem., 43, 2480, 1978, to yield the aldehyde **16.1**. This compound is reacted with a dialkyl aminoalkylphosphonate **16.2** in the presence of a suitable reducing agent to afford the amine product **16.5**. The preparation of amines by means of a reductive amination reaction is described above (Scheme **10**).

For example, 3-(hydroxymethyl)-phenylalanine **16.6**, prepared as described in Acta Chem. Scand. Ser. B, 1977, B31, 109, is converted, as described above, into the formylated derivative **16.8**. This compound is then reacted, in ethanol, at ambient temperature, with one molar equivalent of a dialkyl aminoethylphosphonate **16.9**, prepared as described in J. Org. Chem., 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated product **16.10**.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine **16.6**, different hydroxymethyl phenylalanines **16.3**, and/or different aminoalkyl phosphonates **16.2**, the corresponding products **16.5** are obtained.

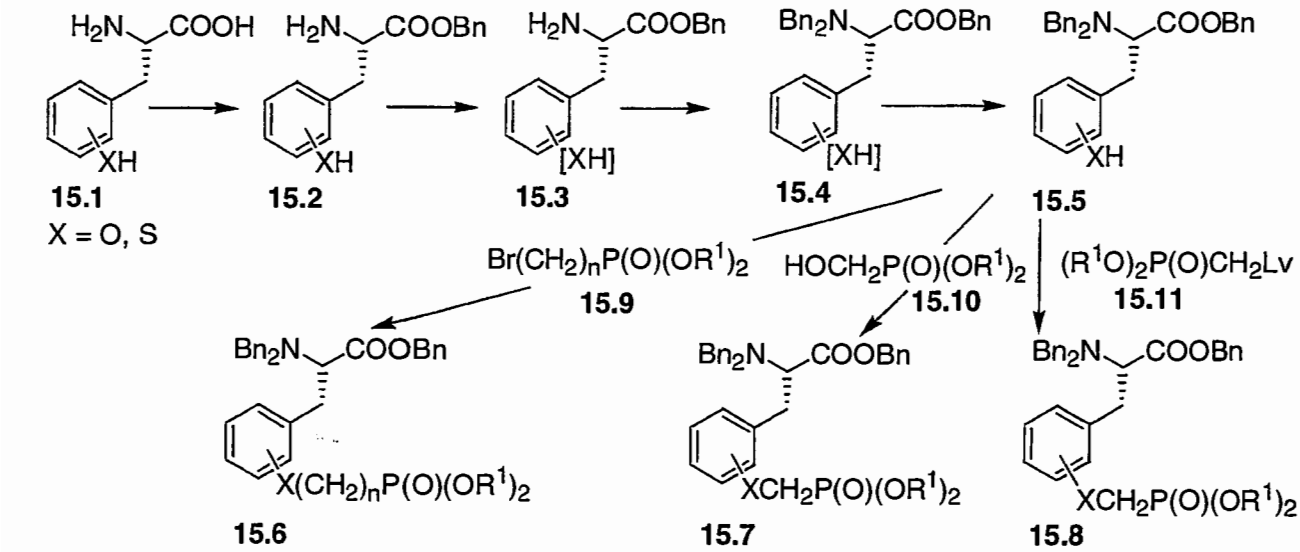
Scheme **17** depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a suitably protected bromo-substituted phenylalanine **17.2** is coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **17.3** to produce the phosphonate ester **17.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.

For example, 3-bromophenylalanine **17.5**, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme **15**) into the tribenzylated compound **17.6**. This compound is then reacted, in toluene solution at reflux, with diethyl phosphite **17.7**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product **17.8**.

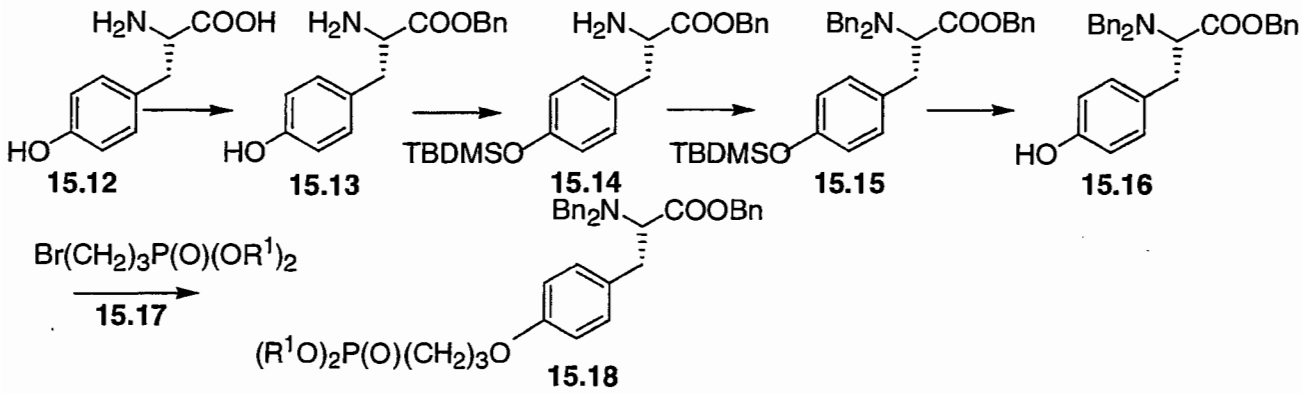
Using the above procedures, but employing, in place of 3-bromophenylalanine **17.5**, different bromophenylalanines **17.1**, and/or different dialkylphosphites **17.3**, the corresponding products **17.4** are obtained.

Scheme 15

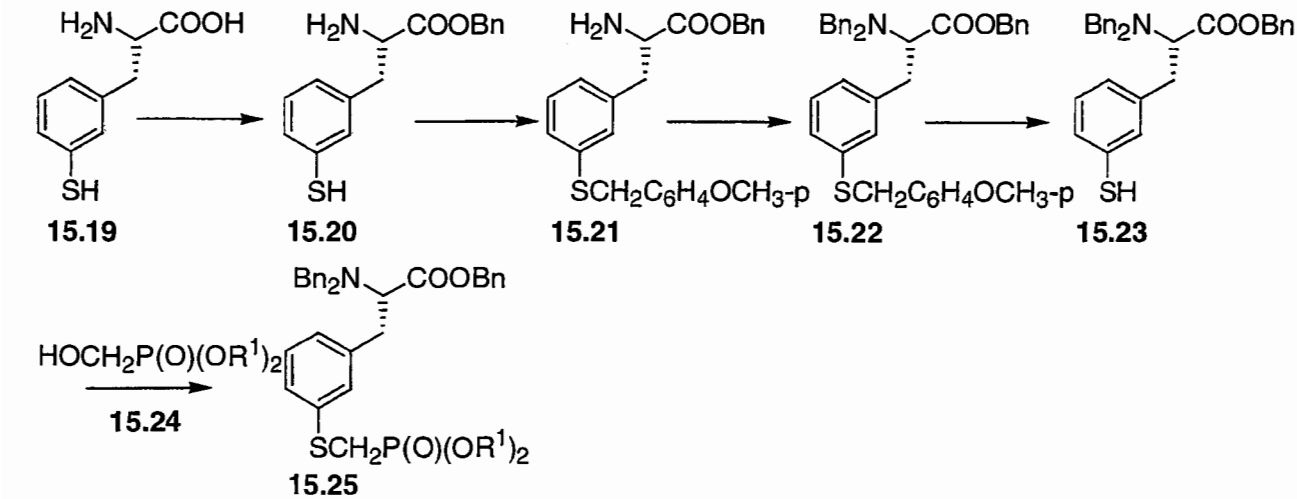
Method



Example1

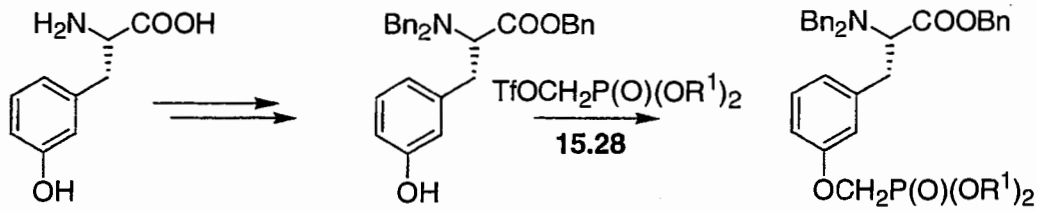


Example 2



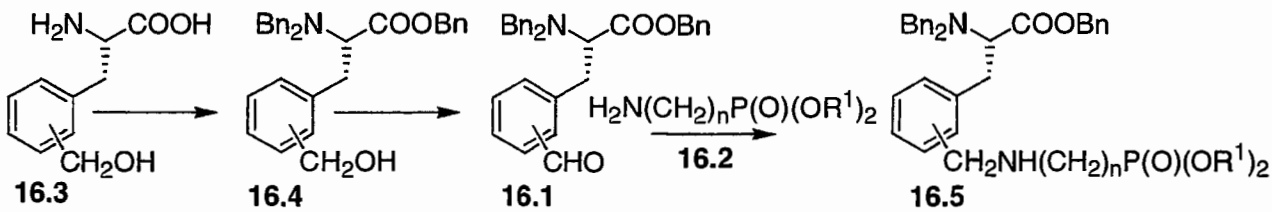
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Example 3

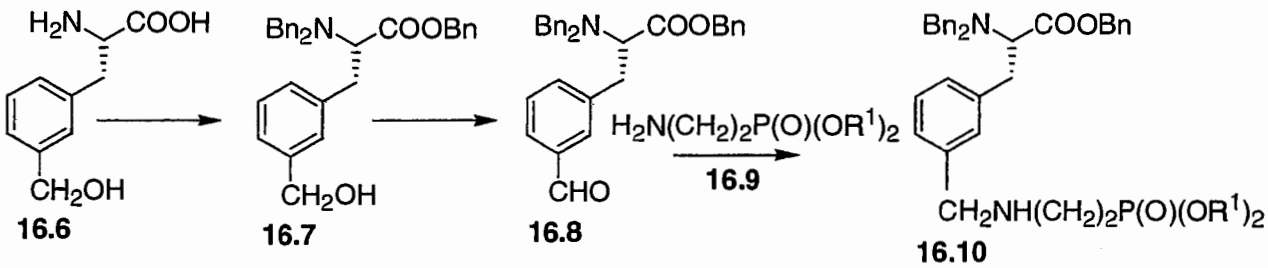


Scheme 16

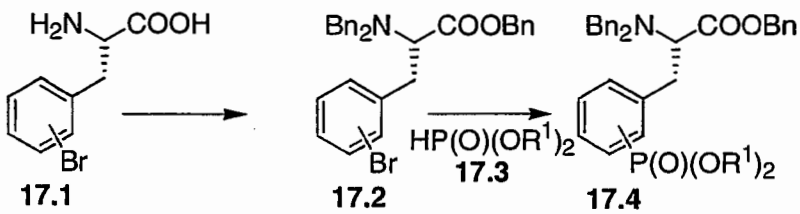
Method



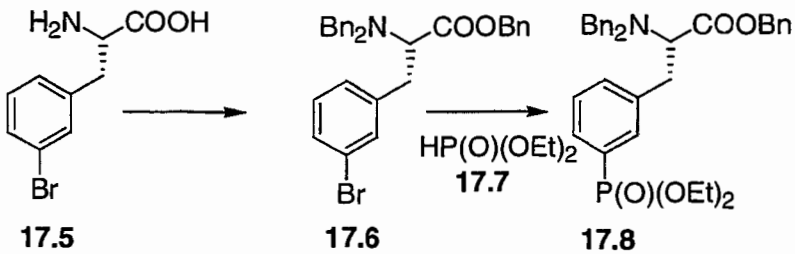
Example



Scheme 17



Example



Preparation of phosphonate esters with structure 3.

Scheme **18** illustrates the preparation of compounds **3** in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, the ketonitrile **7.1**, prepared as described in J. Org. Chem., 1994, 59, 4080, is reacted, as described above (Scheme **n**) with a bromobenzylmagnesium halide reagent **18.1**. The resultant ketoenamine **18.2** is then converted into the diacylated bromophenyl carbinol **18.3**. The conditions required for the conversion of the ketoenamine **18.2** into the carbinol **18.3** are similar to those described above (Scheme **7**), for the conversion of the ketoenamine **7.3** into the carbinol **7.8**. The product **18.3** is then reacted with a dialkyl phosphite **17.3**, in the presence of a palladium (0) catalyst, to yield the phosphonate ester **3**. The conditions for the coupling reaction are the same as those described above (Scheme **17**) for the preparation of the phosphonate ester **17.8**.
For example, the ketonitrile **7.1** is reacted, in tetrahydrofuran solution at 0°, with three molar equivalents of 4-bromobenzylmagnesium bromide **18.4**, the preparation of which is described in Tetrahedron, 2000, 56, 10067, to afford the ketoenamine **18.5**. The latter compound is then converted into the diacylated bromophenyl carbinol **18.6**, using the sequence of reactions described above (Scheme **7**) for the conversion of the ketoenamine **7.3** into the carbinol **7.8**. The resultant bromo compound **18.6** is then reacted with diethyl phosphite **18.7** and triethylamine, in toluene solution at reflux, in the presence of tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product **18.8**.
Using the above procedures, but employing, in place of 4-bromobenzylmagnesium bromide **18.4**, different bromobenzylmagnesium halides **18.1** and/or different dialkyl phosphites **17.3**, there are obtained the corresponding phosphonate esters **3**.

Scheme **19** illustrates the preparation of compounds **3** in which the phosphonate ester moiety is attached to the nucleus by means of a phenyl ring. In this procedure, a bromophenyl-substituted benzylmagnesium bromide **19.1**, prepared from the corresponding bromomethyl compound by reaction with magnesium, is reacted with the ketonitrile **7.1**. The conditions for this transformation are the same as those described above (Scheme **7**). The product of the Grignard addition reaction is then transformed, using the sequence of reactions described

above, (Scheme **7**) into the diacylated carbinol **19.2**. The latter compound is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **17.3**, to afford the phenylphosphonate **3**. The procedure for the coupling reaction is the same as those described above for the preparation of the phosphonate **17.4**.

For example, 4-(4-bromophenyl)benzyl bromide, prepared as described in DE 2262340, is reacted with magnesium to afford 4-(4-bromophenyl)benzylmagnesium bromine **19.3**. This product is then reacted with the ketonitrile **7.1**, as described above, to yield, after the sequence of reactions shown in Scheme **7**, the diacylated carbinol **19.4**. The latter compound is then reacted, as described above, (Scheme **17**) with a diethyl phosphite **17.3**, to afford the phenylphosphonate **19.5**.

Using the above procedures, but employing, in place of 4-(4-bromophenyl)benzyl bromide **19.3**, different bromophenylbenzyl bromides **19.1**, and/or different dialkyl phosphites **17.3**, the corresponding products **3** are obtained.

Scheme **20** depicts the preparation of phosphonate esters **3** in which the phosphonate group is attached by means of a heteroatom and a methylene group. In this procedure, a hetero-substituted benzyl alcohol **20.1** is protected, affording the derivative **20.2**. The protection of phenyl hydroxyl, thiol and amino groups are described, respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277, 309. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. Amino groups can be protected, for example by dibenzylation. The conversion of amines into dibenzylamines, for example by treatment with benzyl bromide in a polar solvent such as acetonitrile or aqueous ethanol, in the presence of a base such as triethylamine or sodium carbonate, is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 364. The resultant protected benzyl alcohol **20.2** is converted into a halo derivative **20.3**, in which Ha is chloro or bromo. The conversion of alcohols into chlorides and bromides is described, for example, in

Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. For example, benzyl alcohols **20.2** can be transformed into the chloro compounds **20.3**, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in J. Am. Chem. Soc., 106, 3286, 1984. Benzyl alcohols can be transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc., 92, 2139, 1970. The resultant protected benzyl halide **20.3** is then converted into the corresponding benzylmagnesium halide **20.4** by reaction with magnesium metal in an ethereal solvent, or by a Grignard exchange reaction treatment with an alkyl magnesium halide. The resultant substituted benzylmagnesium halide **20.4** is then converted, using the sequence of reactions described above (Scheme **7**) for the preparation of **7.8**, into the carbinol **20.5** in which the substituent XH is suitably protected.

The protecting group is then removed to afford the phenol, thiophenol or amine **20.6**. Deprotection of phenols, thiophenols and amines is described respectively in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperature, as described in Chem. Pharm. Bull., 26, 1576, 1978. N,N-dibenzyl amines can be converted into the unprotected amines by catalytic reduction in the presence of a palladium catalyst, as described above (Scheme **1**). The resultant phenol, thiophenol or amine **20.6** is then converted into the phosphonate ester **3** by reaction with an activated derivative of a dialkyl hydroxymethyl phosphonate **15.11**, in which Lv is a leaving group. The reaction is conducted under the same conditions as described above for the alkylation of the phenol **15.5** to afford the ether or thioether **15.8** (Scheme **15**).

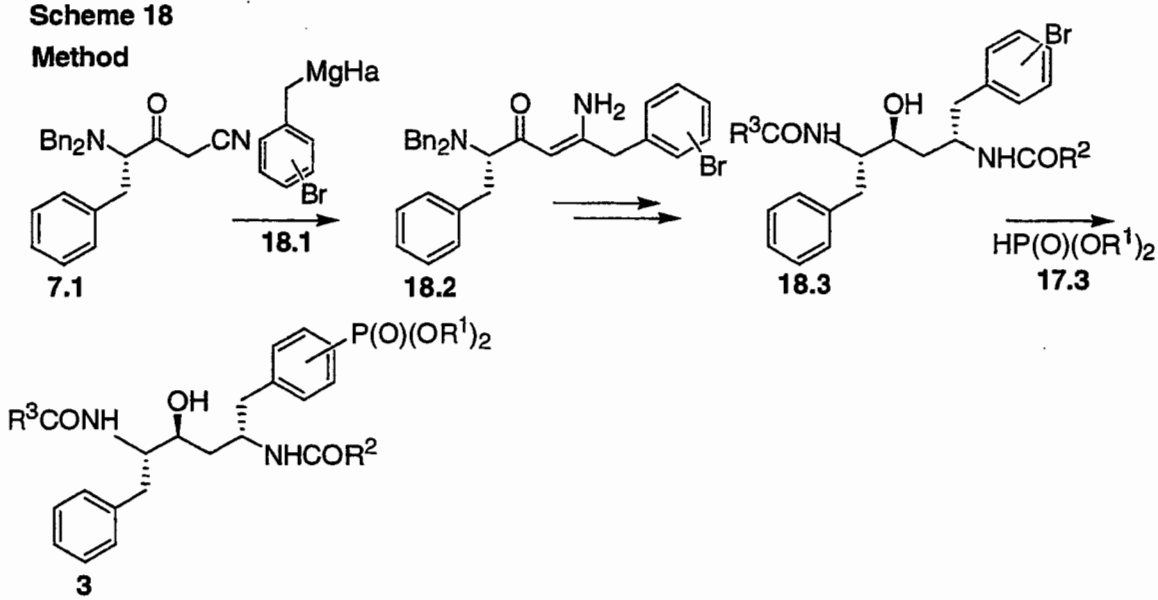
For example, 3-hydroxybenzyl alcohol **20.7** (Aldrich) is reacted with chlorotriisopropylsilane and imidazole in dimethylformamide, as described in Tet. Lett., 2865, 1964, to afford the silyl ether **20.8**. This compound is reacted with carbon tetrabromide and triphenylphosphine in dichloromethane, as described in J. Am. Chem. Soc., 109, 2738, 1987, to afford the brominated product **20.9**. This material is reacted with magnesium in ether to afford the Grignard reagent **20.10**, which is then subjected to the series of reaction shown in Scheme **7** to afford the carbinol **20.11**. The triisopropylsilyl protecting group is then removed by treatment

of the ether **20.11** with tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Org. Chem., 51, 4941, 1986. The resultant phenol **20.12** is then reacted in dimethylformamide solution with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **15.28**, prepared as described in Synthesis, 4, 327, 1998, in the presence of a base such as dimethylaminopyridine, as described above (Scheme **15**) to afford the phosphonate product **20.13**.

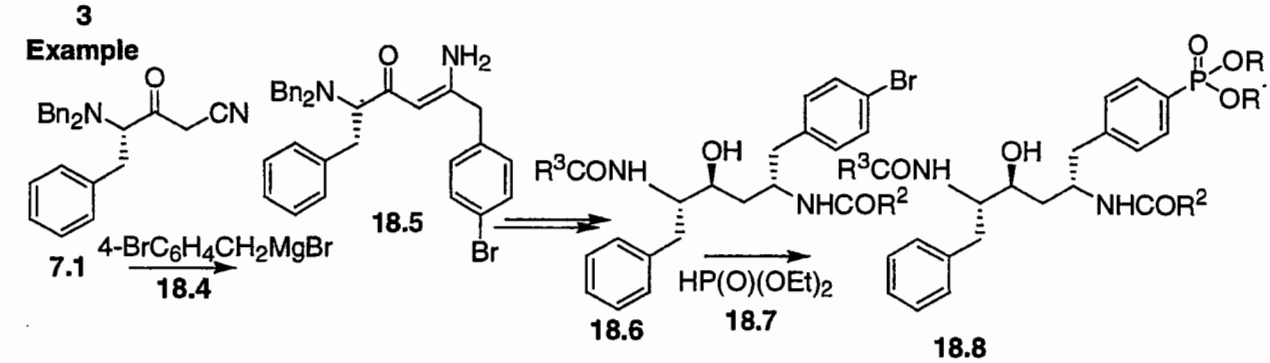
Using the above procedures, but employing, in place of 3-hydroxybenzyl alcohol **20.7**, different hydroxy, mercapto or amino-substituted benzyl alcohols **20.1**, and/or different dialkyl hydroxymethyl phosphonate derivatives **15.11**, the corresponding products **3** are obtained.

Scheme 18

Method

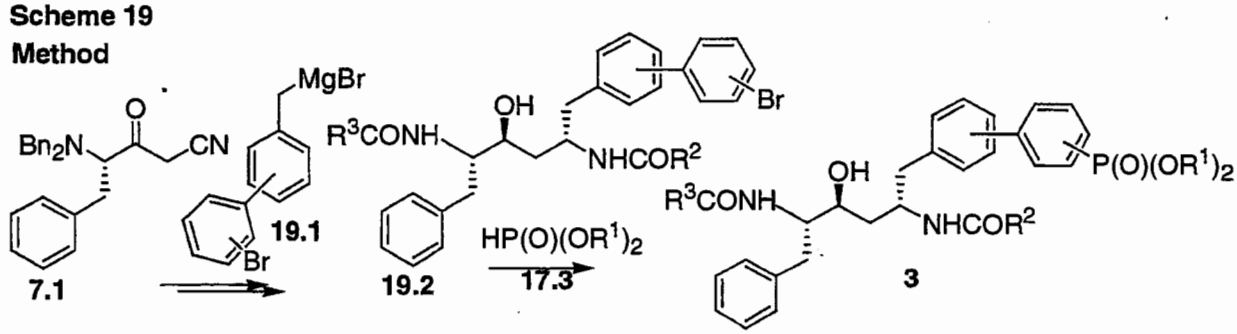


Example

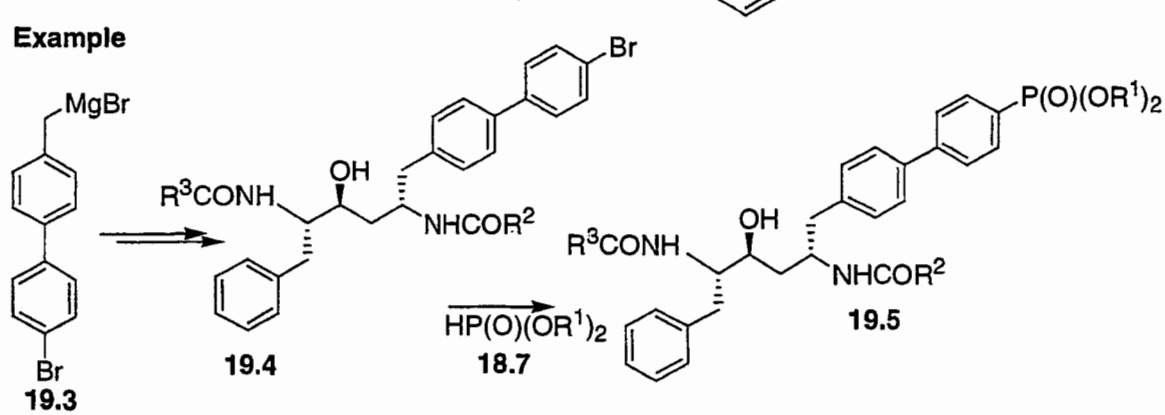


Scheme 19

Method

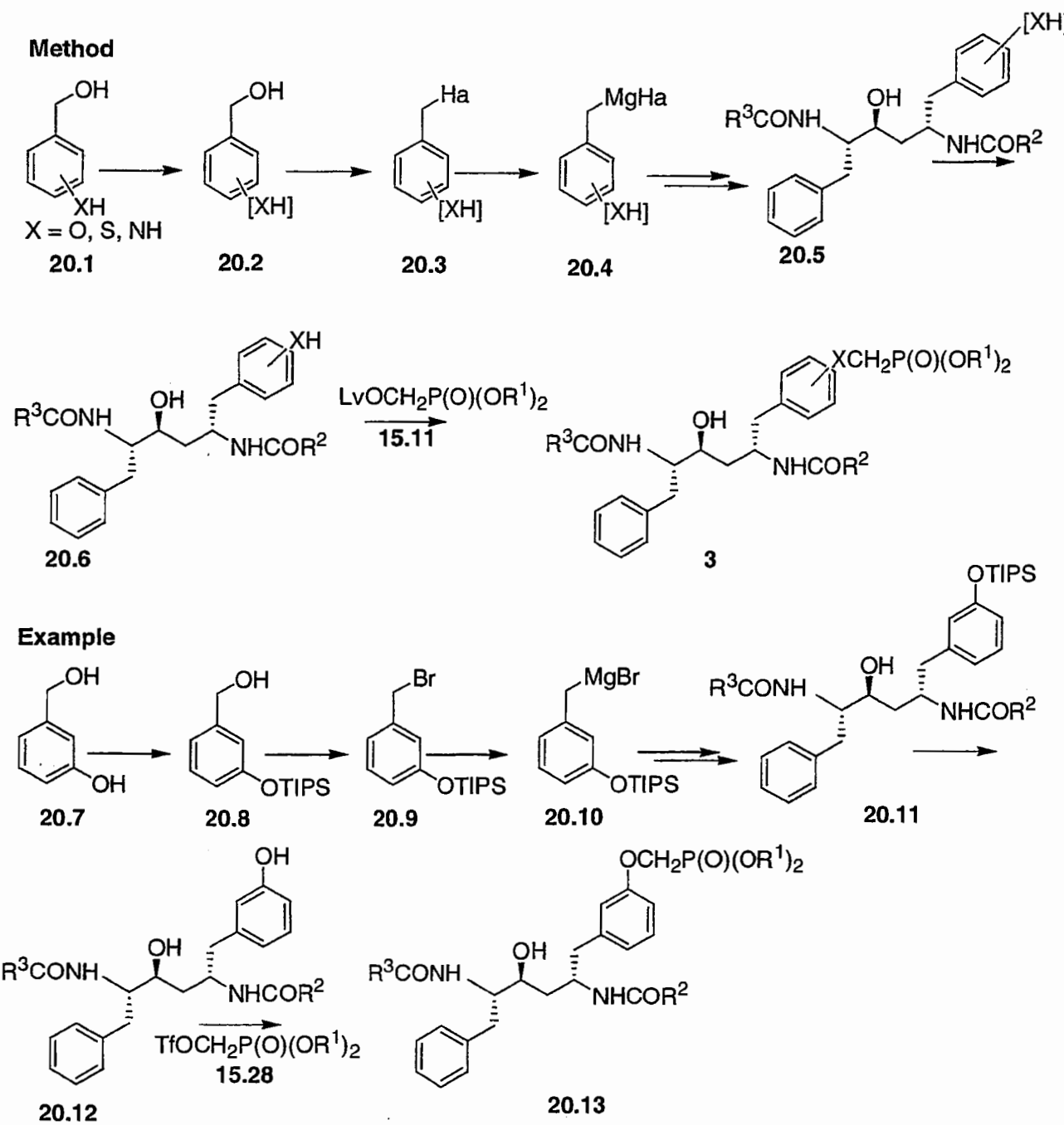


Example



Scheme 20

Method



Interconversions of the phosphonates R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH) and R-link-P(O)(OH)$_2$.

Schemes **1-33** described the preparations of phosphonate esters of the general structure R-link-P(O)$(OR^1)_2$, in which the groups R^1, the structures of which are defined in Chart **1**, may be the same or different. The R^1groups attached to a phosphonate esters **1-5**, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme **21**. The group R in Scheme **21** represents the substructure to which the substituent link-P(O)$(OR^1)_2$ is attached, either in the compounds **1-5** or in precursors thereto. The R^1 group may be changed, using the procedures described below, either in the precursor compounds, or in the esters **1-5**. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **21.1** into the corresponding phosphonate monoester **21.2** (Scheme **21**, Reaction 1) can be accomplished by a number of methods. For example, the ester **21.1** in which $R^1$is an aralkyl group such as benzyl, can be converted into the monoester compound **21.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester **21.1** in which $R^1$is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **21.2** can be effected by treatment of the ester **21.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **21.1** in which one of the groups $R^1$is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **21.2** in which $R^1$is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups $R^1$are alkenyl, such as allyl, can be converted into the monoester **21.2** in which $R^1$is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **21.1** or a phosphonate monoester **21.2** into the corresponding phosphonic acid **21.3** (Scheme **21**, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc.,

Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **21.2** in which $R^1$is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **21.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **21.2** in which $R^1$is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **21.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **21.1** in which $R^1$is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **21.1** in which $R^1$is phenyl is described in J. Amer. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester **21.2** into a phosphonate diester **21.1** (Scheme **21**, Reaction 4) in which the newly introduced R^1group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **21.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **21.2** to the diester **21.1** can be effected by the use of the Mitsonobu reaction, as described above (Scheme **15**). The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **21.2** can be transformed into the phosphonate diester **21.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as

cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **21.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **21.1**.

A phosphonic acid R-link-$P(O)(OH)_2$ can be transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **21**, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ **21.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid R-link-$P(O)(OH)_2$ **21.3** can be transformed into a phosphonate diester R-link-$P(O)(OR^1)_2$ **21.1** (Scheme **21**, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **21.3** can be transformed into phosphonic esters **21.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°. Alternatively, phosphonic acids **21.3** can be transformed into phosphonic esters **21.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **21.1**.

Phosphonate esters 1-5 incorporating carbamate moieties.

The phosphonate esters **1-5** in which the R^2CO or R^3CO groups are formally derived from the carboxylic acid synthons **C38 - C49** as shown in Chart **2c**, contain a carbamate moiety. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme **22** illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme **22**, in the general reaction generating carbamates, a carbinol **22.1** is converted into the activated derivative **22.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **22.2** is then reacted with an amine **22.3**, to afford the carbamate product **22.4**. Examples **1 – 7** in Scheme **22** depict methods by which the general reaction can be effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.

Scheme **22**, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **22.5**. In this procedure, the carbinol **22.5** is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **22.6**. The latter compound is then reacted with the amine component **22.3**, in the presence of an organic or inorganic base, to afford the carbamate **22.7**. For example, the chloroformyl compound **22.6** is reacted with the amine **22.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **22.7**. Alternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme **22**, Example **2** depicts the reaction of the chloroformate compound **22.6** with imidazole, **22.7**, to produce the imidazolide **22.8**. The imidazolide product is then reacted with the amine **22.3** to yield the carbamate **22.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme **22** Example **3**, depicts the reaction of the chloroformate **22.6** with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester **22.10**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **22.19** - **22.24** shown in Scheme **22**, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **22.19**, N-hydroxysuccinimide **22.20**, or pentachlorophenol, **22.21**, the mixed carbonate **22.10** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of

dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **22.22** or 2-hydroxypyridine **22.23** can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme **22** Example **4** illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **22.8** is employed. In this procedure, a carbinol **22.5** is reacted with an equimolar amount of carbonyl diimidazole **22.11** to prepare the intermediate **22.8**. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **22.8** is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **22.7**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate **22.7**.

Scheme **22**, Example **5** illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **22.13**. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **22.12**, to afford the alkoxycarbonyl product **22.13**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine $R'NH_2$ to afford the carbamate **22.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80° as described in Syn., 1977, 704.

Scheme **22**, Example **6** illustrates the preparation of carbamates in which a carbonate $(R"O)_2CO$, **22.14**, is reacted with a carbinol **22.5** to afford the intermediate alkyloxycarbonyl intermediate **22.15**. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate **22.7**. The procedure in which the reagent **22.15** is derived from hydroxybenztriazole **22.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **22.15** is derived from N-hydroxysuccinimide **22.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **22.15** is derived from 2-hydroxypyridine **22.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **22.15** is derived from 4-nitrophenol **22.24** is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate **22.14** is conducted in an inert organic solvent at ambient temperature.

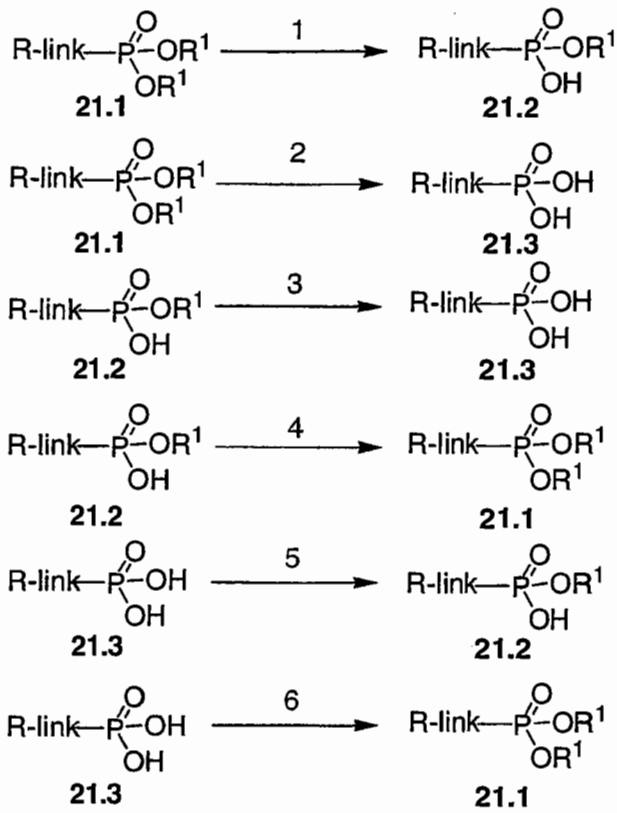
Scheme **22**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides **22.16**. in this procedure, an alkyl chloroformate **22.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **22.16**. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **22.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme **22**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **22.7**.

Scheme **22**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **22.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **22.7**.

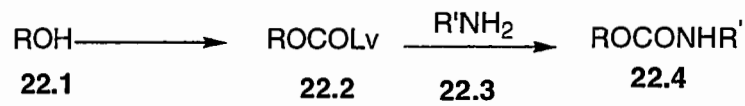
Scheme **22**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **22.7**.

Scheme 21

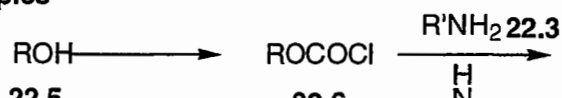

R-link—P(=O)(OR1)(OR1)
1
R-link—P(=O)(OR1)(OH)
21.1
21.2
R-link—P(=O)(OR1)(OR1)
2
R-link—P(=O)(OH)(OH)
21.1
21.3
R-link—P(=O)(OR1)(OH)
3
R-link—P(=O)(OH)(OH)
21.2
21.3
R-link—P(=O)(OR1)(OH)
4
R-link—P(=O)(OR1)(OR1)
21.2
21.1
R-link—P(=O)(OH)(OH)
5
R-link—P(=O)(OR1)(OH)
21.3
21.2
R-link—P(=O)(OH)(OH)
6
R-link—P(=O)(OR1)(OR1)
21.3
21.1

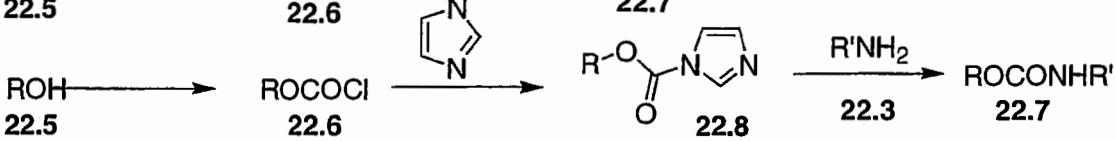
Scheme 22

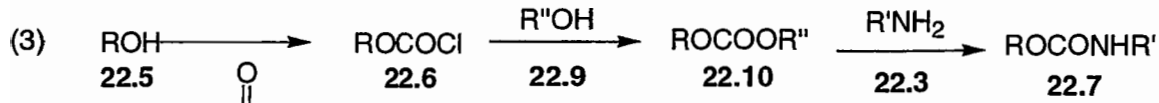
General reaction

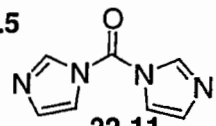


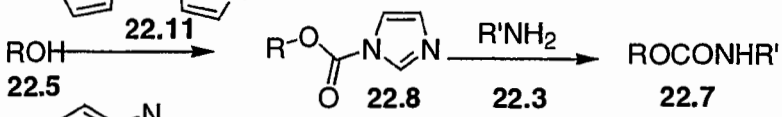
Examples

(1) 

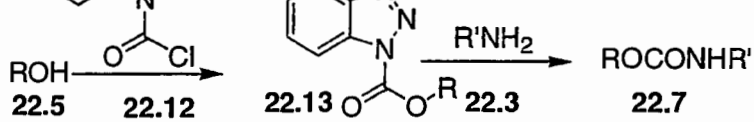
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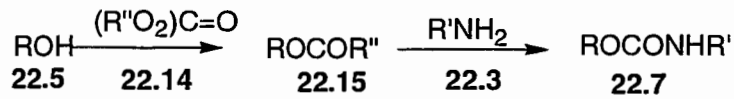
(3) 

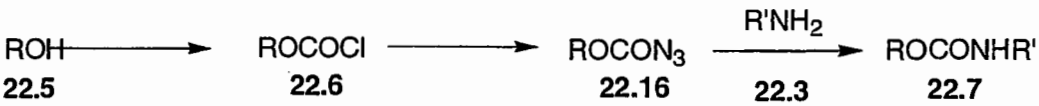


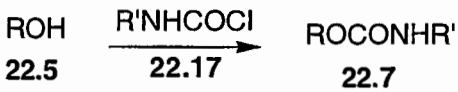
(4) 

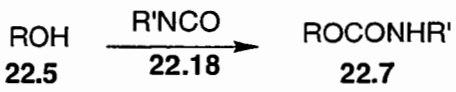


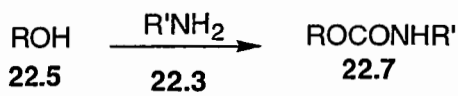
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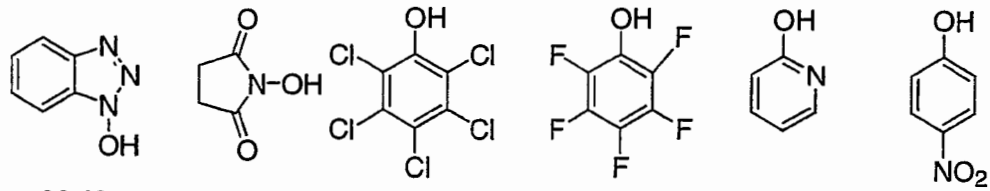
(6) 

(7) 

(8) 

(9) 

(10) 

R"OH = 

Preparation of phosphonate intermediates 4 and 5 with phosphonate moieties incorporated into the groups R^2COOH and R^3COOH.

The chemical transformations described in Schemes **1-22** illustrate the preparation of compounds **1-3** in which the phosphonate ester moiety is attached to the dimethylphenoxyacetyl (R^3) substructure, (Schemes **1-3**), the phenylalanine moiety (Schemes **4-6**), and the benzyl moiety (Schemes **7**, **8**).

The various chemical methods employed herein (Schemes **9-22**) for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds R^2COOH and R^3COOH, as defined in Charts **2a**, **2b**, and **2c**. The resultant phosphonate-containing analogs $R^{2a}COOH$ and $R^{3a}COOH$ can then, using the procedures described above, be employed in the preparation of the compounds **4** and **5**. The procedures required for the introduction of the phosphonate-containing analogs $R^{2a}COOH$ and $R^{3a}COOH$ are the same as those described above (Schemes **4**, **5** and **22**) for the introduction of the R^2CO and R^3CO moieties.

For example, Schemes **23** - **27** illustrate methods for the preparation of hydroxymethyl-substituted benzoic acids (structure **C25**, Chart **2b**) incorporating phosphonate moieties; Schemes **28-30** illustrate the preparation of tetrahydropyrimidine aminoacid derivatives (structure **C27**, Scheme **2b**) incorporating phosphonate ester moieties, and Schemes **31-33** show the syntheses of benzyl carbamate aminoacid derivatives (structure **C4**, Chart **2a**) incorporating phosphonate ester moieties. The thus-obtained phosphonate ester synthons are then incorporated into the compounds **4** and **5**.

Scheme **23** illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid **23.1** is subjected to halogen-methyl exchange to afford the organometallic intermediate **23.2**. This compound is reacted with a chlorodialkyl phosphite **23.3** to yield the phenylphosphonate ester **23.4**, which upon deprotection affords the carboxylic acid **23.5**.

For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, **23.6**, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Amer. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The

acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane **23.7**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester **23.8**. This compound is treated with boron trifluoride at 0° to effect rearrangement to the orthoester **23.9**, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether **23.10**. Halogen-metal exchange is performed by the reaction of **23.10** with butyllithium, and the lithiated intermediate is then coupled with a chlorodialkyl phosphite **23.3**, to produce the phosphonate **23.11**. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid **23.12**.

Using the above procedures, but employing, in place of the bromo compound **23.6**, different bromo compounds **23.1**, there are obtained the corresponding products **23.5**.

Scheme **24** illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

In this method, a suitably protected dimethyl hydroxybenzoic acid, **24.1**, is reacted with a brominating agent, so as to effect benzylic bromination. The product **24.2** is reacted with a sodium dialkyl phosphite, **24.3**, as described in J. Med. Chem., 1992, 35, 1371, to effect displacement of the benzylic bromide to afford the phosphonate **24.4**. Deprotection of the carboxyl function then yields the carboxylic acid **24.5**.

For example, 2,5-dimethyl-3-hydroxybenzoic acid, **24.6**, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p17, to afford the ether ester **24.7**. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or diisopropylethylamine. The product **24.7** is then reacted with a brominating agent, for example N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product **24.8**. This compound is then reacted with a sodium dialkyl phosphite **24.3** in tetrahydrofuran, as described above, to afford the phosphonate **24.9**. Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields the carboxylic acid **24.10**.

Using the above procedures, but employing, in place of the methyl compound **24.6**, different methyl compounds **24.1**, there are obtained the corresponding products **24.5**.

Scheme **25** illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom. In this method, a suitably protected hydroxy- or mercapto-substituted hydroxymethyl benzoic acid **25.1** is reacted, under the conditions of the Mitsonobu reaction, with a dialkyl hydroxymethyl phosphonate **25.2**, to afford the coupled product **25.3**, which upon deprotection affords the carboxylic acid **25.4**.

For example, 3,6-dihydroxy-2-methylbenzoic acid, **25.6**, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester **25.7**, by treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 77, to afford the mono-silyl ether **25.8**. This compound is then reacted with a dialkyl hydroxymethylphosphonate **25.2**, under the conditions of the Mitsonobu reaction, as described above (Scheme **15**) to afford the coupled product **25.9**. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic carboxylic acid **25.10**.

Using the above procedures, but employing, in place of the phenol **25.6**, different phenols or thiophenols **25.1**, there are obtained the corresponding products **25.4**.

Scheme **26** depicts the preparation of phosphonate esters attached to the hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains. In this method, a dialkyl alkenylphosphonate **26.2** is coupled, by means of a palladium catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid **26.1**. The product **26.3** can be deprotected to afford the phosphonate **26.4**, or subjected to catalytic hydrogenation to afford the saturated compound, which upon deprotection affords the corresponding carboxylic acid **26.5**.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid **26.6,** prepared as described in WO 9218490, is converted as described above, into the silyl ether OBO ester **26.7**. This

compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate **26.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above (Scheme **11**) to afford the product **26.9**. Deprotection, or hydrogenation/deprotection, of this compound, as described above, then affords respectively the unsaturated and saturated products **26.10** and **26.11**.

Using the above procedures, but employing, in place of the bromo compound **26.6**, different bromo compounds **26.1**, and/or different phosphonates **26.2**, there are obtained the corresponding products **26.4** and **26.5**.

Scheme **27** illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid **27.1** is converted to the corresponding boronic acid **27.2**, by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82. The product is subjected to a Suzuki coupling reaction with a dialkyl bromophenyl phosphonate **27.3**. The product **27.4** is then deprotected to afford the diaryl phosphonate product **27.5**.

For example, the silylated OBO ester **27.6**, prepared as described above, (Scheme **23**), is converted into the boronic acid **27.7**, as described above. This material is coupled with a dialkyl 4-bromophenyl phosphonate **27.8**, prepared as described in J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, in the presence of sodium bicarbonate, as described, for example, in Palladium reagents and catalysts J. Tsuji, Wiley 1995, p 218, to afford the diaryl phosphonate **27.9**. Deprotection, as described above, then affords the benzoic acid **27.10**.

Using the above procedures, but employing, in place of the bromo compound **27.6**, different bromo compounds **27.1**, and/or different phosphonates **27.3**, there are obtained the corresponding carboxylic acid products **27.5**.

Scheme **28** illustrates the preparation of analogs of the tetrahydropyrimidine carboxylic acid **C27** in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom O, S, or N. In this procedure, an aminoacid **28.1**, in which R^4 is as defined in Chart **2b**, is converted into the corresponding phenyl carbamate **28.2**. The preparation of phenyl carbamates is described in Tet. Lett., 1977, 1936, and in J. Chem. Soc., C, 1967, 2015. The amine substrate is reacted with phenyl chloroformate in the presence of an inorganic or

organic base, such as potassium carbonate or triethylamine, in an organic, aqueous or aqueous organic solvent such as dichloromethane, tetrahydrofuran or water or pyridine. Preferably, the aminoacid **28.1** is reacted with phenyl chloroformate, in water containing lithium hydroxide, lithium chloride and alumina, at a pH of about 9.5, as described in Org. Process Res. Dev., 2000, 4, 264, to afford the phenyl carbamate **28.2**. This compound is then reacted with di(3-chloropropyl)amine **28.3**, prepared as described in Tet. 1995, 51, 1197, to afford the amide product **28.4**. The preparation of amides by reaction of an ester with an amide is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 987. The displacement reaction is effected by treatment of the substrate with the amine, optionally in the presence of a base such as sodium methoxide and the like, to afford the amide product **28.4**. Preferably, the carbamate **28.2** and the amine **28.3** are reacted together in tetrahydrofuran, in the presence of sodium hydroxide or lithium hydroxide, to produce the amide product **28.4**. The latter compound is then transformed, optionally without isolation, into the chloropropyl-substituted tetrahydropyrimidine product **28.5**, by reaction with a strong base such as potassium tert. butoxide in tetrahydrofuran, as described in Org. Process. Res. Dev., 2000, 4, 264. The compound **28.5** is then reacted with a dialkyl hydroxy, mercapto or alkylamino-substituted alkylphosphonate **28.6** to afford the displacement product **28.7**. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as sodium hydride, lithium hexamethyldisilazide, potassium carbonate or the like, optionally in the presence of a catalytic amount of potassium iodide, to afford the ether, thioether or amine product **28.7**.

Alternatively, the chloropropyl-substituted tetrahydropyrimidine compound **28.5** is transformed into the corresponding propylamine **28.8**. The conversion of halo derivatives into amines is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397ff, or Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953 p. 665ff. The chloro compound is reacted with ammonium hydroxide, anhydrous ammonia or hexamethylene tetramine, or with an alkali metal amide such as sodamide to afford the mine product. Preferably, the chloro compound is reacted with potassium phthalimide, and the phthalimido product is then cleaved by treatment with hydrazine, as described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953 p. 679, to afford the amine **28.8**. The product is then subjected to a reductive amination reaction with a dialkyl formylalkyl phosphonate **28.9**, to yield the phosphonate product **28.10**.

For example, as shown in Scheme **28**, Example **1**, 3-methyl-2-phenoxycarbonylamino-butyric acid **28.11**, prepared as described in Org. Process Res. Dev., 2000, 4, 264, is reacted with di(3-chloropropyl)amine, using the conditions described above, to afford 2-[3,3-bis-(3-chloro-propyl)-ureido]-3-methyl-butyric acid **28.4**. The product is then reacted sequentially with sodium hydroxide and then potassium tert. butoxide in tetrahydrofuran, as described in Org. Process Res. Dev., 2000, 4, 264, so as to afford the cyclized product 2-[3-(3-chloro-propyl)-2-oxo-tetrahydro-pyrimidin-1-yl]-3-methyl-butyric acid **28.13**. The latter compound is then reacted in dimethylformamide solution at about 70°, with a dialkyl 2-mercaptoethyl phosphonate **28.14**, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, potassium carbonate and a catalytic amount of potassium iodide, to yield the phosphonate ester **28.13**. Using the above procedures, but employing, in place of the valine carbamate **28.11**, different carbamates **28.2**, and/or different hetero-substituted alkyl phosphonates **28.6**, the corresponding products **28.7** are obtained.

As a further illustration, Scheme **28**, Example **2** depicts the reaction of the chloropropyl tetrahydropyrimidine derivative **28.13** with potassium phthalimide **28.16**. Equimolar amounts of the reactants are combined in dimethylformamide at ca 80°, in the presence of a catalytic amount of potassium iodide, to afford 2-{3-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-2-oxo-tetrahydro-pyrimidin-1-yl}-3-methyl-butyric acid **28.17**. The product is then reacted under reductive amination conditions, as described above (Scheme **10**) with a dialkyl formylphenyl phosphonate **28.19** (Epsilon) to yield the phosphonate ester product **28.20**. Using the above procedures, but employing, in place of the valine carbamate **28.11**, different carbamates **28.2**, and/or different formyl-substituted alkyl phosphonates **28.9**, the corresponding products **28.10** are obtained.

Scheme **29** illustrates the preparation of analogs of the tetrahydropyrimidine carboxylic acid **C27** in which the phosphonate moiety is attached by means of an alkylene chain. In this procedure, an aminoacid **29.1** is subjected to an alkylation reaction with a propanol derivative **29.2** in which Lv is a leaving group such as halo or sulfonyl. The reaction is conducted in aqueous or aqueous organic solution in the presence of a base such as sodium hydroxide, potassium carbonate and the like, to afford the product **29.3**. This compound is then oxidized to the corresponding aldehyde **29.4**. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff.

Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride. The reaction is conducted in an inert aprotic solvent such as pyridine, dichloromethane or toluene. Preferably, the alcohol **29.3** is reacted with an equimolar amount of pyridinium chlorochromate in dichloromethane at ambient temperature, to afford the aldehyde **29.4**. This material is then subjected to a reductive amination reaction with a dialkyl aminoalkyl phosphonate **29.5**, using the conditions described above (Scheme **10**) to produce the phosphonate ester **29.6**. The latter compound is then reacted with phosgene, or carbonyldiimidazole or an equivalent reagent, to yield the tetrahydropyrimidine product **29.7**. Equimolar amounts of the reagents are combined in an inert polar solvent such as tetrahydrofuran or dimethylformamide at ambient temperature, to effect the cyclization reaction.

For example, 2-(3-hydroxy-propylamino)-3-methyl-butyric acid, the preparation of which is described in Toxicol. Appl. Pharm., 1995, 131, 73, is oxidized, as described above, to afford 3-methyl-2-(3-oxo-propylamino)-butyric acid **29.9**. The product is then reacted with a dialkyl aminoethyl phosphonate **29.10**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, under reductive amination conditions, to give the product **29.11**. This compound is then reacted one molar equivalent of carbonyldiimidazole in dichloromethane, as described in US Patent 5914332, to afford the tetrahydropyrimidine product **29.12**.

Using the above procedures, but employing, in place of the valine derivative **29.8**, different aminoacid derivatives **29.3**, and/or different amino-substituted alkyl phosphonates **29.5**, the corresponding products **29.7** are obtained.

Scheme **30** illustrates the preparation of analogs of the tetrahydropyrimidine carboxylic acid **C27** in which the phosphonate moiety is attached by means of an alkylene chain. In this procedure, a tetrahydropyrimidine aminoacid derivative, prepared as described in U.S .Patent 5,914,332, is converted into the carboxyl-protected compound **30.2**. The protection and deprotection of carboxyl groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. For example, the carboxyl group is protected as a benzyl or substituted benzyl ester, removable by means of hydrogenolysis, or as a tert. butyl ester, removable by treatment with anhydrous acid. The carboxyl-protected derivative **30.2** is then reacted with a dialkyl bromoalkyl phosphonate **30.3**, in the presence of a strong base such as sodium hydride, potassium tert. butoxide, lithium

hexamethyldisilazide and the like, in a polar solvent such as dimethylformamide, to afford the alkylation product **30.4**. The carboxyl group is then deprotected to yield the carboxylic acid **30.5**.

For example, 3-methyl-2-(3-methyl-2-oxo-tetrahydro-pyrimidin-1-yl)-butyric acid **30.6**, prepared as described in Org. Process Res. Dev., 200, 4, 264, is converted into the benzyl ester **30.7** by reaction with benzyl alcohol, dicyclohexylcarbodiimide and dimethylaminopyridine in dichloromethane, as described in J. Chem. Soc. Chem. Comm., 1982, 1132. The product is then treated with one molar equivalent of lithium hexamethyldisilazide in dimethylformamide, and the resultant anion is reacted with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **30.8** (Aldrich), to prepare the alkylated product **30.9**. The benzyl ester is then converted into the carboxylic acid **30.10**, by hydrogenolysis over a palladium catalyst, as described in Org. React., VII, 263, 1953. Using the above procedures, but employing, in place of the valine derivative **30.6**, different aminoacid derivatives **30.1**, and/or different bromo-substituted alkyl phosphonates **30.3**, the corresponding products **30.5** are obtained.

Scheme **31** illustrates the preparation of phosphonate-containing derivatives of the carboxylic acid **C4** (Chart **2a**) in which the phosphonate group is attached by means of an alkylene chain and a heteroatom O, S or N. In this procedure, a substituted benzyl alcohol **31.1** is reacted with a dialkyl bromoalkyl phosphonate **31.2** to prepare the ether, thioether or amine product **31.3**. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium carbonate, optionally in the presence of a catalytic amount of potassium iodide. The benzyl alcohol product **31.3** is then transformed into a formyl derivative **31.4**, in which Lv is a leaving group, as described above (Scheme **22**). The formate derivative **31.4** is then reacted with a carboxy-protected amino acid **31.5**, using the procedures described above for the preparation of carbamates (Scheme **22**), to afford the carbamate product **31.6**. The carboxy-protecting group is then removed to afford the carboxylic acid **31.7**. The carboxyl protecting group present in the aminoacid **31.5** is selected so that the conditions for removal do not cleave the benzyl carbamate moiety in the substrate **31.6**.

For example, 3-methylaminobenzyl alcohol **31.8** is reacted in dimethylformamide solution at ca 70° with one molar equivalent of a dialkyl bromoethyl phosphonate **31.9**(Aldrich) and

potassium carbonate, to afford the amine **31.10**. The product is then with reacted one molar equivalent of carbonyldiimidazole in tetrahydrofuran, to give the imidazolide product **31.11**. The compound is then reacted with the tert. butyl ester of valine **31.12**, in pyridine at ambient temperature, to afford the carbamate product **31.13**. The tert. butyl ester is then removed by treatment of the ester **31.13** with trifluoroacetic acid at 0°, as described in J. Am. Chem. Soc., 99, 2353, 1977, to afford the carboxylic acid **31.14**.

Using the above procedures, but employing, in place of the benzyl alcohol derivative **31.8**, different benzyl alcohols **31.1**, and/or different bromo-substituted alkyl phosphonates **31.2**, the corresponding products **31.7** are obtained.

Scheme **32** illustrates the preparation of phosphonate-containing derivatives of the carboxylic acid **C4** (Chart **2a**) in which the phosphonate group is attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted benzyl alcohol **32.1** is coupled, in the presence of a palladium catalyst, with a dialkyl alkenylphosphonate **32.2**. The coupling reaction between aryl bromides and olefins is described above (Scheme **11**). The coupled product **32.3** is then converted into the carbamate derivative **32.5**, by means of the series of reactions illustrated above (Scheme **31**) for the conversion of the benzyl alcohol **31.3** into the carbamate derivative **31.7**. Alternatively, the unsaturated compound **32.3** is reduced, diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p.8, to produce the saturated analog **32.4**. This material as then transformed, as described above, into the carbamate derivative **32.6**.

For example, 4-bromobenzyl alcohol **32.7** is coupled, in the presence of diethyl vinylphosphonate, prepared as described in Synthesis, 1983, 556, in the presence of ca. 3 mol % of palladium(II) acetate, triethylamine and tri(o-tolyl)phosphine in acetonitrile at ca. 100° in a sealed tube, as described in Synthesis, 1983, 556, to produce the coupled product **32.9**. The product is then converted, as described above, into the unsaturated and saturated carbamate derivatives **32.10** and **32.11**.

Using the above procedures, but employing, in place of 4-bromobenzyl alcohol **32.7**, different benzyl alcohols **32.1**, and/or different dialkyl alkenyl phosphonates **32.2**, the corresponding products **32.5** and **32.6** are obtained.

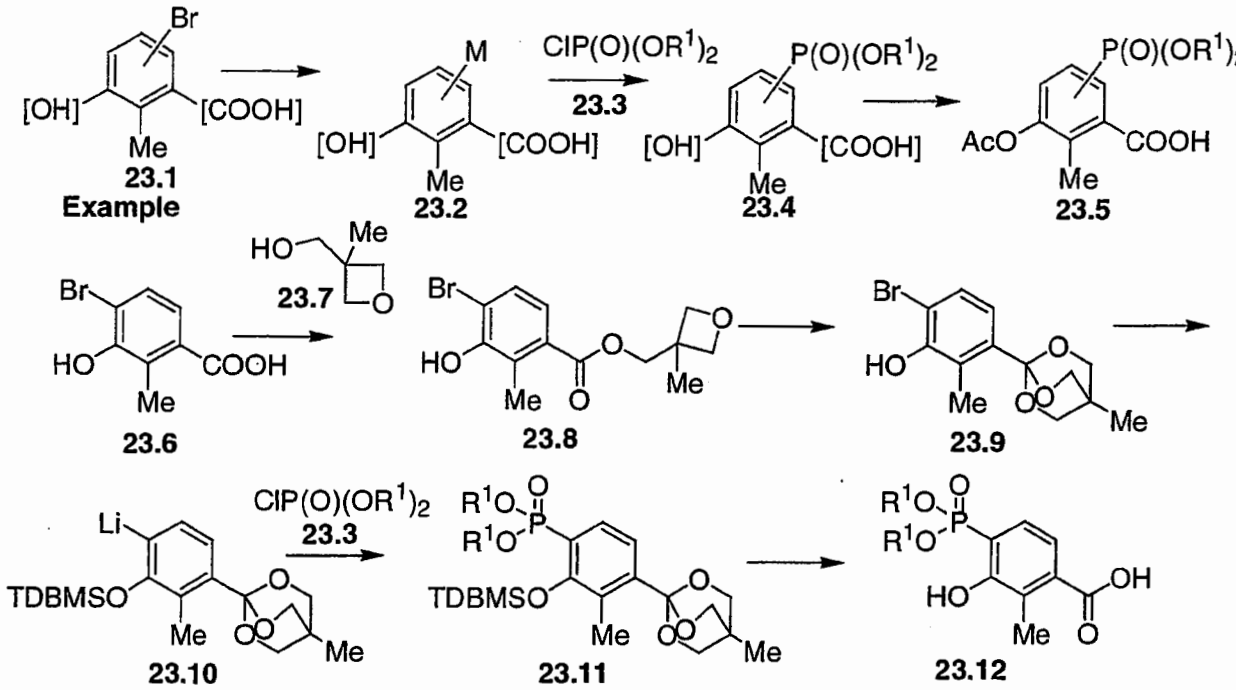
Scheme **33** illustrates the preparation of phosphonate-containing derivatives of the carboxylic acid **C4** (Chart **2a**) in which the phosphonate group is attached by means of a phenyl ring. In this procedure, a benzaldehyde boronic acid **33.1** is coupled, using the procedures described above (Scheme **27**) with a dialkyl bromophenylphosphonate **33.2**, to afford the biphenyl derivative **33.3**. The aldehyde group is then reduced to give the corresponding benzyl alcohol **33.4**. The reduction of aldehydes to afford alcohols is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968. The conversion can be effected by the use of reducing agents such as sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride, diborane and the like. Preferably, the aldehyde **33.3** is reduced to the carbinol **33.4** by reaction with sodium borohydride in ethanol at ambient temperature. The resulting benzyl alcohol is then transformed, using the procedures described above, (Scheme **31**) into the carbamate derivative **33.5**.

For example, 3-formylphenylboronic acid **33.6** (Fluka) is coupled with a dialkyl 4-bromophenylphosphonate **33.7**, prepared as described in J. Organomet. Chem., 1999, 581, 62, in the presence of tetrakis(triphenylphosphine)palladium and sodium bicarbonate, as described in Palladium Reagents and Catalysts, by J. Tsuji, Wiley 1995, p. 218, to yield the diphenyl compound **33.8**. The aldehyde group is reduced to afford the carbinol **33.9**, and the latter compound is then transformed, as described above, into the carbamate derivative **33.10**.

Using the above procedures, but employing, in place of the benzaldehyde **33.6**, different benzaldehydes **33.1**, and/or different dialkyl bromophenyl phosphonates **33.2**, the corresponding products **33.4** are obtained.

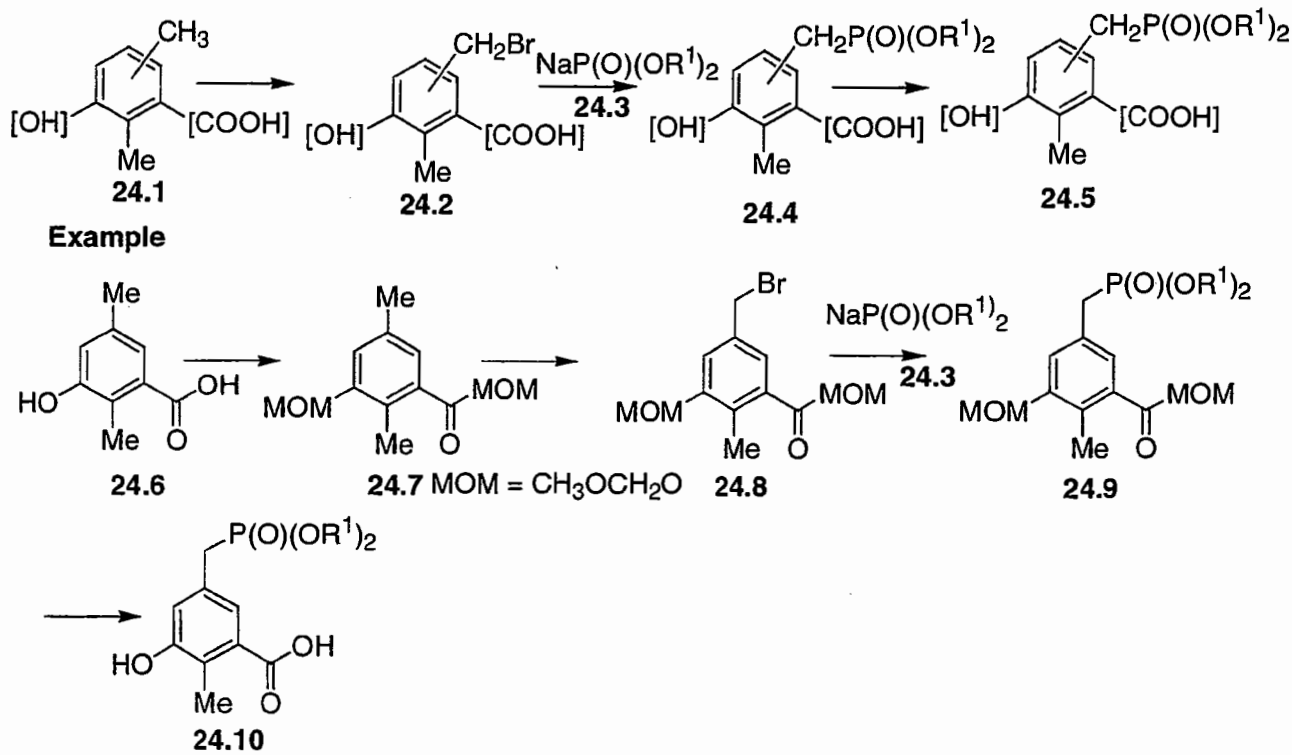
Scheme 23

Method



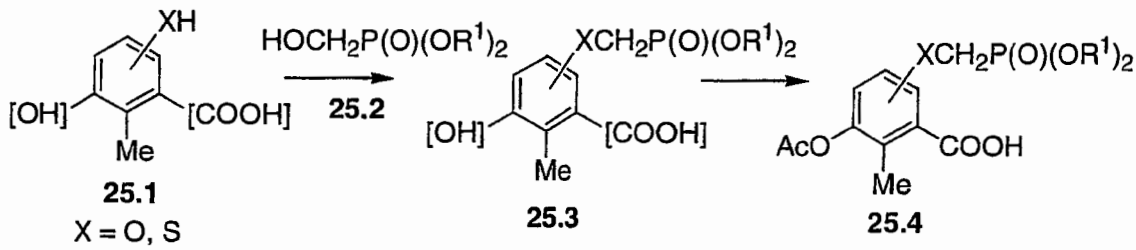
Scheme 24

Method

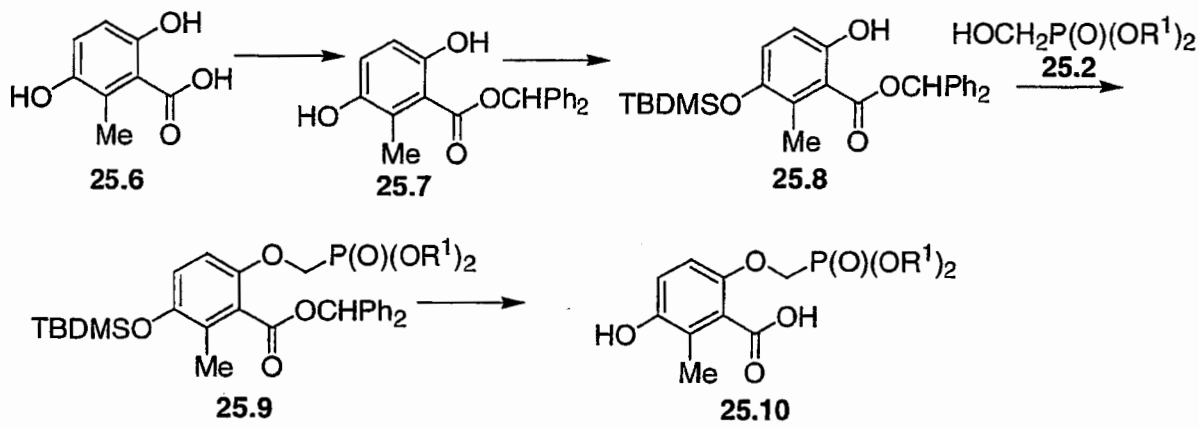


Scheme 25

Method

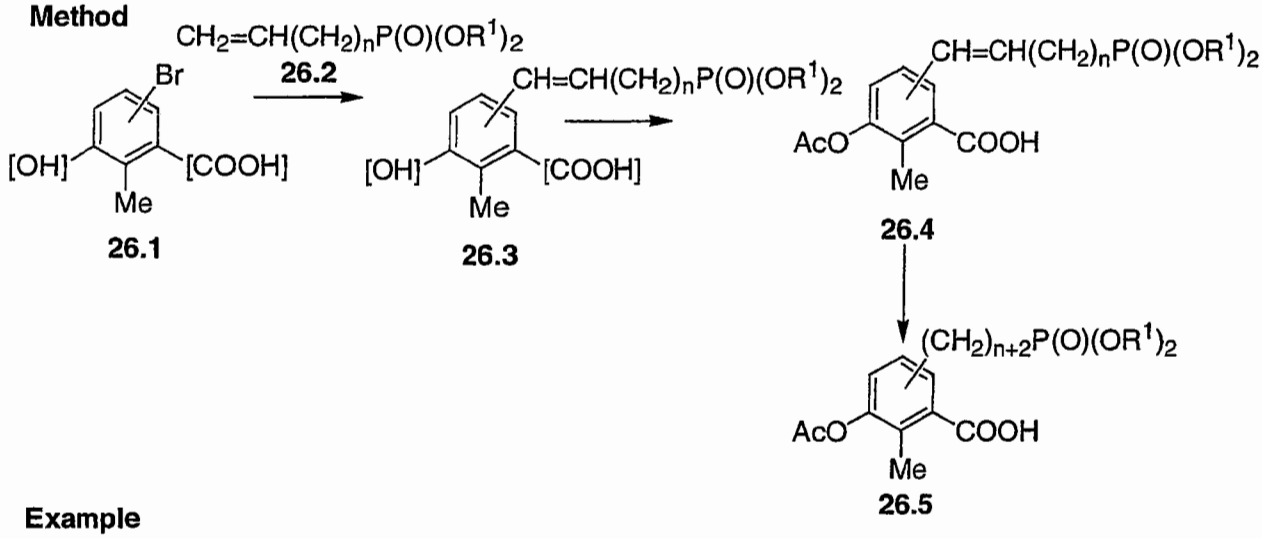


Example

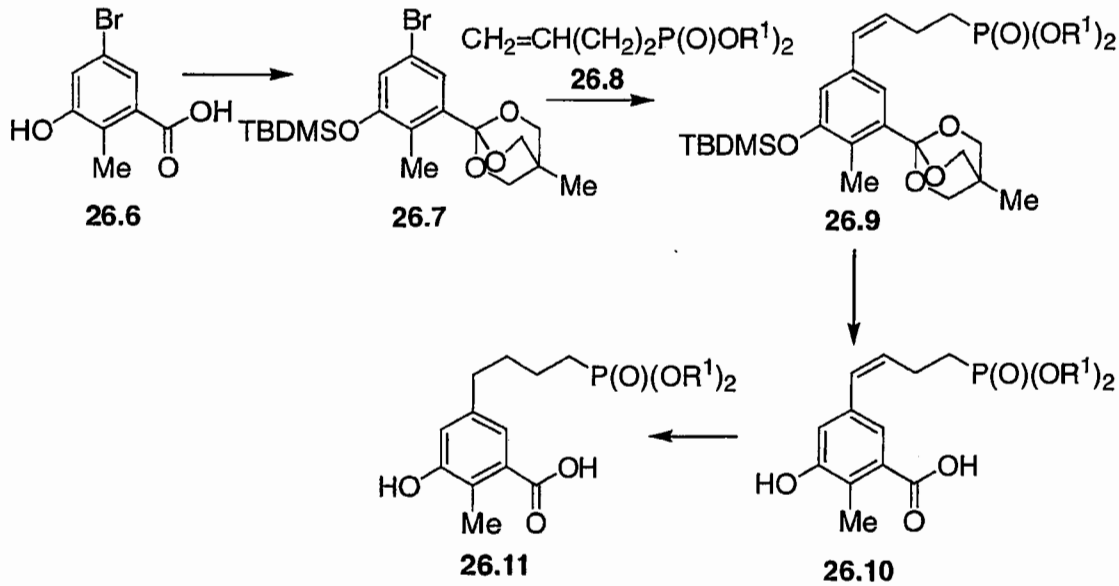


Scheme 26

Method

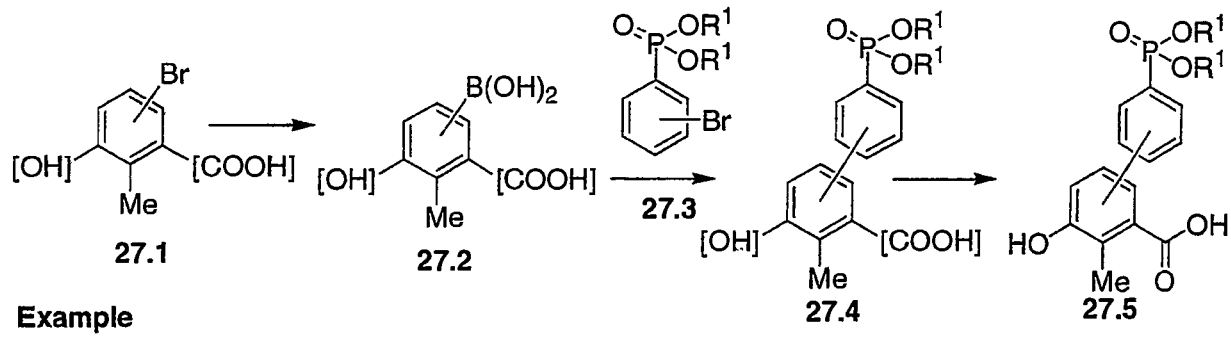


Example

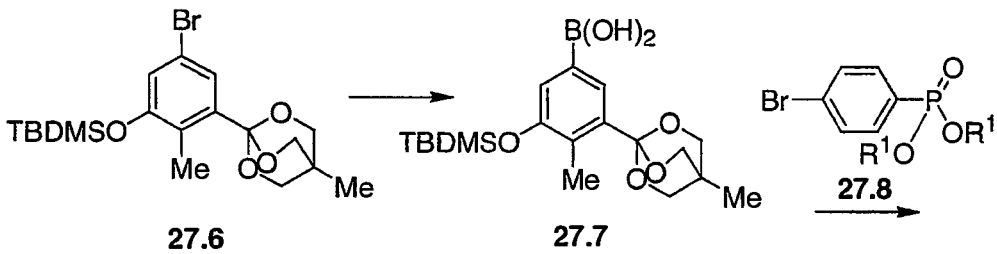


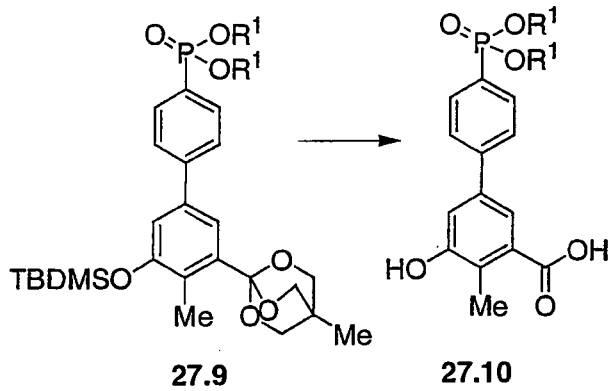
Scheme 27

Method

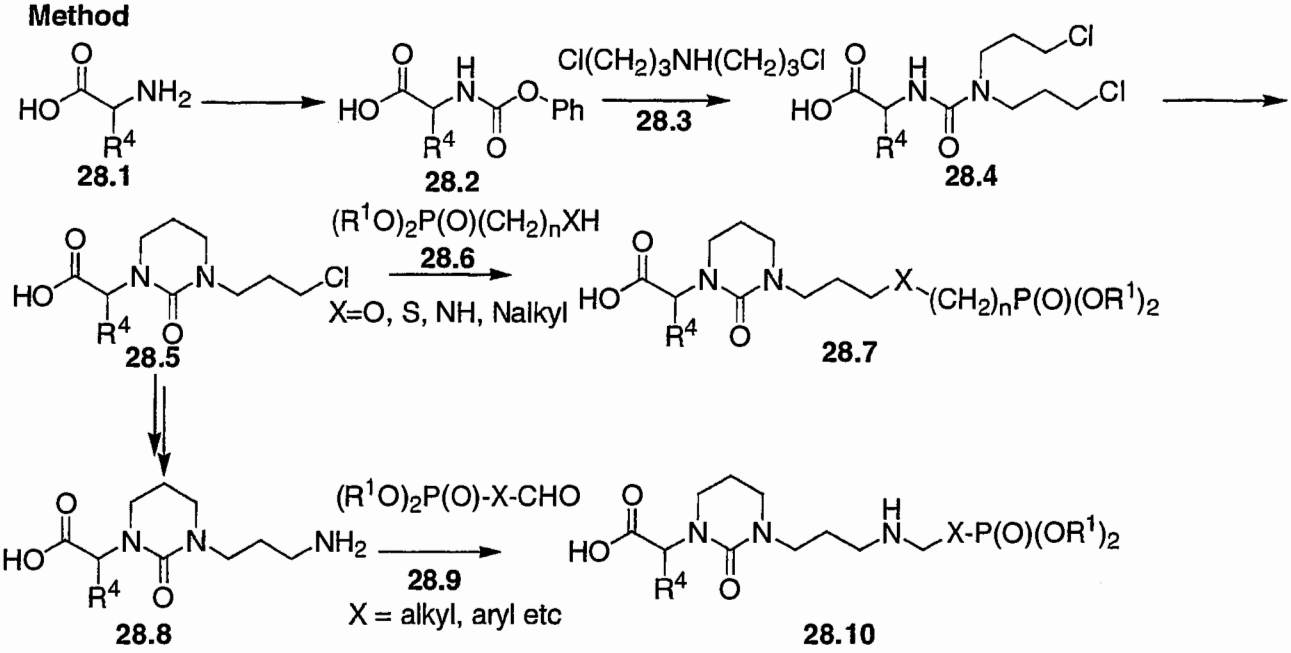


Example

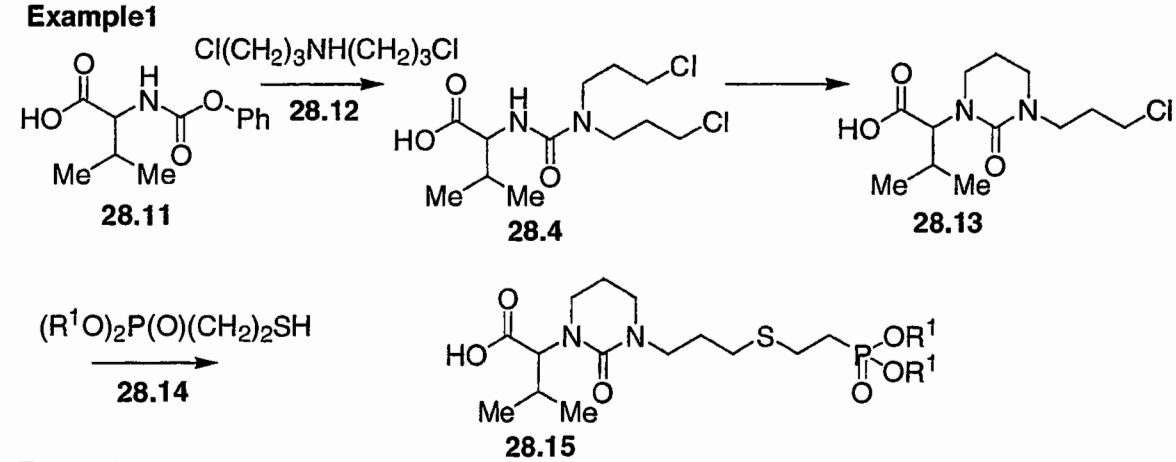




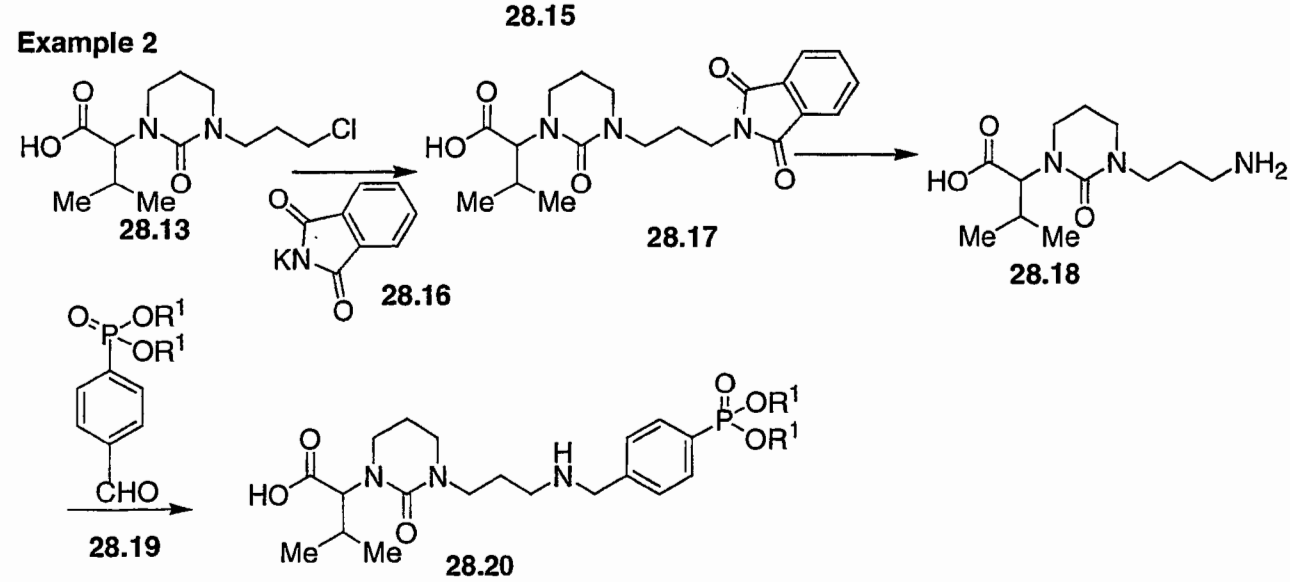
Scheme 28
Method



Example1

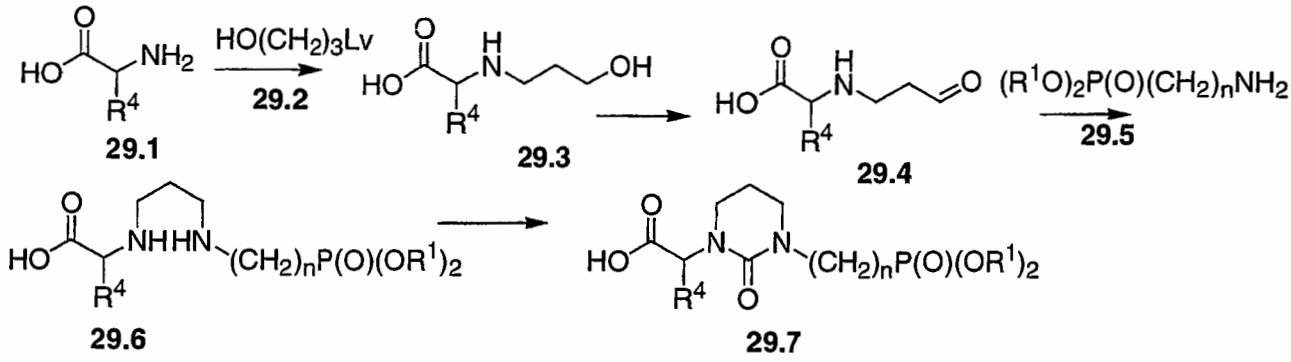


Example 2

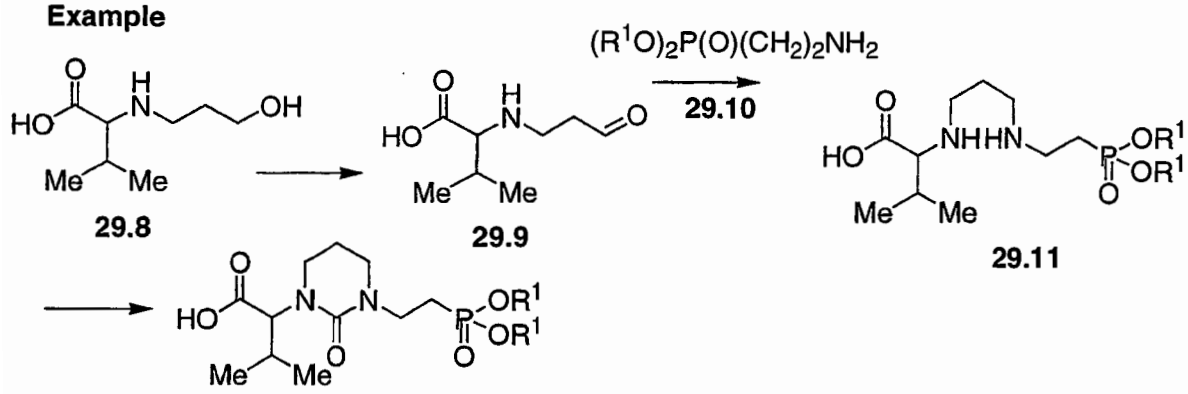


Scheme 29

Method

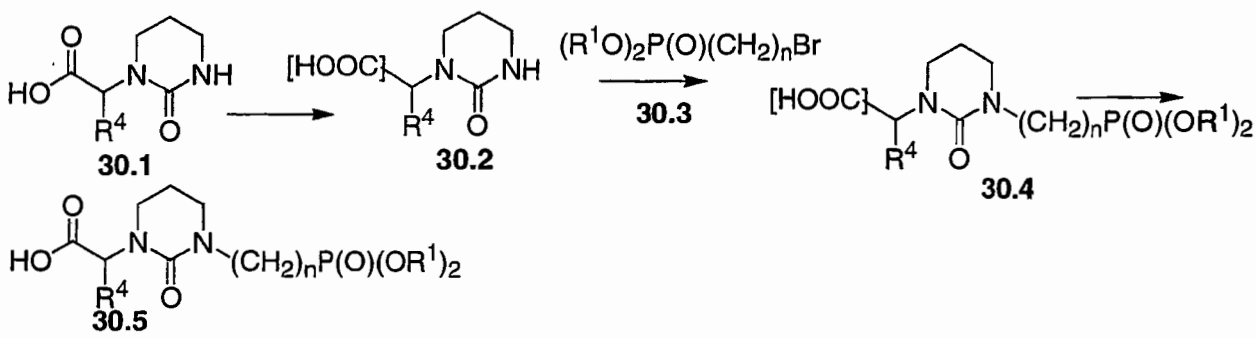


Example

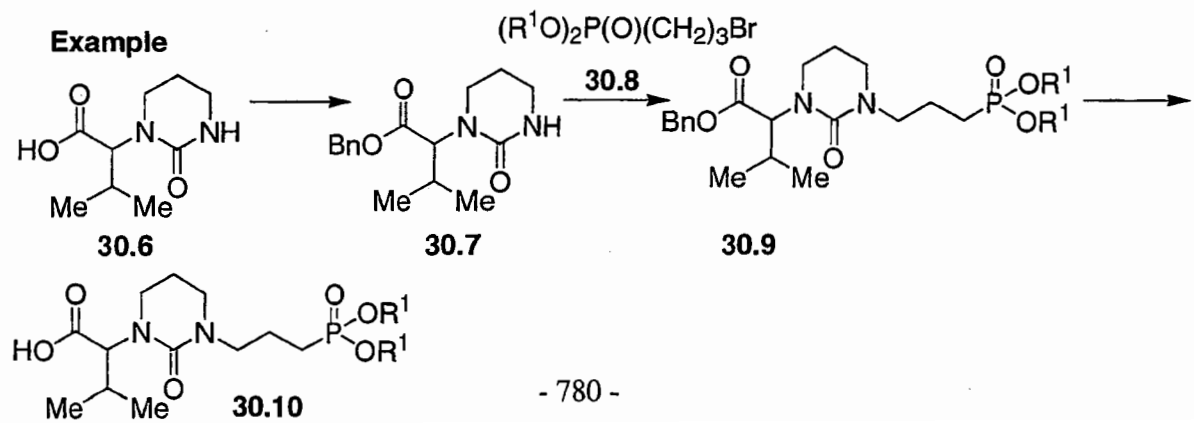


Scheme 30

Method

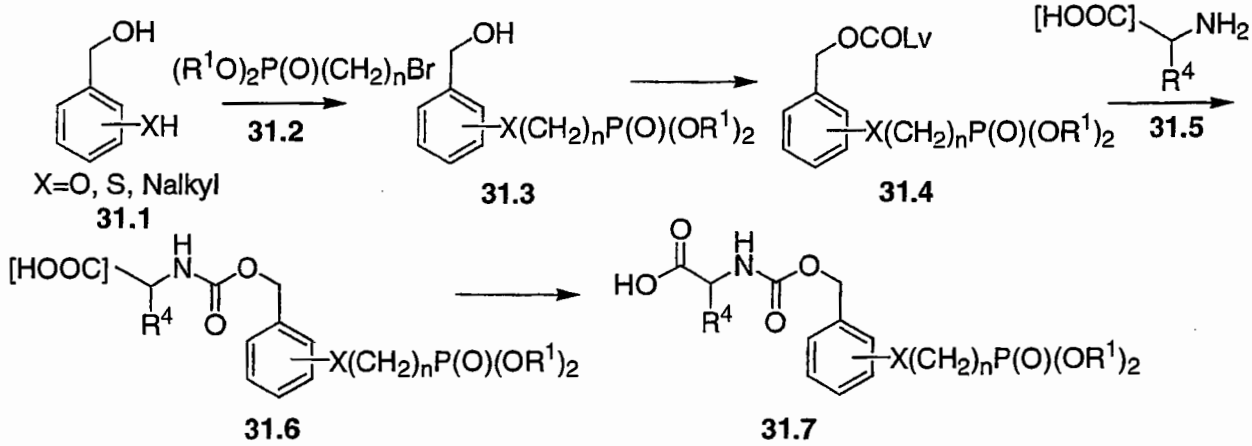


Example

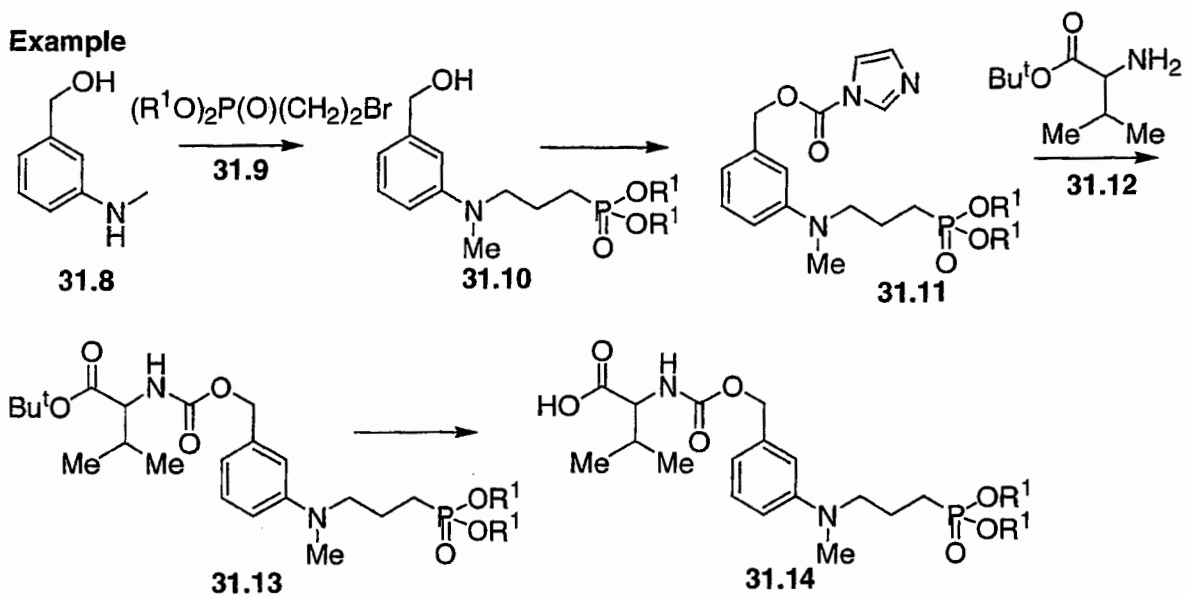


Scheme 31

Method



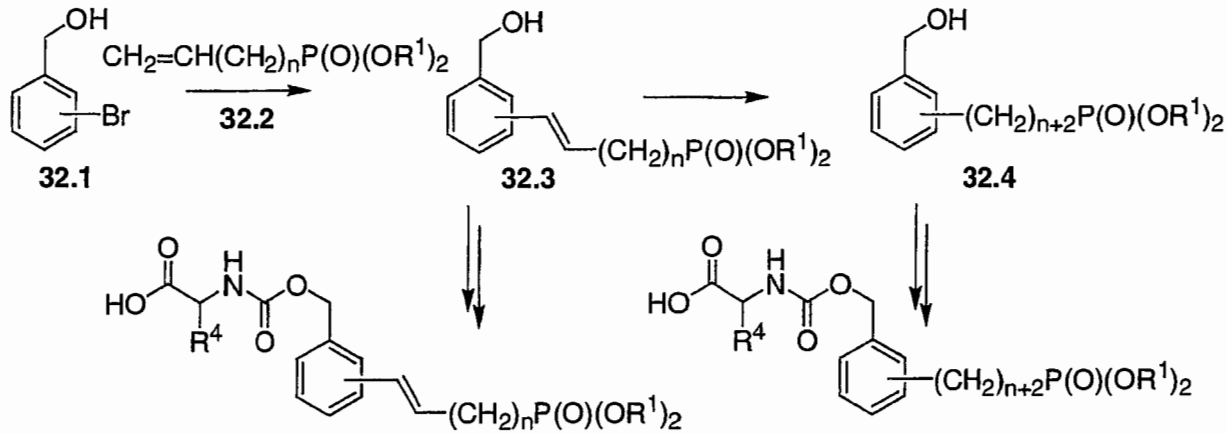
Example



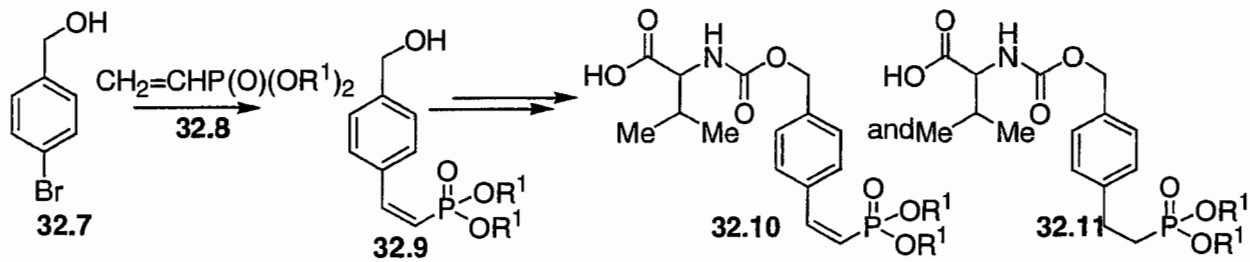
5

Scheme 32

Method

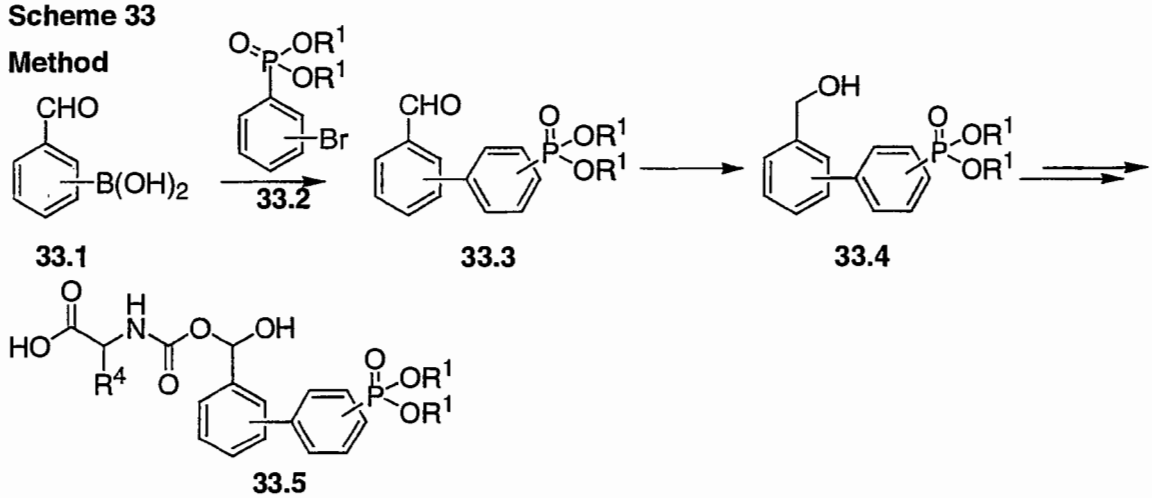


Example

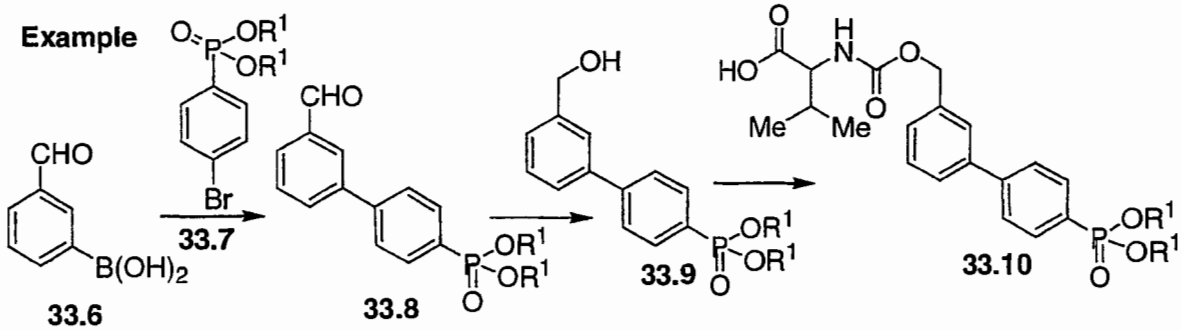


Scheme 33

Method



Example



General applicability of methods for introduction of phosphonate substituents.

The methods described herein for the preparation of phosphonate ester intermediate compounds are, with appropriate modifications, generally applicable to different substrates, such as the carboxylic acids depicted in Charts **2a**, **2b** and **2c**. Thus, the methods described above for the introduction of phosphonate groups into the dimethylphenoxyacetic acid moiety (Schemes **9-14**), can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the phenylalanine synthon for the preparation of the phosphonate esters **3**. Similarly, the methods described above for the introduction of phosphonate groups into the phenylalanine moiety (Schemes **15-17**), the hydroxy methyl substituted benzoic acids (Schemes **23- 27**), the tetrahydropyrimidine analogs (Schemes **28-30**), and the benzyl carbamates (Schemes **31- 33**) can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the dimethylphenoxyacetic acid component.

Atazanavir-like phosphonate protease inhibitors (ATLPPI)

Preparation of the intermediate phosphonate esters.

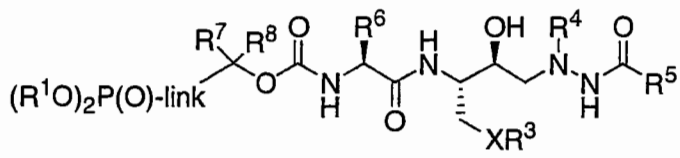
The structures of the intermediate phosphonate esters **1** to **7**, and the structures for the component groups X, R^1, R^7 and R^8 of this invention are shown in Chart **1**. The structures of the R^2COOH and R^5COOH components are shown in Charts **2a**, **2b** and **2c**, and the structures of the R^3XCH_2 components are shown in Chart **3**. The structures of the R^4 components are shown in Chart **4**. Specific stereoisomers of some of the structures are shown in Charts **1-4**; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **7**. Subsequent chemical modifications to the compounds **1** to **7**, as described herein, permit the synthesis of the final compounds of this invention.

The intermediate compounds **1** to **7** incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **5** and **6** illustrate examples of the linking groups present in the structures **1** – **7**. The term "etc" in Charts **3**, **5** and **6**, refers to the scaffold atazanavir.

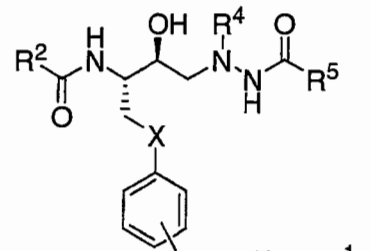
Schemes **1** - **56** illustrate the synthses of the intermediate phosphonate compounds of this invention, **1**- **5**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **6** and **7**, in which the phosphonate moiety is incorporated into the groups R^2COOH and R^5COOH, are also described below.

5

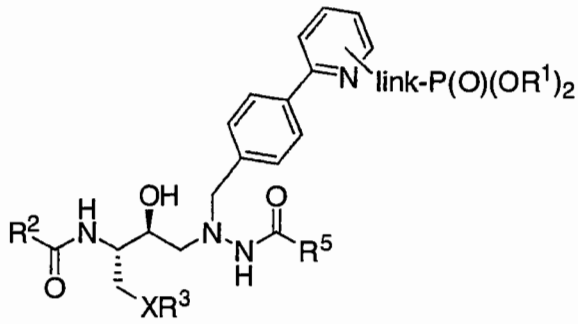
Chart 1. Structures of the phosphonate esters 1 - 7.



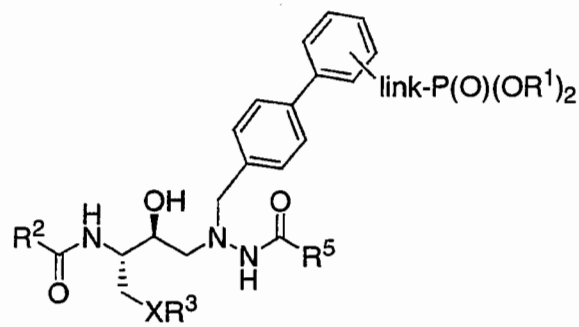
1



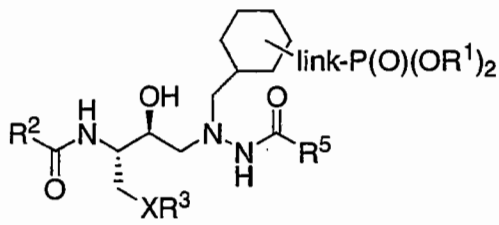
2



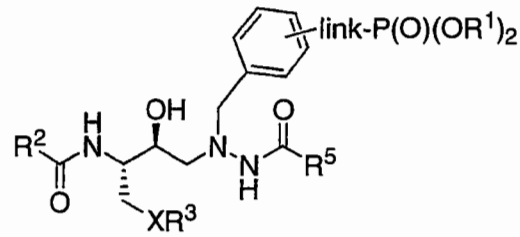
3a



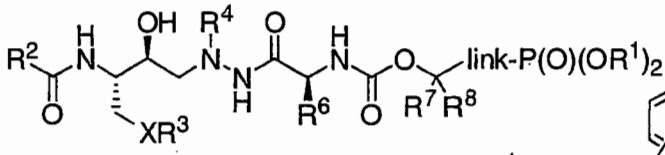
3b



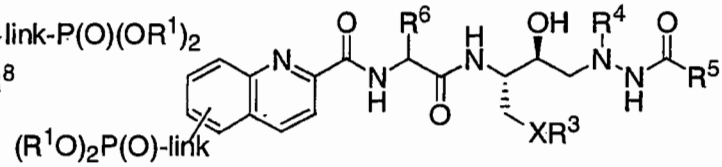
3c



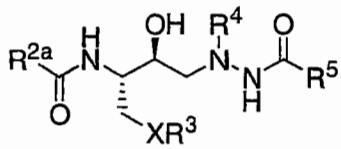
3d



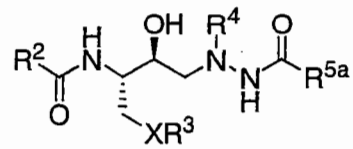
4



5



6



7

R^{5a}= phosphonate-containing R^5

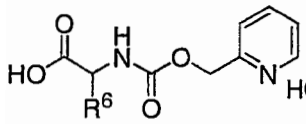
R^{2a}= phosphonate-containing R^2

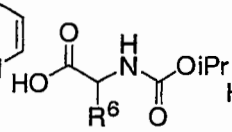
R^1 = H, alkyl, haloalkyl,alkenyl, aralkyl, aryl

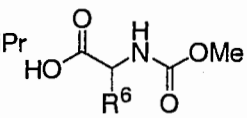
R^7, R^8 = H, alkyl

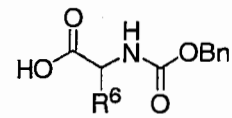
X = direct bond; sulfur.

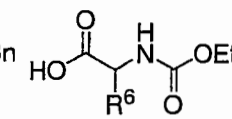
Chart 2a Structures of the R^2COOH and R^5COOH components

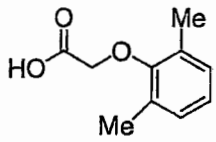

C1

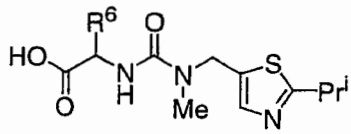

C2

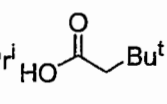

C3

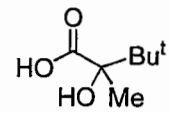

C4

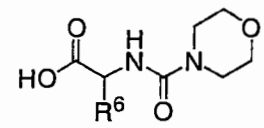

C5

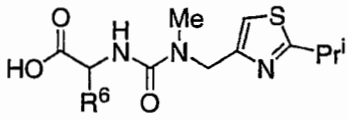

C6

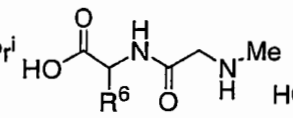

C7

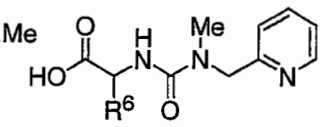

C8

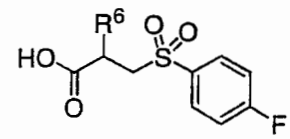

C9

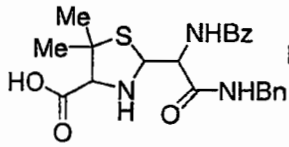

C10

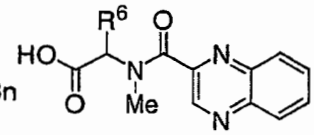

C11

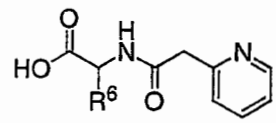

C12

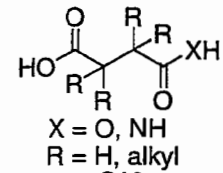

C13

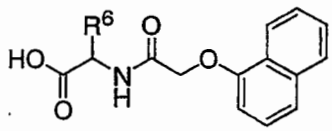

C14

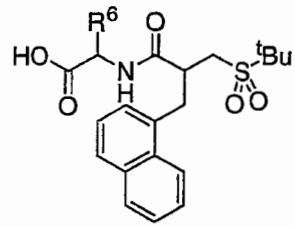

C15

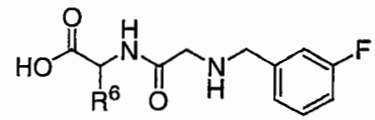

C16

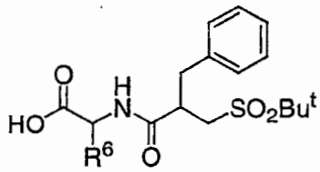

C17

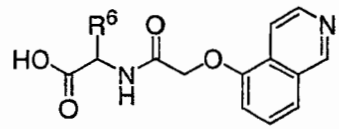

X = O, NH
R = H, alkyl
C18

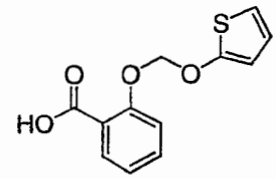

C19


C20


C21

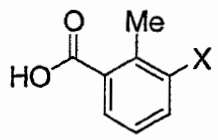

C22


C23

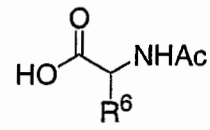

C24

R^6 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

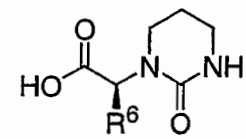
Chart 2b Structures of the R^2COOH and R^5COOH components



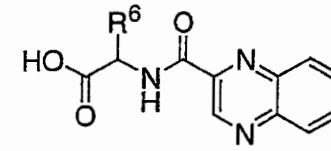
C25
X = OH, NH_2



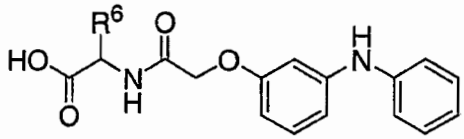
C26



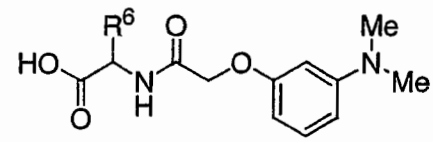
C27



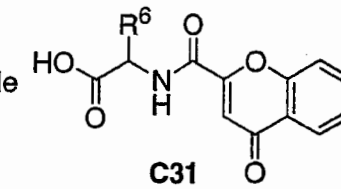
C28



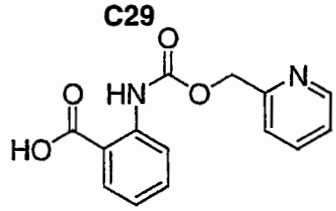
C29



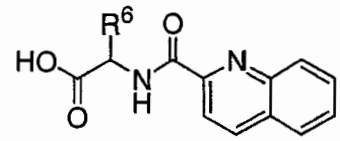
C30



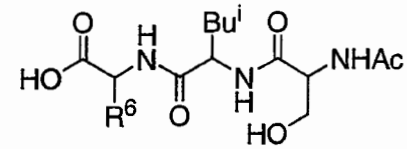
C31



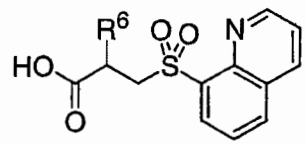
C32



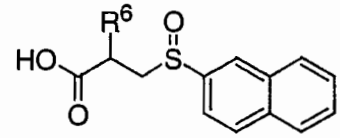
C33



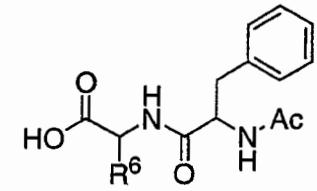
C34



C35



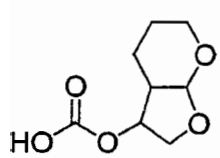
C36

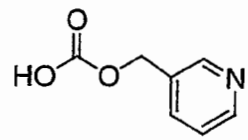


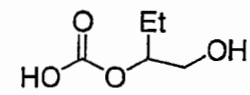
C37

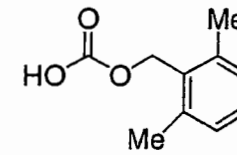
R^6 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, NHAc, $NHCOCF_3$

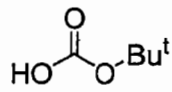
Chart 2c Structures of the R^2COOH and R^5COOH components

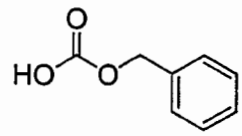

C38

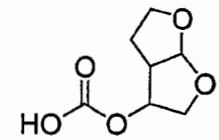

C39

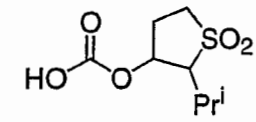

C40

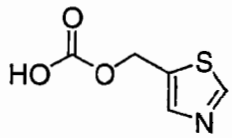

C41

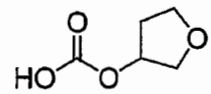

C42

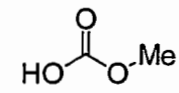

C43


C44


C45


C46


C47


C48

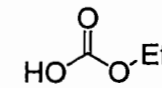
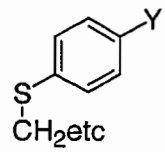
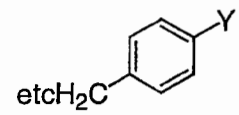

C49

Chart 3 Structures of the R^3XCH_2 groups.

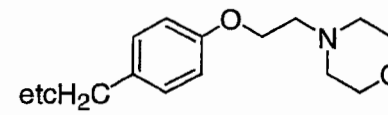
R^3XCH_2 =

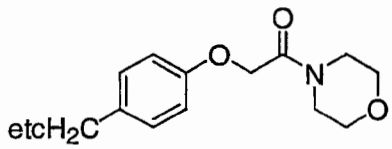

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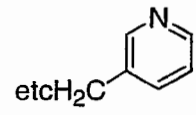
Y = H, F


9

Y = H, OC_2H_5, $OCH_2C_6H_5$


10


11


12

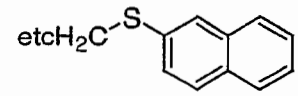
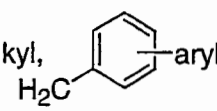

13

Chart 4 Structures of the R^4 groups

R^4 = alkyl, $(CH_2)_n$aryl, $(CH_2)_n$cycloalkyl,



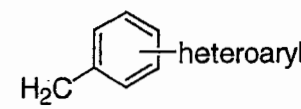
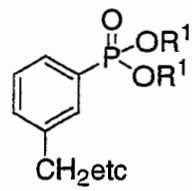


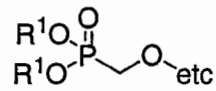
Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.

link **examples**

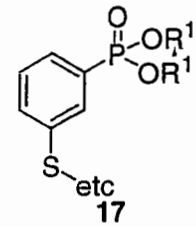
direct bond



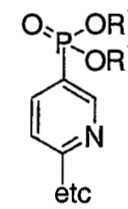
15



16

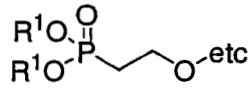


17

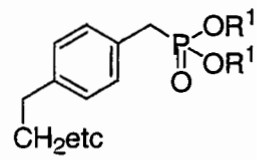


18

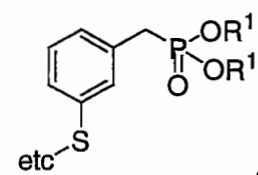
single carbon



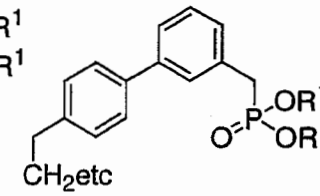
19



20

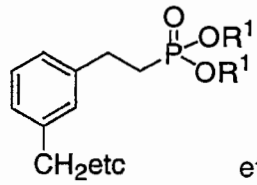


21

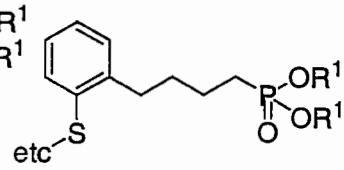


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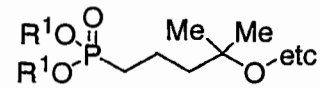
multiple carbon



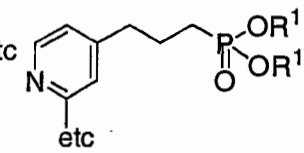
22



23

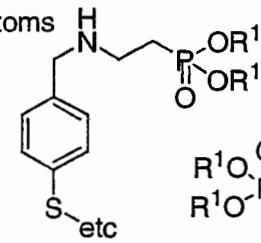


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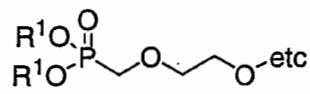


25

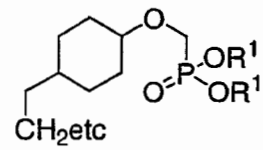
hetero atoms



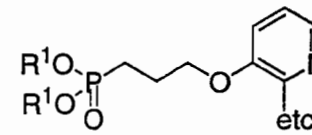
26



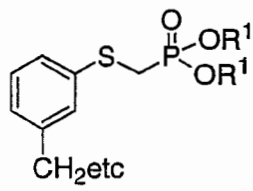
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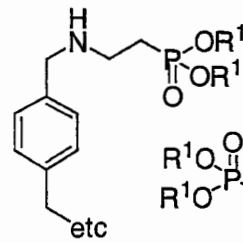
28



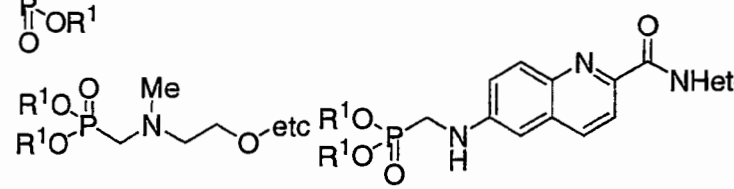
29



30



31

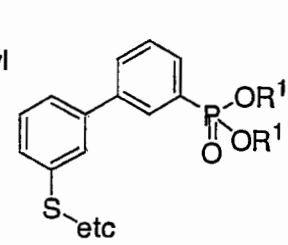


32 **33**

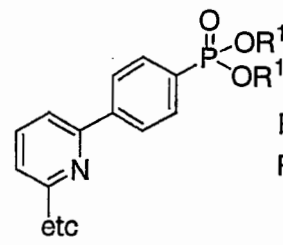
Chart 6 Examples of the linking group between the scaffold and the phosphonate moiety.

link **examples**

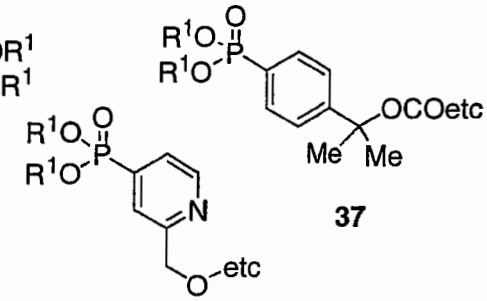
aryl, heteroaryl



34

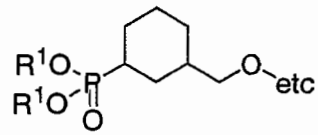


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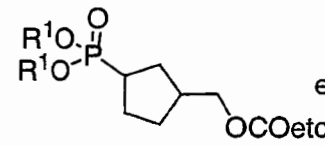


36 **37**

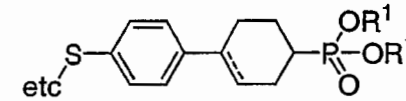
cycloalkyl



38

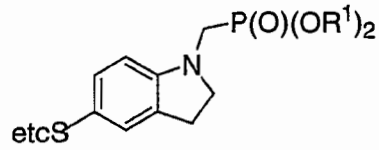


39

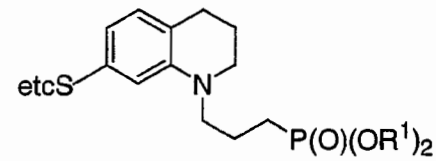


40

cyclized

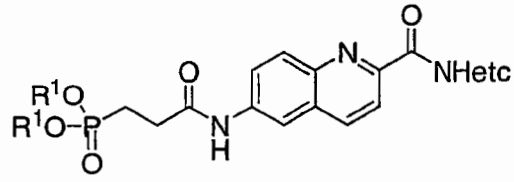


41

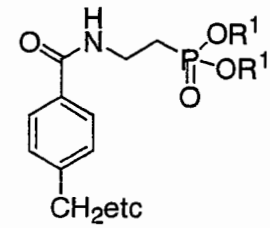


42

amide



43



44

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

Schemes **1** and **2** illustrate the preparation of the phosphonate esters **1** in which X is a direct bond. As shown in Scheme **1**, the oxirane **1.1** is reacted with the BOC-protected hydrazine derivative **1.2** to afford the aminoalcohol **1.3**. The preparation of the oxiranes **1.1**, in which Y is as defined in Scheme **1**, is described below, (Scheme **3**). The preparation of the hydrazine derivatives $R^4NHNHBOC$ is described below, (Scheme **4**). The reaction between the oxirane **1.1** and the hydrazine **1.2** is conducted in a polar organic solvent such as dimethylformamide, acetonitrile or, preferably, a lower alkanol. For example, equimolar amounts of the reactants are combined in isopropanol and heated to ca. 80° for about 16 hours, as described in WO 9740029, to afford the aminoalcohol **1.3**. The cbz protecting group is then removed from the product to yield the free amine **1.4**. The removal of carbobenzyloxy substituents to afford the corresponding amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The conversion can be effected by the use of catalytic hydrogenation, in the presence of hydrogen or a hydrogen donor and a palladium catalyst. Alternatively, the cbz group can be removed by treatment of the substrate with triethylsilane, triethylamine and a catalytic amount of palladium (II) chloride, as described in Chem. Ber., 94, 821, 1961, or by the use of trimethylsilyl iodide in acetonitrile at ambient temperature, as described in J. Chem. Soc., Perkin Trans. I, 1277, 1988. The cbz group can also be removed by treatment with a Lewis acid such as boron tribromide, as described in J. Org. Chem., 39, 1247, 1974, or aluminum chloride, as described in Tet. Lett., 2793, 1979.

Preferably, the protected amine **1.3** is converted into the free amine **1.4** by means of hydrogenation over 10% palladium on carbon catalyst in ethanol, as described in US Patent 5196438.

The amine product **1.4** is then reacted with a carboxylic acid **1.5** to afford the amide **1.6**. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane. Preferably, equimolar amounts of the amine and the carboxylic acid are reacted in tetrahydrofuran at ca. -10°, in the presence of dicyclohexylcarbodiimide, as described in U.S. Patent 5,196,438, to afford the aminoamide **1.6**. The aminoamide is then reacted with a reagent A-CR^7R^8OCOX (**1.7**), in which the substituent A is the group $(R^1O)_2P(O)$-link, or a precursor group thereto, such as [OH], [SH], [NH], Br, as described below, and in which the substituent X is a leaving group, to yield the carbamate **1.8**. The reagent A-CR^7R^8OCOX is derived from the corresponding alcohol A-CR^7R^8OH, using methods described below, (Scheme **20**). The preparation of the reactants A-CR^7R^8OCOX is described in Schemes **21** - **26**. The preparation of carbamates by means of reactions between alcohols and amines is described in Scheme **20**.

The BOC-protected amine present in the carbamate product **1.8** is then deprotected to produce the free amine **1.9**. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid or formic acid, or

by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC group is removed by treatment of the substrate **1.8** with hydrogen chloride in tetrahydrofuran, for example as described in Org. Process Res. Dev., 2002, 6, 323. The resulting amine **1.9** is then coupled with a carboxylic acid or an activated derivative thereof **1.10**, to afford the amide **1.11**, using the conditions described above for the preparation of the amide **1.6**. For example, the amine **1.9** is reacted with the carboxylic acid **1.10**, X = OH, in the presence of a water-soluble carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydroxybenztriazole and triethylamine, as described in J. Med. Chem., 41, 1988, 3387, to yield the amide **1.11**.

The procedures illustrated in Scheme **1** depict the preparation of the compounds **1.11** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br, as described below. Scheme **2** illustrates the conversion of compounds **1.11** in which A is a precursor to the group link-P(O)$(OR^1)_2$ into the compounds **1**. Procedures for the conversion of the substituent A into the group link-P(O)$(OR^1)_2$ are illustrated below, (Schemes **21 - 56**). In the procedures illustrated above, (Scheme **1**) and in the procedures illustrated below (Schemes **3 - 19**) for the preparation of the phosphonate esters **1 - 7**, compounds in which the group A is a precursor to the group link-P(O)$(OR^1)_2$ may be converted into compounds in which A is link-P(O)$(OR^1)_2$ at any appropriate stage in the reaction sequence, or, as shown in Scheme **2**, at the end of the sequence. The selection of an appropriate stage to effect the conversion of the group A into the group link-P(O)$(OR^1)_2$ is made after consideration of the nature of the reactions involved in the conversion, and the stability of the various components of the substrate to those reaction conditions.

Scheme **3** illustrates the preparation of the epoxides **1.1** used above in Scheme **1**. The preparation of the epoxide **1.1** in which R^7 is H is described in J. Org. Chem., 1994, 59, 3656. Analogs in which R^7 is one of the substituents defined in Chart **3** are prepared as shown in Scheme **3**. A substituted phenylalanine **3.1** is first converted into the benzyloxycarbonyl (cbz) derivative **3.2**. The preparation of benzyloxycarbonyl amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The aminoacid **3.1** is reacted with benzyl chloroformate or dibenzyl carbonate in the presence of a suitable base such as sodium carbonate or triethylamine, to afford the protected amine product **3.2**. The conversion of the carboxylic acid **3.2** into the epoxide **1.1**, for

example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, and in J. Org. Chem., 1994, 59, 3656 is then effected. The carboxylic acid is first converted into an activated derivative such as the acid chloride **3.3**, in which X is Cl,, for example by treatment with oxalyl chloride, or into a mixed anhydride, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone **3.4**. The reaction is performed by the addition of a solution of the activated carboxylic acid derivative to an ethereal solution of three or more molar equivalents of diazomethane at 0°. The diazoketone **3.4** is converted into the chloroketone **3.5** by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether, as described in J. Org. Chem., 1994, 59, 3656. The latter compound is then reduced, for example by the use of an equimolar amount of sodium borohydride in an ethereal solvent such as tetrahydrofuran at 0°, to produce a mixture of chlorohydrins from which the minor diastereomer **3.6** is separated by chromatography. The chlorohydrin **3.6** is then converted into the epoxide **1.1** by treatment with a base such as an alkali metal hydroxide in an alcoholic solvent, for example as described in J. Med. Chem., 1997, 40, 3979. Preferably, the compound **3.6** is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide **1.1**. The preparations of analogs of the oxirane **1.1** in which the amino group is protected respectively as the tert-butoxycarbonyl and trifluoroacetyl derivatives are described respectively in J. Med. Chem., 1994, 37, 1758 and J. Med. Chem., 1996, 39, 3203.

Scheme **4** depicts the preparation of the hydrazine derivatives **1.2**, in which R^4 is CH_2-aryl, CH_2-alkyl, CH_2-cycloalkyl as shown in Chart **4**. The general procedure for the preparation of BOC-protected hydrazine derivatives from the corresponding aldehyde RCHO (**4.1**) is shown in Scheme **4**. The aldehyde is reacted with tert. butyl carbazate **4.2**, in a solvent such as an alkanol, a hydrocarbon such as toluene, or a polar organic solvent such as dimethylformamide, to afford the substituted hydrazone **4.3**. Preferably, equimolar amounts of the reactants are heated in a mixture of toluene and isopropanol, as described in Org. Process Res. Dev., 2002, 6, 323, to prepare the hydrazone **4.3.** The product is then reduced to the corresponding hydrazine derivative **4.4**. The transformation can be effected by chemical reduction, for example by the use of sodium borohydride, sodium cyanoborohydride, or sodium triacetoxyborohydride or the like, or by palladium-catalyzed reduction in the presence of hydrogen or a hydrogen donor such as ammonium formate. Preferably, the hydrazone **4.3**

is reduced to the hydrazine **4.4** by hydrogenation at ambient temperature and pressure, in the presence of palladium hydroxide on carbon, as described in Org. Process Res. Dev., 2002, 6, 323.

The preparation of the hydrazine derivatives **1.2** in which a diaryl moiety is present is shown in Scheme **4**, Example **1**. In this procedure, a formyl-substituted phenyl boronate **4.5** (Lancaster Synthesis) is transformed, by means of a palladium-catalyzed coupling with an aryl or heteroaryl bromide **4.6**, to afford the aldehyde **4.7**. The coupling of aryl bromides with aryl boronates is described, for example, in Palladium Reagents and Catalysts, by J. Tsuji, Wiley 1995, p. 218 and in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p 57. Typically, the reactants **4.5** and **4.6** are combined in an aprotic organic solvent such as dimethylformamide in the presence of a palladium (0) catalyst such as tetrakis(triphenylphosphine)palladium and a base such as sodium bicarbonate or potassium acetate, to afford the coupled product **4.7**. This material is then reacted with a protected hydrazine derivative such as tert-butoxycarbonylhydrazine (tert-butyl carbazate) **4.2**, to yield the hydrazone **4.8**. The reaction between equimolar amounts of the aldehyde and the protected hydrazine is conducted in alcoholic solvent such as ethanol, at reflux temperature, for example as described in WO9740029, to produce the hydrazone **4.8**. The latter compound is then reduced, for example by the use of hydrogen in the presence of a palladium catalyst, as described in WO 9740029, or by the use of sodium cyanoborohydride and p-toluenesulfonic acid in tetrahydrofuran, as described in J. Med. Chem., 1998, 41, 3387, to afford the substituted hydrazine **1.2**. Other reactants **1.2**, in which R^4 is as defined in Chart **4**, are prepared from the appropriate aldehydes, using the procedures of Scheme **4**.

Scheme **4**, Example **2** illustrates the preparation of phosphonate-containing pyridylphenyl hydrazine derivatives **4.11**, which are employed in the preparation of the phosphonate esters **3a**. In this procedure, a phosphonate-substituted pyridyl benzaldehyde **4.9**, the preparation of which is described below, (Schemes **40** and **41**) is reacted, as described above, with tert. butyl carbazate **4.2**, to afford the hydrazone **4.10**. This compound is then reduced, in the presence of palladium hydroxide as catalyst, as described above, to yield the hydrazine product **4.11**.

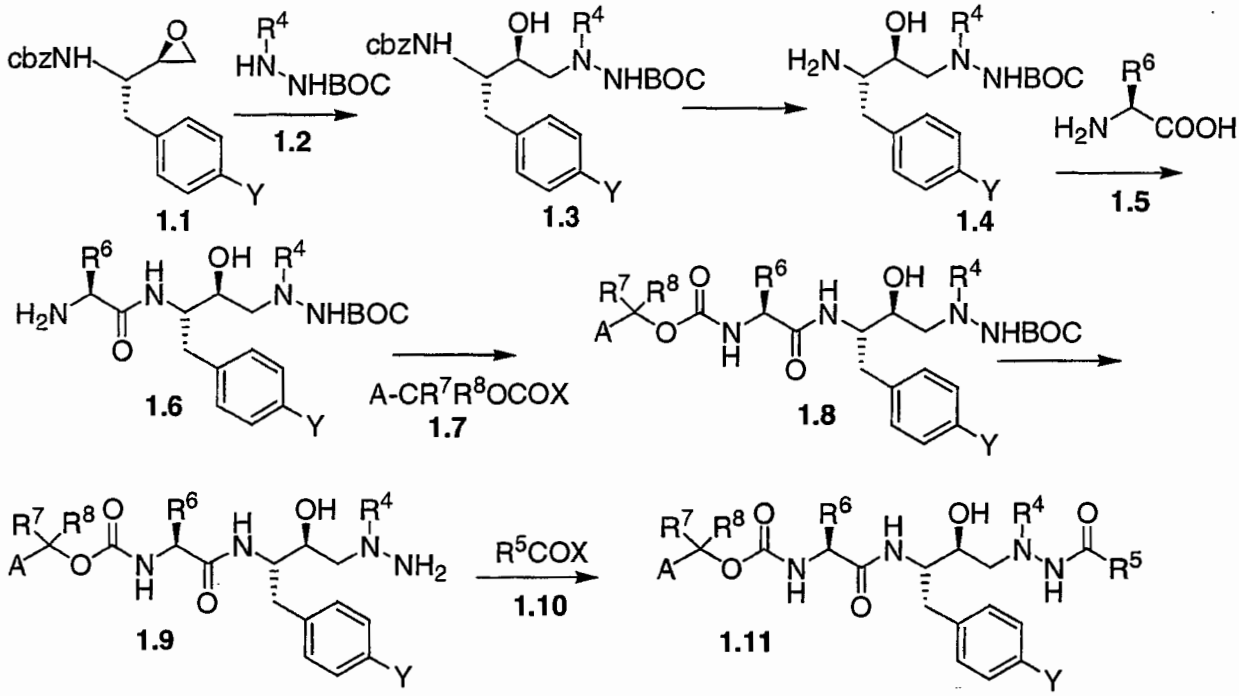
Scheme **4**, Example **3** illustrates the preparation of phosphonate-containing biphenyl hydrazine derivatives **4.13**, which are employed in the preparation of the phosphonate esters **3b**. In this procedure, a phosphonate-substituted phenyl benzaldehyde **4.12** the preparation of which is

described below, (Schemes **42- 44**) is converted, as described above in Example **2** into hydrazine product **4.13**.

Scheme **4**, Example **4** illustrates the preparation of phosphonate-containing phenyl hydrazine derivatives **4.15**, which are employed in the preparation of the phosphonate esters **3d**. In this procedure, a phosphonate-substituted phenyl benzaldehyde **4.14**, the preparation of which is described below, (Schemes **45 - 48**) is converted, as described above in Example **2** into hydrazine product **4.15**.

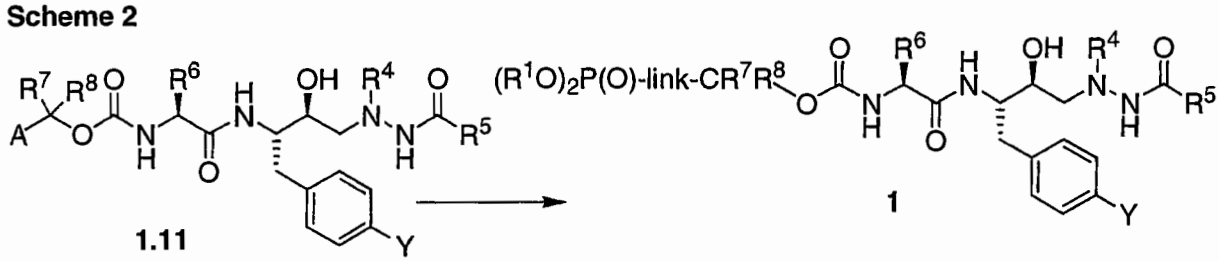
Scheme **4**, Example **5** illustrates the preparation of phosphonate-containing cyclohexyl hydrazine derivatives **4.17**, which are employed in the preparation of the phosphonate esters **3c**. In this procedure, a phosphonate-substituted cyclohexane carboxaldehyde **4.16**, the preparation of which is described below, (Schemes **49 – 52**) is converted, as described above in Example **2** into hydrazine product **4.17.**

Scheme 1

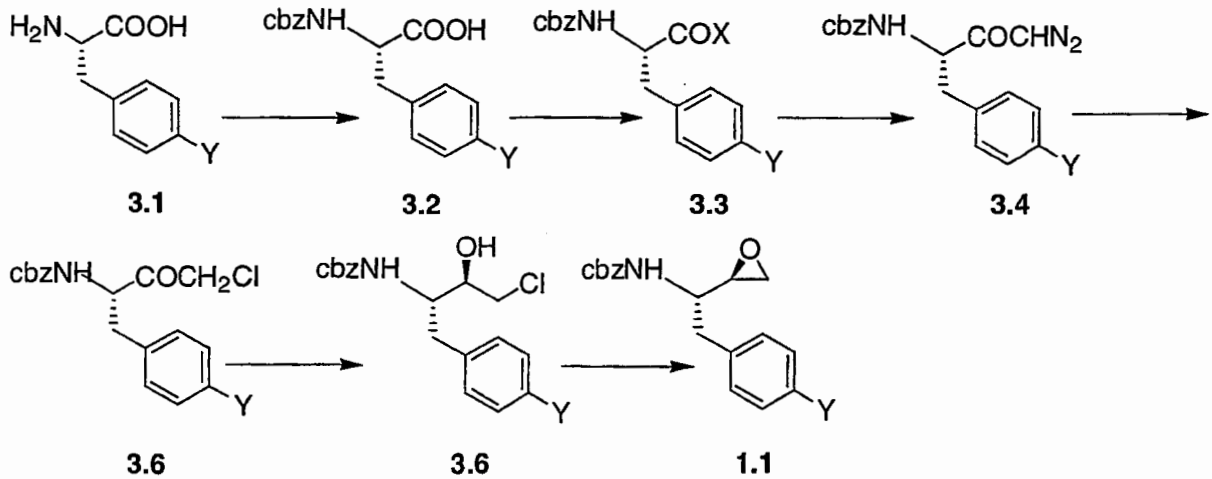


Y = H, OC_2H_5, $OCH_2C_6H_5$, $O(CH_2)_2$morpholino, OCH_2COmorpholino

Scheme 2

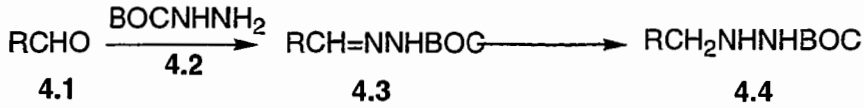


Scheme 3

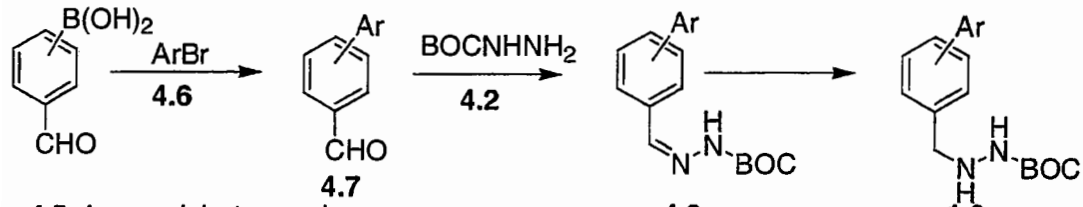


Scheme 4

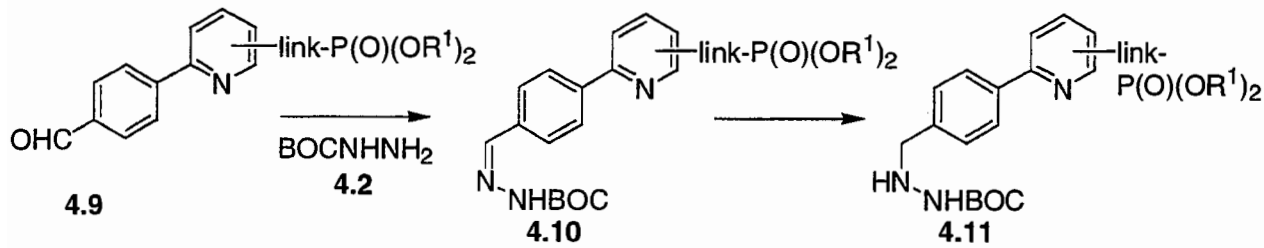
General reaction



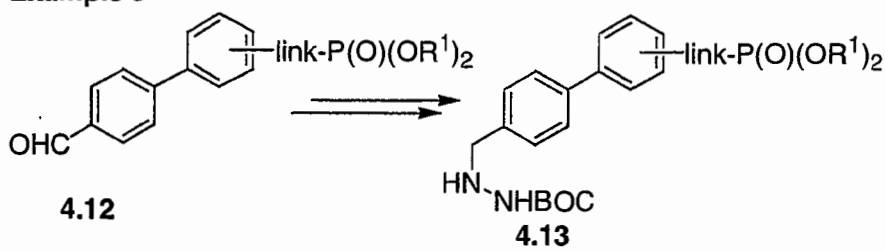
Example 1



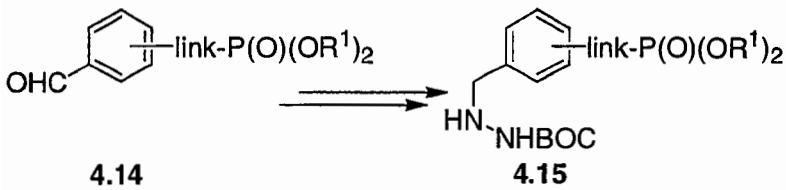
Example 2



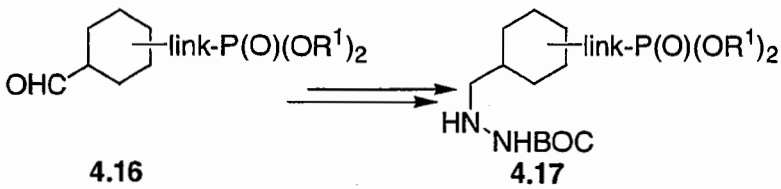
Example 3



Example 4



Example 5



Preparation of the phosphonate ester intermediates 1 in which X is sulfur.

Schemes **5** and **6** illustrate the preparation of the compounds **1** in which X is sulfur. In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, **5.1**, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol R^3SH **5.2**, as defined above, to afford the thioether **5.3**.

The reaction is conducted in an organic solvent such as, for example, pyridine, DMF, toluene and the like, optionally in the presence of water, in the presence of an inorganic or organic base, at from 0° to 80°, for from 1-12 hours. Preferably the mesylate **5.1** is reacted with an equimolar amount of the thiol R^3SH **5.2**, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°, as described in J. Org. Chem., 1994, 59, 3656, to give the product **5.3**. The 1,3-dioxolane protecting group present in the compound **5.3** is then removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol **5.4**. Methods for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p191. For example, the 1,3-dioxolane compound **5.3** is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture. Preferably, the 1,3-dioxolane **5.3** is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°, to yield the diol product **5.4**.

The primary hydroxyl group of the diol **5.4** is then selectively activated by reaction with an electron-withdrawing reagent such as, for example, dinitrobenzoyl chloride or p-toluenesulfonyl chloride. The reaction is conducted in an inert solvent such as pyridine, dichloromethane and the like, in the presence of an inorganic or organic base.

Preferably, equimolar amounts of the diol **5.4** and p-toluenesufonyl chloride are reacted in a solvent such as pyridine, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, as described in J. Org. Chem, 2000, 65, 1623, to afford the p-toluenesulfonate ester **5.5**.

The latter compound is then reacted with the hydrazine derivative **1.2** to afford the hydrazine **5.6**. The displacement reaction is conducted in a polar aprotic solvent such as

dimethylformamide, acetonitrile, dioxan and the like, in the presence of an organic or inorganic base, to afford the product **5.6**. Preferably, equimolar amounts of the reactants are combined in dimethylformamide at ca. 80° in the presence of potassium carbonate, to produce the hydrazine product **5.6**. The cbz protecting group is then removed to afford the amine **5.7**. The removal of carbobenzyloxy substituents to afford the corresponding amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The conversion can be effected by the use of catalytic hydrogenation, in the presence of hydrogen or a hydrogen donor and a palladium catalyst. Alternatively, the cbz group can be removed by treatment of the substrate with triethylsilane, triethylamine and a catalytic amount of palladium (II) chloride, as described in Chem. Ber., 94, 821, 1961, or by the use of trimethylsilyl iodide in acetonitrile at ambient temperature, as described in J. Chem. Soc., Perkin Trans. I, 1277, 1988. The cbz group can also be removed by treatment with Lewis acid such as boron tribromide, as described in J. Org. Chem., 39, 1247, 1974, or aluminum chloride, as described in Tet. Lett., 2793, 1979. Preferably, the cbz protecting group is removed by hydrogenation of the substrate **5.6** in the presence of 5% palladium on carbon catalyst, to yield the amine **5.7**. The amine is then coupled with the aminoacid **5.8** to give the amine **5.9**. The reaction is effected under the same conditions as described above for the preparation of the amide **1.6**.

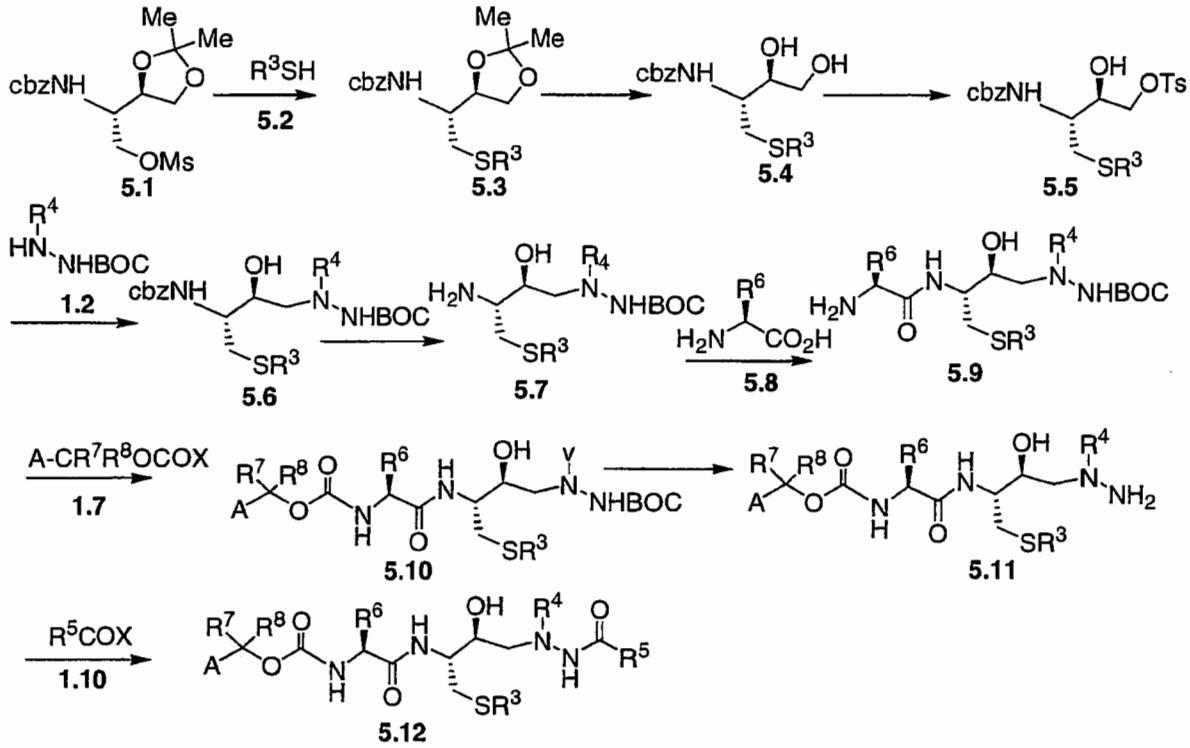
The amine is then reacted with a reagent A-CR^7R^8OCOX (**1.7**), in which the substituent A is the group $(R^1O)_2P(O)$-link, or a precursor group thereto, such as [OH], [SH], [NH], Br, as described below, and in which the substituent X is a leaving group, to yield the carbamate **5.10**. The reagent A-CR^7R^8OCOX is derived from the corresponding alcohol A-CR^7R^8OH, using methods described below, (Scheme **20**). The preparation of the reactants A-CR^7R^8OCOX is described in Schemes **21** - **26**. The preparation of carbamates by means of reactions between alcohols and amines is described below, in Scheme **20**.

The BOC protecting group is then removed from the product **5.10** to produce the hydrazine **5.11**. The conditions for the removal of the BOC group are the same as those described above (Scheme **1**). The product is then acylated with the carboxylic acid or activated derivative thereof, **1.10**, using the conditions described above, (Scheme **1**) to yield the product **5.12**.

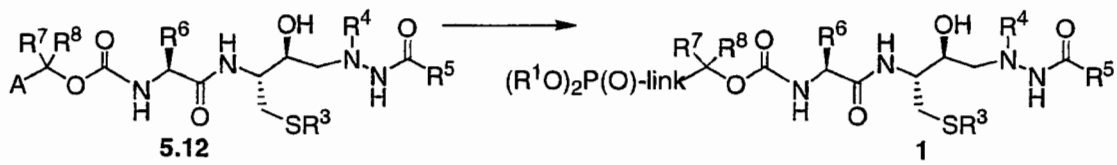
The procedures illustrated in Scheme **5** depict the preparation of the compounds **5.11** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br , as described below. Scheme **6** illustrates the conversion of compounds **5.12** in which

A is a precursor to the group link-P(O)(OR^1)$_2$ into the compounds **1**. Procedures for the conversion of the substituent A into the group link-P(O)(OR^1)$_2$ are illustrated below, (Schemes **21 - 56**).

Scheme 5



Scheme 6



Preparation of the phosphonate ester intermediates 2 in which X is a direct bond.

Schemes **7** and **8** illustrate the preparation of the phosphonate esters **2** in which X is a direct bond. As shown in Scheme **7**, a cbz-protected oxirane **7.1** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br, is reacted with a hydrazine derivative **1.2**, to afford the ring-opened product **7.3**. The conditions for the reaction are the same as those described above for the preparation of the hydrazine derivative

1.3, (Scheme **1**). The preparation of the substituted oxiranes **7.1** are described below, in Scheme **9**. The product **7.3** is then transformed, using the sequence of reactions illustrated in Scheme **7**, into the product **7.8**. The conditions employed for the component reactions of this sequence are the same as for the analogous reaction in Scheme **1**.

The procedures illustrated in Scheme **7** depict the preparation of the compounds **7.8** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **8** illustrates the conversion of compounds **7.8** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **2**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **21 - 56**).

Scheme **9** illustrates the preparation of the oxiranes **7.1**. In this sequence, a substituted phenylalanine **9.1**, in which substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, is transformed into the cbz-protected derivative **9.2**, using the conditions described above for the preparation of the cbz derivative **3.2**, (Scheme **3**). The latter compound is then transformed, using the using the sequence of reactions illustrated in Scheme **3**, into the product **7.1**. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme **3**.

Preparation of the phosphonate ester intermediates 2 in which X is a sulfur.

Schemes **10** and **11** illustrate the preparation of the compounds **2** in which X is sulfur. As shown in Scheme **10**, the mesylate **5.1** is reacted with the substituted thiophenol **10.1**, in which substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below (scheme **30-39**), to afford the thioether **10.2**. The conditions employed for this reaction are the same as those described above for the preparation of the thioether **5.3**, Scheme **5**. The product **10.2** is then transformed, using the series of reactions shown in Scheme **5**, into the diacylated thioether **10.3**. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme **5**.
The procedures illustrated in Scheme **10** depict the preparation of the compounds **10.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as

[OH], [SH] Br, as described below. Scheme **11** illustrates the conversion of compounds **10.3** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **2**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **21 - 56**).

Preparation of the phosphonate ester intermediates 3 in which X is a direct bond.

Schemes **12** and **13** depict the preparation of the phosphonate esters **3a** in which X is a direct bond. As shown in Scheme **12**, the oxirane **1.1** is reacted with a BOC protected phenylhydrazine derivative **12.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. The preparation of the hydrazine derivatives **12.1** is described in Schemes **4**, **40** and **41**. The reaction is conducted under the same conditions as described above for the preparation of the hydrazine **7.3**, Scheme **7**. The product **12.2** is then transformed, using the sequence of reactions shown in Scheme **7** for the transformation of the hydrazine **7.3** into the diacylated compound **7.8**, into the diacylated compound **12.3**. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme **7**.

The procedures illustrated in Scheme **12** depict the preparation of the phosphonate esters **12.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **13** illustrates the conversion of compounds **12.3** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **3a** in which X is a direct bond. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **21 - 56**).

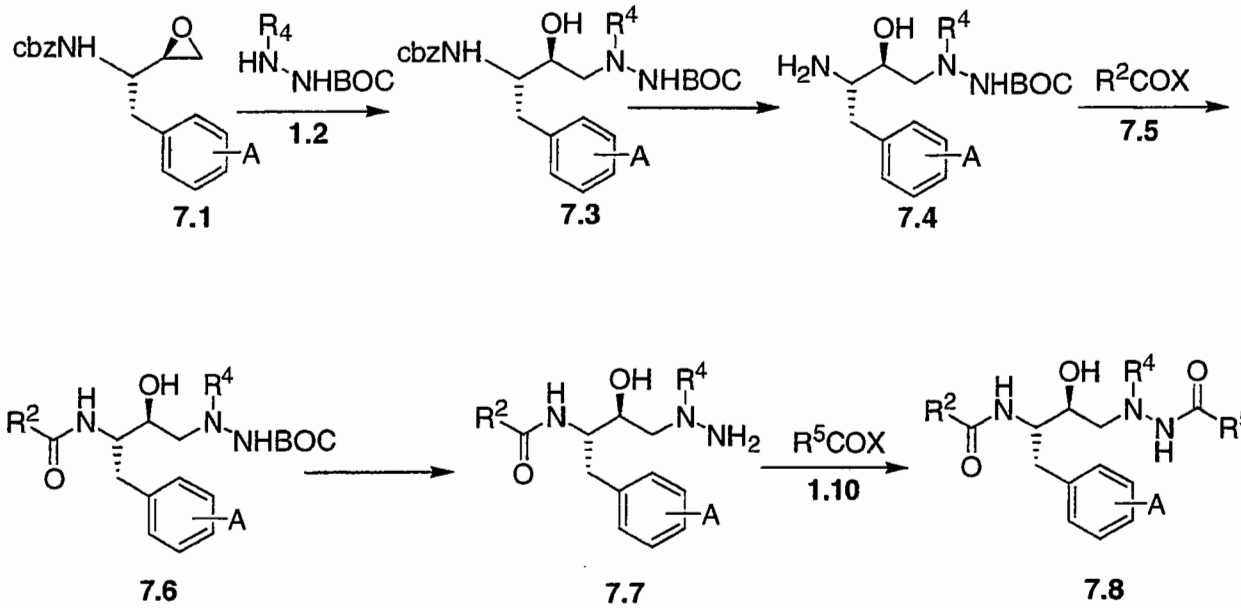
The phosphonate esters **3b**, **3c** and **3d**, in which X is a direct bond, are prepared using the procedures of Schemes **12** and **13**, except that the hydrazine derivatives **4.13**, **4.17** and **4.15**, prepared as described in Schemes **42 – 52**, are used in place of the hydrazine derivative **12.1**.

Preparation of the phosphonate ester intermediates 3 in which X is sulfur.

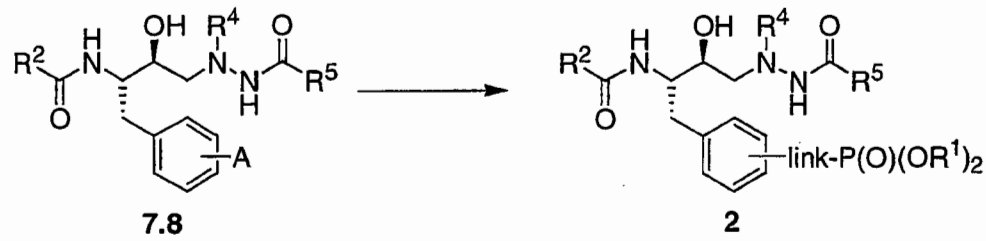
Schemes **14** and **15** illustrate the preparation of the phosphonate esters **3a** in which X is sulfur. As shown in Scheme **14**, the p-toluenesulfonate ester **5.5** is reacted with the phenylhydrazine derivative **12.1**, in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, to afford the hydrazine derivative **14.1**. The reaction is conducted under the same conditions as described above for the preparation of the hydrazine **5.6**, Scheme **5**. The product **14.1** is then transformed into the diacylated product **14.2**, using the sequence of reactions shown in Scheme **5**. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme **5**. The procedures illustrated in Scheme **14** depict the preparation of the phosphonate esters **14.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **15** illustrates the conversion of compounds **14.2** in which A is a precursor to the group link-P(O)$(OR^1)_2$ into the compounds **3a** in which X is S. Procedures for the conversion of the substituent A into the group link-P(O)$(OR^1)_2$ are illustrated below, (Schemes **21 - 56**).

The phosphonate esters **3b**, **3c** and **3d**, in which X is S, are prepared using the procedures of Schemes **12** and **13**, except that the hydrazine derivatives **4.13**, **4.17** and **4.15**, prepared as described in Schemes **42 – 52**, are used in place of the hydrazine derivative **12.1**.

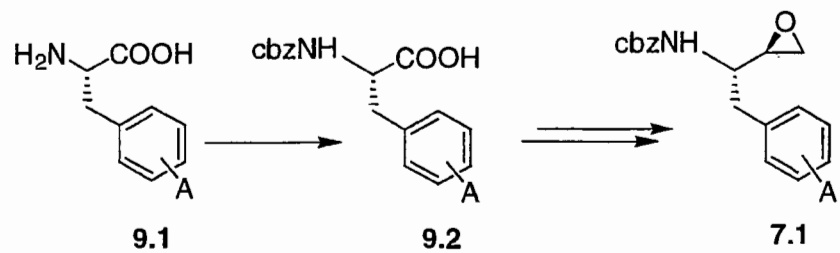
Scheme 7



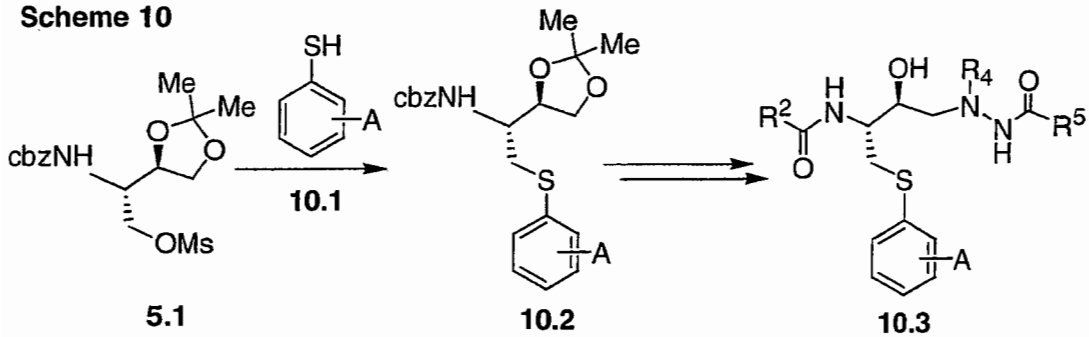
Scheme 8



Scheme 9

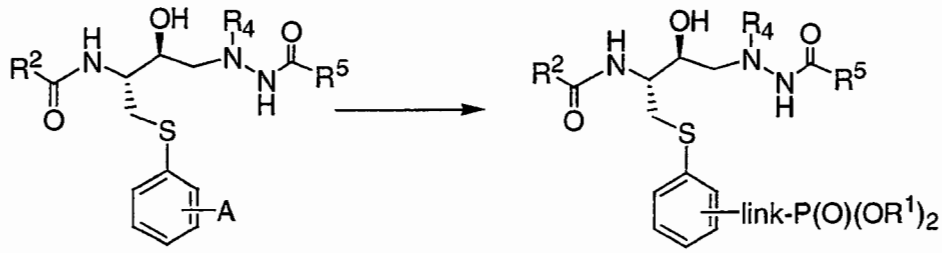


Scheme 10



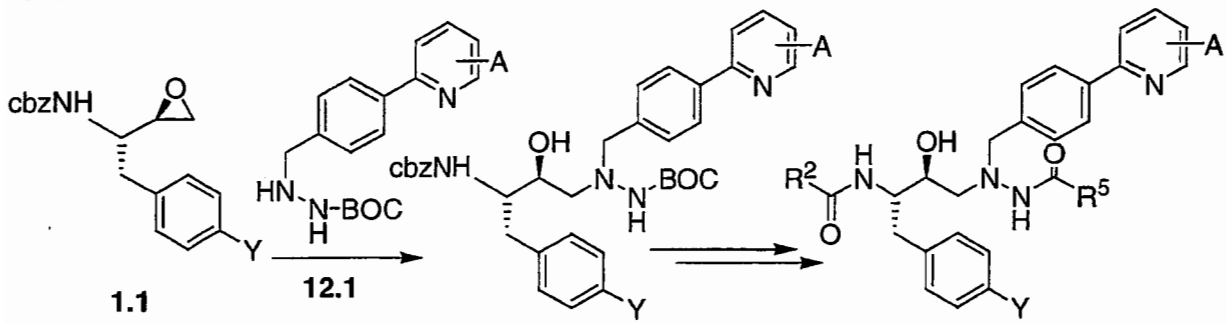
5.1 10.2 10.3

Scheme 11



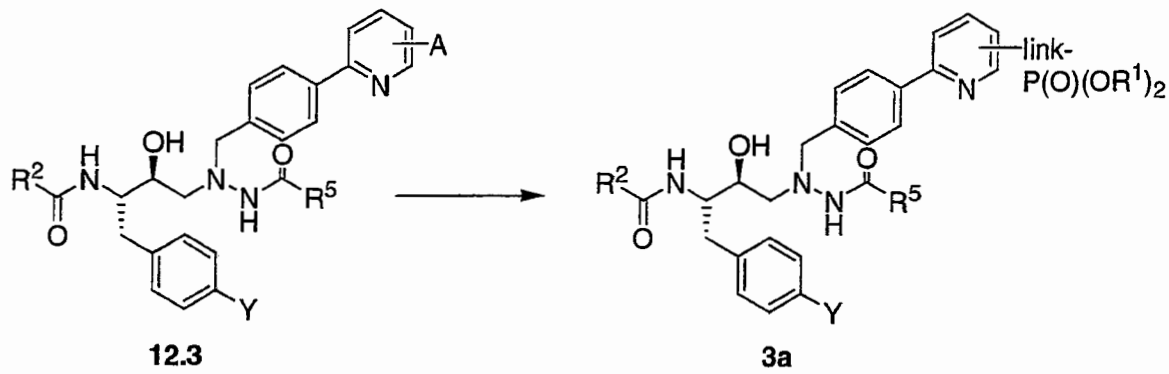
10.3 2

Scheme 12

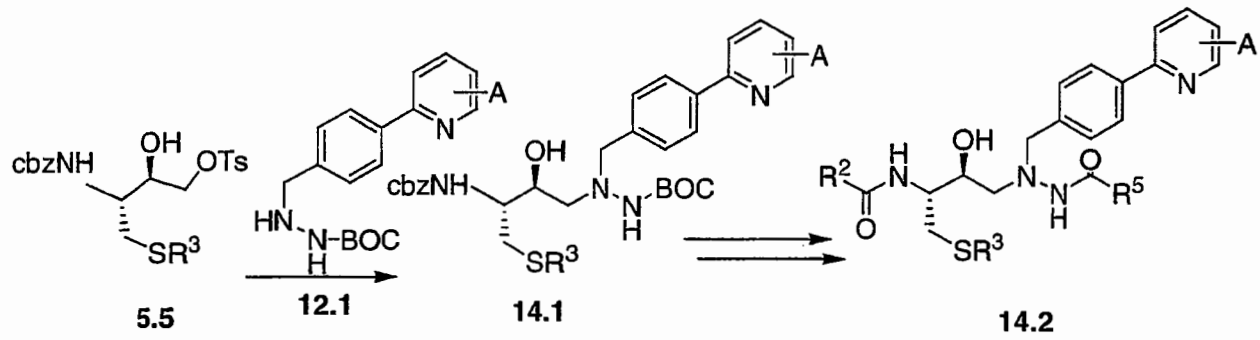


1.1 12.1 12.2 12.3

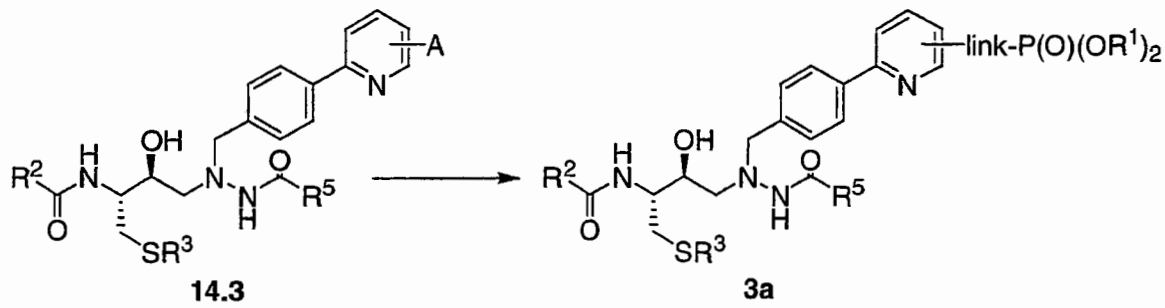
Scheme 13



Scheme 14



Scheme 15



Preparation of the phosphonate ester intermediates 4 in which X is a direct bond.

Schemes **16** and **17** illustrate the preparation of the phosphonate esters **4** in which X is a direct bond. As shown in Scheme **16**, the amine **1.4**, prepared as described in Scheme **1**, is reacted with the carboxylic acid or activated derivative thereof R^2COX **7.5**, to afford the amide **16.1**. The conditions for the amide forming reaction are the same as those described above for the

preparation of the amide **1.11**, (Scheme **1**). The product is then deprotected by removal of the BOC group, using the procedures described above (Scheme **1**), to yield the hydrazine **16.2**. This material is then coupled with the aminoacid **1.5**, using the coupling procedures described above for the preparation of the amide **1.6**, to produce the amide **16.3**. The product is then reacted with the acylating agent A-CR^7R^8OCOX, **1.7**, in which A and X are as described above, Scheme **1**, to afford the carbamate product **16.4**.

The procedures illustrated in Scheme **16** depict the preparation of the phosphonate esters **16.4** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **17** illustrates the conversion of compounds **16.4** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **4**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **21 - 56**).

Preparation of the phosphonate ester intermediates 4 in which X is sulfur.

Schemes **18** and **19** illustrate the preparation of the phosphonate esters **4** in which X is sulfur. As shown in Scheme **18**, the amine **5.7**, prepared as described in Scheme **5**, is reacted with the carboxylic acid or activated derivative thereof **7.5**, to produce the amide **18.1**. The reaction is performed under the conditions described above for the preparation of the amide **1.11**. The BOC group present in the amide **18.1** is then removed using the procedures described above, (Scheme **1**) to afford the amine **18.2**. This material is then coupled with the aminoacid **1.5**, using the procedures described above for the preparation of the amide **1.6**, to produce the amide **18.3**. The latter compound is then reacted with the acylating agent A-CR^7R^8OCOX, **1.7**, in which A and X are as described above, Scheme **1**, to afford the carbamate product **18.4**.

The procedures illustrated in Scheme **18** depict the preparation of the phosphonate esters **18.4** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **19** illustrates the conversion of compounds **18.4** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **4**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **21 - 56**).

Preparation of the phosphonate ester intermediates 5 in which X is a direct bond.

Schemes **19a** and **19b** illustrate the preparation of the phosphonate esters **5** in which X is a direct bond. As shown in Scheme **19a**, the amine **1.6** is reacted with a quinoline-2-carboxylic acid derivative **19a.1**, in which the substituent A is either the group $(R^1O)_2P(O)$-link or a precursor group thereto, such as OH, SH, Br to afford the amide **19a.2**. The reaction is performed as described above for the preparation of the amide **1.6** (Scheme **1**). The BOC protecting group is then removed, using the procedures described in Scheme **1**, to yield the amine **19a.3**. This compound is then reacted, as described above, with the carboxylic acid R^5COOH, or an activated derivative thereof **19a.4**, to give the amide **19a.5**.

The procedures illustrated in Scheme **19a** depict the preparation of the phosphonate esters **19a.5** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **19b** illustrates the conversion of compounds **19a.5** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **5**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **21 - 56**). The preparation of the quinoline carboxylic acid reagents **19a.1** is described below, (Schemes **53 - 56**).

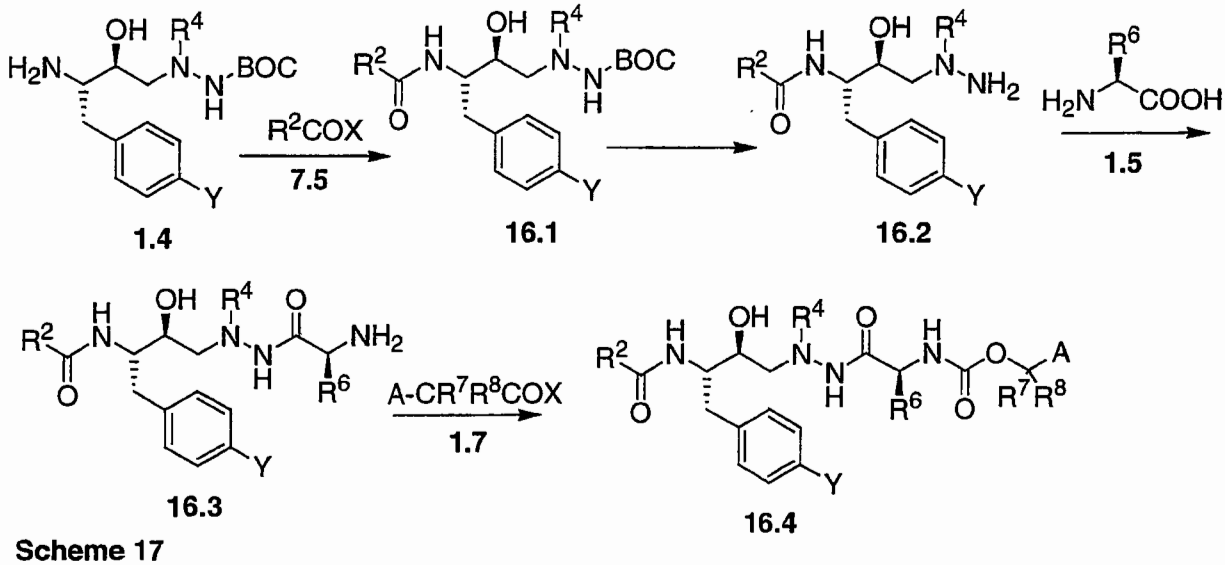
Preparation of the phosphonate ester intermediates 5 in which X is sulfur.

Schemes **19c** and **19d** illustrate the preparation of the phosphonate esters **5** in which X is sulfur. As shown in Scheme **19c**, the amine **5.9** is reacted, as described above, with the quinoline carboxylic acid derivative **19a.1** to yield the amide product **19c.1**. The BOC protecting group is then removed, as described above, to give the amine **19c.2**. The latter compound is then reacted, as described above, with the carboxylic acid R^5COOH, or an activated derivative thereof **19a.4**, to give the amide **19c.3**.

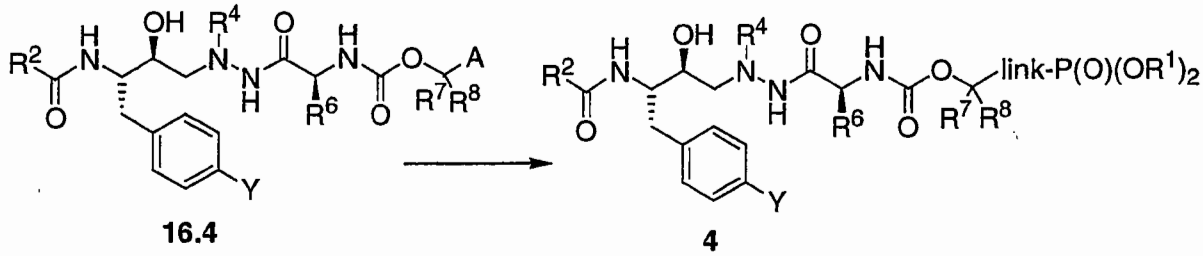
The procedures illustrated in Scheme **19c** depict the preparation of the phosphonate esters **19c.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme **19d** illustrates the conversion of compounds **19c.3** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **5**. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are

illustrated below, (Schemes **21 - 56**). The preparation of the quinoline carboxylic acid reagents **19a.1** is described below, (Schemes **53 - 56**).

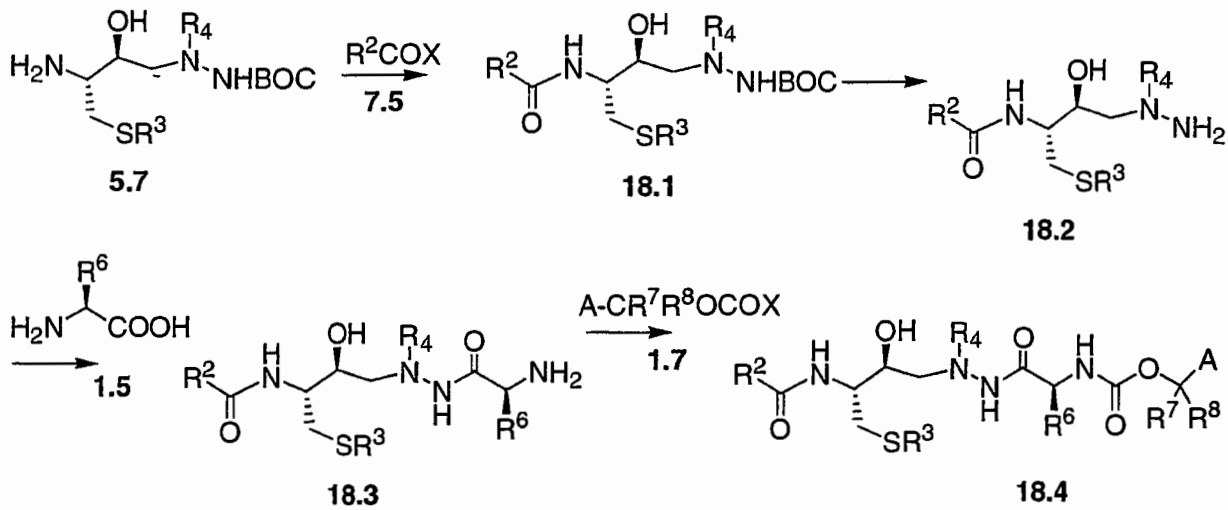
Scheme 16



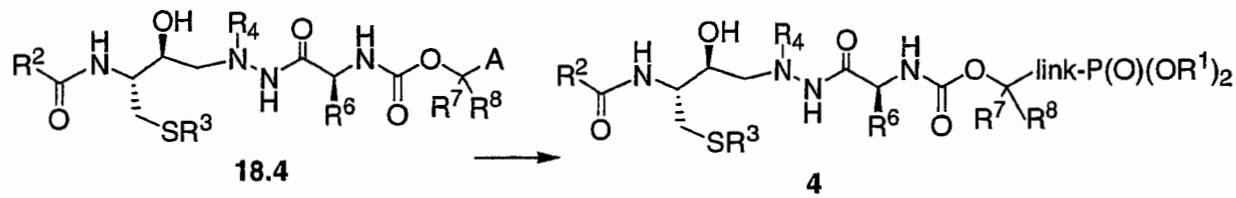
Scheme 17



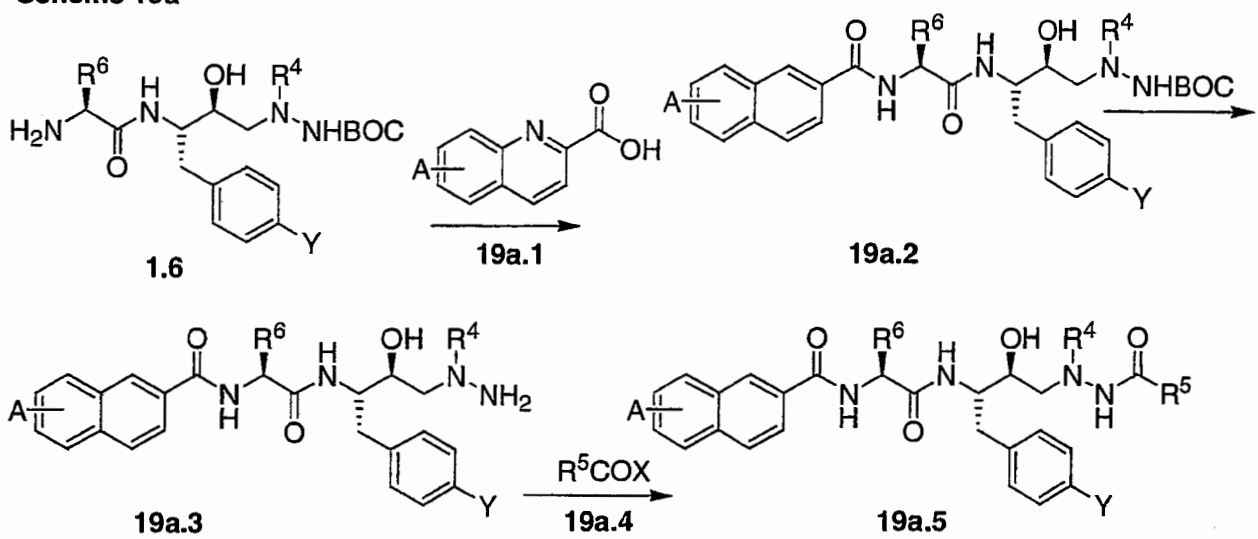
Scheme 18



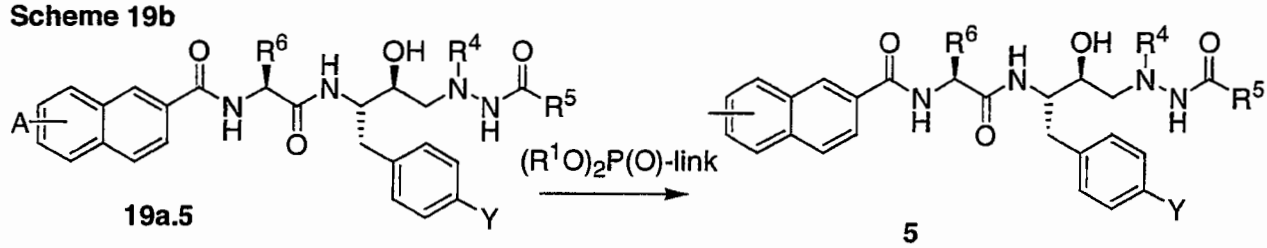
Scheme 19



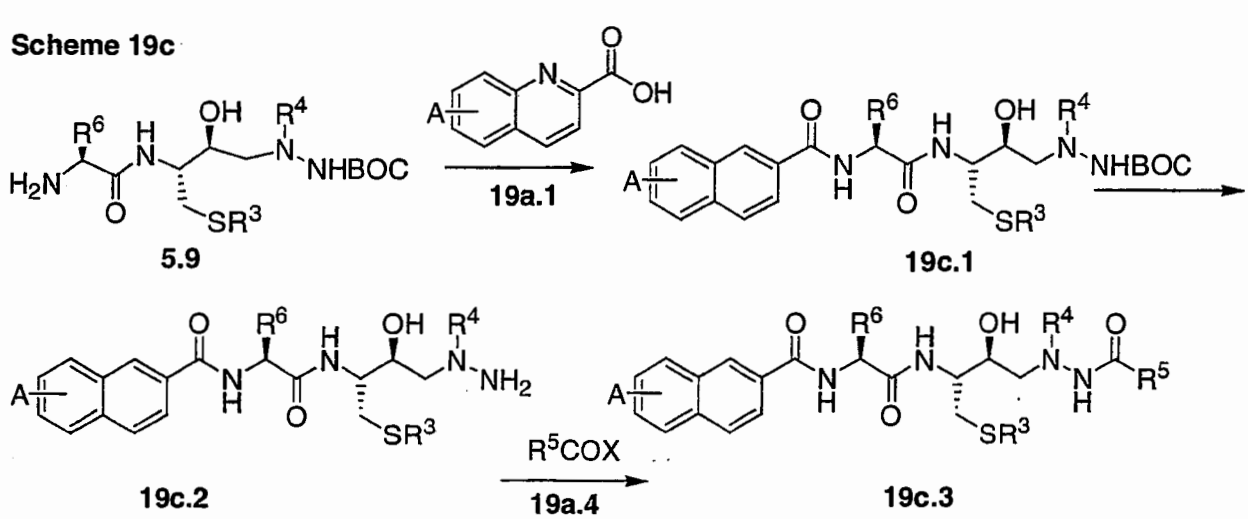
Scheme 19a



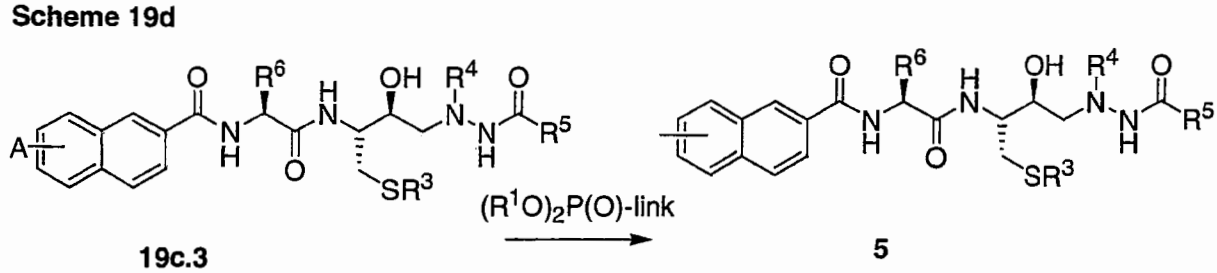
Scheme 19b



Scheme 19c



Scheme 19d



Preparation of carbamates.

The phosphonate esters **1** and **4**, and the phosphonate ester **1-7** in which the R^2CO or R^5CO groups are formally derived from the carboxylic acids **C38 - C49** (Chart **2c**) contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme **20** illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme **20**, in the general reaction generating carbamates, a carbinol **20.1**, is converted into the activated derivative **20.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **20.2** is then reacted with an amine **20.3**, to afford the carbamate product **20.4**. Examples **1 – 7** in Scheme **20** depict methods by which the general reaction can be effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.

Scheme **20**, Example **1** illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **20.5**. In this procedure, the carbinol **20.5** is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **20.6**. The latter compound is then reacted with the amine component **20.3**, in the presence of an organic or inorganic base, to afford the carbamate **20.7**. For example, the chloroformyl compound **20.6** is reacted with the amine **20.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **20.7**. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme **20**, Example **2** depicts the reaction of the chloroformate compound **20.6** with imidazole to produce the imidazolide **20.8**. The imidazolide product is then reacted with the amine **20.3** to yield the carbamate **20.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is

conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme **20** Example **3**, depicts the reaction of the chloroformate **20.6** with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester **20.10**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **20.19** - **20.24** shown in Scheme **20**, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **20.19**, N-hydroxysuccinimide **20.20**, or pentachlorophenol, **20.21**, the mixed carbonate **20.10** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **20.22** or 2-hydroxypyridine **20.23** can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme **20** Example **4** illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **20.8** is employed. In this procedure, a carbinol **20.5** is reacted with an equimolar amount of carbonyl diimidazole **20.11** to prepare the intermediate **20.8**. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **20.8** is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **20.7**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate **20.7**.

Scheme **20**, Example **5** illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **20.13**. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **20.12**, to afford the alkoxycarbonyl product **20.13**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. The product is then reacted with the amine $R'NH_2$ to afford the carbamate **20.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80° as described in Syn., 1977, 704.

Scheme **20**, Example **6** illustrates the preparation of carbamates in which a carbonate $(R"O)_2CO$, **20.14**, is reacted with a carbinol **20.5** to afford the intermediate alkyloxycarbonyl

intermediate **20.15**. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate **20.7**. The procedure in which the reagent **20.15** is derived from hydroxybenztriazole **20.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **20.15** is derived from N-hydroxysuccinimide **20.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **20.15** is derived from 2-hydroxypyridine **20.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **20.15** is derived from 4-nitrophenol **20.24** is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate **20.14** is conducted in an inert organic solvent at ambient temperature.

Scheme **20**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides **20.16**. In this procedure, an alkyl chloroformate **20.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **20.16**. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **20.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

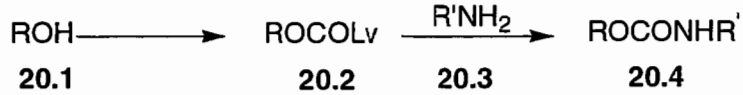
Scheme **20**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine **20.17**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **20.7**.

Scheme **20**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **20.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **20.7**.

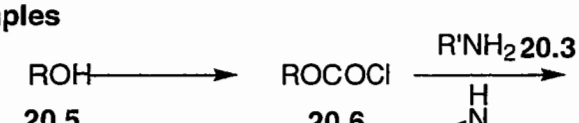
Scheme **20**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **20.7**.

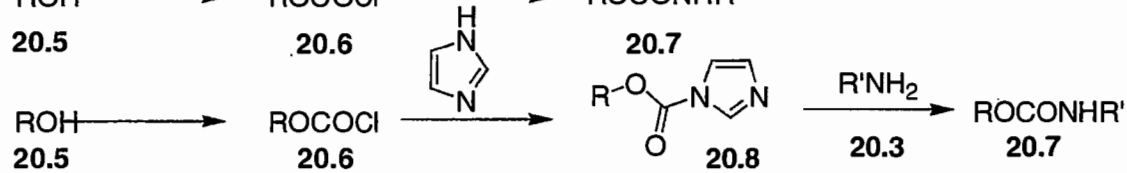
Scheme 20

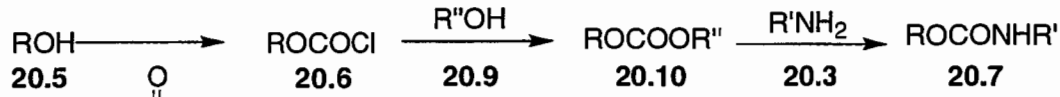
General reaction

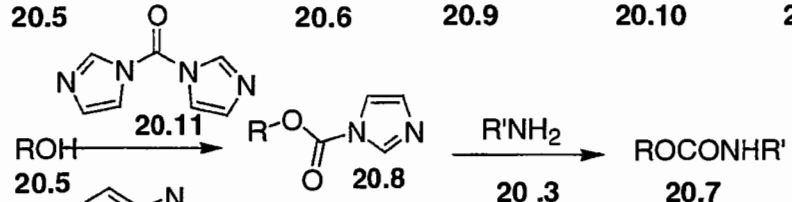


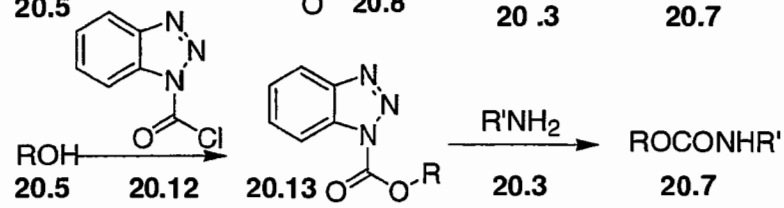
Examples

(1) 

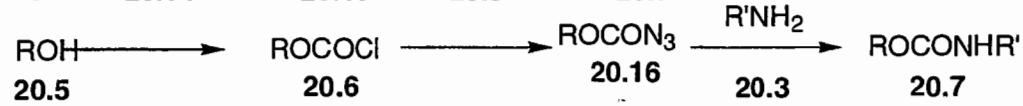
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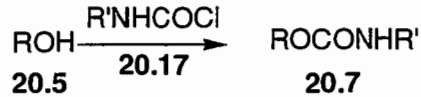
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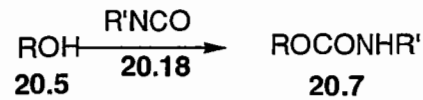
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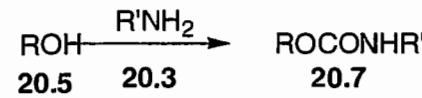
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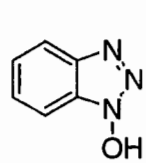
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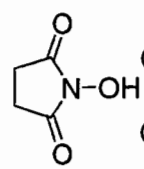
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(9) 

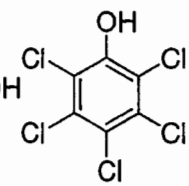
(10) 

R"OH = 

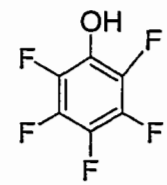
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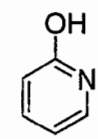
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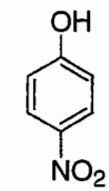
20.21



20.22



20.23



20.24

Preparation of the reagents A-CR^7R^8OCOX.

The reagents A-CR^7R^8OCOX **1.7** are prepared from the corresponding carbinols A-CR^7R^8OH, using procedures such as those described above in Scheme **20**. Examples of the preparation of the carbinols A-CR^7R^8OH and the derived reagents **1.7** are shown below in Schemes **21-26**. The activation methods for the conversion of the carbinols A-CR^7R^8OH to the reagents A-CR^7R^8OCOX are interchangeable between the different alcohols A-CR^7R^8OH.

Scheme **21** depicts the preparation of phosphonate-containing reagents **21.2** in which the phosphonate is linked by means of an alkylene chain. In this procedure, a dialkyl hydroxyalkyl phosphonate **21.1** is reacted with phosgene, or an equivalent reagent, to afford the chloroformate **21.2**, as described above in Scheme **20**, Example **1**. The reaction is conducted in an inert organic solvent such as dichloromethane or toluene, at from about 0° to ambient temperature.

For example, as shown in Scheme **21**, Example **1**, a dialkyl hydroxymethylphosphonate **21.3** (Aldrich) is reacted with excess phosgene in toluene at 0°, as described in Org. Syn. Coll. Vol. 3, 197, 1965, to afford the chloroformyl product **21.4**.

Scheme **21**, Example **2** illustrates the analogous conversion of a dialkyl hydroxyethyl phosphonate **21.5** (Aldrich) into the chloroformate derivative **21.6**. The reaction is performed as described above for the preparation of the chloroformate **21.4**.

Scheme **21**, Example **3** illustrates the analogous conversion of a dialkyl phosphono-substituted tert. butanol **21.7**, prepared as described in Fr.2462440, into the chloroformate derivative **21.8**. The reaction is performed as described above for the preparation of the chloroformate **21.4**.

Using the above procedures, but employing, in place of the phosphonates **21.3**, **21.5** or **21.7**, different dialkyl hydroxyalkyl phosphonates **21.1**, the corresponding products **21.2** are obtained.

Scheme **22** depicts the preparation of phosphonate-containing reagents **22.2** in which the phosphonate is linked by means of a phenyl ring. In this procedure, a dialkyl

hydroxyalkylphenyl phosphonate **22.1** is converted, as described above, into an activated chloroformyl derivative **22.2**, using the procedures described above in Scheme **20**.
For example, a dialkyl 4-hydroxymethylphenylphosphonate **22.3** (Aldrich) is reacted in tetrahydrofuran with an equimolar amount of the 2-pyridyl carbonate **22.4**, prepared as described in Tet. Let., 1991, 4251, to afford the product **22.5**.
Using the above procedure, but employing, in place of a dialkyl hydroxyphenylphosphonate **22.3**, different dialkyl hydroxyphenyl phosphonates **22.1**, the corresponding products **22.2** are obtained.

Scheme **23** depicts the preparation of phosphonate containing reagents **23.4** in which the phosphonate group is linked by means of an alkylene chain incorporating a heteroatom O, S or N. In this procedure, a dialkyl hydroxy-, thio- or alkylaminoalkylphosphonate **23.1** is alkylated by reaction with a bromoalkanol **23.2**. The alkylation reaction is conducted at from ambient temperature to about 70° in a polar organic solvent such as dimethylformamide, dioxan or acetonitrile, in the presence of a base. In cases in which X is oxygen, a strong base such as lithium hexamethyldisilylazide or potassium tert-butoxide is employed. In cases in which X is sulfur or alkylamino, an inorganic base such as potassium carbonate or cesium carbonate is used. The product **23.3** is then converted into an activated derivative **23.4** by means of one of the methods described above in Scheme **20**.
For example, as shown in Scheme **23**, Example **1**, a dialkyl 2-mercaptoethyphosphonate **23.5**, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, is reacted with one molar equivalent of bromoethanol **23.6**, in dimethylformamide at 60° in the presence of cesium carbonate, to afford the thioether product **23.7**. This compound is then reacted with pentafluorophenyl carbonate **23.8**, (Fluorochem) in dimethylformamide solution at ambient temperature in the presence of triethylamine, to afford the pentafluorophenoxycarbonyl product **23.9**.
As a further example of the method of Scheme **23**, as shown in Example **2**, a dialkyl methylaminomethyl phosphonate **23.10**, (AsInEx Inc.) is reacted in dimethylformamide at 70° with one molar equivalent of 5-bromo-2-hydroxy-2-methylpentane **23.11**, prepared as described in J. Med. Chem., 1994, 37, 2343, and potassium carbonate, to afford the amine product **23.12**. The product is then converted, as described above, into the pentafluorophenyl formate derivative **23.13**.

Using the above procedures, but employing, in place of a dialkyl 2-mercaptoethyphosphonate **23.5**, or a dialkyl methylaminomethyl phosphonate **23.10**, different hydroxy, mercapto or aminoalkylphosphonates **23.1**, and/or different bromoalkanols **23.2**, and/or different activation methods, the corresponding products **23.4** are obtained.

Scheme **24** illustrates the preparation of phosphonate containing reagents **24.4** in which the phosphonate group is linked by means of an alkylene chain incorporating an N-alkyl group. In this procedure, a dialkyl formylalkyl phosphonate **24.1** is reacted with an alkylaminoalkanol **24.2** under reductive amination conditions, so as to afford the product **24.3**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this reaction, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The reduction reaction can also be performed by hydrogenation in the presence of a palladium catalyst and hydrogen or a hydrogen donor. The reaction product **24.3** is then transformed into the activated derivative **24.4** by means of one of the procedures described above in Scheme **20**.

As shown in Scheme **24**, Example **1**, a dialkyl formylmethylphosphonate **24.5** (Aurora) is reacted with methylaminoethanol **24.6**, in the presence of sodium cyanoborohydride, to afford the coupled product **24.7**. This compound is then reacted with an equimolar amount of chlorocarbonylbenztriazole **20.13**, **in** toluene at 80°, in the presence of one molar equivalent of triethylamine, as described in Syn., 1977, 704, to yield the product **24.8**.

As a further example of the method of Scheme **24**, as shown in Example **2**, the aldehyde **24.5** is reacted with 2-hydroxy-2-methyl-3-methylaminopropane **24.10**, under reductive amination conditions, to afford the amine product **24.11**. The latter compound is then reacted with phosgene, or an equivalent thereof, as described above, to afford the chloroformyl product **24.12**.

Using the above procedures, but employing, in place of the phosphonates **24.5**, different phosphonates **24.1**, and/or in place of the aminoalkanols **24.6** or **24.10**, different

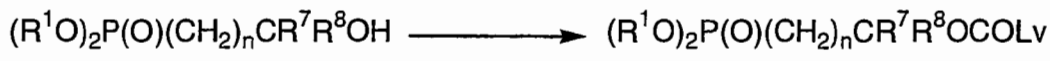
aminoalkylalkanols **24.2**, and/or different activation methods described in Scheme **20**, the corresponding products **24.4** are obtained.

Scheme **25** illustrates the preparation of phosphonate containing reagents **25.2** in which the phosphonate group is linked by means of an alkylene chain incorporating an acetylenic linkage. In this procedure, a dialkyl hydroxyalkynyl phosphonate **25.1** is converted, by means of one of the procedures described in Scheme **20**, into the activated formyl derivative **25.2**.
For example, a dialkyl hydroxypropynyl phosphonate **25.3** prepared as described in J. Org. Chem., 1987, 52, 4810, is reacted with one molar equivalent of di(succinimidyloxy)carbonate **25.4**, prepared as described in Tet. Lett, 1992, 2781, in dichloromethane at ambient temperature, to afford the product **25.5**.
Using the above procedures, but employing, in place of the dialkyl hydroxypropynyl phosphonate **25.3**, different dialkyl hydroxyalkynyl phosphonates **25.1**, the corresponding products **25.2** are obtained.

Scheme **26** illustrates the preparation of phosphonate containing reagents **26.2** in which the phosphonate group is linked by means of an alkylene chain incorporating an olefinic linkage. In this procedure, a dialkyl hydroxyalkenyl phosphonate **26.1** is converted, by means of one of the procedures described in Scheme **20**, into the activated formyl derivative **26.2**.
For example, a dialkyl propenylphosphonate **26.3**, prepared as described in Zh. Obschei. Khim., 1974, 44, 18343, is reacted with phosgene in toluene at 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to afford the chloroformyl product **26.4**.
Using the above procedures, but employing, in place of the dialkyl hydroxypropenyl phosphonate **26.3**, different dialkyl hydroxyalkynyl phosphonates **26.1**, the corresponding products **26.2** are obtained.

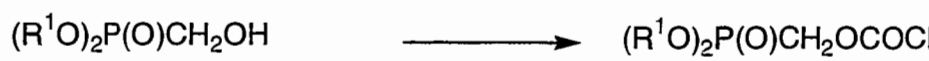
Scheme 21

Method



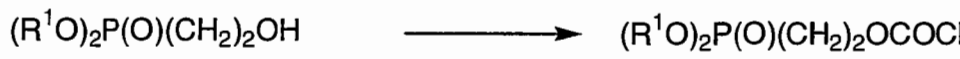
21.1 **21.2**

Example 1



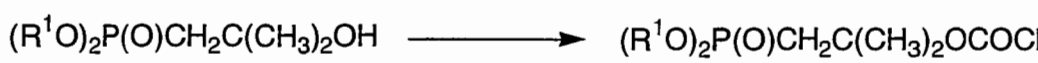
21.3 **21.4**

Example 2



21.5 **21.6**

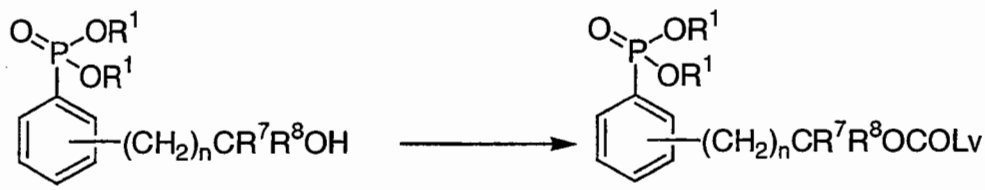
Example 3



21.7 **21.8**

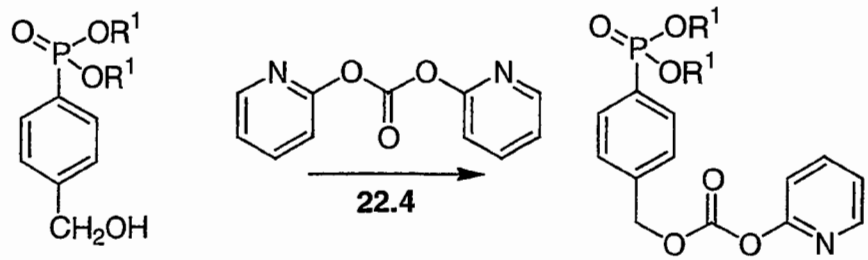
Scheme 22

Method



22.1 **22.2**

Example



22.3 **22.5**

Scheme 23

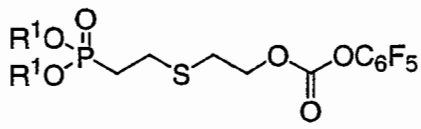
Method

$(R^1O)_2P(O)(CH_2)_nXH$ **23.1** (X = O, S, N-alkyl) $\xrightarrow{Br(CH_2)_mCR^7R^8OH}$ **23.2** $(R^1O)_2P(O)(CH_2)_nX(CH_2)_mCR^7R^8OH$ **23.3** $\longrightarrow$

$(R^1O)_2P(O)(CH_2)_nX(CH_2)_mCR^7R^8OCOLv$ **23.4**

Example 1

$(R^1O)_2P(O)CH_2SH$ **23.5** $\xrightarrow{Br(CH_2)_2OH}$ **23.6** $(R^1O)_2P(O)CH_2S(CH_2)_2OH$ **23.7** $\xrightarrow{(C_6F_5O)_2CO}$ **23.8**



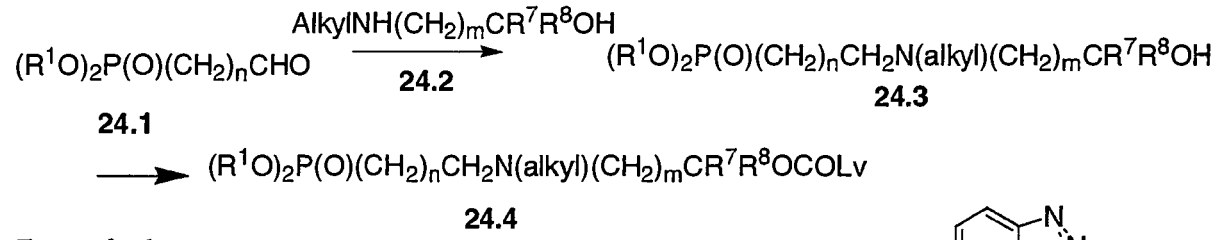
23.9

Example 2

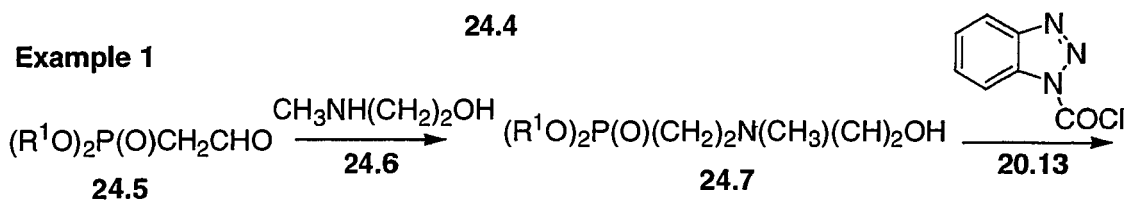
$(R^1O)_2P(O)CH_2NHCH_3$ **23.10** $\xrightarrow{Br(CH_2)_3C(CH_3)_2OH}$ **23.11** $(R^1O)_2P(O)CH_2N(CH_3)(CH_2)_3C(CH_3)_2OH$ **23.12** $\longrightarrow$

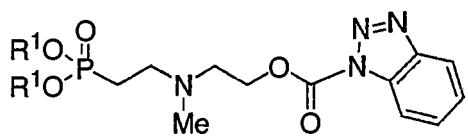
$(R^1O)_2P(O)CH_2N(CH_3)(CH_2)_3C(CH_3)_2OCOC_6F_5$ **23.13**

Scheme 24
Method



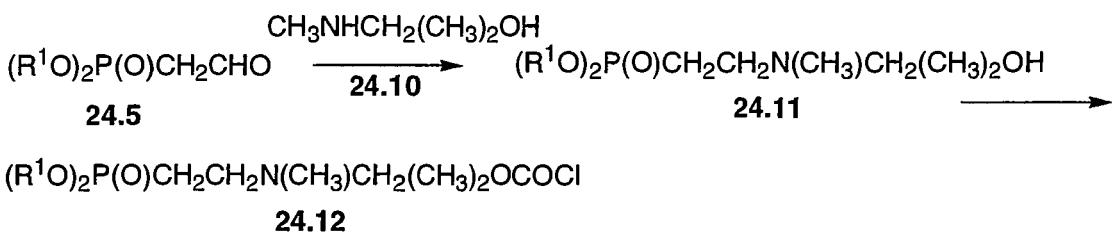
Example 1



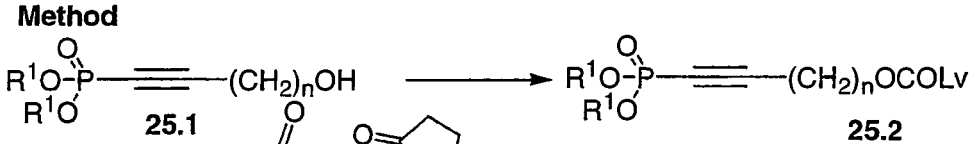


24.8

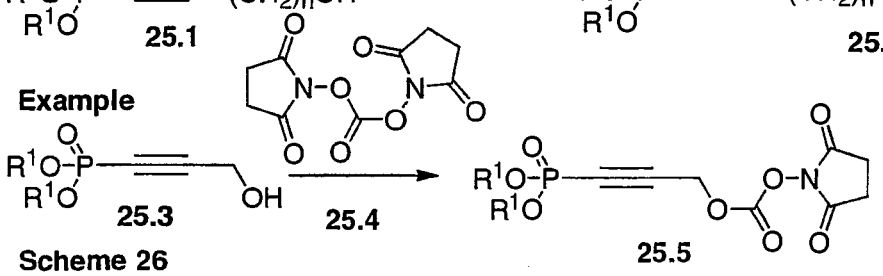
Example 2



Scheme 25
Method



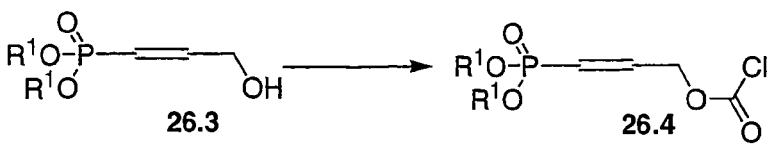
Example



Scheme 26
Method



Example



Preparation of the oxirane reactants 7.1.

The oxirane reactants **7.1** are obtained by means of chemical transformations applied to variously substituted phenylalanine derivatives. In the methods described below, the phosphonate moiety can be introduced into the molecule at any appropriate stage in the synthetic sequence, or after the intermediates are incorporated into the phosphonate esters **2**.

Scheme **27** depicts the preparation of oxirane reactants **27.5** in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **27.1** is converted into the cbz-protected derivative, using the procedures described above in Scheme **3**. The protected product **27.2** is then converted, by means of the series of reactions shown in Scheme **3**, into the oxirane **27.3**. The latter compound is then reacted with a dialkyl phosphite **27.4**, in the presence of a palladium catalyst, to afford the phosphonate ester **27.5**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.
For example, 4-bromophenylalanine **27.6**, prepared as described in Biotech. Lett., 1994, 16, 373, is converted, as described above, (Scheme **3**), into the oxirane **27.7**. This compound is then reacted, in toluene solution at reflux, with a dialkyl phosphite **27.4**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product **27.8**.
Using the above procedures, but employing, in place of 4-bromophenylalanine **27.6**, different bromo-substituted phenylalanines **27.1**, and/or different dialkyl phosphites, the corresponding products **27.5** are obtained.

Scheme **28** illustrates the preparation of oxiranes **28.4** in which the phosphonate moiety is attached by means of an alkylene chain. In this procedure, a carbobenzyloxy protected bromo-substituted phenylalanine **27.2**, prepared as described above, is coupled, in the presence of a palladium catalyst, with a dialkyl alkenylphosphonate **28.1**, to afford the coupled product **28.2**. The preparation of aryl alkenyl phosphonates by means of a coupling reaction between aryl bromides and alkenyl phosphonates is described in Syn., 1983, 556. The reaction is performed

in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a palladium (II) catalyst, a tertiary base such as triethylamine and a phosphine such as triphenylphosphine and the like, to afford the aryl alkenyl phosphonate product **28.2**. The latter compound is then reduced, for example by reaction with diimide, as described in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 262, to afford the saturated product **28.3**. The latter compound is then converted, by means of the series of reactions shown in Scheme **3**, into the oxirane **28.4**.

For example, the cbz-protected 3-bromophenylalanine **28.5**, prepared as described in Pept. Res., 1990, 3, 176, is coupled, in acetonitrile solution at 100° in a sealed tube, with a dialkyl vinylphosphonate **28.6**, in the presence of palladium (II)acetate, tri-(o-tolyl)phosphine and triethylamine, as described in Syn., 1983, 556, to afford the coupled product **28.7**. The product is then reduced with diimide, generated by treatment of disodium azodicarboxylate with acetic acid, as described in J. Am. Chem. Soc., 83, 3725, 1961, to yield the saturated product **28.8**. This material is then converted, using the procedures shown in Scheme **3**, into the oxirane **28.9**.

Using the above procedures, but employing, in place of the 3-bromophenylalanine derivative **28.5**, different bromo compounds **27.2**, and/or different alkenyl phosphonates **28.1**, the corresponding products **28.4** are obtained.

Scheme **29** illustrates the preparation of oxiranes **29.9** in which the phosphonate group is linked by means of an alkylene chain and an oxygen or sulfur atom. In this procedure, a substituted phenylalanine **29.1** is converted into the methyl ester **29.2** by means of a conventional acid-catalyzed esterification reaction. The hydroxy or mercapto substituent is then protected to afford the derivative **29.3**. The protection of phenyl hydroxyl and mercapto groups is described respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, and p. 277. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl, 9-fluorenylmethyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-

methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The protected compound **29.3** is then transformed into the cbz derivative **29.4**, using the procedure described above (Scheme **3**). The O or S-protecting group is then removed to produce the phenol or thiol **29.5**. Deprotection of phenols and thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978 or by the use of mercuric acetate in trifluoroacetic acid. The resultant phenol or thiophenol **29.5** is then reacted with a dialkyl halo or alkylsulfonyloxyalkyl phosphonate **29.6**, to yield the ether or thioether product **29.7**. The alkylation reaction is performed at from ambient temperature to about 80°, in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of an organic or inorganic base such as dimethylaminopyridine, triethylamine, potassium carbonate or cesium carbonate. The methyl ester is then hydrolyzed, for example by treatment with lithium hydroxide in aqueous tetrahydrofuran, to afford the carboxylic acid **29.8**. The latter compound is then transformed, by means of the reactions shown in Scheme **3**, into the oxirane **29.9**.

For example, as illustrated in Scheme **29**, Example **1**, 4-mercaptophenylalanine **29.10**, prepared as described in J. Amer. Chem. Soc., 1997, 119, 7173, is reacted with methanol at reflux temperature in the presence of p-toluenesulfonic acid, to yield the methyl ester **29.11**. The thiol substituent is then protected by conversion to the S-adamantyl derivative **29.12**, for example by reaction with adamantanol in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978. The amino group in the product **29.12** is then protected by conversion to the cbz derivative **29.13**, using the procedure described in Scheme **3**. Removal of the S-protecting group, for example by treatment of the thioether **29.13** with mercuric trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978, then affords the thiophenol **29.14**. The latter compound is then reacted in dimethylformamide solution with a dialkyl bromoalkylphosphonate, for example a dialkyl bromoethylphosphonate **29.15**, (Aldrich) in the presence of a base such as cesium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the thioether **29.16**. The methyl

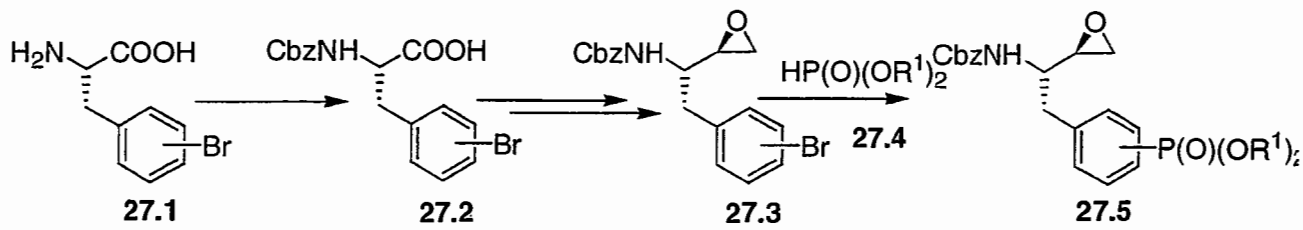
ester is then hydrolyzed as described above, and the resultant carboxylic acid **29.17** is transformed, by means of the reactions shown in Scheme **3**, into the oxirane **29.18**.

As a further example of the method of Scheme **29**, as shown in Example **2**, 3-hydroxyphenylalanine **29.19** (Fluka) is converted into the methyl ester **29.20**, and the phenolic hydroxyl group is then protected by reaction with one molar equivalent of tert-butylchlorodimethylsilane and imidazole in dimethylformamide, as described in J. Amer. Chem. Soc., 94, 6190, 1972, to produce the silyl ether **29.21**. Conversion to the cbz derivative **29.22**, as described above, followed by desilylation, using tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Amer. Chem. Soc., 94, 6190, 1972, then affords the phenol **29.23**. The phenolic hydroxyl group is then reacted in dimethylformamide solution with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate, **29.24**, prepared as described in Tet. Lett., 1986, 27, 1477, and a base such as triethylamine, to afford the ether **29.25**. The methyl ester is then hydrolyzed, as described above, and the resultant carboxylic acid **29.26** is then transformed, by means of the series of reactions shown in Scheme **3**, into the oxirane **29.27**.

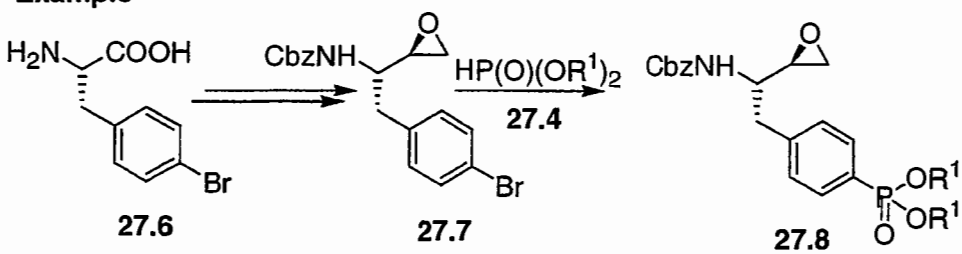
Using the above procedures, but employing, in place of the bromoethyl phosphonate **29.15**, or the trifluoromethanesulfonyloxymethyl phosphonate **29.24**, different bromoalkyl or trifluoromethanesulfonyloxyalkyl phosphonates **29.6**, and/or different phenylalanine derivatives **29.1**, the corresponding products **29.9** are obtained.

Scheme 27

Method

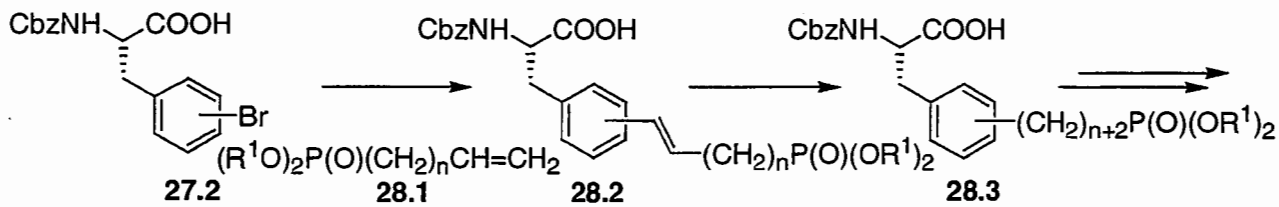


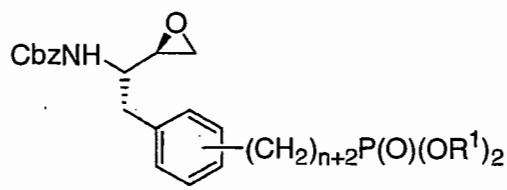
Example



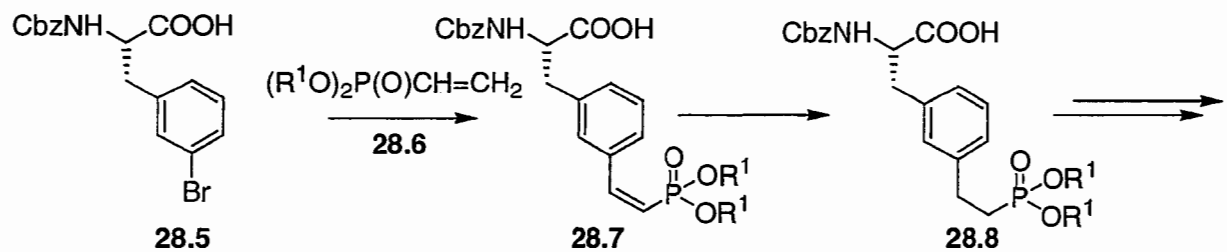
Scheme 28

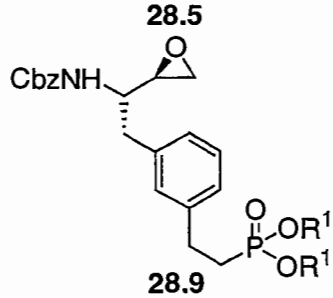
Method



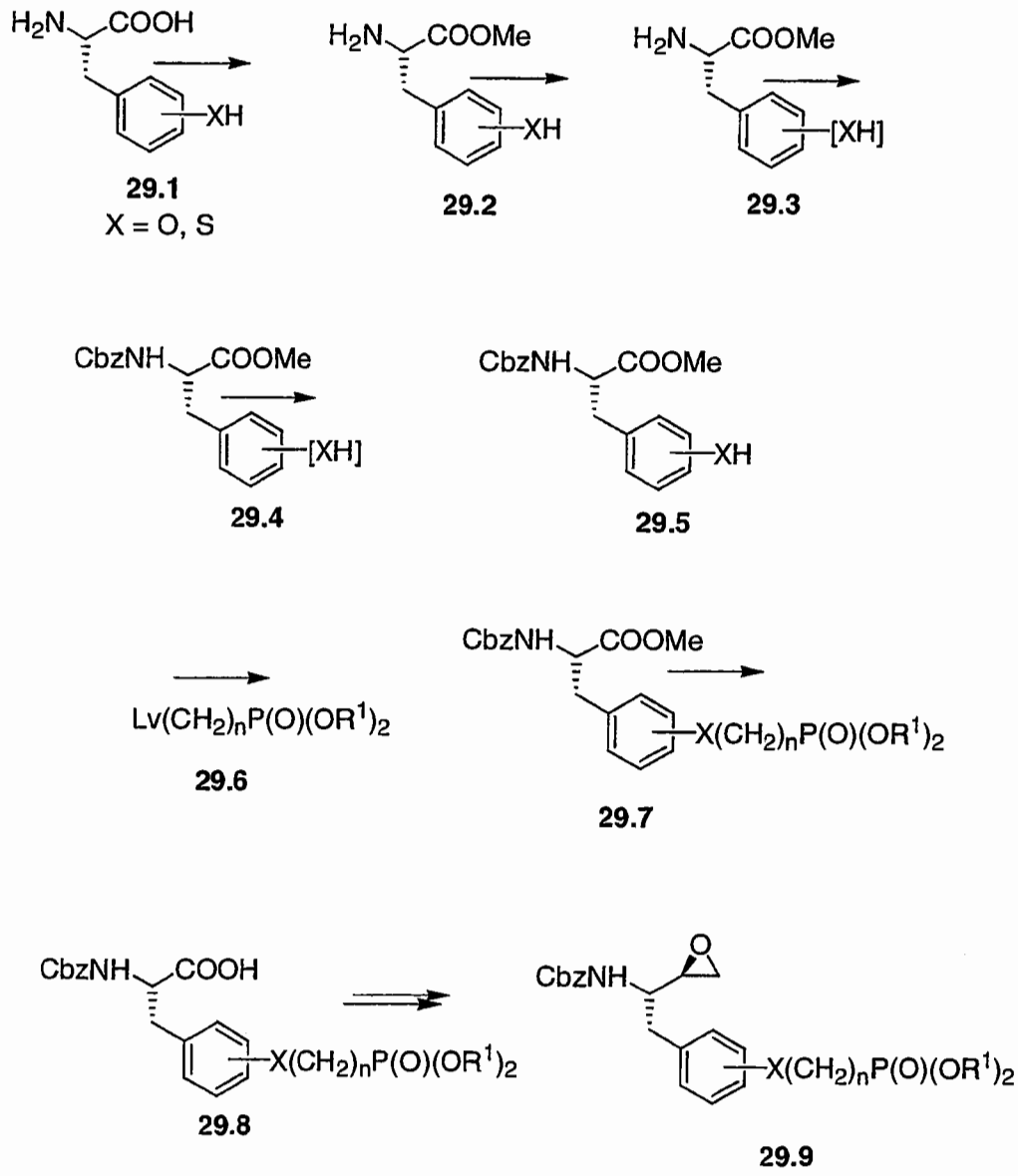


Example

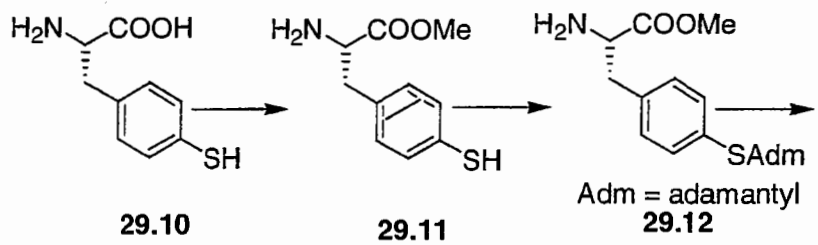




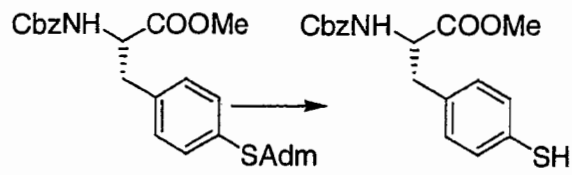
Scheme 29


H2N COOH
XH
29.1
X = O, S
H2N COOMe
XH
29.2
H2N COOMe
[XH]
29.3
CbzNH COOMe
[XH]
29.4
CbzNH COOMe
XH
29.5
Lv(CH2)nP(O)(OR1)2
29.6
CbzNH COOMe
X(CH2)nP(O)(OR1)2
29.7
CbzNH COOH
X(CH2)nP(O)(OR1)2
29.8
CbzNH
O
X(CH2)nP(O)(OR1)2
29.9

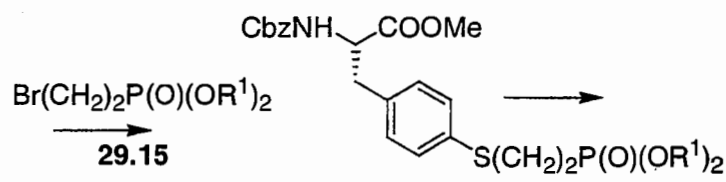
Example 1



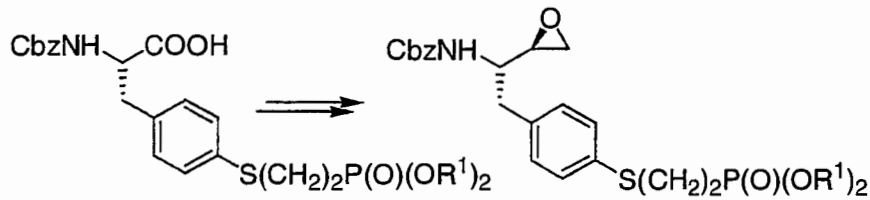
29.10 **29.11** **29.12**



29.13 **29.14**

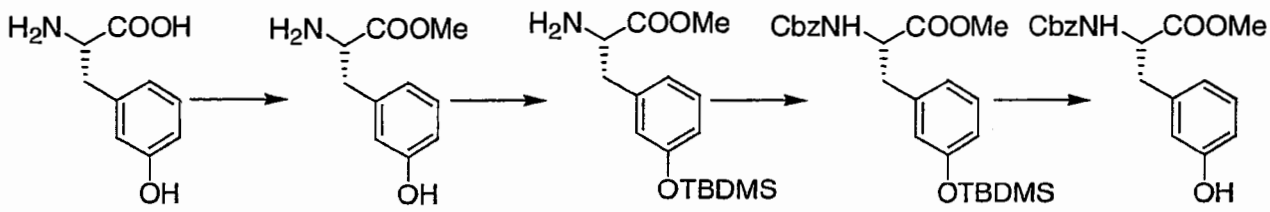


29.16

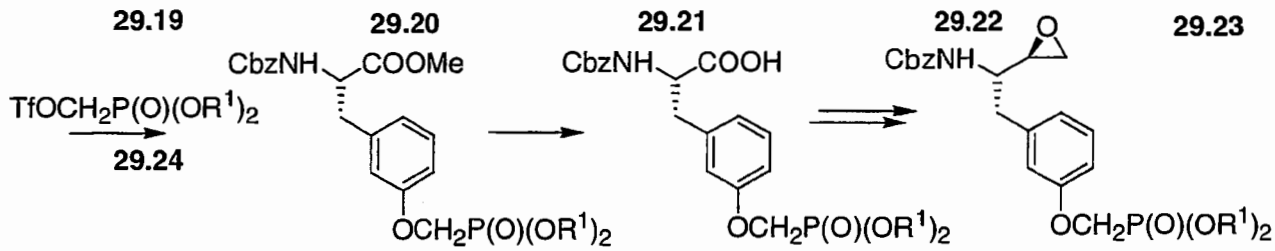


29.17 **29.18**

Example 2



29.19 **29.20** **29.21** **29.22** **29.23**



29.25 **29.26** **29.27**

Preparation of the phosphonate-containing thiophenol derivatives 10.1.

Schemes **30** - **39** describe the preparation of phosphonate-containing thiophenol derivatives **10.1** which are employed as described above (Schemes **10** and **11**) in the preparation of the phosphonate ester intermediates **2**.

Scheme **30** depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol **30.1** is protected, as described above (Scheme **29**) to afford the protected product **30.2**. The product is then coupled, in the presence of a palladium catalyst, with a dialkyl phosphite **30.3**. The preparation of arylphosphonates by the coupling of aryl halides with dialkyl phosphites us described above, (Scheme **29**). The thiol protecting group is then removed, as described above, to afford the thiol **30.4**.

For example, 3-bromothiophenol **30.5** is converted into the 9-fluorenylmethyl (Fm) derivative **30.6** by reaction with 9-fluorenylmethyl chloride and diisopropylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite **30.3**, as described for the preparation of the phosphonate **27.8** (Scheme **27**), to afford the phosphonate ester **30.7**. The Fm protecting group is then removed by treatment of the product with piperidine in dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol **30.8**.

Using the above procedures, but employing, in place of 3-bromothiophenol **30.5**, different thiophenols **30.1**, and/or different dialkyl phosphites **30.3**, the corresponding products **30.4** are obtained.

Scheme **31** illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol **31.2** is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative **31.3**. The latter compound is reacted with a halodialkyl phosphite **31.4** to afford the product **31.5**; deprotection then affords the thiophenol **31.6**

For example, 4-bromothiophenol **31.7** is converted into the S-triphenylmethyl (trityl) derivative **31.8**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and

P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **31.9** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorodialkyl phosphite **31.10** to afford the phosphonate **31.11**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **31.12**.
Using the above procedures, but employing, in place of the bromo compound **31.7**, different halo compounds **31.2**, and/or different halo dialkyl phosphites **31.4**, there are obtained the corresponding thiols **31.6**.

Scheme **32** illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol is subjected to free-radical bromination to afford a bromomethyl product **32.1**. This compound is reacted with a sodium dialkyl phosphite **32.2** or a trialkyl phosphite, to give the displacement or rearrangement product **32.3**, which upon deprotection affords the thiophenol **32.4**.
For example, 2-methylthiophenol **32.5** is protected by conversion to the benzoyl derivative **32.6**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **32.7**. This material is reacted with a sodium dialkyl phosphite **32.2**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **32.8**.
Alternatively, the bromomethyl compound **32.7** can be converted into the phosphonate **32.8** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **32.7** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100^0 to produce the phosphonate **32.8**. Deprotection of the phosphonate **32.8**, for example by treatment with aqueous ammonia, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiol **32.9**.
Using the above procedures, but employing, in place of the bromomethyl compound **32.7**, different bromomethyl compounds **32.1**, there are obtained the corresponding thiols **32.4**.

Scheme **33** illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **33.1** is reacted with a dialkyl hydroxyalkylphosphonate **33.2** under

the conditions of the Mitsonobu reaction, for example as described in Org. React., 1992, 42, 335, to afford the coupled product **33.3**. Deprotection then yields the O- or S-linked products **33.4**.

For example, the substrate 3-hydroxythiophenol, **33.5**, is converted into the monotrityl ether **33.6**, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **33.7** in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound **33.8**. Removal of the trityl protecting group, as described above, then affords the thiophenol **33.9**.

Using the above procedures, but employing, in place of the phenol **33.5**, different phenols or thiophenols **33.1**, and different dialkylphosphonates **33.2** there are obtained the corresponding thiols **33.4**.

Scheme **34** illustrates the preparation of thiophenols **34.4** bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **34.1** is reacted with an activated ester, for example the trifluoromethanesulfonate **34.2**, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product **34.3**. Deprotection then affords the thiol **34.4**.

For example, 4-methylaminothiophenol **34.5** is reacted with one equivalent of acetyl chloride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the product **34.6**. This material is then reacted with, for example, a dialkyl trifluoromethanesulfonylmethyl phosphonate **34.7**, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product **34.8**. Preferably, equimolar amounts of the phosphonate **34.7** and the amine **34.6** are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product **34.8**. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiophenol **34.9**.

Using the above procedures, but employing, in place of the thioamine **34.5**, different phenols, thiophenols or amines **34.1**, and/or different phosphonates **34.2**, there are obtained the corresponding products **34.4**.

Scheme **35** illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate **35.2**. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol **35.1** is reacted with a dialkyl bromoalkyl phosphonate **35.2** to afford the product **35.3**. Deprotection then affords the free thiophenol **35.4.**

For example, 3-hydroxythiophenol **35.5** is converted into the S-trityl compound **35.6**, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate **35.7**, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°, to yield the ether product **35.8**. Deprotection, as described above, then affords the thiol **35.9**.

Using the above procedures, but employing, in place of the phenol **35.5**, different phenols, thiophenols or amines **35.1**, and/or different phosphonates **35.2**, there are obtained the corresponding products **35.4**.

Scheme **36** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **36.2** is coupled with an aromatic bromo compound **36.1**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **36.4**, or the saturated analog **36.6**.

For example, 3-bromothiophenol is converted into the S-Fm derivative **36.7**, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate **36.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a

palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product **36.9**. Deprotection, as described above, then affords the thiol **36.10**. Optionally, the initially formed unsaturated phosphonate **36.9** is subjected to reduction, for example using diimide, as described above, to yield the saturated product **36.11**, which upon deprotection affords the thiol **36.12**.

Using the above procedures, but employing, in place of the bromo compound **36.7**, different bromo compounds **36.1**, and/or different phosphonates **36.2**, there are obtained the corresponding products **36.4** and **36.6**

Scheme **37** illustrates the preparation of an aryl-linked phosphonate ester **37.4** by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **37.1** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product **37.3** which is deprotected to yield the thiol **37.4**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **37.5**. This material is reacted with diethyl 4-bromophenylphosphonate **37.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **37.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **37.8**.

Using the above procedures, but employing, in place of the boronate **37.5**, different boronates **37.1**, and/or different phosphonates **37.2**, there are obtained the corresponding products **37.4**.

Scheme **38** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol

38.1 is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **38.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **38.3** is then deprotected to afford the thiol **38.4**. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **38.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **38.5** is then reacted with, for example diethyl 4-(bromomethyl)phenylphosphonate, **38.6**, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The thioether product **38.7** thus obtained is deprotected, as described above, to afford the thiol **38.8**.

Using the above procedures, but employing, in place of the thiophenol **38.5**, different phenols, thiophenols or amines **38.1**, and/or different phosphonates **38.2**, there are obtained the corresponding products **38.4**.

Scheme **39** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

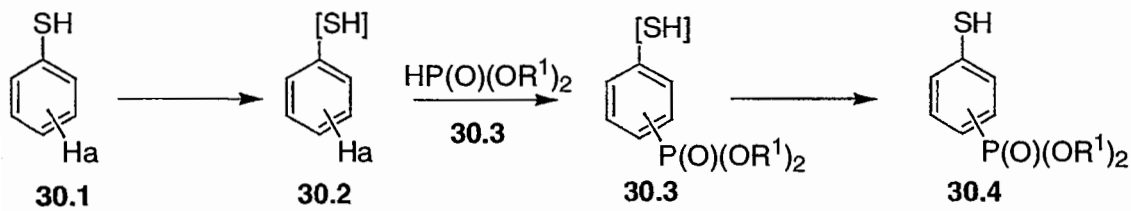
In this procedure, a suitably protected thiophenol **39.1**, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **39.2**, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **39.3**. Deprotection, as described above, then affords the thiol **39.4**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived

organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p. 707. For example, 2,3-dihydro-1H-indole-5-thiol, **39.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **39.6**, as described above, and the ester is then reacted with the trifluoromethanesulfonate **39.7**, using the conditions described above for the preparation of the phosphonate **34.8**, (Scheme **34**), to yield the phosphonate **39.8**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **39.9**.

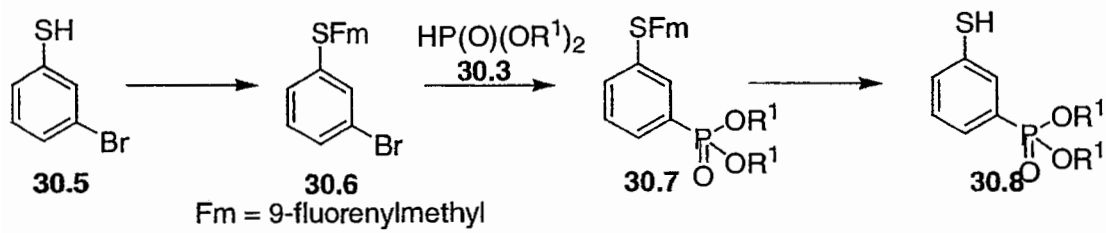
Using the above procedures, but employing, in place of the thiol **39.5**, different thiols **39.1**, and/or different triflates **39.2**, there are obtained the corresponding products **39.4**.

Scheme 30

Method



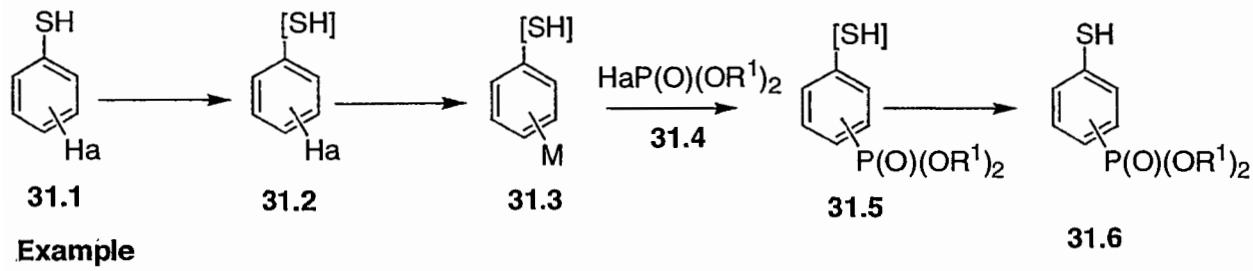
Example



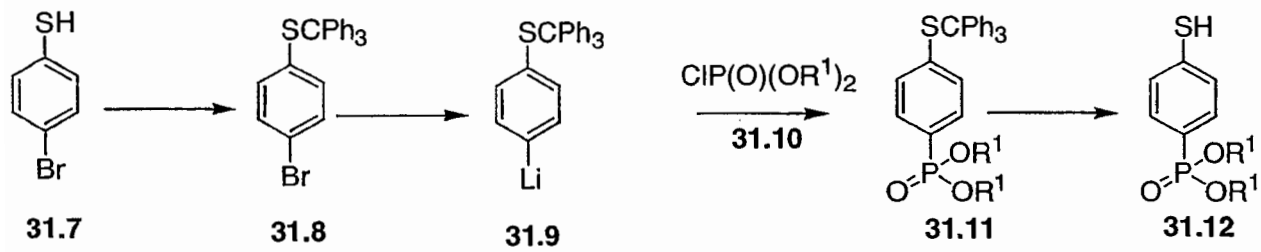
Fm = 9-fluorenylmethyl

Scheme 31

Method

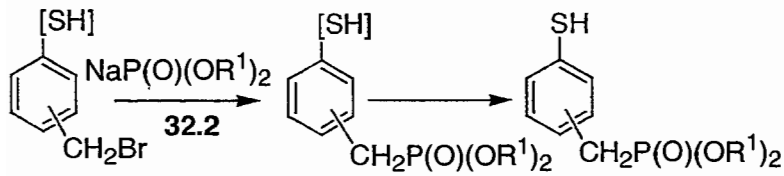


Example



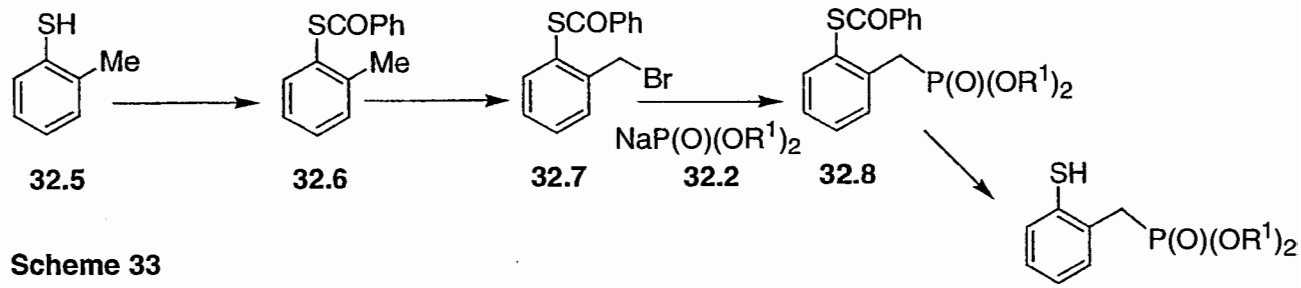
Scheme 32

Method



32.1 **32.3** **32.4**

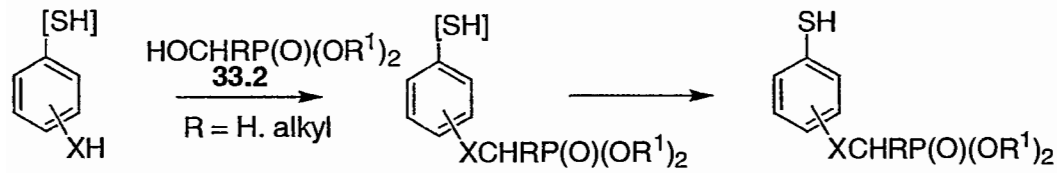
Example



32.5 **32.6** **32.7** **32.2** **32.8** **32.9**

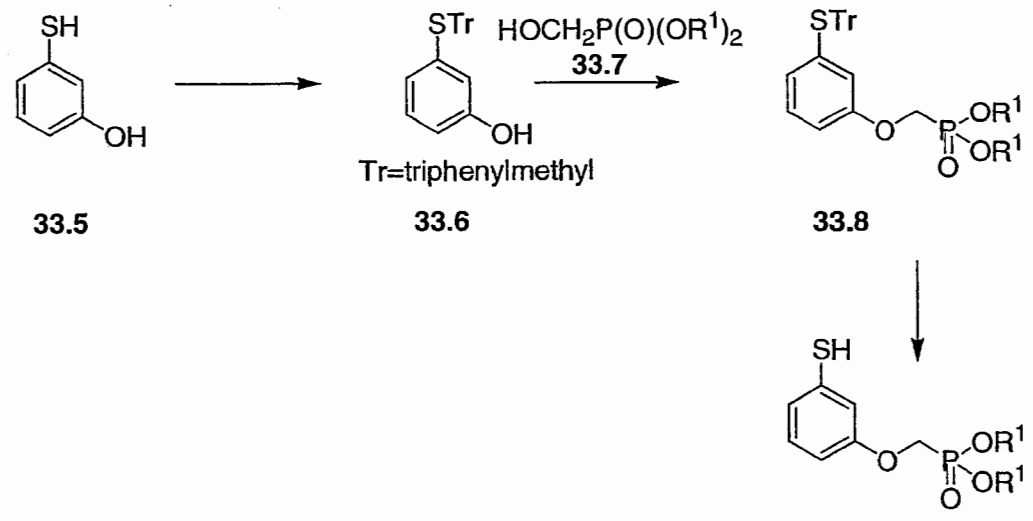
Scheme 33

Method



33.1 **33.3** **33.4**

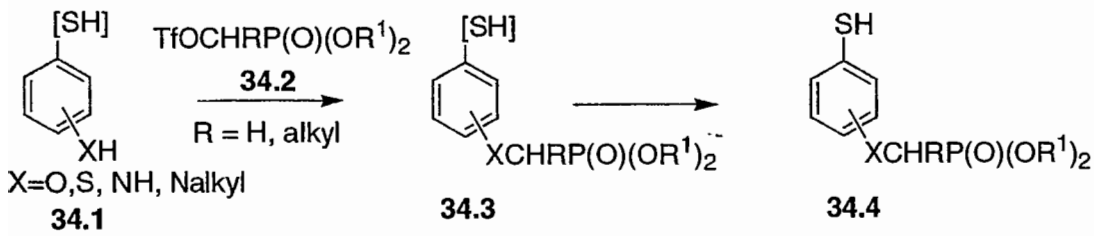
Example



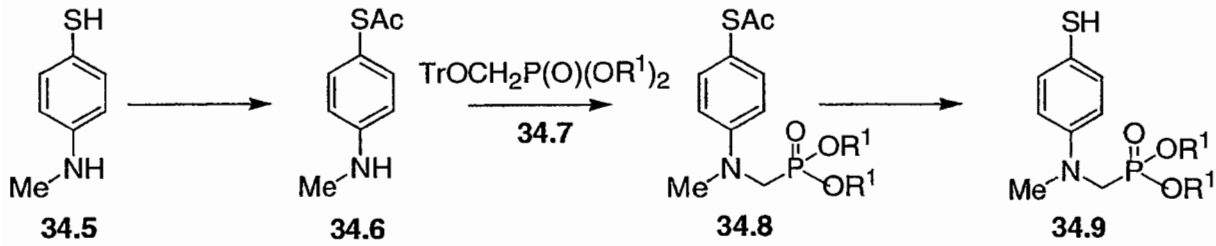
33.5 **33.6** **33.8** **33.9**

Scheme 34

Method

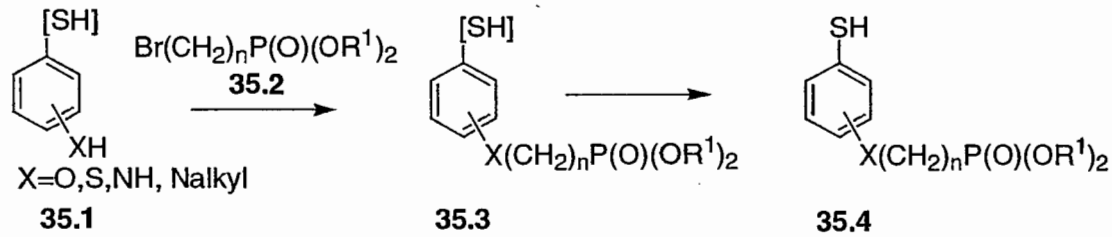


Example

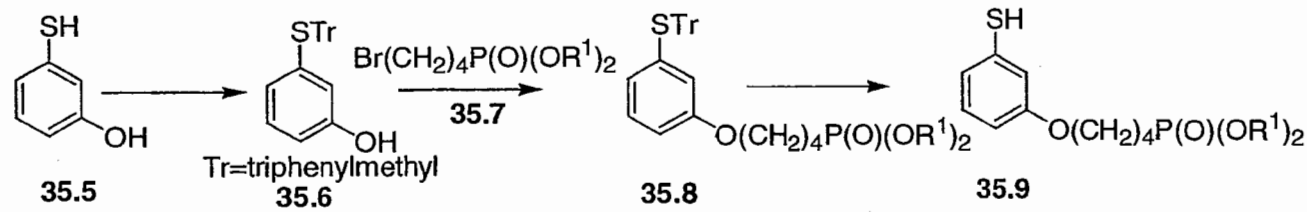


Scheme 35

Method

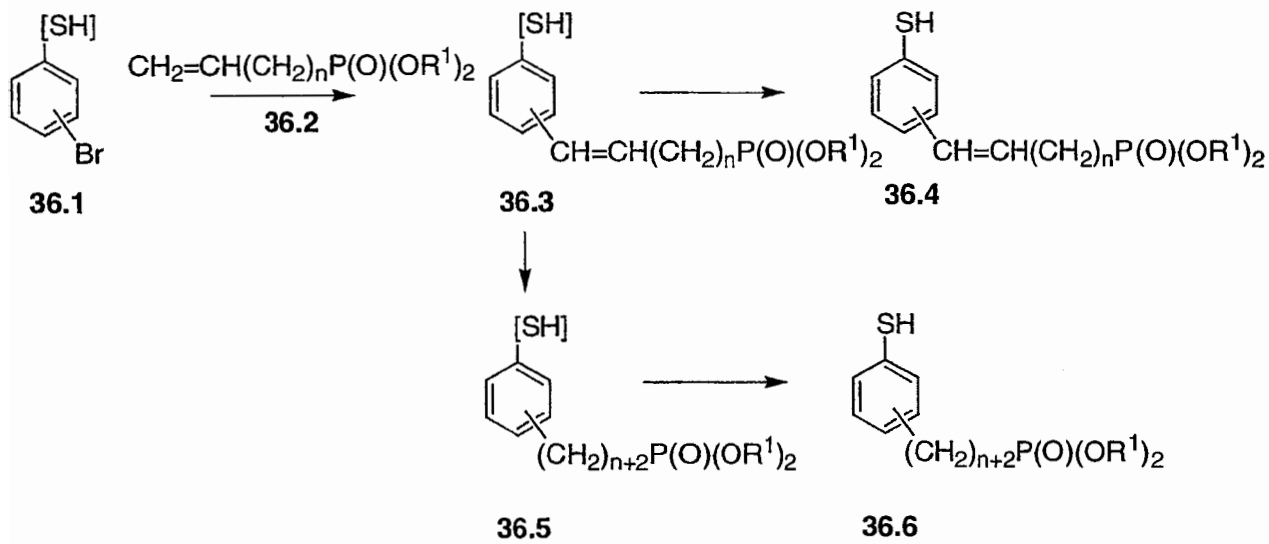


Example

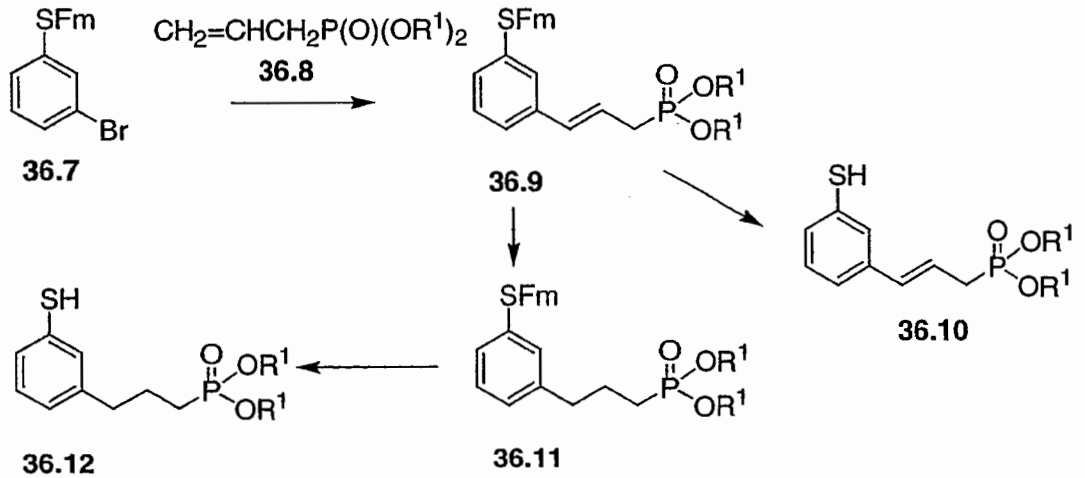


Scheme 36

Method

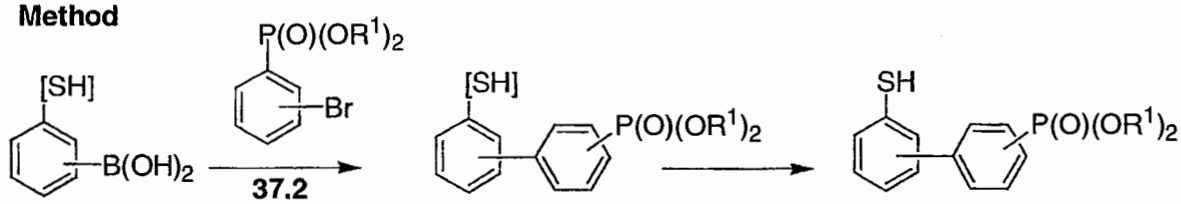


Example



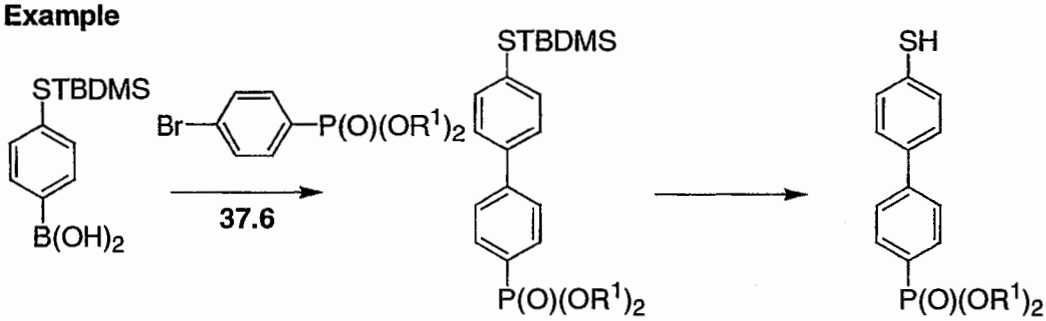
Scheme 37

Method



37.1 **37.3** **37.4**

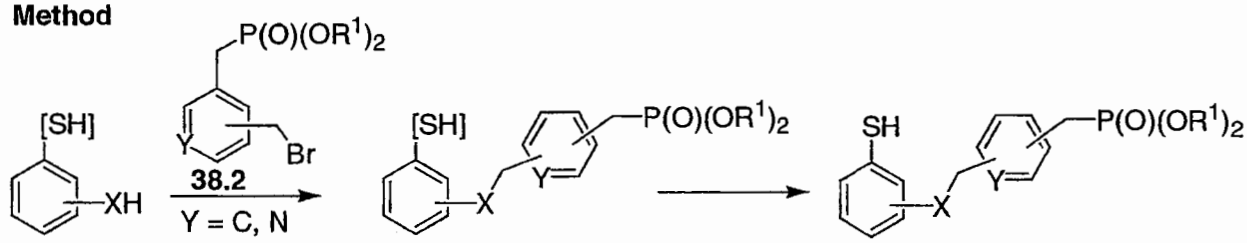
Example



37.5 **37.7** **37.8**

Scheme 38

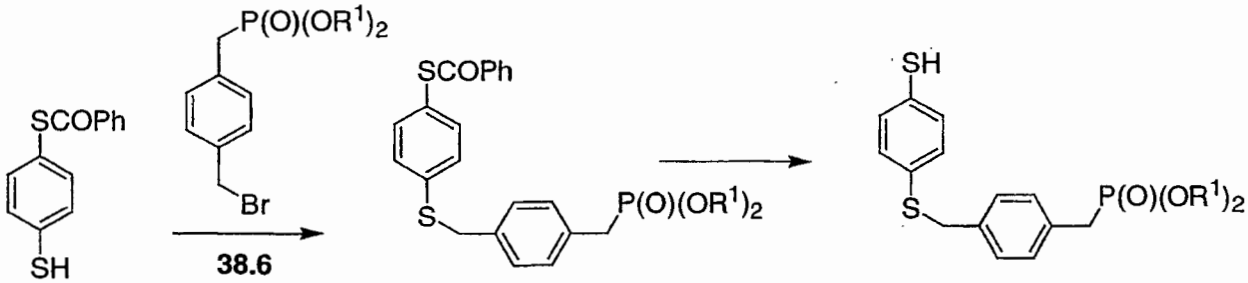
Method



X =O, S, NH, Nalkyl

38.1 **38.3** **38.4**

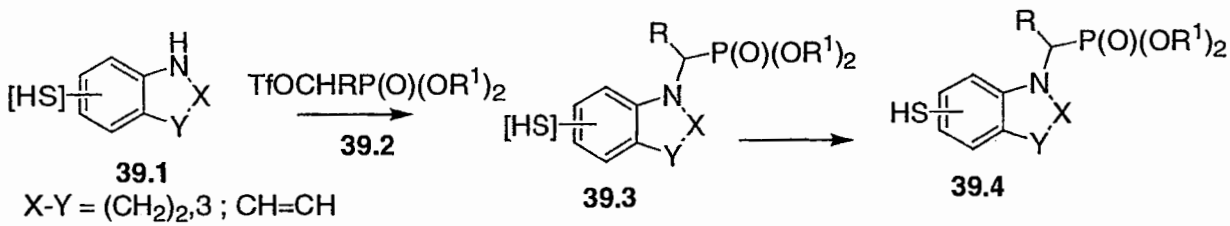
Example



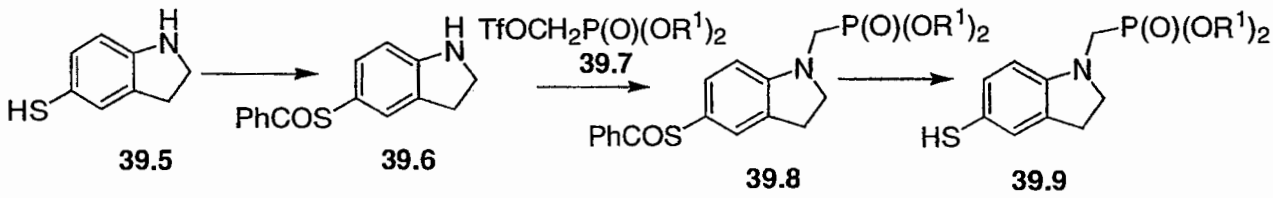
38.5 **38.7** **38.8**

Scheme 39

Method



Example



Preparation of the phenylpyridylphosphonate aldehydes 4.9.

Schemes **40** and **41** illustrate methods for the preparation of 4-(2-pyridyl)benzaldehydes **4.9** incorporating phosphonate groups, which are employed in the preparation of the phosphonate ester intermediates **3a**.

Scheme **40** illustrates the preparation of benzaldehydes substituted at the 4 position with a bromo-substituted 2-pyridine group, and the conversion of the bromo substituent into various phosphonate substituents, linked to the pyridine ring either directly, or by means of a saturated or unsaturated alkylene chain, or by a heteroatom and an alkylene chain.

In this procedure, a 4-formylphenylboronate **40.1** (Lancaster Synthesis) is coupled with a dibromopyridine **40.2** to afford the bromopyridyl benzaldehyde product **40.3**. Equimolar amounts of the reactants are combined in the presence of a palladium catalyst, as described above (Scheme **4**). The bromopyridine product **40.3** is then reacted with a dialkyl phosphite **40.4**, in the presence of a palladium catalyst, as described above (Scheme **27**) to afford the pyridylphosphonate ester **40.5**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.

Alternatively, the bromopyridine compound **40.3** is coupled, in the presence of a palladium catalyst, with a dialkyl alkenylphosphonate **40.6**, to yield the alkenyl phosphonate **40.9**, using

the procedures described above, (Scheme **28**). The olefinic bond present in the product is then reduced to afford the saturated analog **40.8**. The reduction reaction is performed catalytically, for example by the use of palladium on carbon and hydrogen or a hydrogen donor, or chemically, for example by employing diimide, generated by treatment of disodium azodicarboxylate with acetic acid, as described in J. Am. Chem. Soc., 83, 3725, 1961.

Alternatively, the bromopyridine compound **40.3**, in which the bromo substituent is in either the 4 or 6 position, is transformed, by reaction with a dialkyl hydroxy, mercapto or aminoalkyl phosphonate **40.7**, into the ether, thioether or amine product **40.10**. The preparation of pyridine ethers, thioethers and amines by means of displacement reactions of 2- or 4-bromopyridines by alcohols, thiols and amines is described, for example, in Heterocyclic Compounds, Volume 3, R. A. Abramovitch, ed., Wiley, 1975, p. 597, 191, and 41 respectively. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide at ca 100° in the presence of a base such as potassium carbonate, to effect the displacement reaction.

Scheme **40**, Example **1**, illustrates the coupling reaction of 4-formylphenylboronic acid **40.1** with 2,5-dibromopyridine **40.11**, using the procedure described above, to afford 4-(5-bromo-2-pyridyl)benzaldehyde **40.12**. This compound is then coupled, as described above, with a dialkyl phosphite **40.4**, to afford the pyridyl phosphonate **40.13**.

Using the above procedures, but employing, in place of 2,5-dibromopyridine **40.11**, different dibromopyridines **40.2**, and/or different dialkyl phosphites **40.4**, the corresponding products **40.5** are obtained.

Alternatively, as illustrated in Scheme **40**, Example **2**, the phenylboronic acid **40.1** is coupled, as described above, with 2,4-dibromopyridine **40.14** to afford 4-(4-bromo-2-pyridyl)benzaldehyde **40.15**. The product is then reacted with a dialkyl mercaptoethyl phosphonate **40.16**, the preparation of which is described in Zh. Obschei. Khim., 1973, 43, 2364, to yield the thioether **40.17**. Equimolar amounts of the reactants are combined in dimethylformamide at 80° in the presence of potassium carbonate, to effect the displacement reaction.

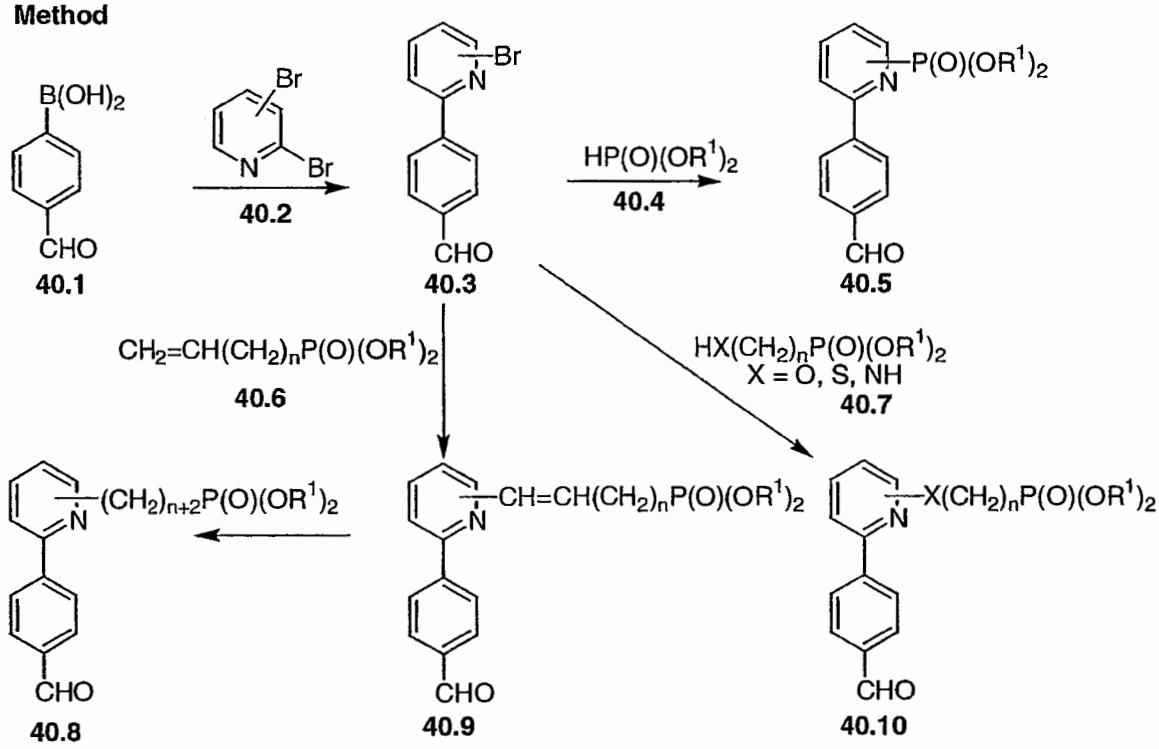
Using the above procedures, but employing, in place of the dialkyl mercaptoethyl phosphonate **40.16**, different dialkyl hydroxy, mercapto or aminoalkyl phosphonates **40.7**, the corresponding products **40.10** are obtained.

Alternatively, as shown in Scheme **40**, Example **3**, 4-(5-bromo-2-pyridyl)benzaldehyde **40.12** is coupled with a dialkyl vinyl phosphonate **40.18**, in the presence of a palladium catalyst, as described above, to afford the unsaturated phosphonate **40.19**. Optionally, the product can be reduced to the saturated analog **40.20**, for example by the use of diimide, as described above. Using the above procedures, but employing, in place of the bromoaldehyde **40.12**, different bromoaldehydes **40.3**, and/or, in place of the dialkyl vinylphosphonate **40.18**, different dialkyl alkenylphosphonates **40.6**, the corresponding products **40.8** and **40.9** are obtained.

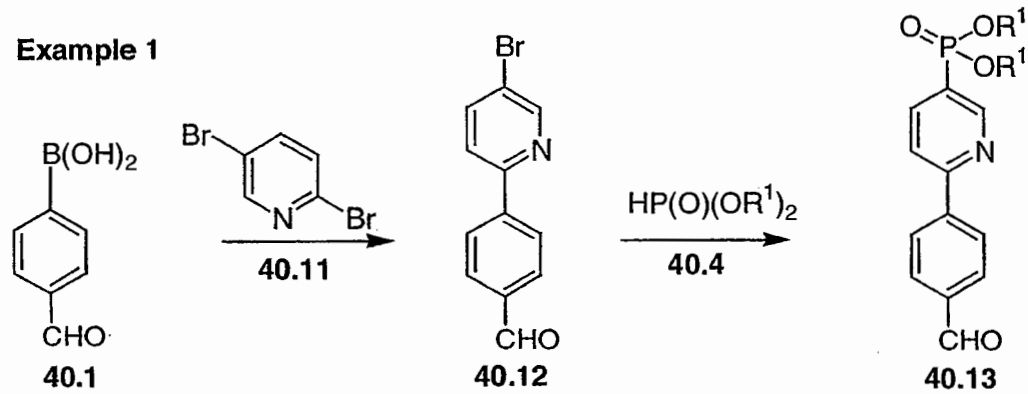
Scheme **41** illustrates the preparation of 4-(2-pyridyl)benzaldehydes incorporating phosphonate group linked by means of a alkylene chain incorporating a nitrogen atom. In this procedure, a formyl-substituted 2-bromopyridine **41.2** is coupled, as described above, (Scheme **40**) with a 4-(hydroxymethyl)phenylboronic acid **41.1**. prepared as described in Macromolecules, 2001, 34, 3130, to afford the 4-(2-pyridyl)benzyl alcohol **41.3**. The product is then reacted with a dialkyl aminoalkyl phosphonate **41.4**, under reductive amination conditions. The preparation of amines by means of a reductive amination of an aldehyde is described above (Scheme **24**). The resultant benzyl alcohol **41.5** is then oxidized to yield the corresponding benzaldehyde **41.6**. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride. The reaction is conducted in an inert aprotic solvent such as dichloromethane or toluene. Preferably, the alcohol **41.5** is oxidized to the aldehyde **41.6** by reaction with pyridinium chlorochromate in dichloromethane.
For example, the phenylboronic acid **41.1** is coupled with 2-bromopyridine-4-carboxaldehyde **41.7**, the preparation of which is described in Tet. Lett. 2001, 42, 6815, to afford 4-(4-formyl-2-pyridyl)benzyl alcohol **41.8**. The aldehyde is then reductively aminated by reaction with a dialkyl aminoethylphosphonate **41.9**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, and a reducing agent, to afford the amine product **41.10**. The latter compound is then oxidized, for example by treatment with pyridinium chlorochromate, to afford the aldehyde phosphonate **41.11**.
Using the above procedures, but employing, in place of the bromopyridine aldehyde **41.7**, different aldehydes **41.2**, and/or different dialkyl aminoalkyl phosphonates **41.4**, the corresponding products **41.6** are obtained.

Scheme 40

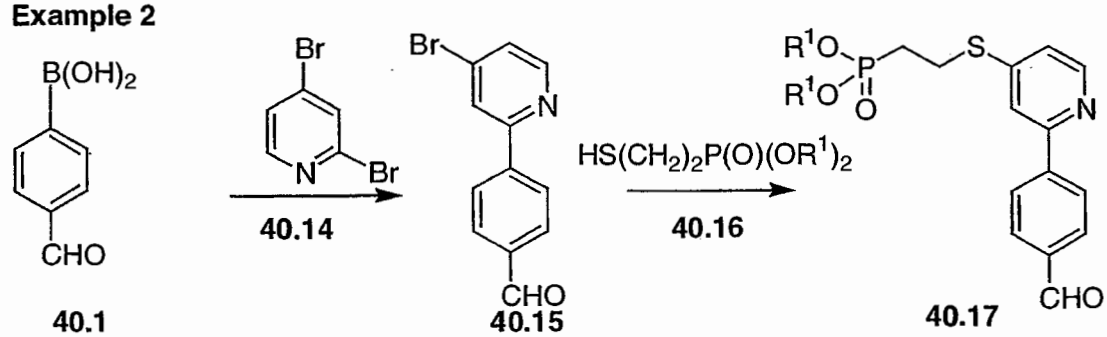
Method



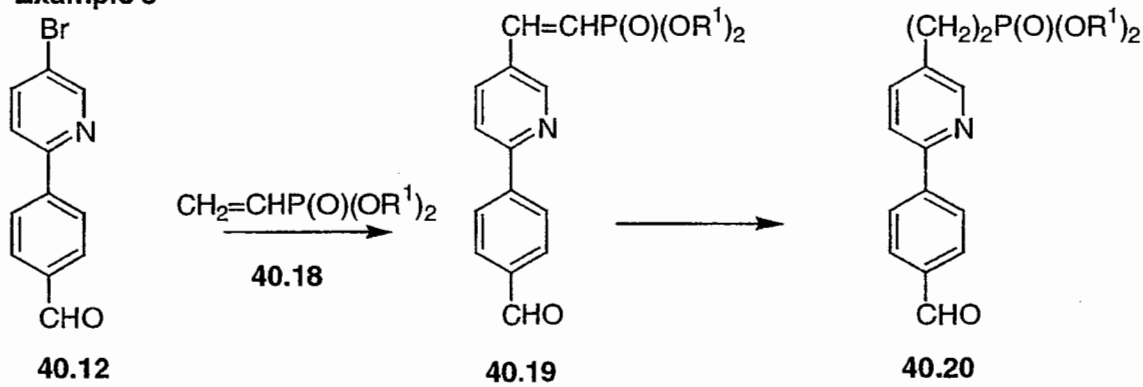
Example 1



Example 2

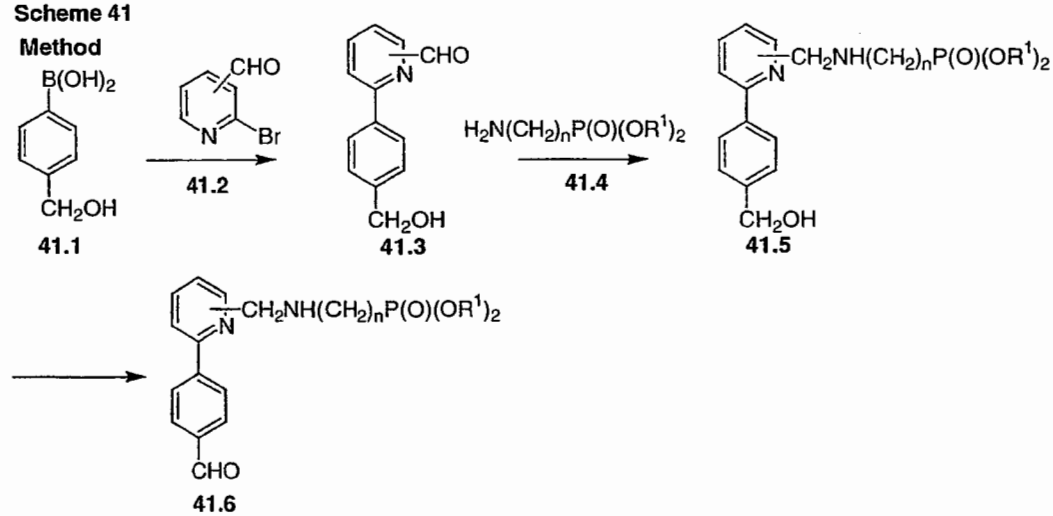


Example 3

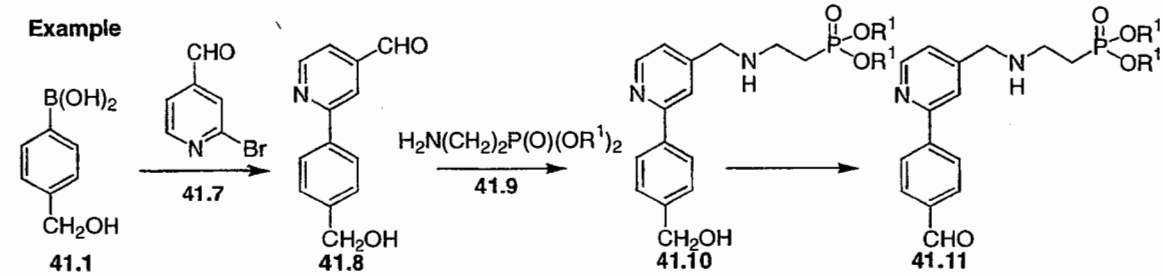


Scheme 41

Method



Example



Preparation of the biphenyl phosphonate aldehydes 4.12.

Schemes **42 - 44** illustrate methods for the preparation of the biphenylphosphonate aldehydes **4.12** which are employed in the synthesis of the phosphonate esters **3b**.

Scheme **42** depicts the preparation of biphenyl aldehyde phosphonates in which the phosphonate moiety is attached to the phenyl ring either directly, or by means of a saturated or unsaturated alkylene chain. In this procedure, 4-formylbenzeneboronic acid **42.1** and a

dibromobenzene **42.2** are coupled in the presence of a palladium catalyst, as described above, to produce the bromobiphenyl aldehyde **42.3**. The aldehyde is then coupled, as described above, with a dialkyl phosphite **42.4**, to afford the phosphonate ester **42.5**. Alternatively, the bromoaldehyde **42.3** is coupled with a dialkyl alkenylphosphonate **42.6**, using the procedures described above, to afford the alkenyl phosphonate **42.8**. Optionally, the latter compound is reduced to yield the saturated analog **42.7**.

For example, as shown in Scheme **42**, Example **1**, 4-formylbenzeneboronic acid **42.1** is coupled with 1,3-dibromobenzene **42.9** to give 3'-bromo-4-formylbiphenyl **42.10**. The product is then coupled, as described above, with a dialkyl phosphite **42.4** to give the biphenyl phosphonate ester **42.11**.

Using the above procedures, but employing, in place of 1,3-dibromobenzene **42.9**, different dibromobenzenes **42.2**, and/or different dialkyl phosphites **42.4**, the corresponding products **42.5** are obtained.

As a further example of the methods of Scheme **42**, as shown in Example **2**, 4'-bromobiphenyl-4-aldehyde **42.12** is coupled with a dialkyl propenylphosphonate **42.13** (Aldrich) in the presence of a palladium catalyst, to produce the propenyl phosphonate **42.15**. Optionally, the product is reduced, for example by catalytic hydrogenation over a palladium catalyst, to yield the saturated product **42.16**.

Using the above procedures, but employing, in place of the 4-bromobiphenyl aldehyde **42.12**, different bromobiphenyl aldehydes, and/or different alkenyl phosphonates **42.6**, the corresponding products **42.7** and **42.8** are obtained.

Scheme **43** illustrates the preparation of biphenyl phosphonates in which the phosphonate group is attached by means of a single carbon or by a heteroatom O, S or N and an alkylene chain. In this procedure, a bromotoluene **43.2** is coupled with 4-formylbenzeneboronic acid **43.1** to yield the methyl-substituted biphenyl aldehyde **43.3**. The product is then subjected to a free radical bromination to produce the bromomethyl compound **43.4**. The conversion of aromatic methyl groups into the corresponding benzylic bromide is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 313. The transformation is effected, for example, by the use of bromine, N-bromosuccinimide, carbon tetrabromide or bromotrichloromethane. The reaction is performed in an inert organic solvent such as carbon tetrachloride, ethyl acetate and the like, at reflux temperature, optionally in the

presence of an initiator such as dibenzoyl peroxide. Preferably, the conversion of the methyl compound **43.3** to the bromomethyl product **43.4** is effected by the use of one molar equivalent of N-bromosuccinimide in refluxing carbon tetrachloride. The bromomethyl compound is then reacted with a sodium dialkyl phosphonate **43.5** to afford the phosphonate product **43.6**. The displacement reaction is performed in an inert solvent such as tetrahydrofuran, at from ambient temperature to reflux, as described in J. Med. Chem., 1992, 35, 1371.

Alternatively, the bromomethyl compound **43.4** is reacted with a dialkyl hydroxy, mercapto or aminoalkyl phosphonate **43.7** to prepare the corresponding ether, thioether or aminoalkyl phosphonate products **43.8**. The reaction is performed in a polar organic solvent such as dimethylformamide, acetonitrile and the like, at from ambient temperature to about 80°, in the presence of an inorganic or organic base. For the preparation of the ethers **43.8** in which X is O, a strong base such as sodium hydride or potassium tert. butoxide is employed. For the preparation of the thioethers or amines **43.8**, a base such as cesium carbonate, dimethylaminopyridine or diisopropylethylamine is employed.

Scheme **43**, Example **1** depicts the coupling reaction of 4-formylbenzeneboronic acid **43.1** with 3-bromotoluene **43.9** to afford 3'-methylbiphenyl-4-aldehyde **43.10**. The product is then reacted with N-bromosuccinimide, as described above, to afford the bromomethyl product **43.11**. This material is reacted with a sodium dialkyl phosphonate **43.5** to afford the phosphonate ester **43.12**.

Using the above procedures, but employing, in place of 3-bromotoluene **43.9**, different bromotoluenes **43.2**, the corresponding products **43.6** are obtained.

Scheme **43**, Example **2** shows the free-radical bromination of 4'-methylbiphenyl-4-aldehyde to give the 4'-bromomethylbiphenyl-4-aldehyde **43.14**. The product is then reacted in acetonitrile solution at 70° with one molar equivalent of a dialkyl aminoethyl phosphonate **43.15**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, and cesium carbonate, to yield the amine product **43.16**.

Using the above procedures, but employing, in place of the aminoethyl phosphonate **43.15**, different hydroxy, mercapto or aminoalkyl phosphonates **43.7**, and/or different biphenyl aldehydes **43.3**, the corresponding products **43.8** are obtained.

Scheme **44** illustrates the preparation of the biphenyl phosphonates **44.3** in which the phosphonate group is attached by means of a heteroatom and an alkylene chain. In this procedure, a hydroxy, mercapto or amino-substituted biphenyl aldehyde **44.1** is reacted with a dialkyl bromoalkyl phosphonate **44.2** to afford the alkylation product **44.3**. The reaction is conducted between equimolar amounts of the reactants in a polar organic solvent such as dimethylformamide and the like, at from ambient temperature to about 80°, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of an inorganic iodide such as potassium iodide.

For example, 3'-hydroxybiphenyl-4-aldehyde **44.4** is reacted with a dialkyl bromoethyl phosphonate **44.5** (Aldrich) and potassium carbonate in dimethylformamide at 80°, to produce the ether **44.6**.

Using the above procedures, but employing, in place of 3'-hydroxybiphenyl-4-aldehyde **44.4**, different hydroxy, mercapto or aminobiphenyl-4-aldehydes **44.1**, and/or different bromoalkyl phosphonates **44.2**, the corresponding products **44.3** are obtained.

Preparation of the benzaldehyde phosphonates 4.14.

Schemes **45 - 48** illustrate methods for the preparation of the benzaldehyde phosphonates **4.14** which are employed in the synthesis of the phosphonate esters **3d**.

Scheme **45** illustrates the preparation of benzaldehyde phosphonates **45.3** in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde **45.1** is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate **45.2**, under reductive amination conditions, as describe above in Scheme **24**, to yield the phosphonate product **45.3**.

For example, benzene-1,3-dialdehyde **45.4** is reacted with a dialkyl aminopropyl phosphonate **45.5**, (Acros) and sodium triacetoxyborohydride, to afford the product **45.6**.

Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde **45.4**, different benzene dialdehydes **45.1**, and/or different phosphonates **45.2**, the corresponding products **45.3** are obtained.

Scheme **46** illustrates the preparation of benzaldehyde phosphonates either directly attached to the benzene ring or attached by means of a saturated or unsaturated carbon chain. In this

procedure, a bromobenzaldehyde **46.1** is coupled, under palladium catalysis as described above, with a dialkyl alkenylphosphonate **46.2**, to afford the alkenyl phosphonate **46.3**. Optionally, the product can be reduced, as described above, to afford the saturated phosphonate ester **46.4**. Alternatively, the bromobenzaldehyde can be coupled, as described above, with a dialkyl phosphite **46.5** to afford the formylphenylphosphonate **46.6**.

For example, as shown in Example **1**, 3-bromobenzaldehyde **46.7** is coupled with a dialkyl propenylphosphonate **46.8** to afford the propenyl product **46.9**. Optionally, the product is reduced to yield the propyl phosphonate **46.10**.

Using the above procedures, but employing, in place of 3-bromobenzaldehyde **46.7**, different bromobenzaldehydes **46.1**, and/or different alkenyl phosphonates **46.2**, the corresponding products **46.3** and **46.4** are obtained.

Alternatively, as shown in Example **2**, 4-bromobenzaldehyde **46.11** is coupled with a dialkyl phosphite **46.5** to afford the 4-formylphenyl phosphonate product **46.12**.

Using the above procedures, but employing, in place of 4-bromobenzaldehyde **46.11**, different bromobenzaldehydes **46.1**, the corresponding products **46.6** are obtained.

Scheme **47** illustrates the preparation of formylphenyl phosphonates in which the phosphonate moiety is attached by means of alkylene chains incorporating two heteroatoms O, S or N. In this procedure, a formyl phenoxy, phenylthio or phenylamino alkanol, alkanethiol or alkylamine **47.1** is reacted with a an equimolar amount of a dialkyl haloalkyl phosphonate **47.2**, to afford the phenoxy, phenylthio or phenylamino phosphonate product **47.3**. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile **47.1**. In cases in which Y is O, a strong base such as sodium hydride or lithium hexamethyldisilazide is employed. In cases in which Y is O or N, a base such as cesium carbonate or dimethylaminopyridine is employed.

For example, 2-(4-formylphenylthio)ethanol **47.4**, prepared as described in Macromolecules, 1991, 24, 1710, is reacted in acetonitrile at 60° with one molar equivalent of a dialkyl iodomethyl phosphonate **47.5**, (Lancaster) to give the ether product **47.6**.

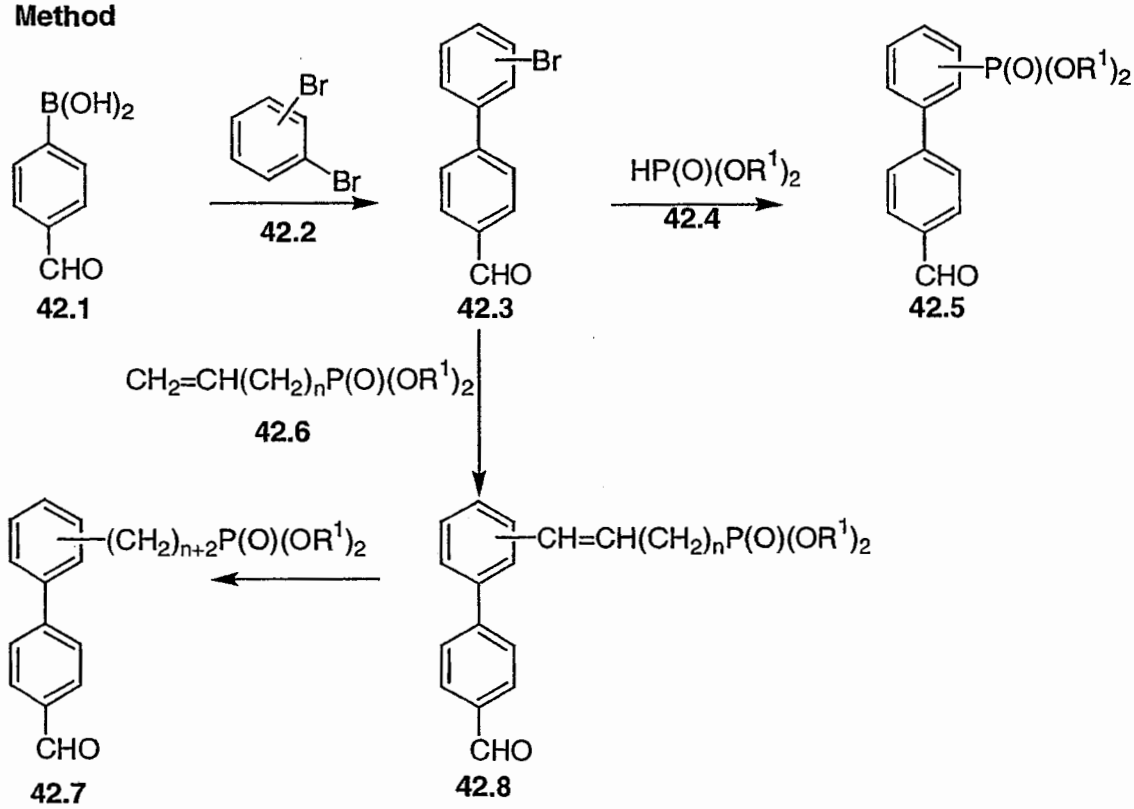
Using the above procedures, but employing, in place of the carbinol **47.4**, different carbinols, thiols or amines **47.1**, and/or different haloalkyl phosphonates **47.2**, the corresponding products **47.3** are obtained.

Scheme **48** illustrates the preparation of formylphenyl phosphonates in which the phosphonate group is linked to the benzene ring by means of an aromatic or heteroaromatic ring. In this procedure, 4-formylbenzeneboronic acid **43.1** is coupled, as described previously, with one molar equivalent of a dibromoarene, **48.1**, in which the group Ar is an aromatic or heteroaromatic group. The product **48.2** is then coupled, as described above (Scheme **46**) with a dialkyl phosphite **40.4** to afford the phosphonate **48.3**.

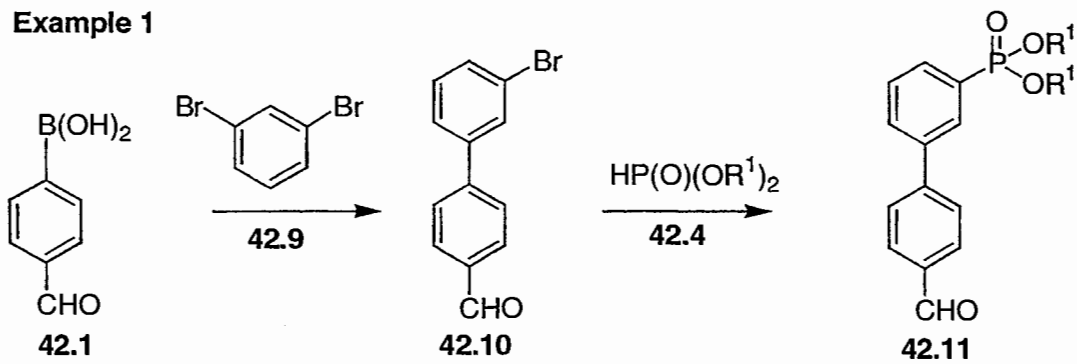
For example, 4-formylbenzeneboronic acid **43.1** is coupled with 2,5-dibromothiophene **48.4** to yield the phenylthiophene product **48.5**. This compound is then coupled with the dialkyl phosphite **40.4** to afford the thienyl phosphonate **48.6**.

Using the above procedures, but employing, in place of dibromothiophene **48.4**, different dibromoarenes **48.1**, the corresponding products **48.3** are obtained.

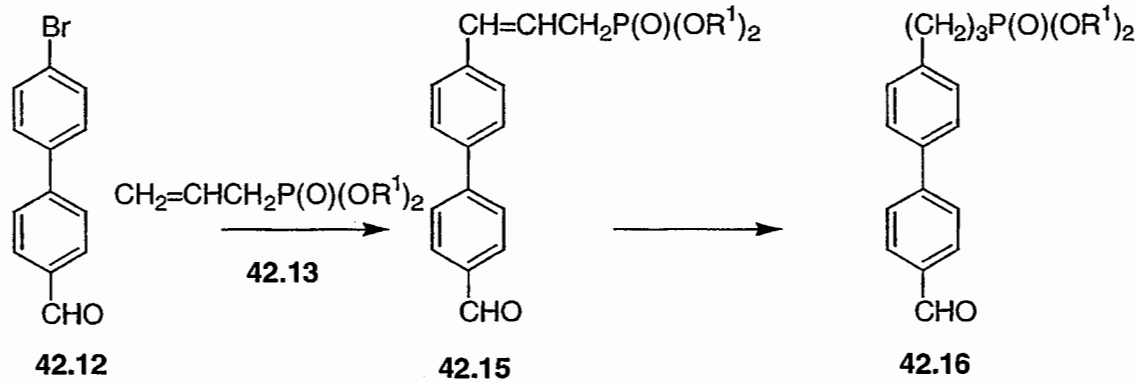
Scheme 42
Method



Example 1

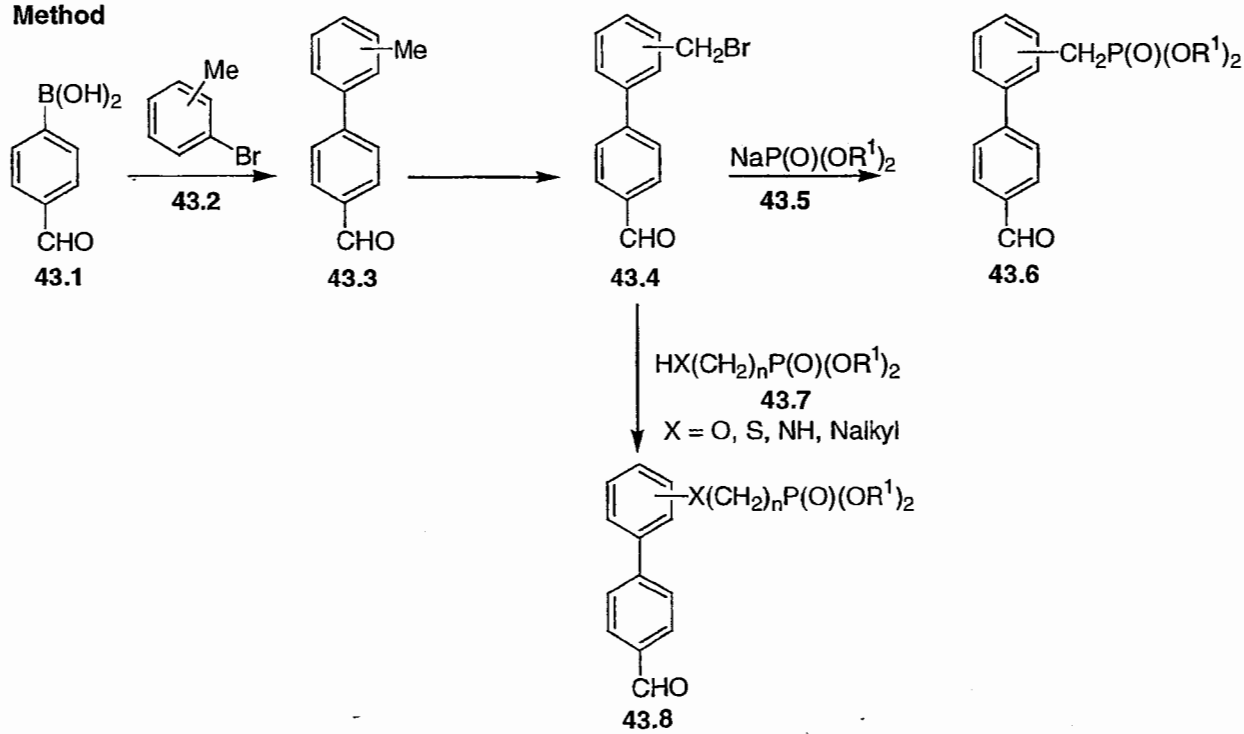


Example 2

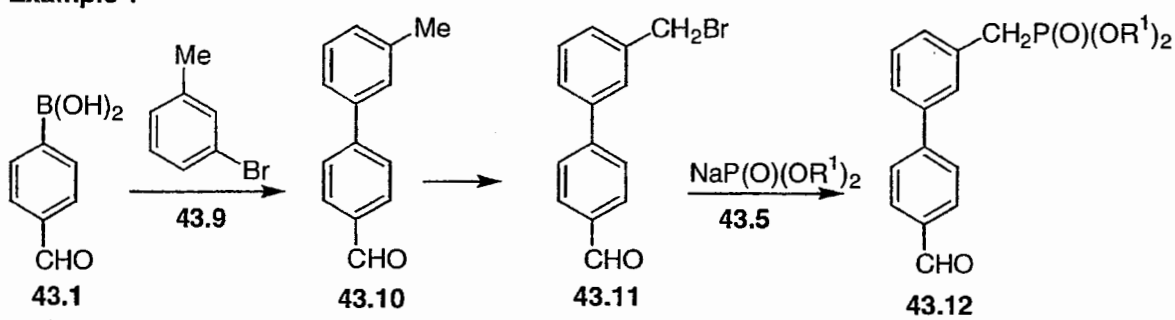


Scheme 43

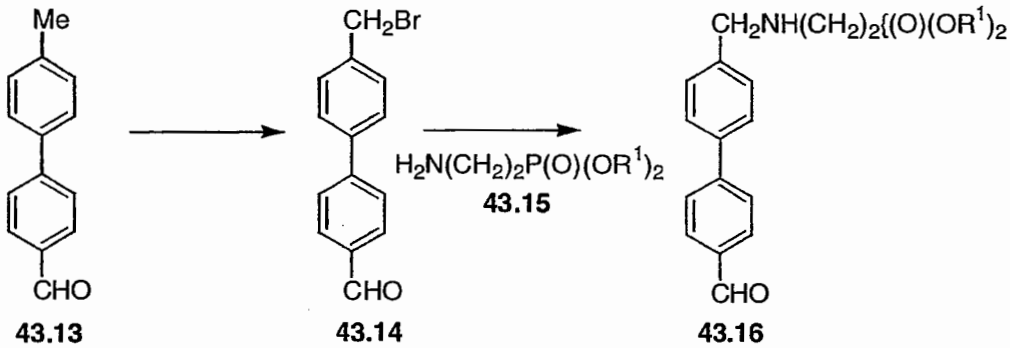
Method



Example 1

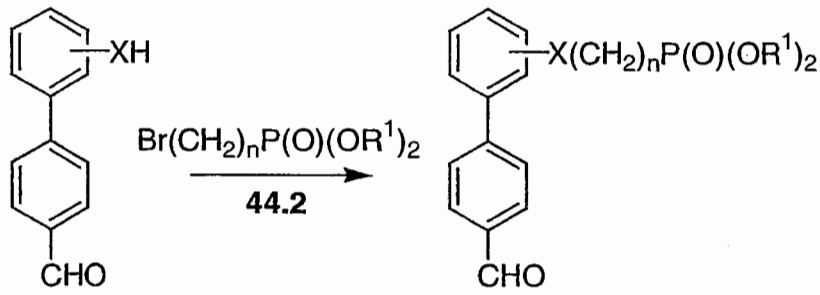


Example 2



Scheme 44

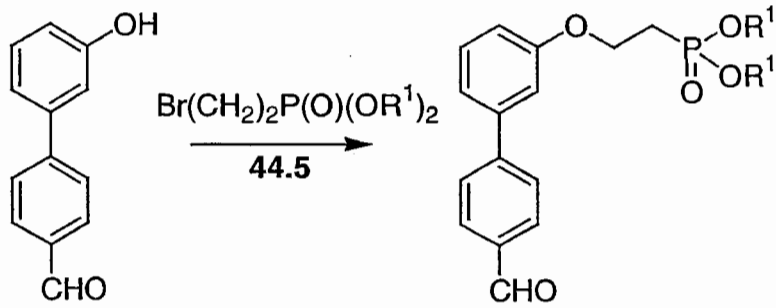
Method



X = O, S, NH, Nalkyl

44.1 **44.3**

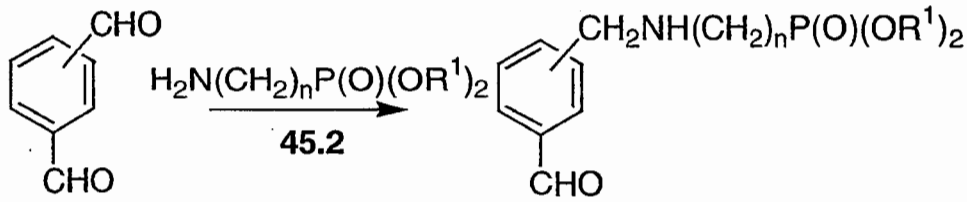
Example



44.4 **44.6**

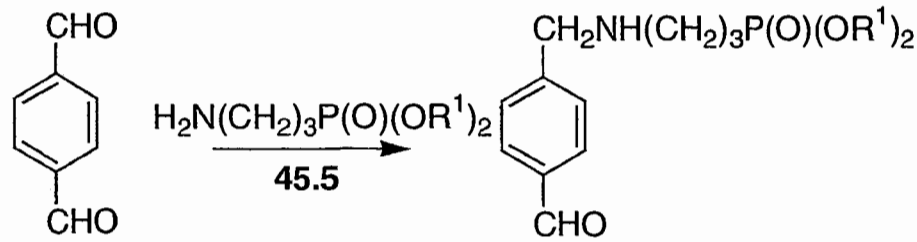
Scheme 45

Method



45.1 **45.3**

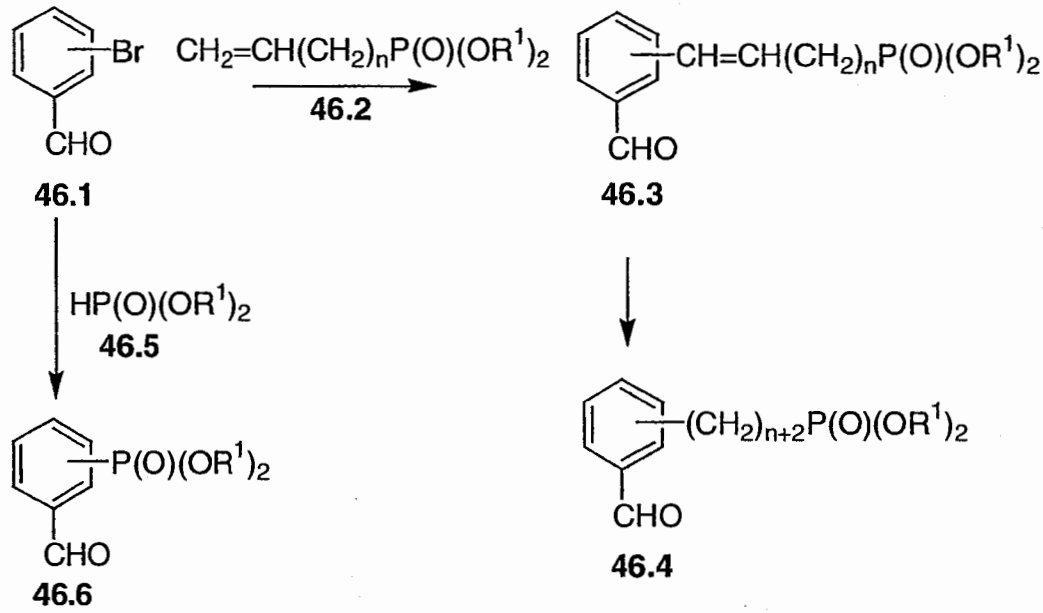
Example



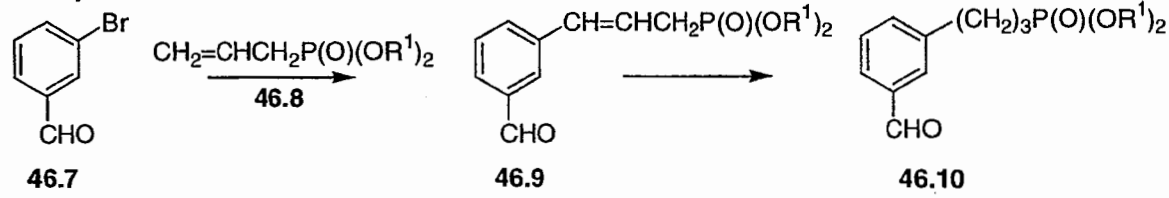
45.4 **45.6**

Scheme 46

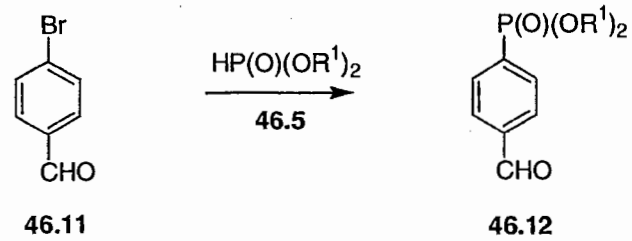
Method



Example 1



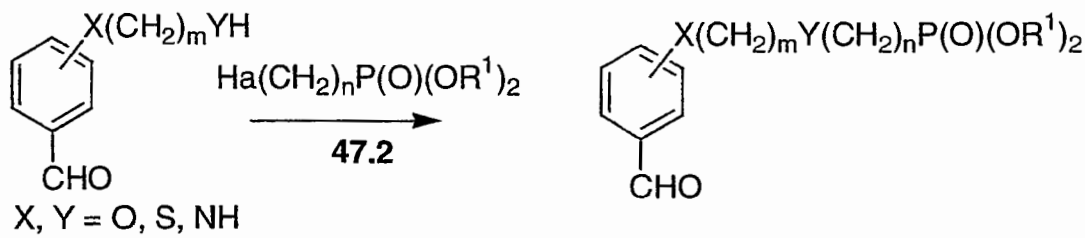
Example 2



5

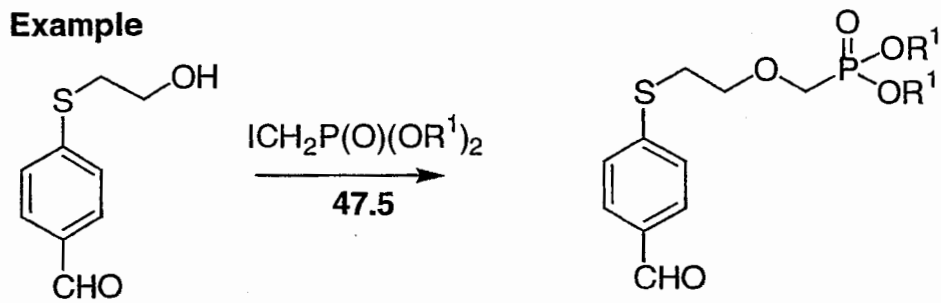
Scheme 47

Method



47.1 **47.3**

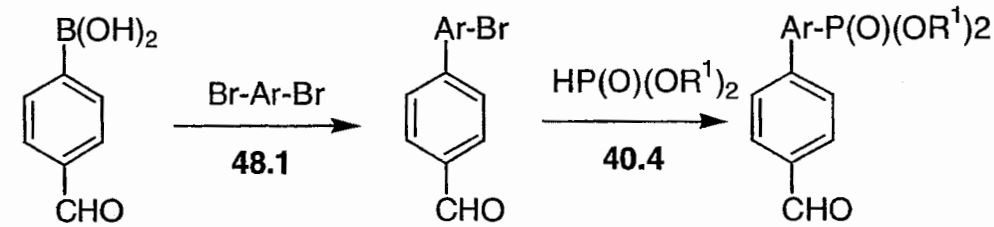
Example



47.4 **47.6**

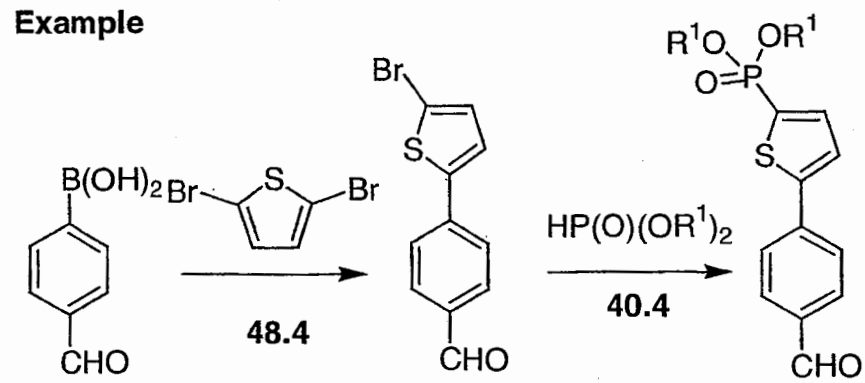
Scheme 48

Method



43.1 **48.2** **48.3**

Example



43.1 **48.5** **48.6**

Preparation of the cyclohexanecarboxaldehyde phosphonates 4.16.

Schemes **49 - 52** illustrate methods for the preparation of the cyclohexanecarboxaldehyde phosphonates **4.16** which are employed in the synthesis of the phosphonate esters **3c**. Scheme **49** depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is attached by means of a nitrogen and an alkylene chain. In this procedure, a cyclohexane dicarboxaldehyde **49.1** is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate **49.2** under reductive amination conditions, as described above, to afford the phosphonate product **49.3**.

For example, cyclohexane-1,3-dialdehyde **49.4**, the preparation of which is described in J. Macromol. Sci. Chem., 1971, 5, 1873, is reacted with a dialkyl aminopropyl phosphonate **49.5**, (Acros) and one molar equivalent of sodium triacetoxyborohydride, to yield the phosphonate product **49.6**.

Using the above procedures, but employing, in place of cyclohexane-1,3-dialdehyde **49.4**, different cyclohexane dialdehydes **49.1**, and /or different aminoalkyl phosphonates **49.2**, the corresponding products **49.3** are obtained.

Scheme **50** depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is attached by means of a vinyl or ethylene group and a phenyl ring. In this procedure, a vinyl-substituted cyclohexane carboxaldehyde **50.1** is coupled, in the presence of a palladium catalyst, as described above, (Scheme **36**) with a dialkyl bromophenylphosphonate **50.2**, to afford the phosphonate product **50.3**. Optionally, the product is reduced to afford the ethylene-linked analog **50.4**. The reduction reaction is effected catalytically, for example by the use of hydrogen in the presence of a palladium catalyst, or chemically, for example by the use of diimide.

For example, 4-vinylcyclohexanecarboxaldehyde **50.5**, the preparation of which is described in WO 9935822, is coupled with a dialkyl 3-bromophenyl phosphonate **50.6**, prepared as described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, to give the coupled product **50.7**. The product is then reduced with diimide, generated by treatment of disodium azodicarboxylate with acetic acid, as described in J. Am. Chem. Soc., 83, 3725, 1961, to yield the saturated product **50.8**.

Using the above procedures, but employing, in place of 4-vinylcyclohexanecarboxaldehyde **50.5**, different vinylcyclohexane carboxaldehydes **50.1**, and /or different bromophenyl phosphonates **50.2**, the corresponding products **50.3** and **50.4** are obtained.

Scheme **51** depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is attached by means of an alkylene chain incorporating an oxygen atom. In this procedure, a hydroxymethyl-substituted cyclohexane carboxaldehyde **51.1** is reacted, in the presence of a strong base such as sodium hydride or potassium tert. butoxide, with one molar equivalent of a dialkyl bromoalkyl phosphonate **51.2**, to prepare the phosphonate **51.3**. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide, tetrahydrofuran or acetonitrile, at from ambient temperature to about 60°.
For example, 3-(hydroxymethyl)cyclohexanecarboxaldehyde **51.4**, prepared as described in WO 0107382, is treated with one molar equivalent of sodium hydride in tetrahydrofuran at 50°, and one molar equivalent of a dialkyl bromoethyl phosphonate **51.5** (Aldrich) to afford the alkylation product **51.6**.
Using the above procedures, but employing, in place of 3-(hydroxymethyl)cyclohexanecarboxaldehyde **51.4** different hydroxymethylcyclohexane carboxaldehydes **51.1**, and /or different bromoalkyl phosphonates **51.2**, the corresponding products **51.3** are obtained.

Scheme **52** depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is directly attached to the cyclohexane ring. In this procedure, a hydroxy-substituted cyclohexanecarboxaldehyde **52.1** is converted into the corresponding bromo derivative **52.2**. The conversion of alcohols into the corresponding bromides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. The transformation is effected by treatment of the alcohol with hydrobromic acid, or by reaction with hexabromoethane and triphenylphosphine, as described in Synthesis, 139, 1983. The resulting bromo compound **52.2** is then subjected to an Arbuzov reaction, by treatment with a trialkyl phosphite **52.3** at ca 100°. The preparation of phosphonates by mean of the Arbuzov reaction is described in Handb. Organophosphorus Chem., 1992, 115.
For example, 4-hydroxycyclohexanecarboxaldehyde **52.5** is reacted with one molar equivalent of hexabromoethane and triphenyl phosphine in dichloromethane, to yield 4-

bromocyclohexanecarboxaldehyde **52.6**. The product is heated at 100° with a trialkyl phosphite **52.3** to afford the cyclohexyl phosphonate **52.7**.

Using the above procedures, but employing, in place of 4-(hydroxymethyl)cyclohexanecarboxaldehyde **52.5**, different hydroxy-substituted cyclohexanecarboxaldehydes **52.1**, the corresponding products **52.4** are obtained.

Preparation of quinoline 2-carboxylic acids 19a.1 incorporating phosphonate moieties or precursors thereto.

The reaction sequence depicted in Schemes **19a** - **19d** require the use of a quinoline-2-carboxylic acid reactant **19a.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br.

A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het. Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines is described, for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.

Scheme **53** illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde **53.1** is reacted with an alkyl pyruvate ester **53.2**, in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester **53.3**. Hydrolysis of the ester, for example by the use of aqueous base, then afford the corresponding carboxylic acid **53.4**. The carboxylic acid product **53.4** in which X is NH_2 can be further transformed into the corresponding compounds **53.6** in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The

conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoborate, is then heated in aqueous solution, for example as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol **53.6**, X = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, **53.6**, Y = Br. Alternatively, the diazonium tetrafluoborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 200, 24, 123, to afford the thiol **53.6**, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters **53.3** instead of the carboxylic acids **53.5**.

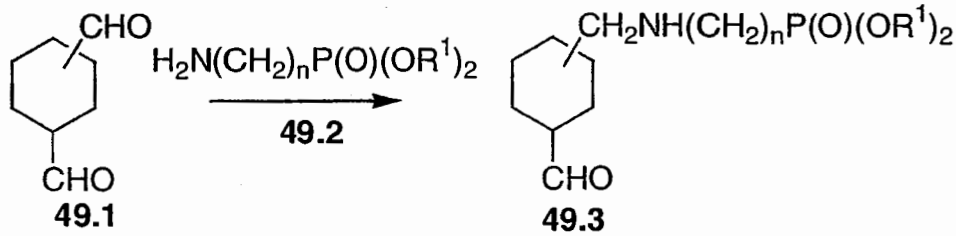
For example, 2,4-diaminobenzaldehyde **53.7** (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate **53.2** in methanol, in the presence if a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate **53.8**. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **53.9**. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoborate **53.10** by reaction with sodium nitrite and tetrafluoboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, **53.11**, Z = OH. Alternatively, the diazonium tetrafluoborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-bromoquinoline-2-carboxylic acid **53.11**, X = Br. Alternatively, the diazonium tetrafluoborate **53.10** is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid **53.11**, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde **53.7**, different aminobenzaldehydes **53.1**, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids **53.6** are obtained. The variously substituted quinoline

carboxylic acids and esters can then be transformed, as described below, (Schemes **54 – 56**) into phosphonate-containing derivatives.

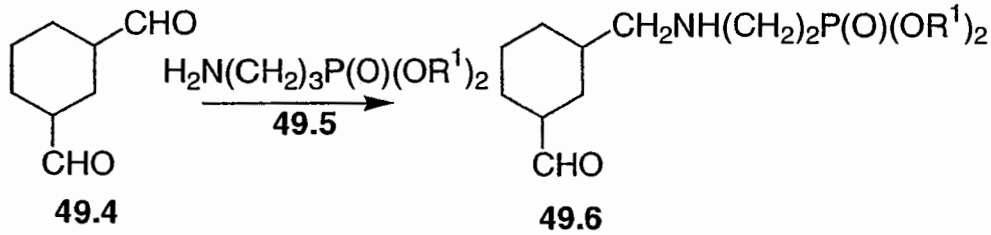
Scheme 49

Method



49.1 **49.3**

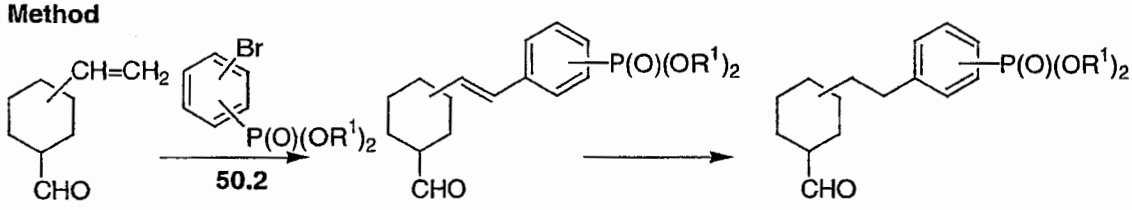
Example



49.4 **49.6**

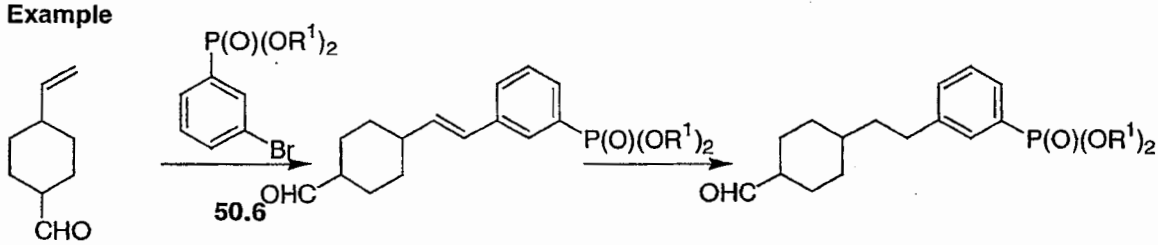
Scheme 50

Method



50.1 **50.3** **50.4**

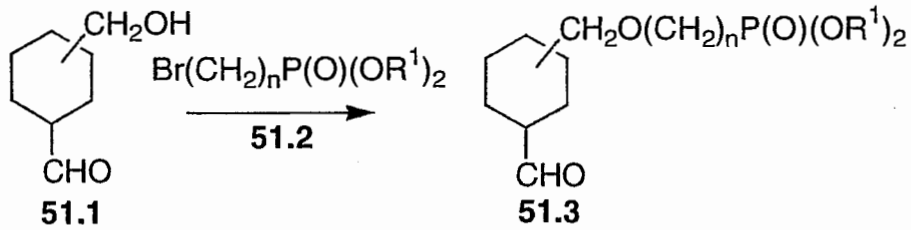
Example



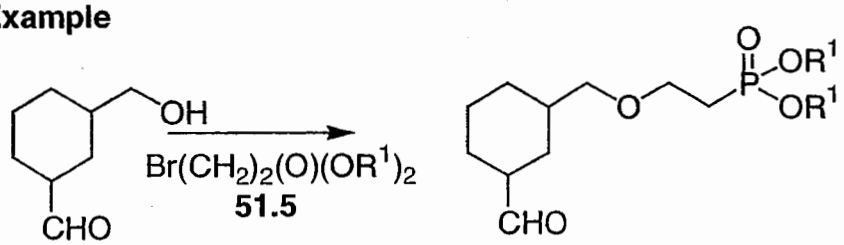
50.5 **50.7** **50.8**

Scheme 51

Method

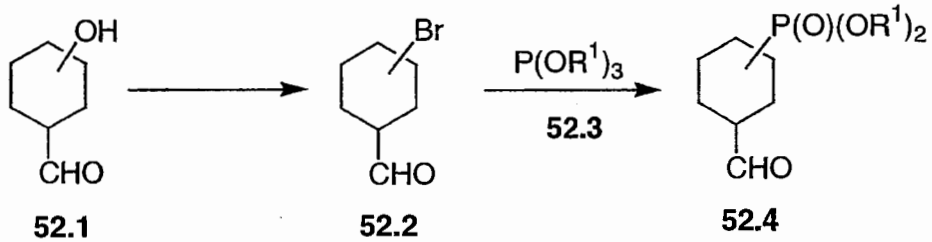


Example

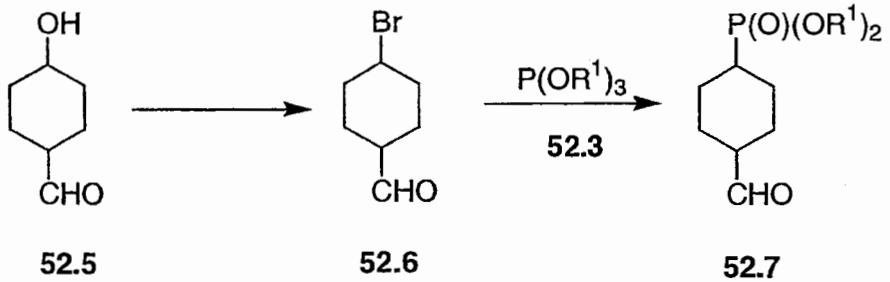


Scheme 52

Method

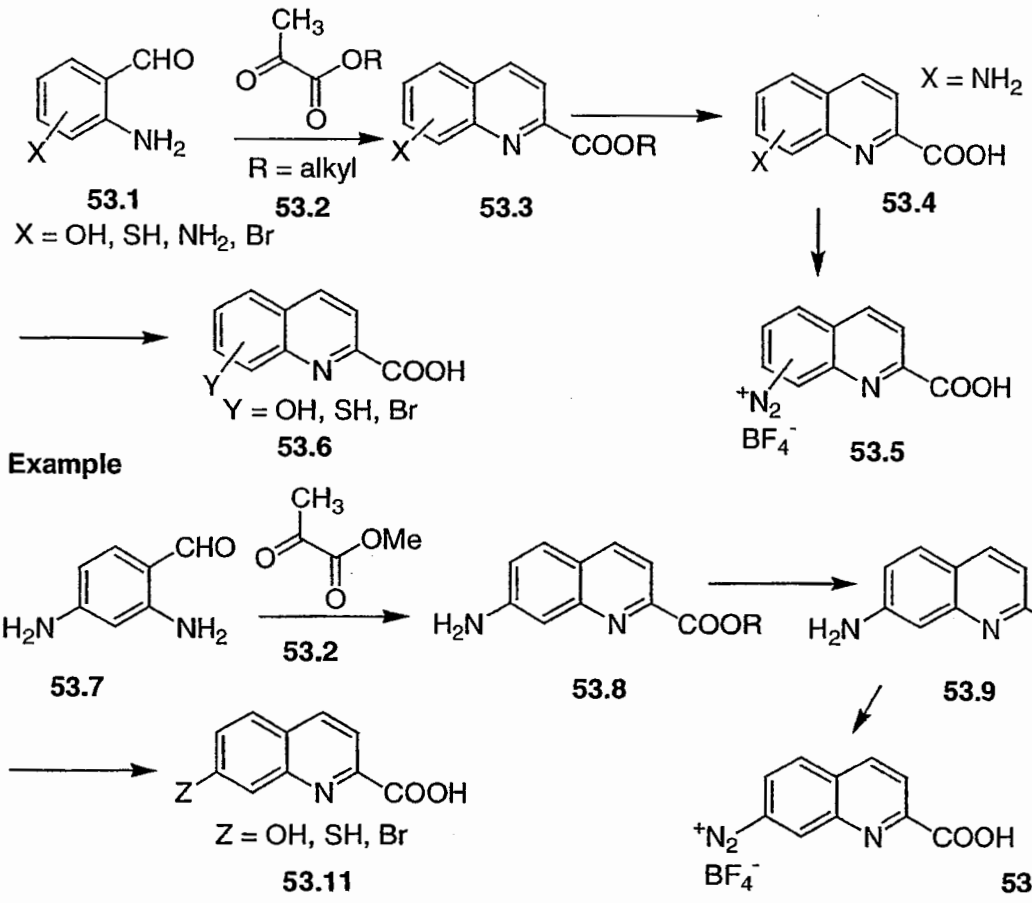


Example



Scheme 53

Method



Example

Scheme **54** depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester **54.1** is transformed, via a diazotization procedure as described above (Scheme **53**) into the corresponding phenol or thiol **54.2**. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate **54.3**, under the conditions of the Mitsonobu reaction, to afford the phosphonate ester **54.4**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the thioether products **54.5**. Basic

hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **54.6**.

For example, methyl 6-amino-2-quinoline carboxylate **54.7**, prepared as described in J. Het. Chem., 1989, 26, 929, is converted, by means of the diazotization procedure described above, into methyl 6-mercaptoquinoline-2-carboxylate **54.8**. This material is reacted with a dialkyl hydroxymethylphosphonate **54.9** (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether **54.10**. Basic hydrolysis then afford the carboxylic acid **54.11**.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline carboxylate **54.7**, different aminoquinoline carboxylic esters **54.1**, and/or different dialkyl hydroxymethylphosphonates **54.3** the corresponding phosphonate ester products **54.6** are obtained.

Scheme **55** illustrates the preparation of quinoline-2-carboxylic acids incorporating phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester **55.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate **55.2**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Thus, Heck coupling of the bromo compound **55.1** and the olefin **55.2** affords the olefinic ester **55.3**. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid **55.4**. Optionally, the unsaturated carboxylic acid **55.4** can be reduced to afford the saturated analog **55.5**. The reduction reaction can be effected chemically, for example by the use of diimide, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5.

For example, methyl 7-bromoquinoline-2-carboxylate, **55.6**, prepared as described in J. Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60° with a dialkyl vinylphosphonate **55.7** (Aldrich) in the presence of 2 mol% of

tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product **55.8**. The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid **55.9**. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product **55.10**.

Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate **55.6**, different bromoquinoline carboxylic esters **55.1**, and/or different dialkyl alkenylphosphonates **55.2**, the corresponding phosphonate ester products **55.4** and **55.5** are obtained.

Scheme **56** depicts the preparation of quinoline-2-carboxylic acids **56.5** in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate **56.1** is reacted with a phosphonate aldehyde **56.2** under reductive amination conditions, to afford the aminoalkyl product **56.3**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product **56.4** is then hydrolyzed to yield the free carboxylic acid **56.5**.

For example, methyl 7-aminoquinoline-2-carboxylate **56.6**, prepared as described in J. Amer. Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **56.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **56.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **56.9**.

Using the above procedures, but employing, in place of the formylmethyl phosphonate **56.2**, different formylalkyl phosphonates, and/or different aminoquinolines **56.1**, the corresponding products **56.5** are obtained.

Interconversions of the phosphonates R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH) and R-link-P(O)(OH)$_2$.

Schemes **1** - **56** described the preparations of phosphonate esters of the general structure R-link-P(O)$(OR^1)_2$, in which the groups R^1, the structures of which are defined in Chart **1**, may be the same or different. The R^1 groups attached to a phosphonate esters **1-7**, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme **57**. The group R in Scheme **57** represents the substructure to which the substituent link-P(O)$(OR^1)_2$ is attached, either in the compounds **1-7** or in precursors thereto. The R^1 group may be changed, using the procedures described below, either in the precursor compounds, or in the esters **1-7**. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **57.1** into the corresponding phosphonate monoester **57.2** (Scheme **57**, Reaction **1**) can be accomplished by a number of methods. For example, the ester **57.1** in which R^1 is an aralkyl group such as benzyl, can be converted into the monoester compound **57.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester **57.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **57.2** can be effected by treatment of the ester **57.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **57.1** in which one of the groups R^1 is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **57.2** in which R^1 is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, can be converted into the monoester **57.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **57.1** or a phosphonate monoester **57.2** into the corresponding phosphonic acid **57.3** (Scheme **57**, Reactions **2** and **3**) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc.,

Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **57.2** in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **57.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **57.2** in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **57.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **57.1** in which R^1 is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **57.1** in which R^1 is phenyl is described in J. Amer. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester **57.2** into a phosphonate diester **57.1** (Scheme **57**, Reaction **4**) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **57.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **57.2** to the diester **57.1** can be effected by the use of the Mitsonobu reaction, as described above (Scheme **54**). The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **57.2** can be transformed into the phosphonate diester **57.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the

phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **57.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **57.1.**

A phosphonic acid R-link-$P(O)(OH)_2$ can be transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **57**, Reaction **5**) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ **57.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid R-link-$P(O)(OH)_2$ **57.3** can be transformed into a phosphonate diester R-link-$P(O)(OR^1)_2$ **57.1** (Scheme **57**, Reaction **6**) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **57.3** can be transformed into phosphonic esters **57.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°. Alternatively, phosphonic acids **57.3** can be transformed into phosphonic esters **57.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **57.1.**

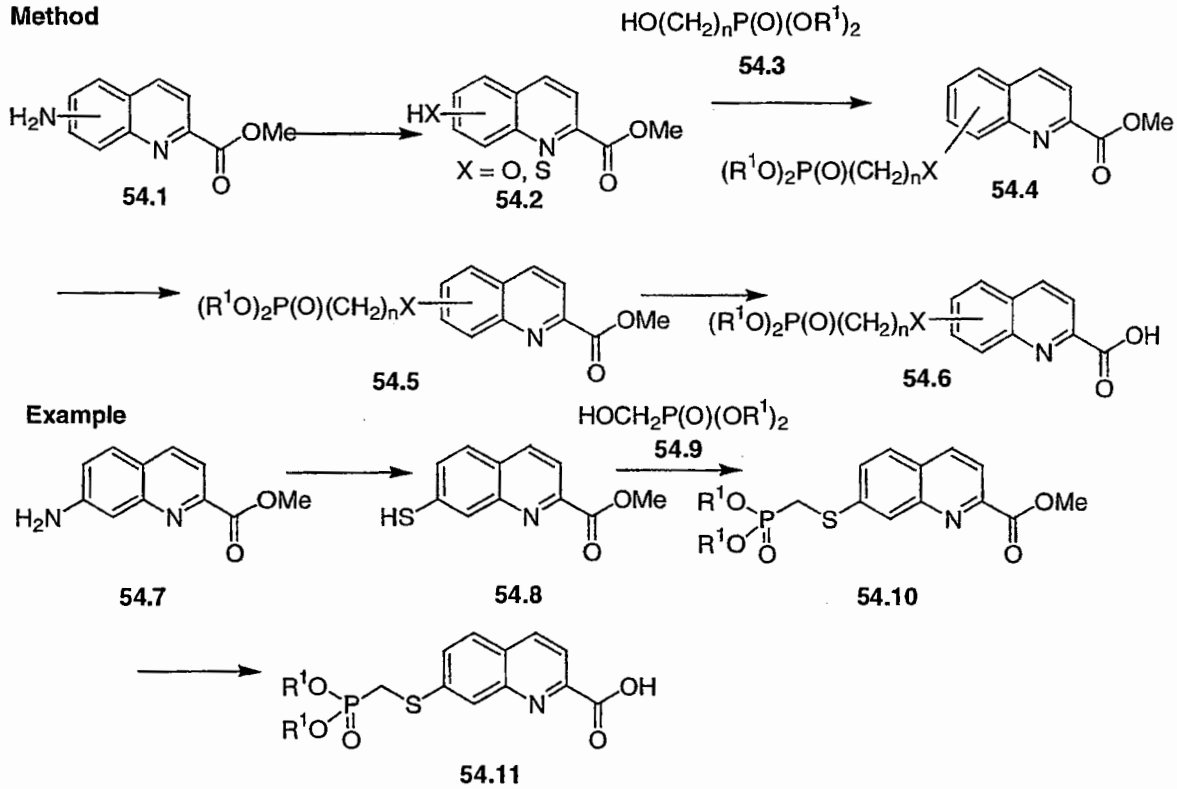
General applicability of methods for introduction of phosphonate substituents.

The procedures described herein for the introduction of phosphonate moieties (Schemes **21** - **56**) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into carbinols (Schemes **21** - **26**) are applicable to the introduction of phosphonate moieties into the oxirane, thiophenol, aldehyde and quinoline substrates, and the methods described herein for the introduction of phosphonate moieties into the oxirane,

thiophenol, aldehyde and quinoline substrates, (Schemes **27 - 56**) are applicable to the introduction of phosphonate moieties into carbinol substrates.

Scheme 54

Method

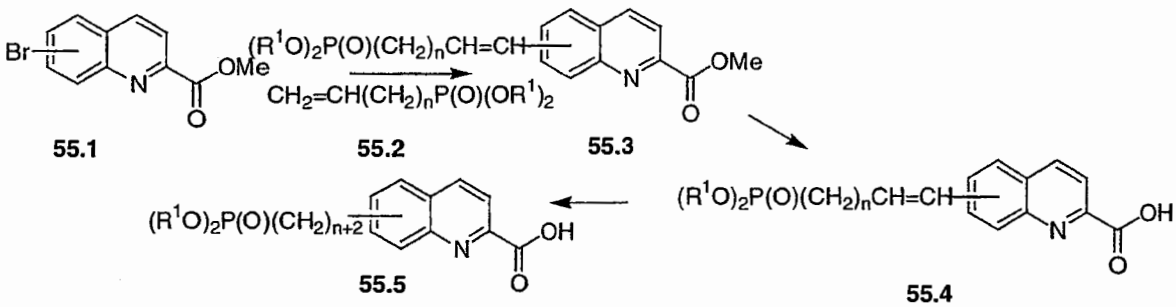


Example

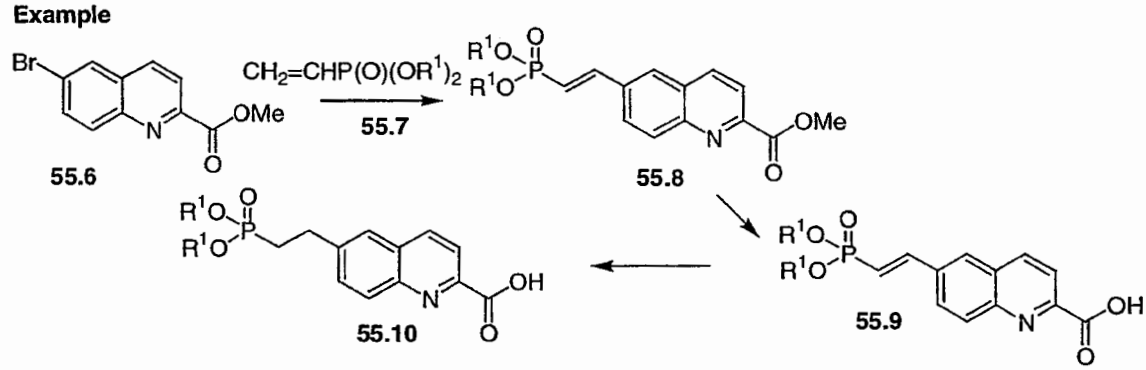
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Scheme 55

Method

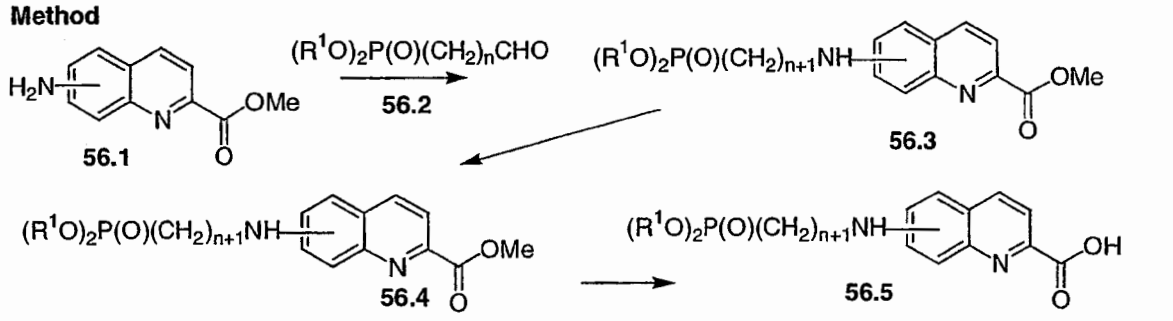


Example

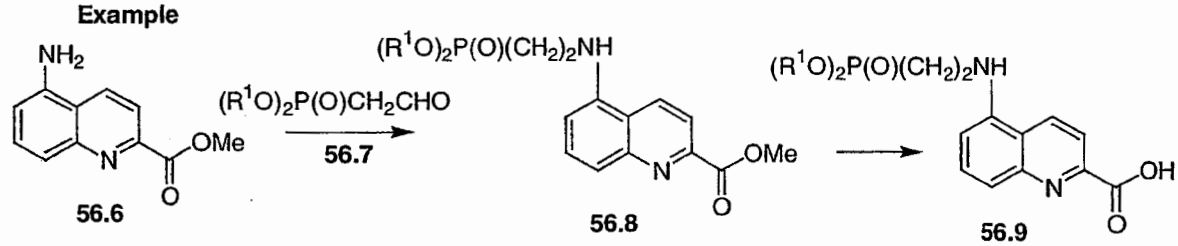


Scheme 56

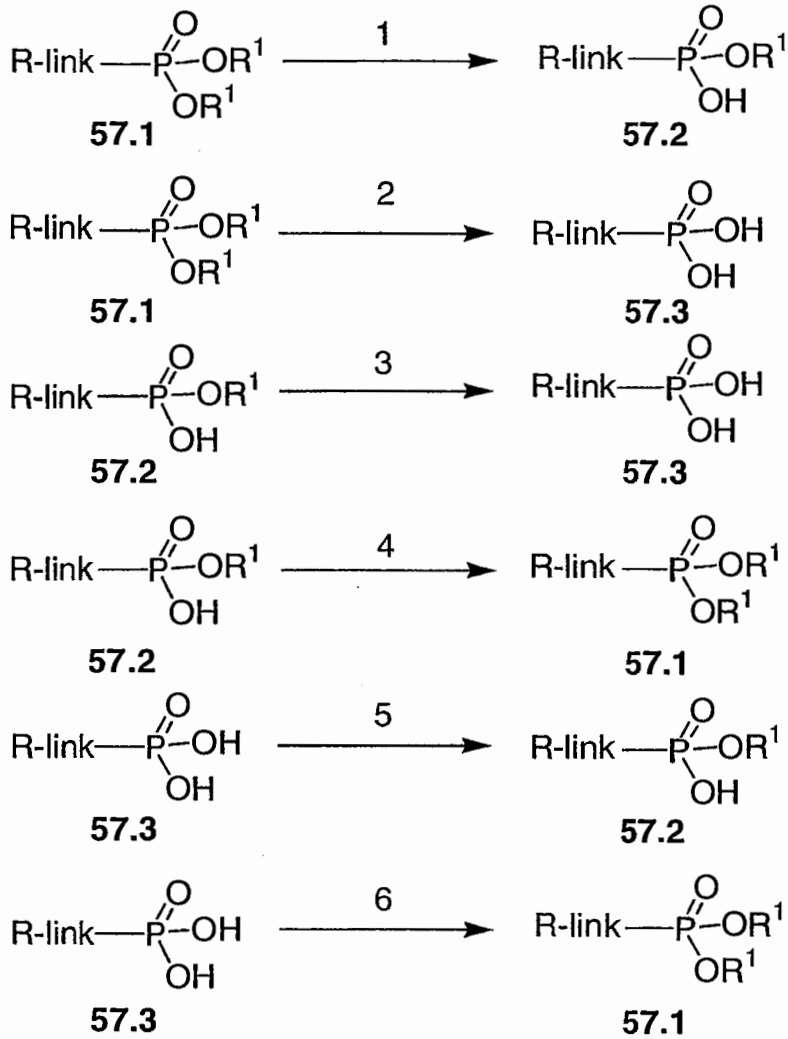
Method



Example



Scheme 57



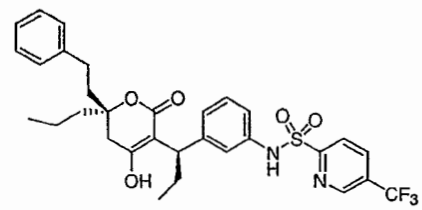
Preparation of phosphonate intermediates 6 and 7 with phosphonate moieties incorporated into the group R^2COOH and R^5COOH.

The chemical transformations described in Schemes **1 - 56** illustrate the preparation of compounds **1-5** in which the phosphonate ester moiety is attached to the carbinol moiety, (Schemes **21 - 26**), the oxirane moiety (Schemes **27 - 29**), the thiophenol moiety (Schemes **30 - 39**), the aldehyde moiety (Schemes **40 - 52**) or the quinoline moiety (Schemes **53 - 56**). The various chemical methods employed for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds R^2COOH and R^5COOH, as defined in Charts

2a, **2b** and **2c**. The resultant phosphonate-containing analogs, designated as $R^{2a}COOH$ and $R^{5a}COOH$ can then, using the procedures described above, be employed in the preparation of the compounds **6** and **7**. The procedures required for the introduction of the phosphonate-containing analogs $R^{2a}COOH$ and $R^{5a}COOH$ are the same as those described above (Schemes **1**, **5**, **7** and **10**) for the introduction of the R^2CO and R^5CO moieties.

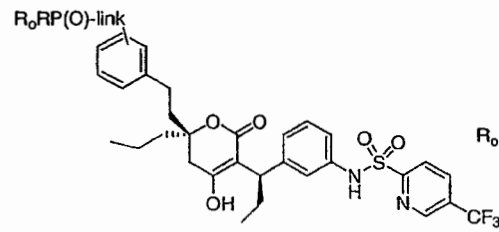
Tipranavir-like phosphonate protease inhibitors (TLPPI)

Chart **1** illustrates the target compounds of the invention. A linkage group (link) is a portion of the structure that links two substructures, one of which is the scaffold having the structures shown above, the other a phosphonate moiety bearing the appropriate R and R^0 groups, as defined below. The link has at least one uninterrupted chain of atoms, other than hydrogen, typically ranging in up to 25 atoms, more preferably less than 10 atoms (hydrogen excluded). The link can be formed using a variety of functional groups such as heteroatom, carbon, alkenyl, aryl etc. Chart **2** illustrates the intermediate phosphonate compounds of this invention that are used in the preparation of the targets, Chart **1**. Chart **3** shows some examples illustrated below of linking groups present in the structures in Chart **1** and **2**. The R and R^0 groups can be both natural and un-natural amino acid esters linked through the amine nitrogen, or alternatively, one of the groups can be substituted for an oxygen linked aryl, alkyl, aralkyl group etc. Alternatively one of the groups may be an oxygen linked aryl, alkyl, aralkyl group etc and the other a lactate ester.

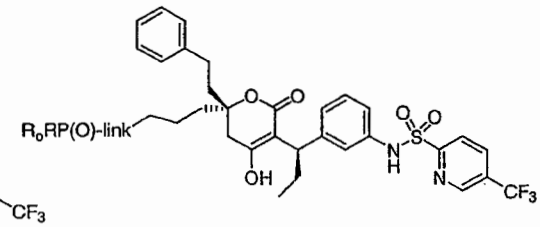


Tipranavir
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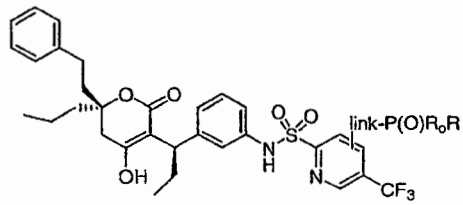
Chart 1



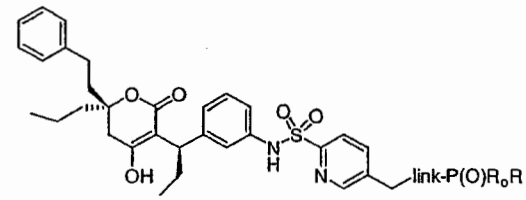
1a



2a

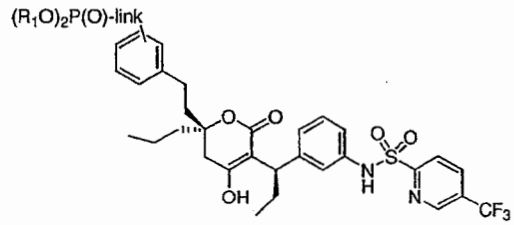


3a

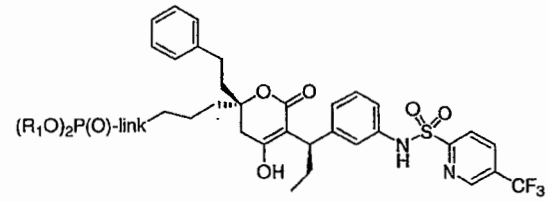


4a

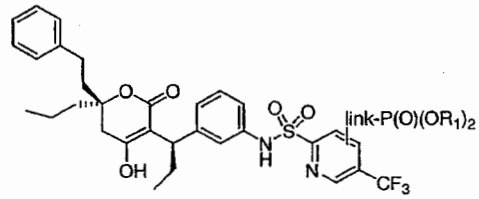
Chart 2



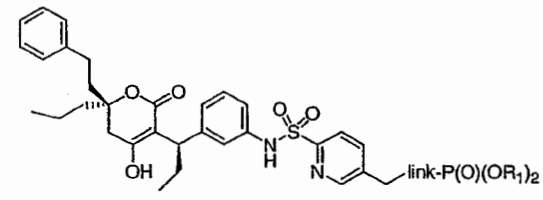
1



2



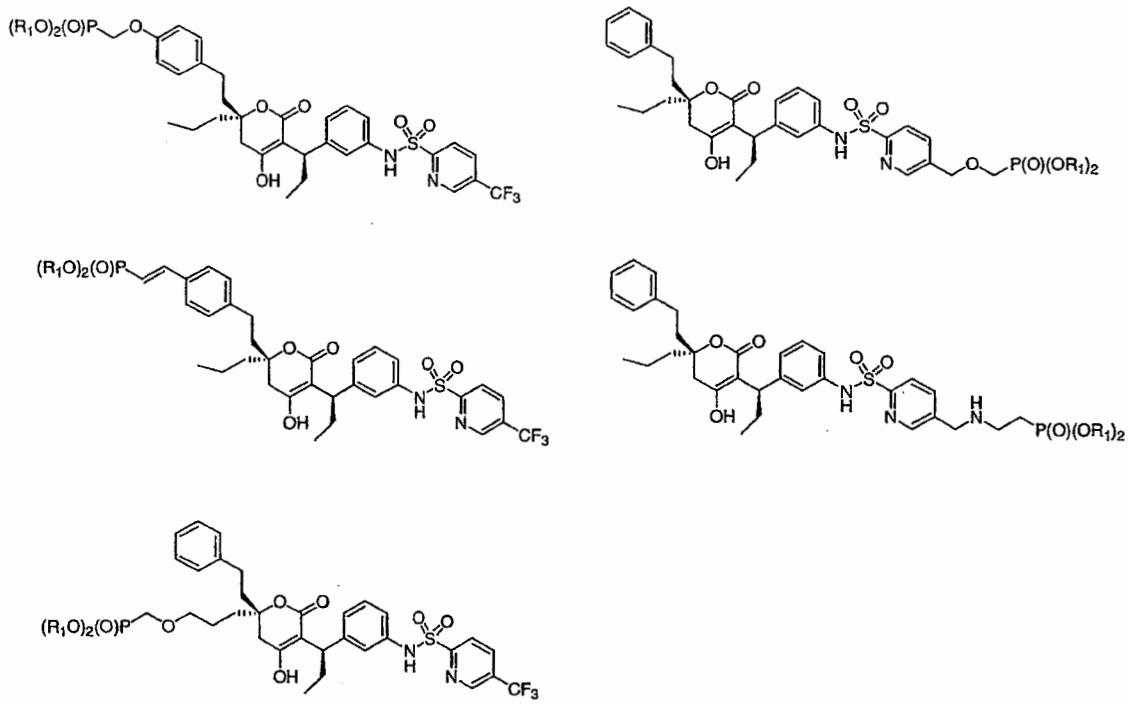
3



4

R_1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

Chart 3



Phosphonate Interconversions

The final compounds described above are synthesized according to the methods described in the following Schemes **1-16**. The intermediate phosphonate esters are shown in Chart **2** and these compounds can be used to prepare the final compounds illustrated above in Chart **1**, by one skilled in the art, using known methods for synthesis of substituted phosphonates. These methods are similar to those described for the synthesis of amides. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274. Further methods are described in Scheme **16** below for the synthesis of the phosphonate diesters and can in some cases be applied to the synthesis of phosphor-amides.

In the following schemes, the conversion of various substituents into the group link-$P(O)(OR^1)_2$, where R^1 is defined in Chart **2**, or indeed the final stage of $P(O)RR^o$, as defined above, can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the

substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, amino, during the introduction of the group link-$P(O)(OR^1)_2$ or $P(O)RR^o$

In the succeeding examples, the nature of the phosphonate ester group $P(O)(OR^1)_2$ can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme **16**). Examples shown in charts **1-3** indicate a specific stereochemistry. However, the methods are applicable to the synthesis all of the possible stereoisomers and the separation of possible isomers can be effected at any stage of the sequence after introduction of the stereocenter. The point in the synthetic sequence would be determined by the resolution that could be achieved in the separation by one skilled in the art.

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], etc.

Preparation of Intermediate Phosphonates shown in Chart 2

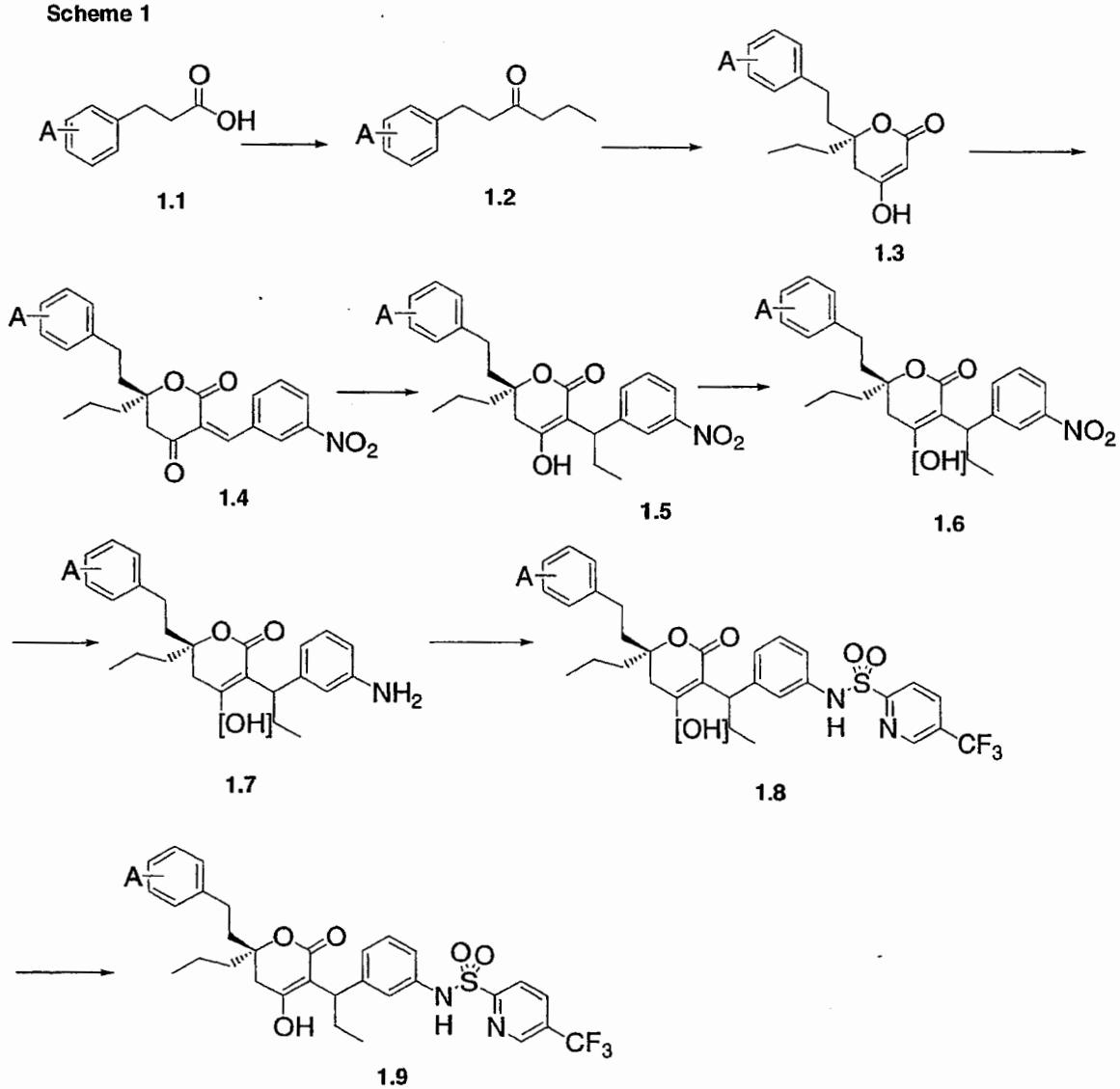
Scheme **1-3** illustrates the synthesis of target molecules of type **1**, chart **2**, in which A is Br, Cl, [OH], [NH], or the group link-$P(O)(OR^1)_2$. The procedures described in J. Med. Chem. 1998, 41, p3467 are used to generate compounds of the type **1** from **1.2** in which A is Hydrogen. The conversion of **1.1** into **1.2** follows procedures described in Bioorg Med. Chem 1999, 7, p2775 for the preparation of a similar compound. The preparation of **1.1** is described in Scheme **13-14**. For example, acid **1.1** is converted via the Weinreb amide to the ketone **1.2**. The ketone **1.2** is then treated with 3-oxo-butyric acid methyl ester, as described in J. Med Chem. 1998, 41, 3467, to give the pyrone **1.3**. A mixture of R and S isomers can be carried forward or alternatively separated by chiral chromatography at this stage. Aluminium chloride catalysed condensation of 3-nitrobenzaldehyde onto the pyrone **1.3,** as described in J. Med

Chem. 1998, 41, 3467-3476, affords nitro pyrone **1.4**. Nitro pyrone **1.4** upon treatment with triethylaluminum in the presence of copper(1) bromide-dimethylsulfide as described in J. Med Chem. 1998, 41, 3467-3476 affords the dihydropyrone **1.5**. Protection of the dihydropyran hydroxyl in **1.5** with a suitable protecting group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.249ff gives the hydroxyl protected compound **1.6.** For example, treatment with SEMCl in the presence of base e.g. potassium carbonate, generates the SEM ether protected **1.6.** Catalytic hydrogenolysis of the nitro group, as described in J. Med Chem. 1998, 41, 3467-3476, affords the aryl amine **1.7** which is then coupled with the 5-trifluoromethyl-pyridine-2-sulfonyl chloride in the presence of pyridine, as described in J. Med Chem. 1998, 41, 3467-3476 to afford the sulfonamide **1.8.** Finally, removal of the protecting group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.249ff affords the product **1.9**. For example, treatment of the SEM protected product indicated above with TBAF produces the de-silylated (6R, 3R/S) product **1.9**. The diastereoisomers are then separated through silica gel chromatography.

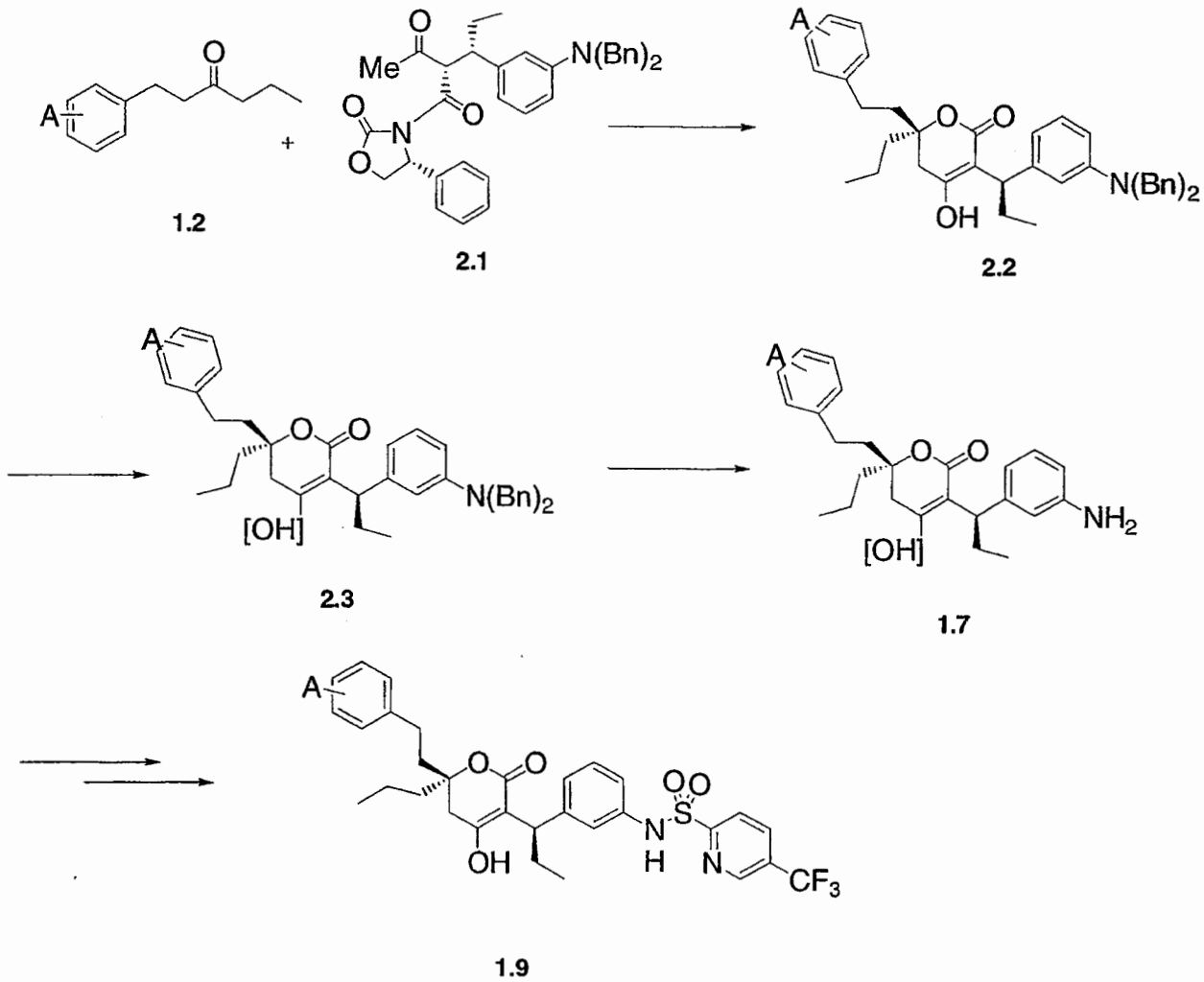
Scheme **2** also illustrates the synthesis of target molecules of type **1**, chart **2**, in which A is Br, Cl, [OH], [NH], or the group link-P(O)$(OR^1)_2$ but the products in this example have the absolute stereochemistry (6R, 3R) . The ketone **1.2**, prepared in Scheme **1**, is transformed into the dihydropyrone **2.2** as described in Drugs of the Future, 1998, 23(2), p146. This 2 step reaction involves reaction of the ketone with dioxalone **2.1**, prepared as described in Drugs of the Future, 1998, 23(2), p146 in the presence of $Ti(OBu)Cl_3$, followed by treatment with a base such as potassium tert-butoxide. Treatment of the dihydropyrone **2.2** with the same procedures reported in Scheme **1** for the conversion of **1.5** into **1.9** then affords the final product **1.9** in chiral form (6R, 3R). For example, the pyrone hydroxyl **2.2** is first protected as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.249ff, to afford **2.3** and then the dibenzyl groups are removed from **2.3** by catalytic hydrogenolysis as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.579 to afford the amine product **1.7**. Amine **1.7** is then converted into **1.9** as described in Scheme **1.**

The reactions shown in Scheme **1-2** illustrate the preparation of the compounds **1.9** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **3** depicts the conversion of the compounds **1.9** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **1**. In this procedure, the compounds **1.9** are converted, using the procedures described below, Schemes **10-15**, into the compounds **1**.

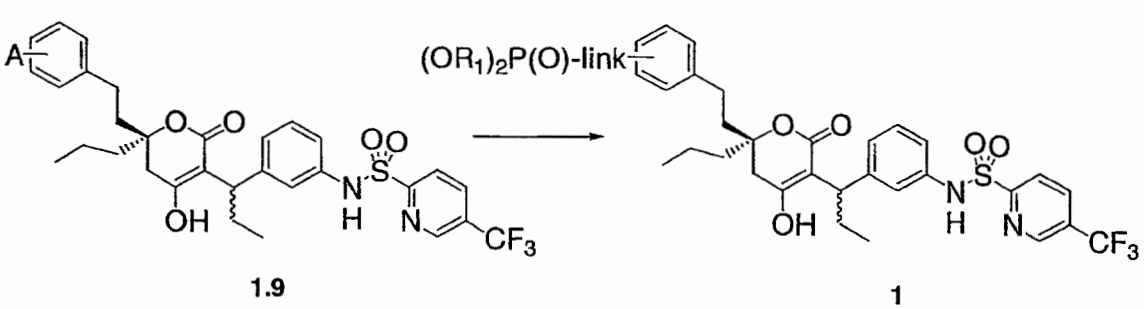
Scheme 1



Scheme 2



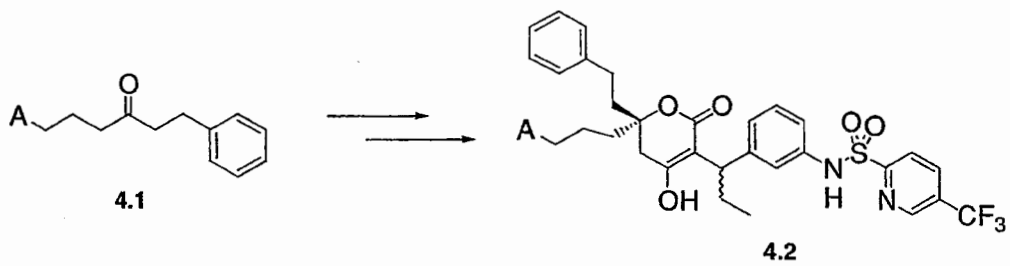
Scheme 3



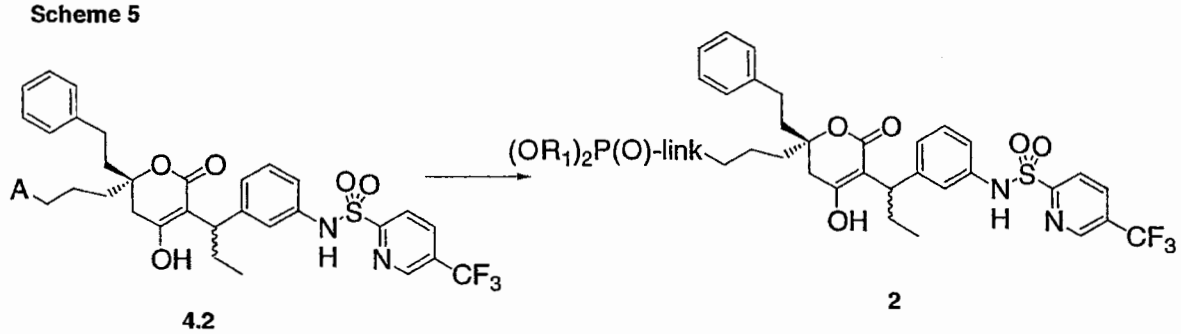
Scheme **4** illustrates the synthesis of target molecules of type **2**, chart **2**, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR^1)$_2$. The acid **4.1** prepared as described below (Scheme **15**), is converted into **4.2** using the procedures described in Scheme **1** or Scheme **2.**

The reactions shown in Scheme **4** illustrate the preparation of the compounds **4.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **5** depicts the conversion of the compounds **4.2** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **2**. In this procedure, the compounds **4.2** are converted, using the procedures described below, Schemes **10-15**, into the compounds **2.**

Scheme 4



Scheme 5

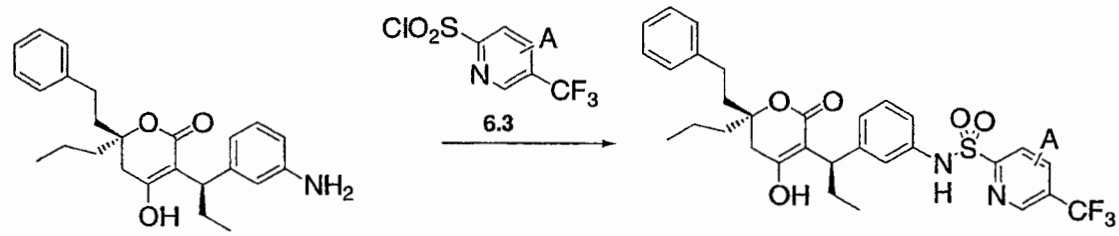


Scheme **6-7** illustrates the synthesis of target molecules of type **3**, chart **2**, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR^1)$_2$. The amine **6.1** prepared as described in Drugs of the Future, 1998, 23(2), p146 or US 5852195, is converted into the sulfonamide **6.2** using the procedures described in Scheme **1** or Scheme **2** for the preparation of **1.8** from **1.7.** The synthesis of the sulfonyl chlorides **6.3** is shown below in Schemes **11-12.**

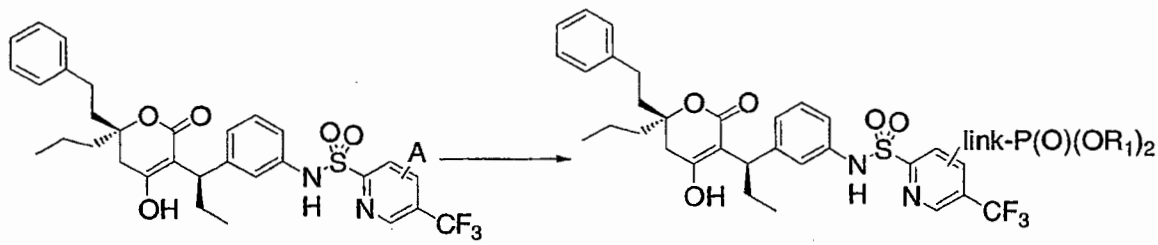
The reactions shown in Scheme **6** illustrate the preparation of the compounds **6.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **7** depicts the conversion of the compounds **6.2** in which A is [OH], [SH], [NH],

Br etc, into the phosphonate esters **3**. In this procedure, the compounds **6.2** are converted, using the procedures described below, Schemes **10-15**, into the compounds **3**.

Scheme 6



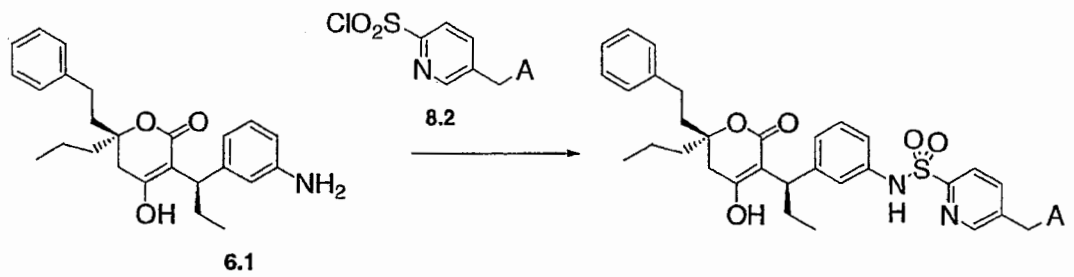
Scheme 7



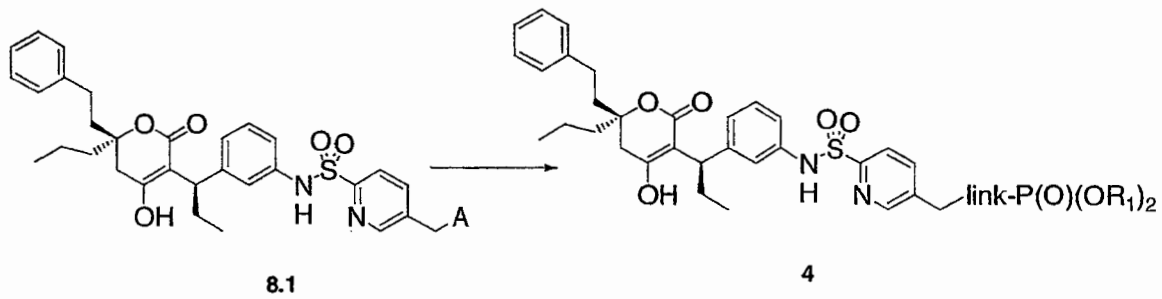
Scheme **8** illustrates the synthesis of target molecules of type **4**, chart **2**, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR^1)$_2$. The amine **6.1** prepared as described in Drugs of the Future, 1998, 23(2), p146 or US 5852195, is converted into the sulfonamide **8.1** by treatment with **8.2** using the procedures described in Scheme **1** or Scheme **2.** The synthesis of the sulfonyl chlorides **8.2** is shown below in Scheme **10**.

The reactions shown in Scheme **8** illustrate the preparation of the compounds **8.1** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **9** depicts the conversion of the compounds **8.1** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **4**. In this procedure, the compounds **8.1** are converted, using the procedures described below, Schemes **10-15**, into the compounds **4**.

Scheme 8



Scheme 9



Preparation of phosphonate reagents used in the synthesis of compounds 1-4

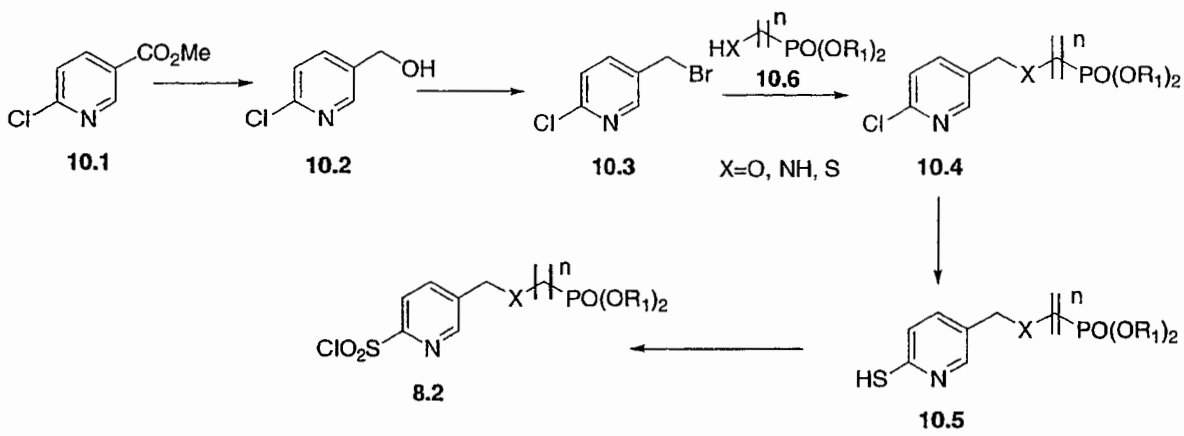
Schemes **10** describes the preparation of phosphonate-containing derivatives **8.2,** in which the phosphonate is linked through a heteroatom, which are employed in the preparation of the phosphonate ester intermediates **4.** The pyridyl ester **10.1** (Acros) is first reduced to the alcohol **10.2**. This transformation involves reducing the ester with lithium aluminium hydride, or other reducing agent, in an inert solvent such as THF or dioxane. Alcohol **10.2** is then converted to the bromide **10.3** through typical hydroxyl to bromide conversion conditions described in Comprehensive Organic Transformations, R.C. Larock, 2nd edition, p693-697. For instance, treatment of **10.2** with carbon tetrabromide and triphenylphosphine in THF or dioxane affords the bromide **10.3.** Treatment of the bromide **10.3** with a thiol, amino, or hydroxyl alkyl phosphonate **10.6** then affords the phosphonate product **10.4.** The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxane or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant **10.6**. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed. The chloride **10.4** is then treated KHS in methanol, as described in Justus Liebigs Annalen Chemie, 1931, p105 or thiourea followed by

potassium hydroxide treatment, as described in Heterocycles 1984, p117, to give the α-sulfide **10.5**. If appropriate, reactive groups e.g. amines in the phosphonate chain, are protected using methods known to one skilled in the art. The α-sulfide **10.5** is then converted to the sulfonyl chloride **8.2** by treatment with chlorine in HCl, as described in Synthesis 1987, 4, p409, or J. Med. Chem 1980,12, p1376.

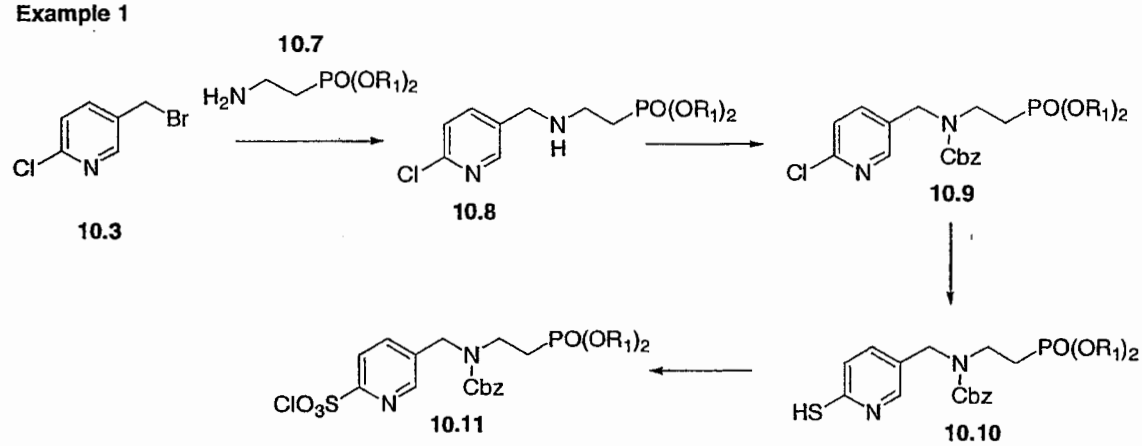
For example, the pyridyl bromide **10.3**, described above, is treated with amino phosphonate **10.7,** prepared as described in J. Org. Chem. 2000, 65, p676, in the presence of potassium carbonate and DMF to afford the phosphonate product **10.8**. Protection of the amine by conversion to the CBZ carbamate **10.9** is performed by treatment of **10.8** with benzyl chloroformate in the presence of triethylamine. Further treatment of **10.9** with thiourea in ethanol at reflux followed by treatment with potassium hydroxide in water then affords the thiol **10.10.** Thiol **10.10** is then treated with chlorine in HCl (aqueous) to afford the sulfonyl chloride **10.11.** Using the above procedures, but employing, in place of the amino alkyl phosphonate **10.7,** different alkyl phosphonates **10.6,** the corresponding products **8.2** are obtained.

Alternatively (Example 2), illustrates the preparation of phosphonates in which the link is through an oxyen atom. The pyridyl bromide **10.3** described above, is treated with hydroxyl phosphonate **10.12,** prepared as described in Synthesis 1998, 4, p327, in the presence of potassium carbonate and DMF to afford the phosphonate product **10.13**. Further treatment of **10.13,** as described above, for the conversion of **10.8** into **10.11** affords the sulfonyl chloride **10.16**. Using the above procedures, but employing, in place of the hydroxy alkyl phosphonate **10.12,** different alkyl phosphonates **10.6** the corresponding products **8.2** are obtained.

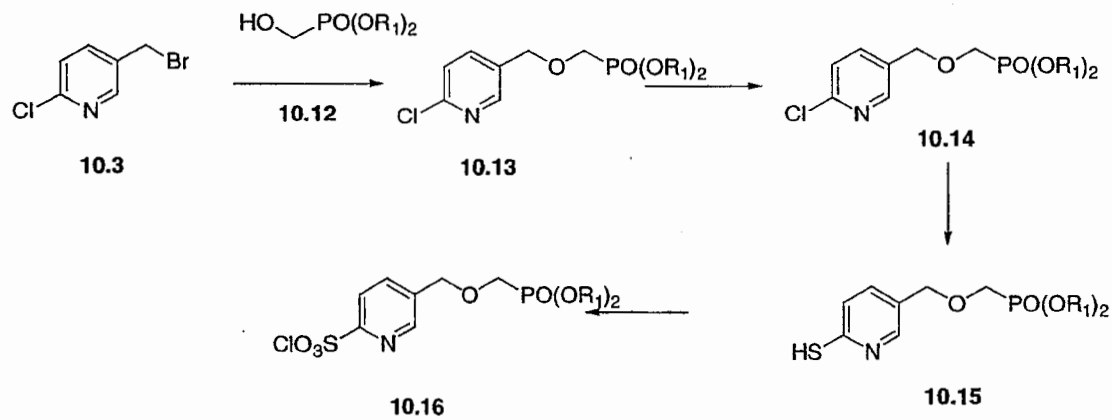
Scheme 10



Example 1



Example 2



Schemes **11-12** describe the preparation of phosphonate-containing derivatives **6.3,** which are employed in the preparation of the phosphonate ester intermediates **3.** Scheme **11** illustrates compounds of type **6.3** in which the link is through a oxygen, sulfur or nitrogen heteroatom.

Pyridyl halide **11.1** is treated with the dialkyl hydroxy, thio or amino-substituted alkylphosphonate **10.6** to give the product **11.3**. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant **10.6**. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed. Upon formation of **11.3** the pyridine is converted to the α-chloro pyridine **11.4** by treatment with chlorine at high temperature in a sealed vessel as described in Recl. Trav. Chim Pays-Bas 1939, 58, p709 or, preferably, the α-chloro compound is generated by treatment of **11.3** with butyl lithium in hexane and $Me_2N(CH_2)_2OLi$ followed by addition of a chloride source such as hexachloroethane, as described in Chem Commun. 2000, 11, p951. Chloride **11.4** is then converted to the thiol **11.4** as described above (Scheme **10**). Thiol **11.5** is then converted to the sulfonyl chloride **6.3** as described in Scheme **10**.

For example, bromo pyridine (Apollo) **11.6** is treated with amine **10.7** in the presence of cesium carbonate in THF or alternative solvent at reflux to give the amine **11.7.** The amine is then converted to the sulfonyl chloride **11.9** through the intermediate chloride **11.8** as described in Scheme **10**. Using the above procedures, but employing, in place of the amino alkyl phosphonate **10.7,** different alkyl phosphonates **10.6,** and in place of the pyridine **11.6** different halo pyridines **11.1**, the corresponding products **6.3** are obtained.

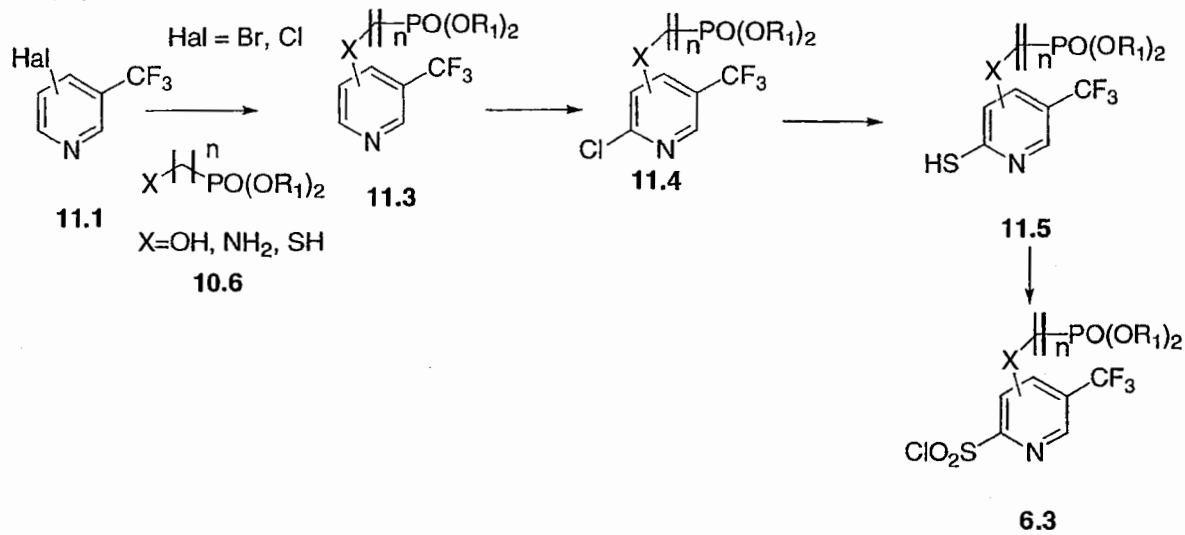
Alternatively the bromo pyridine **11.6** (Apollo) is treated with thiol **11.10,** prepared as described in Zh. Obschei. Khim 1973, 43. p2364, in the presence of cesium carbonate in THF or alternative solvent at reflux to give the thiol **11.11.** The thiol is then converted to the sulfonyl chloride **11.12** as described above for the conversion of **11.7** into **11.9**. Using the above procedures, but employing, in place of the thiol alkyl phosphonate **11.10,** different alkyl phosphonates **10.6,** and in place of the pyridine **11.6** different halo pyridines **11.1**, the corresponding products **6.3** are obtained.

Scheme **12** illustrates compounds of type **6.3** in which the phosphonate is attached through an unsaturated or saturated carbon linker. In this procedure, pyridyl bromo compound **11.1** is treated under a palladium catalyzed Heck coupling conditions with the alkene **12.1** to give the

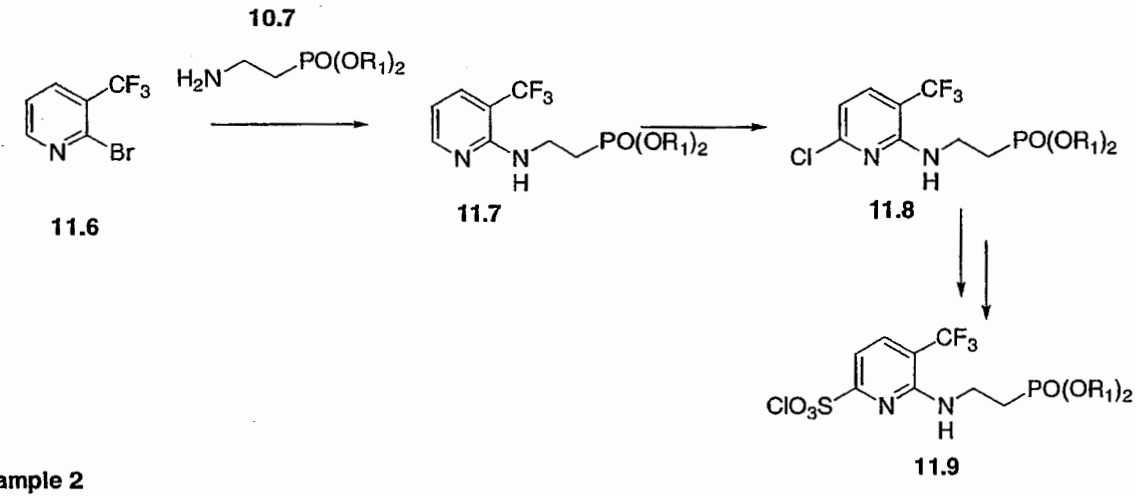
coupled alkene **12.2**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxane, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **12.2**. Optionally, the product **12.2** can be reduced to afford the saturated phosphonate **12.4**. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, and chemical reduction, the latter for example employing diborane or diimide. Following the Heck reaction or reduction the pyridyl compounds **12.2** and **12.4** are converted to the sulfonyl chlorides **12.3** and **12.5** respectively, using the same procedures described in Scheme 11 for the conversion of **11.3** into **6.3**

For example, pyridine **11.6** (Aldrich) is reacted with a dialkyl propenyl phosphonate **12.6**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of bis(triphenylphosphine) palladium(II) chloride , as described in J. Med. Chem., 1992, 35, 1371, to afford the coupled product **12.7.** The product **12.7** is then reduced, for example by reaction with diimide, as described in J. Org. Chem., 30, 3965, 1965, to afford the saturated product **12.9.** Conversion of the products **12.7** and **12.9** into the sulfonyl chlorides **12.8** and **12.10** respectively follows the same procedures described above for the conversion of pyridine **11.7** into **11.9.** Using the above procedures, but employing, in place of the halo pyridine compound **11.6**, different pyridines **11.1**, and/or different phosphonates **12.1** in place of **12.6,** the corresponding products **12.3** and **12.5** are obtained.

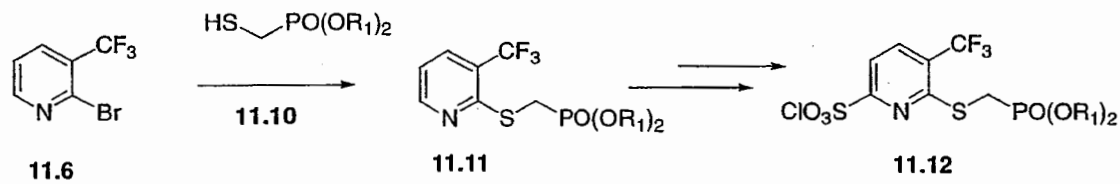
Scheme 11



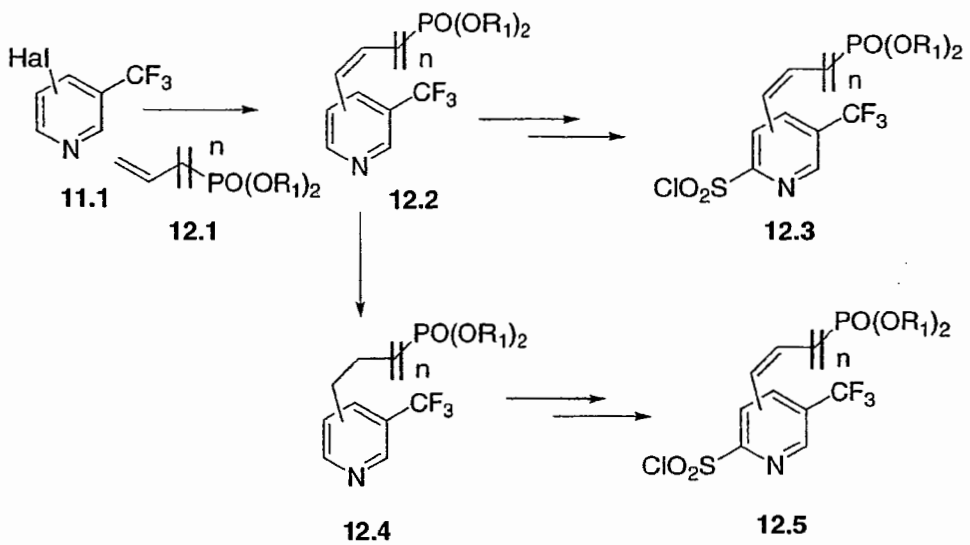
Example 1



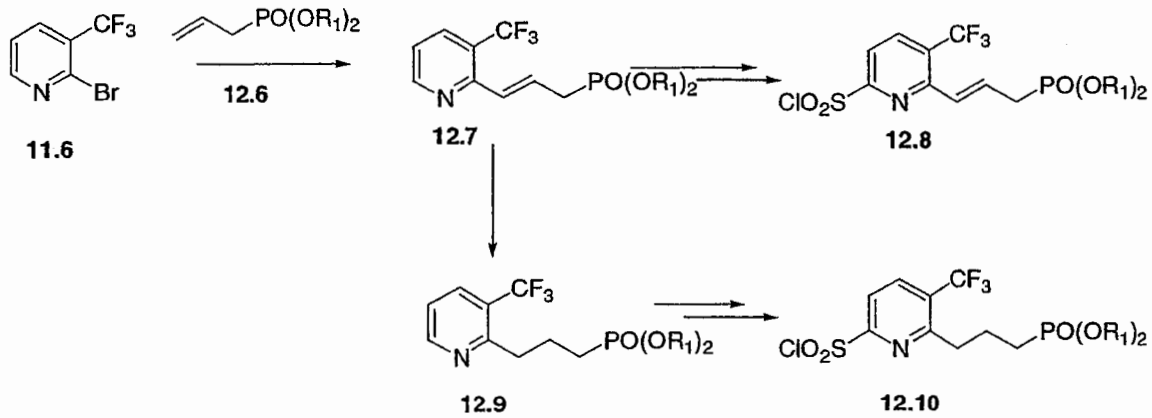
Example 2



Scheme 12



Example 1



Schemes **13-14** illustrate the preparation of phosphonate containing compounds **1.1** that are used in the preparation of the compounds of type **1**, chart **2.** Scheme **13** illustrates the preparation of phosphonates **1.1** in which the phosphonate is attached through a heteroatom such as S, O or N. The aryl halide **13.1** bearing a hydroxyl, amino or thiol group, is treated with one equivalent of the phosphonate alkylating agent **13.2**, in which Lv is a group such as mesyl, trifluoromethanesulfonyl, Br, I, Cl, tosyl etc, in the presence of base e.g. potassium or cesium carbonate in DMF, to give the compound **13.3.** The product **13.3** is then converted to the alkene **13.4** using a palladium mediated Heck coupling with Methyl acrylate as described

above, Scheme **12**. The acrylate is reduced as described in Scheme **12** and then the ester is hydrolyzed by treatment with base such as lithium or sodium hydroxide to afford the acid **1.1**.

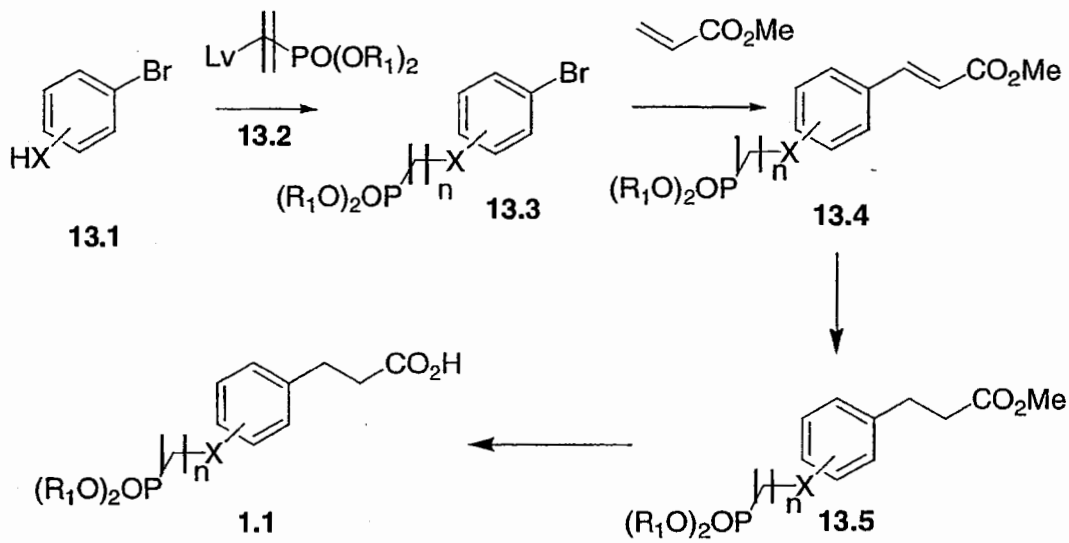
For example, the halide **13.6** (Aldrich) is treated with triflate phosphonate **13.7**, prepared as described in Tet. Lett. 1986, 27, p1497, and potassium carbonate in DMF, to give the ether **13.8.** The ether is then treated with methyl acrylate under Heck coupling conditions as described in J. Med. Chem. 1992, 35, p1371, to give the alkene **13.9**. **13.9** is reduced by treament with diimide, as described analogously in Bioorg Med. Chem. 1999, 7, p2775 to give the saturated aryl ester **13.10.** Treatment of **13.10** with lithium hydroxide in THF and water then affords the acid **13.11.** Using the above procedures, but employing, in place of the aryl halide **13.6**, different aryl halides **13.1**, and/or different phosphonates **13.2** in place of **13.7,** the corresponding products **1.1** are obtained.

Scheme **14** illustrates the preparation of phosphonates **1.1** in which the link is through a carbon bond and a nitrogen heteroatom. The aryl halide bearing an carbonyl group is treated with one equivalent of the amino alkyl phosphonate **14.2** under reductive amination conditions to give the amine **14.3**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, 2nd edition, p. 835. In this procedure, the amine component and the aldehyde component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product **14.3**. The amine product **14.3** is then converted to the alkene **14.4** using a palladium mediated Heck coupling with Methyl acrylate as described above, Scheme **13**. The acrylate is then reduced as described in Scheme **13** to giev **14.5**, and then the ester is hydrolyzed by treatment with base such as lithium or sodium hydroxide to afford the acid **1.1**.

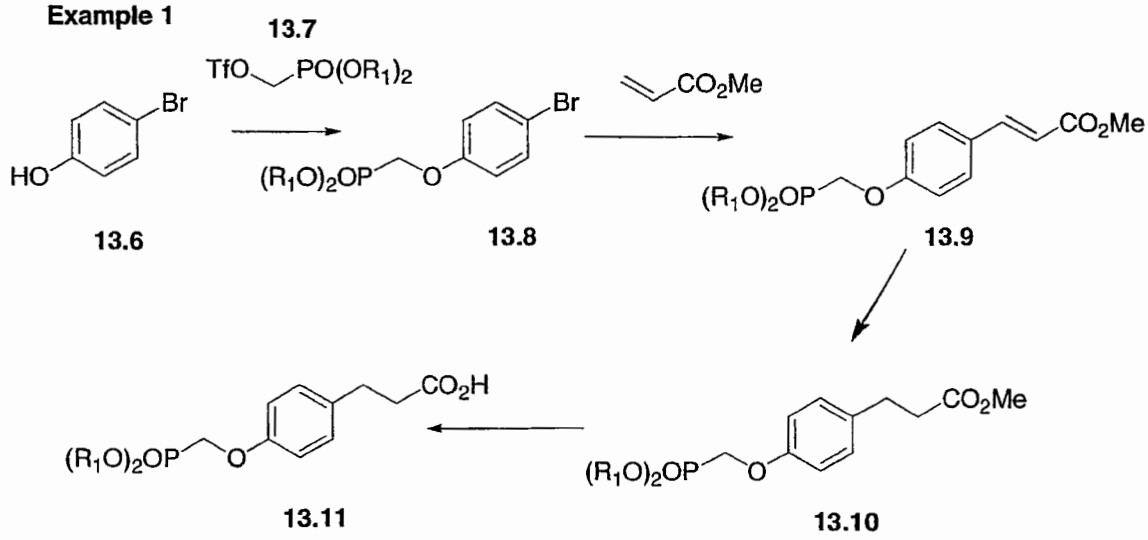
For example, the halide **14.6** (Aldrich) is treated with amino phosphonate **10.7**, prepared as described above, in methanol for 30 min. After 30 min sodium borohydride is added to give the amine **14.7.** The amine **14.7** is then treated with methyl acrylate under Heck coupling conditions as described above, to give the alkene **14.8.** Alkene **14.8** is reduced as described in Scheme **13** to give the saturated ester **14.9.** Treatment of **14.9** with lithium hydroxide in THF and water then affords the acid **14.10.** Using the above procedures, but employing, in place of

the aryl halide **14.6**, different aryl halides **14.1**, and/or different amino phosphonates **14.2** in place of **10.7**, the corresponding products **1.1** are obtained.

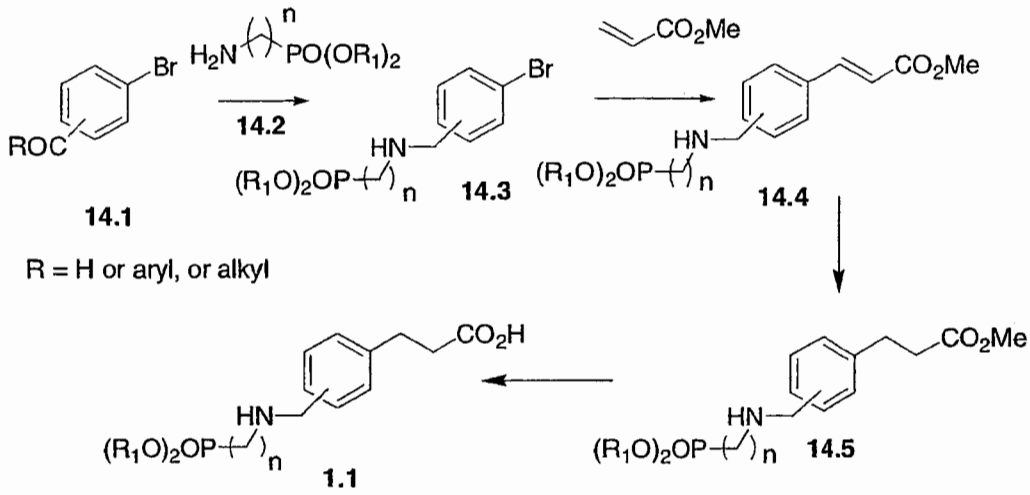
Scheme 13



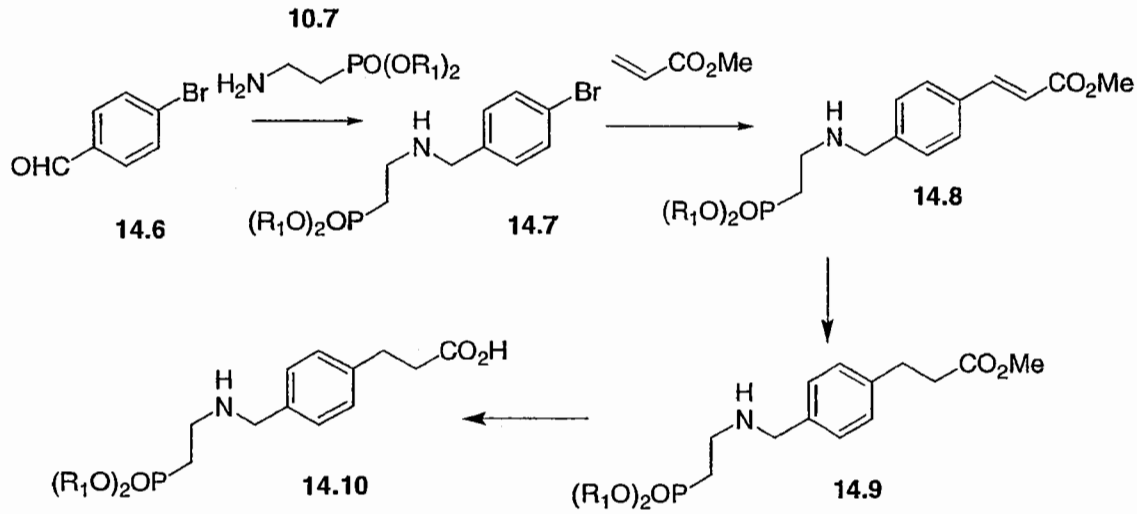
Example 1



Scheme 14



Example 1

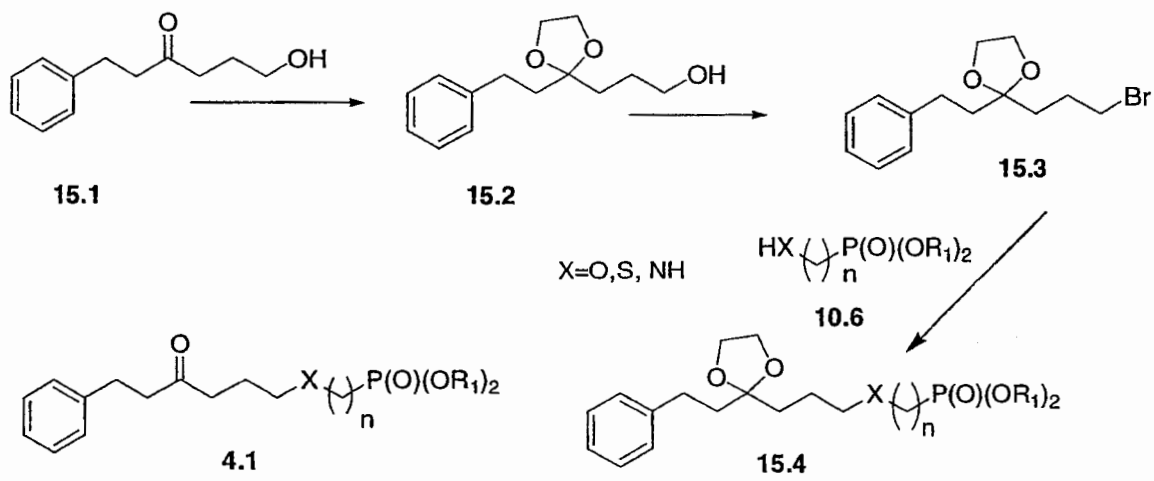


Scheme **15** describes the preparation of phosphonate-containing derivatives **4.1**which are employed in the preparation of the phosphonate ester intermediates **2**, chart **2.** The alcohol **15.1** prepared as described in J. Org Chem. 1994, 59, p3445, is treated with ethylene glycol and a catalytic amount of tosic acid in benzene at reflux to give the 1,3-dioxalone **15.2.** The dioxalone is then treated with carbon tetrabromide and triphenyl phosphine in acetonitrile, or alternate conditions as described in Comprehensive Organic Transformations, R.C. Larock, 2nd editions, p693-697, to generate the bromide **15.3.** Bromide **15.3** is then treated with the dialkyl hydroxy, thio or amino-substituted alkylphosphonate **10.6** to give the product **15.4.** The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan

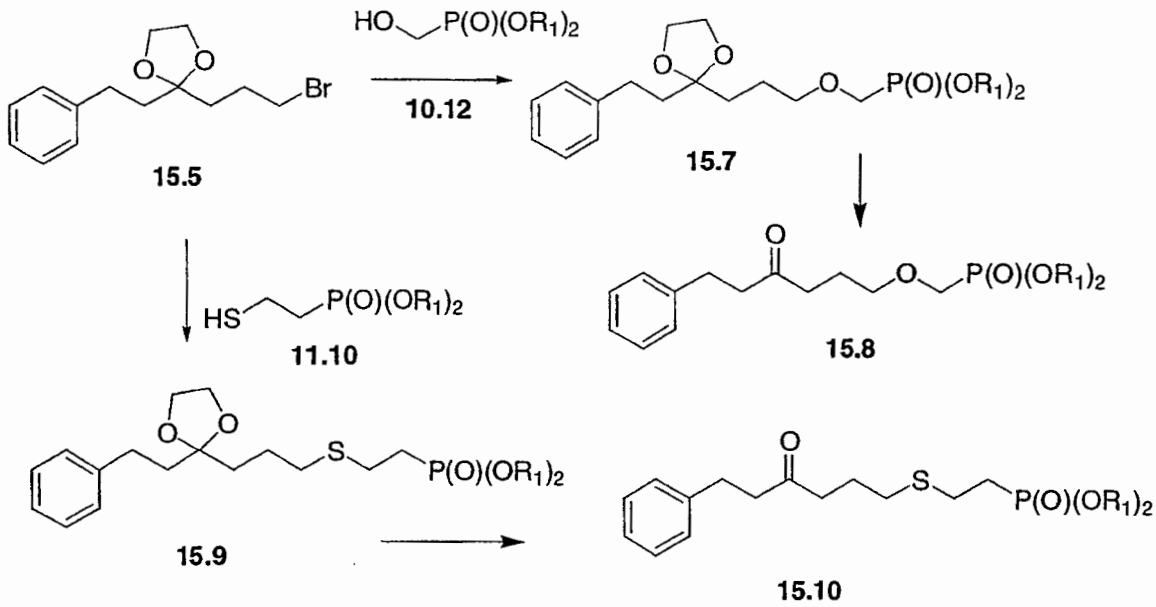
or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant **10.6**. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed. Following preparation of **15.4** the dioxalone is removed as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.317.

For example, **15.5** described above, is treated with alcohol **10.12**, prepared as described in Scheme **10**, in DMF and potassium carbonate at ca 80 °C to give the phosphonate **15.7**. Alternatively bromide **15.5** is then heated at reflux with an equimolar amount of a dialkyl 2-mercaptoethylphophonate **11.10**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990, in the presence of sodium carbonate, to afford the thioether product **15.9.** Treatment of **15.7** and **15.9** with aqueous HCl in THF then affords the ketones **15.8** and **15.10** respectively. Using the above procedures, but employing, in place of **10.12** and **11.10,** different alkyl phosphonates **10.6** the corresponding products, **4.1** are obtained.

Scheme 15



Example 1



General applicability of methods for introduction of phosphonate substituents.

The procedures described for the introduction of phosphonate moieties (Schemes **10-15**) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, for example, the methods described above for the introduction of phosphonate groups onto the pyridyl ring of **11.1**, are also applicable to the introduction of phosphonate moieties onto the aryl rings of **13.1** and **14.1**, and the reverse is also true.

Interconversions of the phosphonates between R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH) and R-link-P(O)(OH)$_2$.

The schemes above describe the preparation of phosphonates of general structure R-link-P(O)(OR^1)$_2$ in which the R^1 groups are defined as indicated in Chart **2**, and the R group refers to the scaffold. The R^1 groups attached to the phosphonate esters in Chart **2** may be changed using established chemical transformations. The interconversion reactions of the phosphonates attached through the link group to the scaffold (R) are illustrated in Scheme **16.** The interconversions may be carried out in the precursor compounds or the final products using the methods described below. The methods employed for a given phosphonate

transformation depend on the nature of the substituent R^1 . The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **16.1** into the corresponding phosphonate monoester **16.2** (Scheme **16**, Reaction 1) can be accomplished by a number of methods. For example, the ester **16.1** in which $R^1$is an aralkyl group such as benzyl, can be converted into the monoester compound **16.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester **16.1** in which $R^1$is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **16.2** can be effected by treatment of the ester **16.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **16.2** in which one of the groups $R^1$is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **16.2** in which $R^1$is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups $R^1$are alkenyl, such as allyl, can be converted into the monoester **16.2** in which $R^1$is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

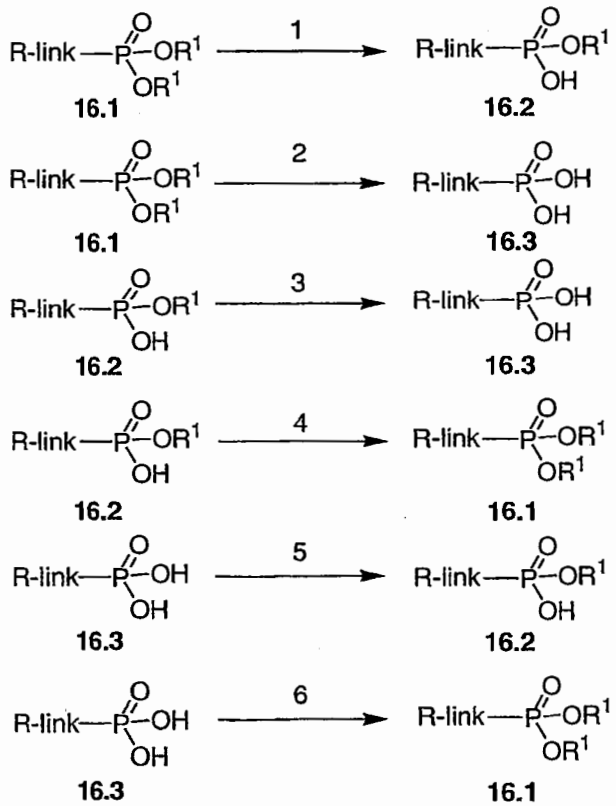
The conversion of a phosphonate diester **16.1** or a phosphonate monoester **16.2** into the corresponding phosphonic acid **16.3** (Scheme **16**, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **16.2** in which $R^1$is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **16.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **16.2** in which $R^1$is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **16.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous

ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **16.1** in which $R^1$is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **16.1** in which $R^1$is phenyl is described in J. Amer. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester **16.2** into a phosphonate diester **16.1** (Scheme **16**, Reaction 4) in which the newly introduced R^1group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **16.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine.. Alternatively, the conversion of the phosphonate monoester **16.1** to the diester **16.1** can be effected by the use of the Mitsonobu reaction. The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **16.2** can be transformed into the phosphonate diester **16.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **16.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **16.1**.

A phosphonic acid R-link-P(O)$(OH)_2$ can be transformed into a phosphonate monoester RP(O)(OR^1)(OH) (Scheme **16**, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester R-link-P(O)$(OR^1)_2$ **16.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed. A phosphonic acid R-link-P(O)$(OH)_2$ **16.3** can be transformed into a phosphonate diester R-link-P(O)$(OR^1)_2$ **16.1** (Scheme **16**, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **16.3** can be transformed into phosphonic esters **16.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°. Alternatively, phosphonic acids **16.3** can be transformed into phosphonic esters **16.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **16.1**.

Scheme 16



Amprenavir-like phosphonate protease inhibitors (AMLPPI)

Preparation of the intermediate phosphonate esters 1-13.

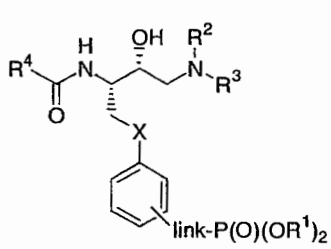
The structures of the intermediate phosphonate esters **1** to **13** and the structures of the component groups R^1, R^5, X of this invention are shown in Charts **1** - **2**. The structures of the R^2NH_2 components are shown in Chart **3**; the structures of the R^3-Cl components are shown in Chart **4**; the structures of the R_4COOH groups are shown in Chart **5a-c**; and the structures of the $R^9CH_2NH_2$ amine components are illustrated in Chart **6**.

Specific stereoisomers of some of the structures are shown in Charts **1** - **6**; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **13**. Subsequent chemical modifications to the compounds **1** to **10**, as described herein, permit the synthesis of the final compounds of this invention.

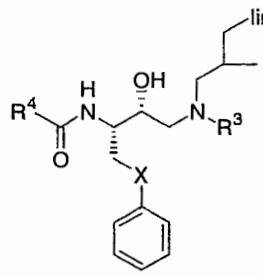
The intermediate compounds **1** to **10** incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **7**, and **8** illustrate examples of the linking groups present in the structures **1** - **10**.

Schemes **1** – **99** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1** - **10**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **11, 12** and **13**, in which a phosphonate moiety is incorporated into one of the groups R^4, R^3, R^2, respectively, is also described below.

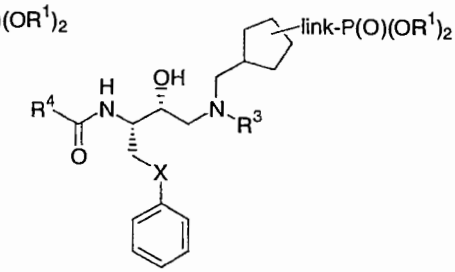
Chart 1



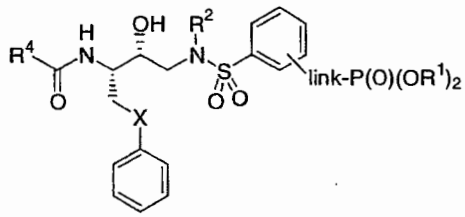
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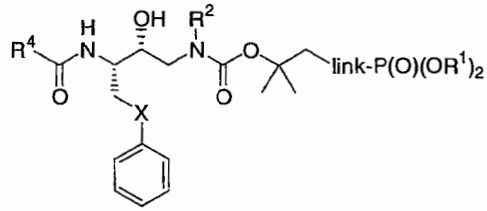
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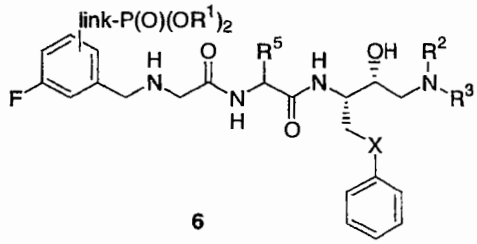
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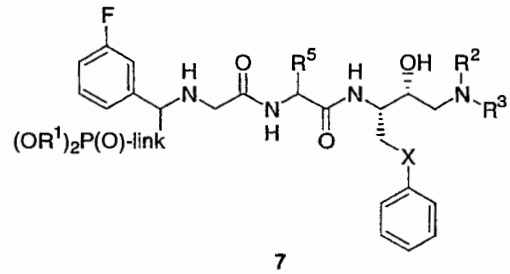
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5



6



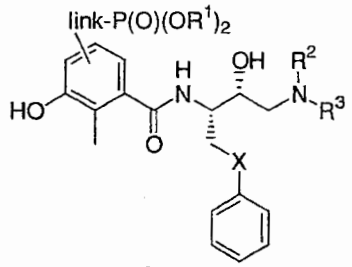
7

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

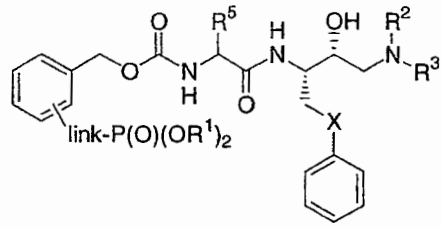
X = S or direct bond

R^5 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$, tert-butyl

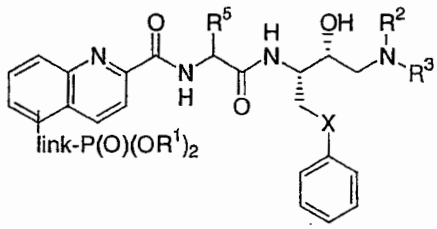
Chart 2



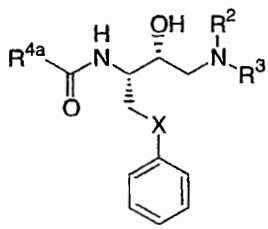
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9

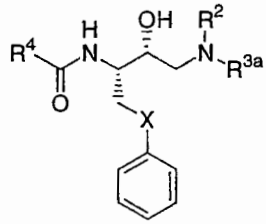


10



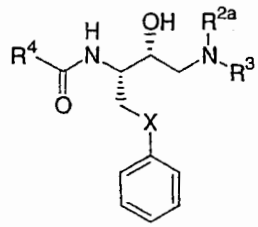
R^{4a} = phosphonate containing R^4

11



R^{3a} = phosphonate containing R^3

12



R^{2a} = phosphonate containing R^2

13

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

X = S or direct bond

R^5 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$, tert-butyl

Chart 3 Structures containing the R^2-NH_2 components

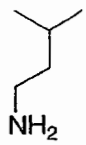
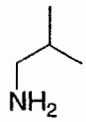
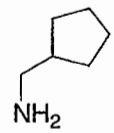




Chart 4 Structures containing the R^3-Cl components

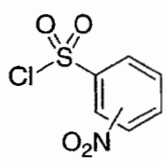
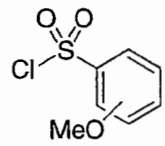
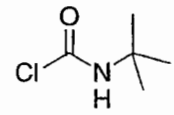
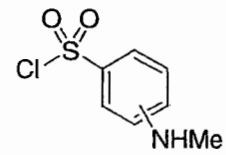
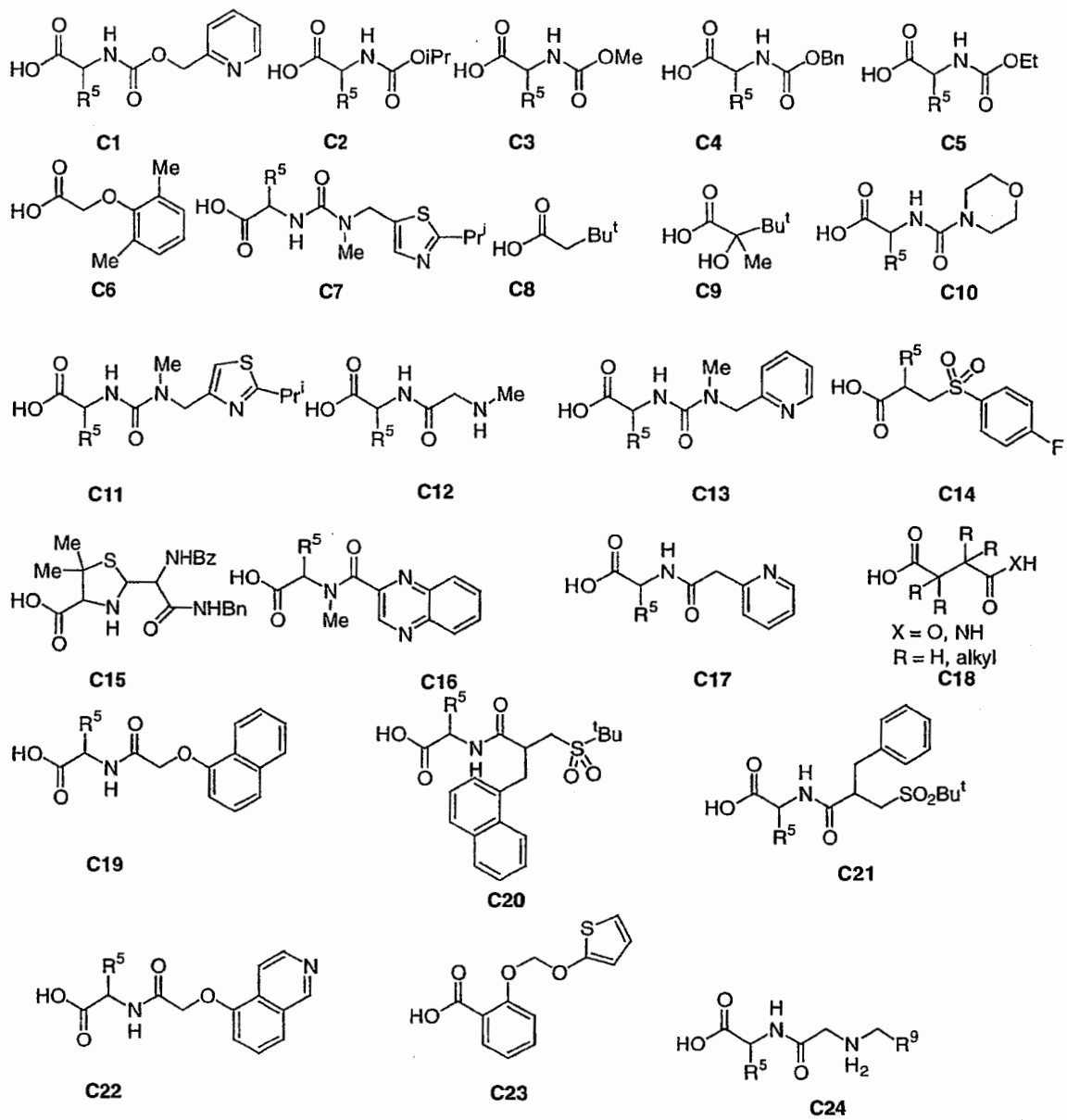
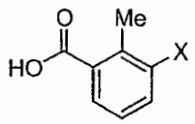





Chart 5a Structures of the R^4COOH components

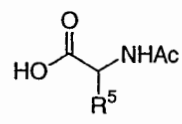


R^5 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$, tert-butyl

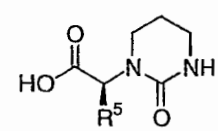
Chart 5b Structures of the R^4COOH components



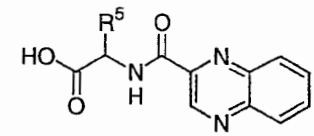
C25
X = OH, NH_2



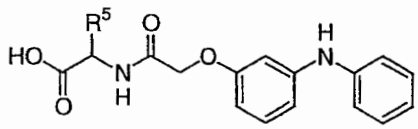
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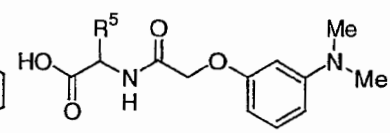
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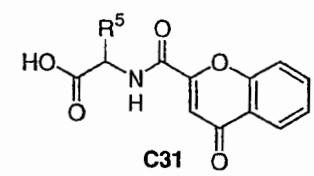
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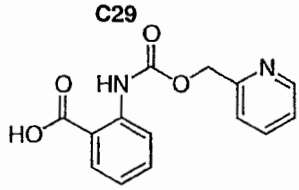
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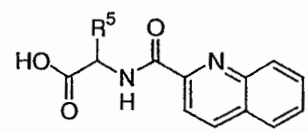
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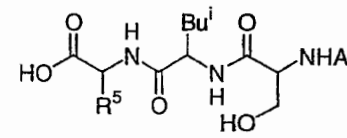
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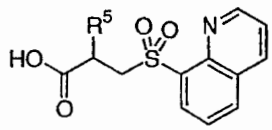
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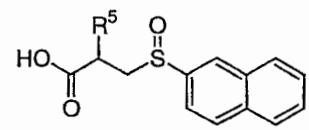
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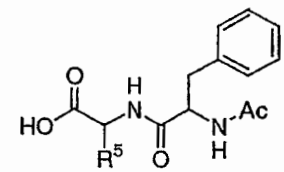
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C35



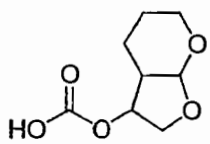
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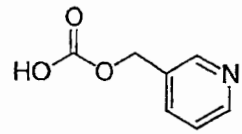
C37

R^5 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$, tert-butyl

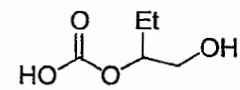
Chart 5c Structures of the R^4COOH components



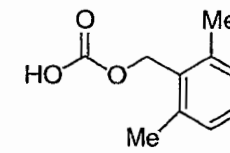
C38



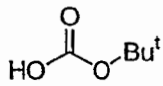
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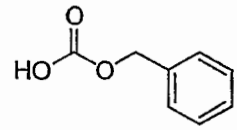
C40



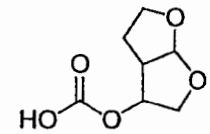
C41



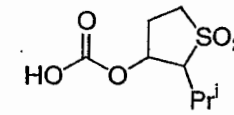
C42



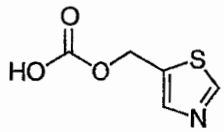
C43



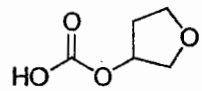
C44



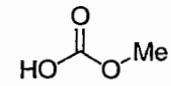
C45



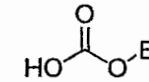
C46



C47

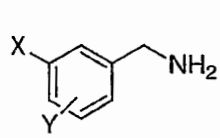


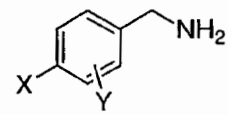
C48

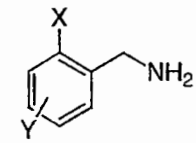


C49

Chart 6 Structures of the $R^9CH_2NH_2$ components



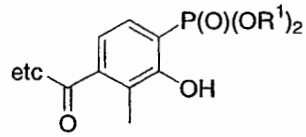


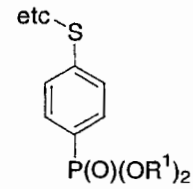


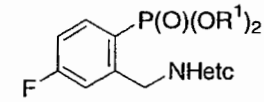
X = F, Br, Cl ; Y = H, F, Br, Cl

Chart 7

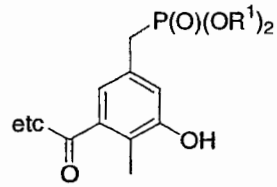
direct bond

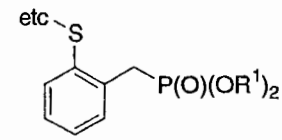




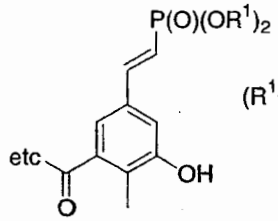


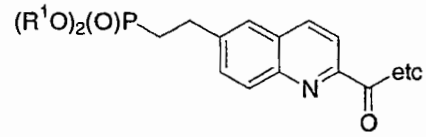
single carbon



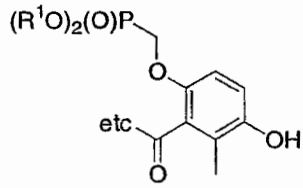


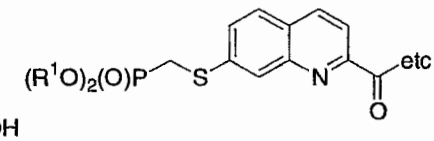
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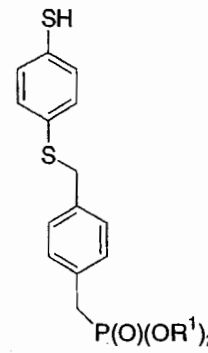


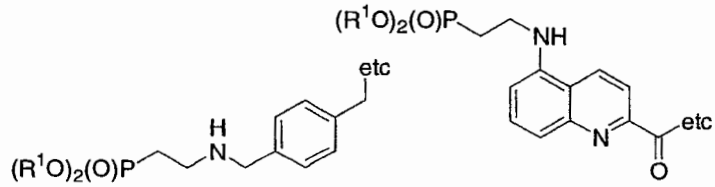


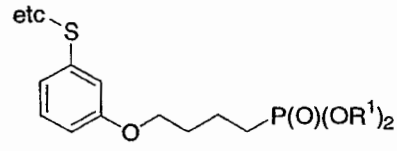
heteroatom











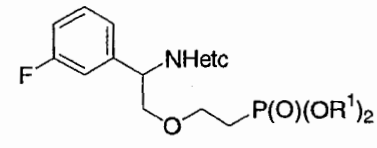
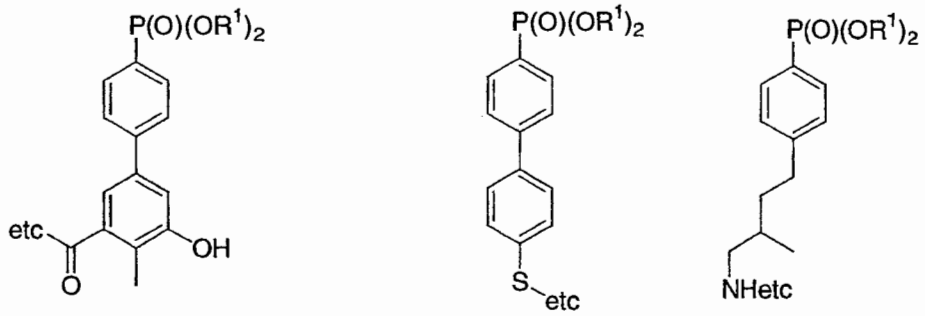
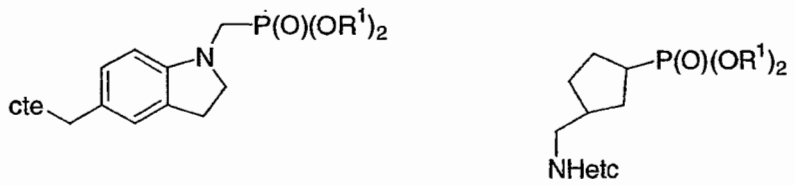


Chart 8

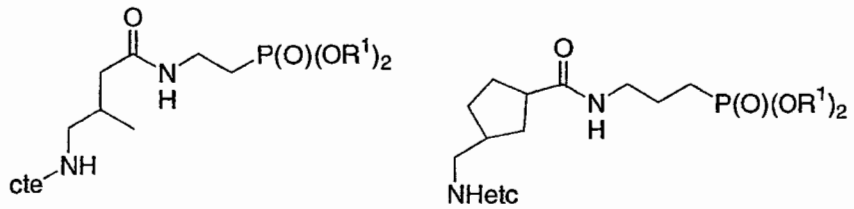
aryl

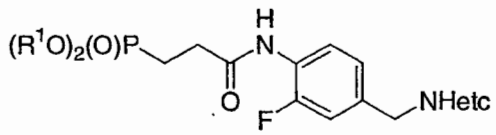


cyclized



amide





Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 or Third Edition 1999. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], etc.

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

The intermediate phosphonate esters **1**, in which the group A is attached to the aryl moiety, the R_4COOH group does not contain an secondary amine, and in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc are prepared as shown in Schemes **1-2**. The epoxide **1.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br is prepared as described in Schemes **56-59** below. Treatment of the epoxide **1.1** with the amine **1.2** affords the aminoalcohol **1.3.** The preparation of aminoalcohols by reaction between an amine and an epoxide is described, for example, in Advanced Organic Chemistry, by J. March, McGraw Hill, 1968, p 334. In a typical procedure, equimolar amounts of the reactants are combined in a polar solvent such as an alcohol or dimethylformamide and the like, at from ambient to about 100°, for from 1 to 24 hours, to afford the product **1.3**. The amino alcohol **1.3** is then treated with an acylating agent **1.4** to afford the product **1.5.** The acylating agent is typically a chloroformate or a sulfonyl chloride as shown in chart **4**. Coupling conditions for amines with sulfonyl chlorides is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 603-615 or for chloroformates, p494ff. Preferably, the amine **1.3** is treated with the sulfonyl chloride **1.4** in the presence of a base such as pyridine, potassium carbonate etc and THF / water to give the product **1.5**. Product **1.5** is deprotected using conditions described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 503ff. Preferably, the BOC amine is treated with TFA in an aprotic solvent such as THF. Conversion to the amide **1.8** is performed using standard coupling conditions between an acid **1.7** and the amine. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride or anhydride, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

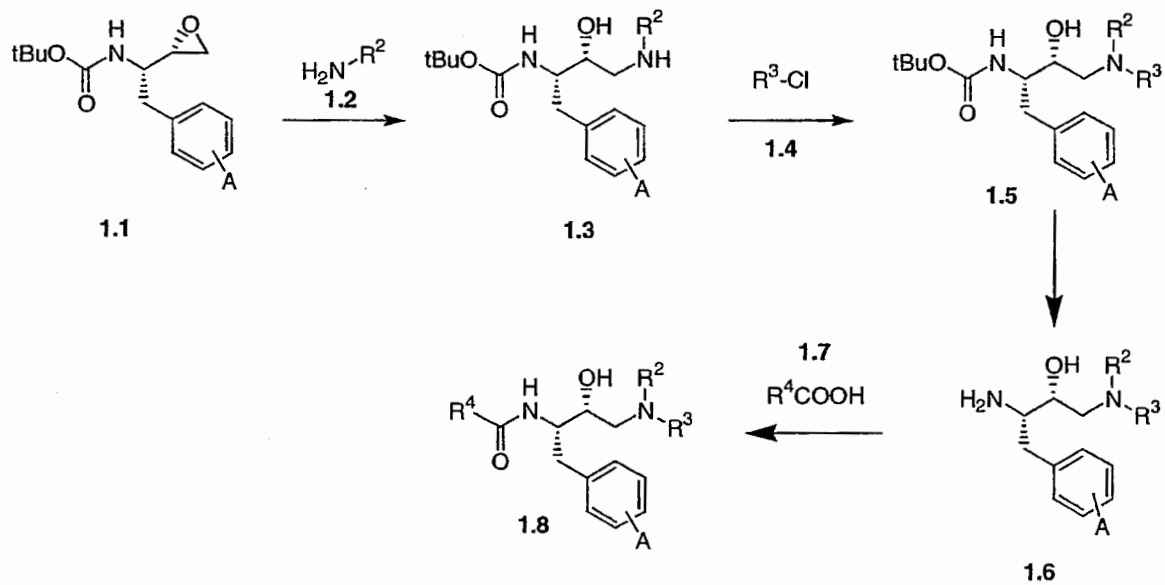
The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid **1.7** is reacted with an equimolar amount of the amine **1.6** in the presence of dicyclohexylcarbodiimide and hydroxybenztriazole, in an aprotic solvent such as, for example, tetrahydrofuran, at about ambient temperature, so as to afford the amide product **1.8.** The compound **1.8**, and analogous acylation products described below, in which the carboxylic acid R^4COOH is one of the carbonic acid derivatives **C38-C49**, as defined in Chart **5c**, are carbamates. Methods for the preparation of carbamates are described below, Scheme **98.**

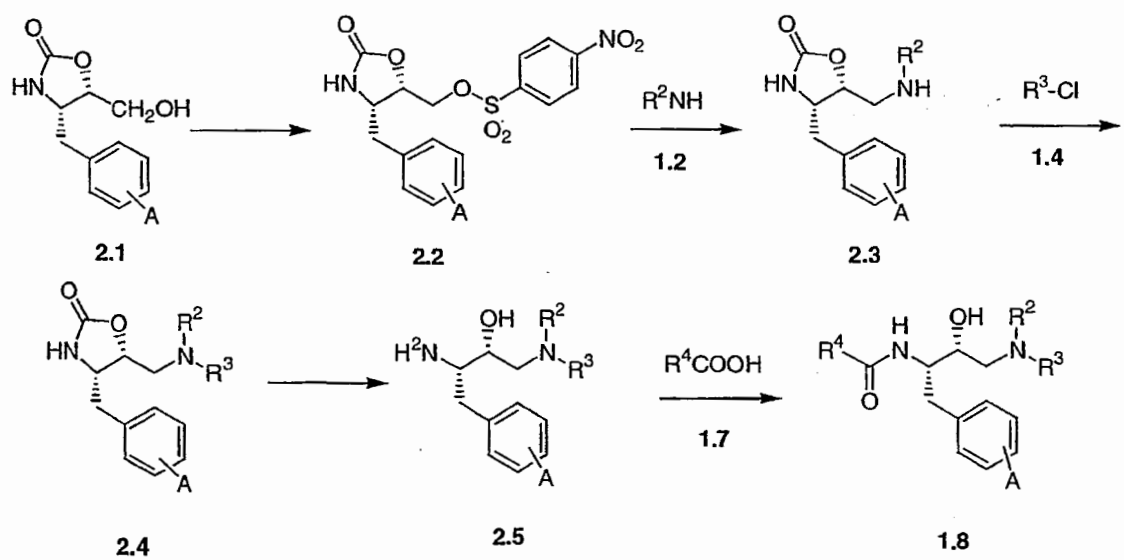
Scheme **2** illustrates an alternative method for the preparation of intermediate phosphonate esters **1**, in which the group A is attached to the aryl moiety, the R_4COOH group does not contain an secondary amine, and in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. The oxazolidinone **2.1**, prepared as described in Schemes **60-62**, is first activated as shown in **2.2** and then treated with amine **1.2** to afford the secondary amine **2.3.** The hydroxyl group can be activated by converting into a bromo derivative, for example by reaction with triphenylphosphine and carbon tetrabromide, as described in J. Am. Chem. Soc., 92, 2139, 1970, or a methanesulfonyloxy derivative, by reaction with methanesulfonyl chloride and a base, or, preferably, into the 4-nitrobenzenesulfonyloxy derivative **2.2**, by reaction in a solvent such as ethyl acetate or tetrahydrofuran, with 4-nitrobenzenesulfonyl chloride and a base such as triethylamine or N-methylmorpholine, as described in WO 9607642. The nosylate product **2.2** is then reacted with the amine component **1.2** to afford the displacement product **2.3.** Equimolar amounts of the reactants are combined in an inert solvent such as dimethylformamide, acetonitrile or acetone, optionally in the presence of an organic or inorganic base such as triethylamine or sodium carbonate, at from about 0°C to 100°C to afford the amine product **2.3.** Preferably, the reaction is performed in methyl isobutyl ketone at 80°C, in the presence of sodium carbonate, as described in WO 9607642. Treatment of the amine product **2.3** with the R3 chloride **1.4** as described in Scheme **1** then affords the product **2.4.** The oxazolidinone group present in the product **2.4** is then hydrolyzed to afford the hydroxyamine **2.5.** The hydrolysis reaction is effected in the presence of aqueous solution of a

base such as an alkali metal hydroxide, optionally in the presence of an organic co-solvent. Preferably, the oxazolidinone compound **2.4** is reacted with aqueous ethanolic sodium hydroxide at reflux temperature, as described in WO 9607642, to afford the amine **2.5**. This product is then reacted with the R^4COOH carboxylic acid or activated derivative thereof, **1.7**, to afford the product **1.8**. The amide-forming reaction is conducted under the same conditions as described above, (Scheme **1**).

Scheme 1



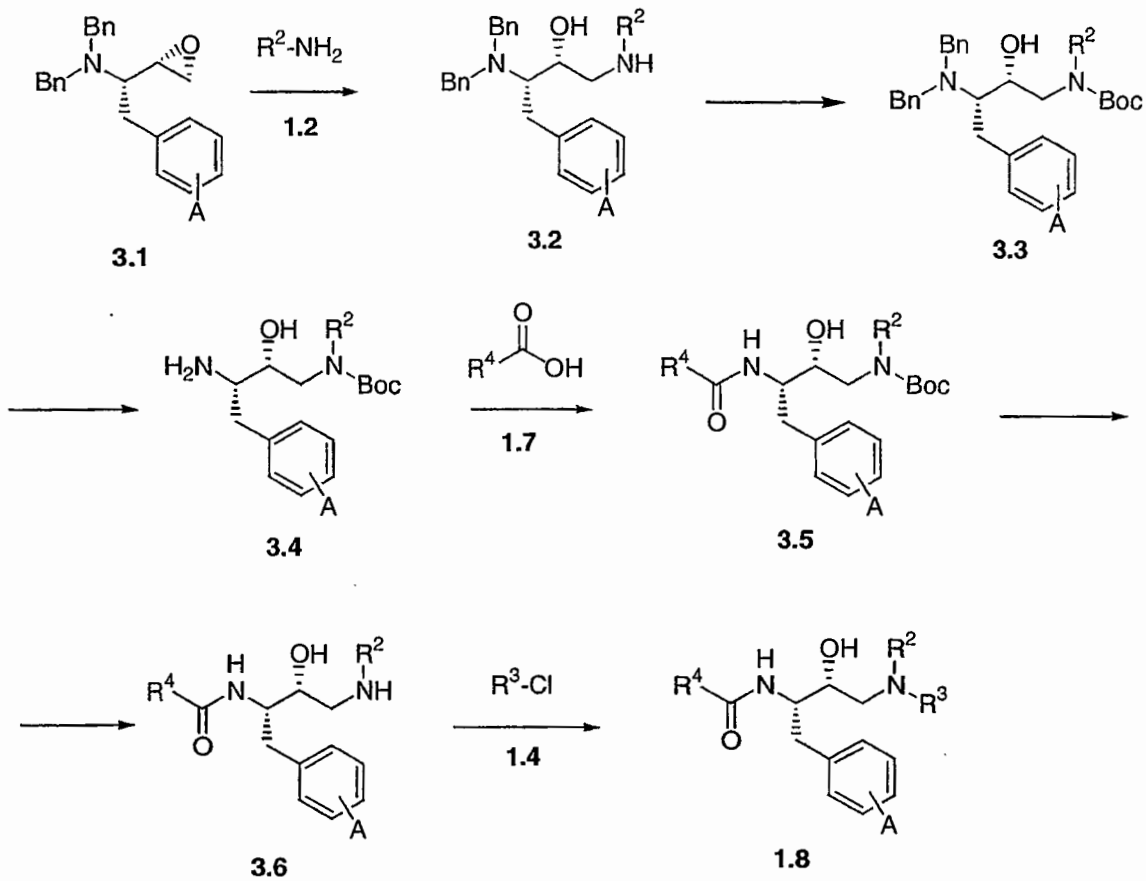
Scheme 2



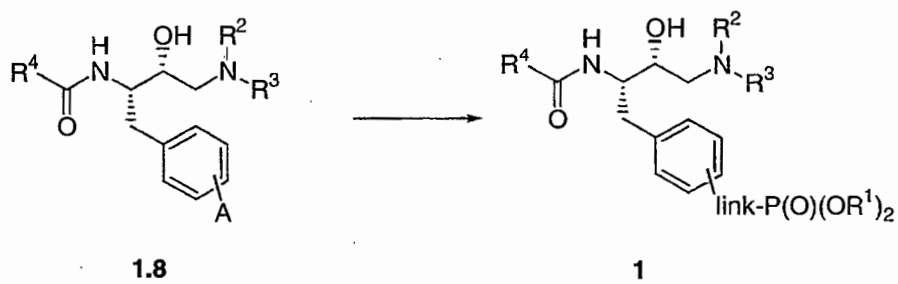
Scheme 3 illustrates the preparation of intermediate phosphonate esters **1**, in which the group A is attached to the aryl moiety, the R_4COOH group contains an secondary amine, and in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. The dibenzyl amine **3.2** is prepared from epoxide **3.1** and amine **1.2** , following the same procedures described in Scheme **1** for the preparation of **1.3**. Epoxide **3.1** is prepared as described below in Schemes **56a**. The amine **3.2** is then converted to the amine **3.4** as described inUS6391919. Preferably, the amine is first protected as the BOC carbamate and then treated with palladium hydroxide on carbon (20%) in methanol under hydrogen at high pressure to give the amine **3.4**. Treatment of **3.4** with the R_4COOH acid **1.7** which contains a secondary or primary amine, under standard amide bond forming conditions as described above, Scheme **1,** then affords the amide **3.5**. Preferably, the acid **1.7**, EDC and n-hydroxybenzotriazole in DMF is treated with the amine **3.4** to give the amide **3.5.** Removal of the BOC group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 520-525 then affords the amine **3.6.** Preferably the BOC amine **3.5** is treated with HCl in dioxane and water to give the free amine **3.6.** The amine **3.6** is then treated with an acylating agent such as an acid, chloroformate or sulfonyl chloride to give the final product **1.8.** Standard coupling conditions for amines with acids or sulfonyl chlorides is indicated above Scheme **1**. Preferably, the amine **3.6** is treated with nitro-sulfonyl chloride in THF and water in the presence of a base such as potassium carbonate to give the sulfonamide **1.8**.

The reactions shown in Scheme **1-3** illustrate the preparation of the compound **1.8** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **4** depicts the conversion of **1.8** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **1** in which X is a direct bond. In this procedure **1.8** is converted, using the procedures described below, Schemes **47-99**, into the compound **1**. Also, in the preceding and following Schemes, the amino substituted sulfonamide reagents are typically introduced as a nitro-sulfonamide reagents. Therefore, where appropriate, an additonal step of nitro group reduction as described in Comprehensive Organic Transformations, by R. C. Larock, 2nd Edition, 1999, p.821ff, is performed to give the final amino products.

Scheme 3



Scheme 4



Scheme **5** illustrates an alternative method for the preparation of the compound **1** in which the group A is attached to the aryl moiety, the R_4COOH group contains a primary or secondary amine and in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. The amine **3.4**, (Scheme 3) is treated with an amino acid **5.1**

under typical amide bond forming conditions to give the amide **5.2** as described above, Scheme **1**. Preferably the acid **5.1** is first treated with EDC and n-hydroxybenzotriazole in DMF and then the amine **3.4** is added in DMF followed by N-methyl morpholine to give the amide **5.2**. Reduction of the amide under the same catalytic hydrogenation conditions as described above in Scheme **3** gives the free amine **5.3**. The amine is further treated with chloroacetyl chloride to provide the chloro compound **5.4**. Preferably treatment with the chloroacetyl chloride is performed in ethyl acetate and water mixture in the presence of a base such as potassium hydrogen carbonate. The chloro compound **5.4** is treated with hydrochloric acid in dioxane and ethyl acetate to give the salt of the free amine **5.5** . The salt **5.5** is then treated with a nitro-sulfonyl chloride **1.4** in THF and water in the presence of a base such as potassium carbonate to give the sulfonamide **5.6**. Alternatively the free amine **5.5** is treated with a chloroformate **1.4** in the presence of a base such as triethylamine to afford the carbamate. Methods for the preparation of carbamates are also described below, Scheme **98.** Compound **5.6** is then treated with the amine **5.7** to give the secondary amine **5.8**. Preferably the chloride is refluxed in the presence of the amine **5.7** in THF.

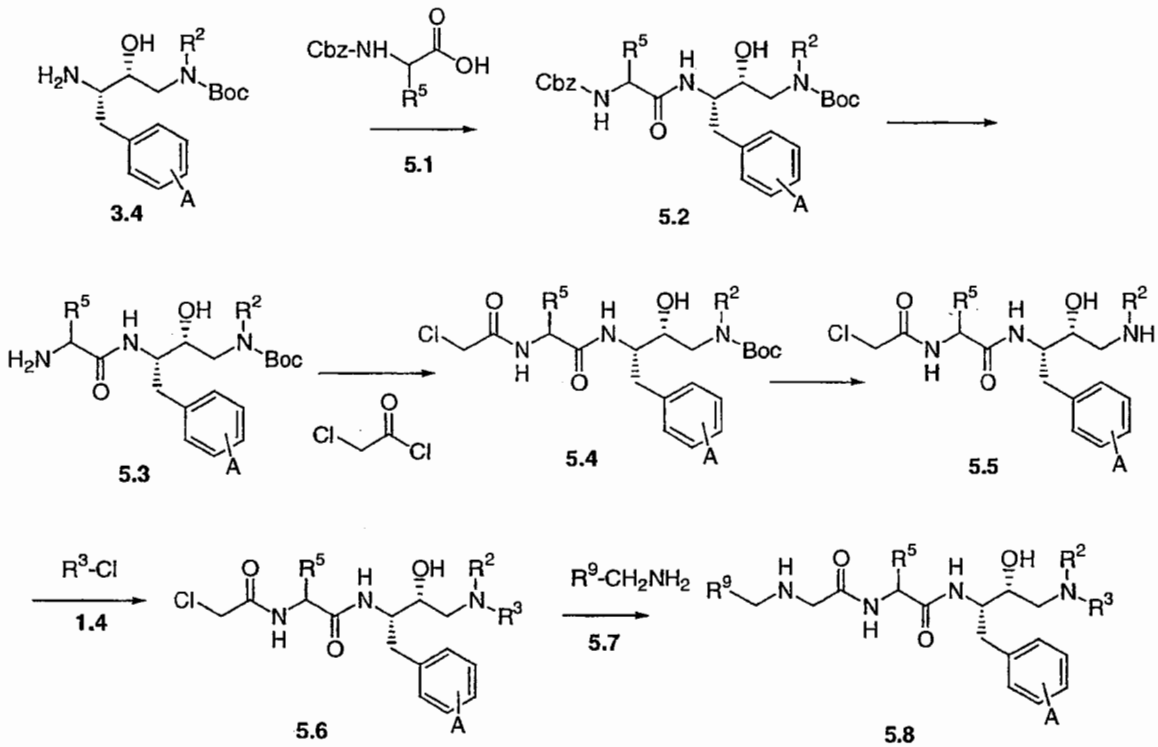
The reactions shown in Scheme **5** illustrate the preparation of the compound **5.8** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **6** depicts the conversion of **5.8** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **1** in which X is a direct bond. In this procedure **5.8** is converted, using the procedures described below, Schemes **47-99**, into the compound **1**.

In the preceding and following schemes, the conversion of various substituents into the group link-$P(O)(OR^1)_2$ can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, during the introduction of the group link-$P(O)(OR^1)_2$.

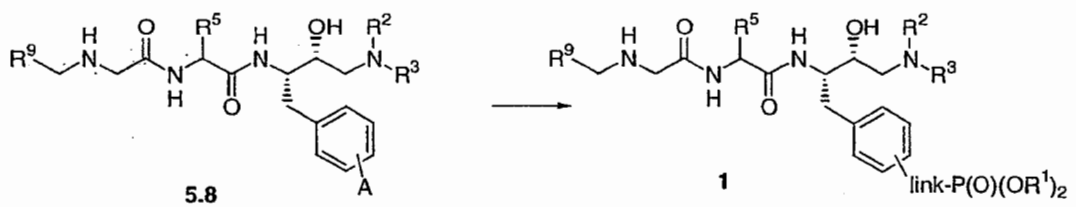
In the preceding and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical

transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme **99**).

Scheme 5



Scheme 6



Preparation of the phosphonate ester intermediates 1 in which X is a sulfur.

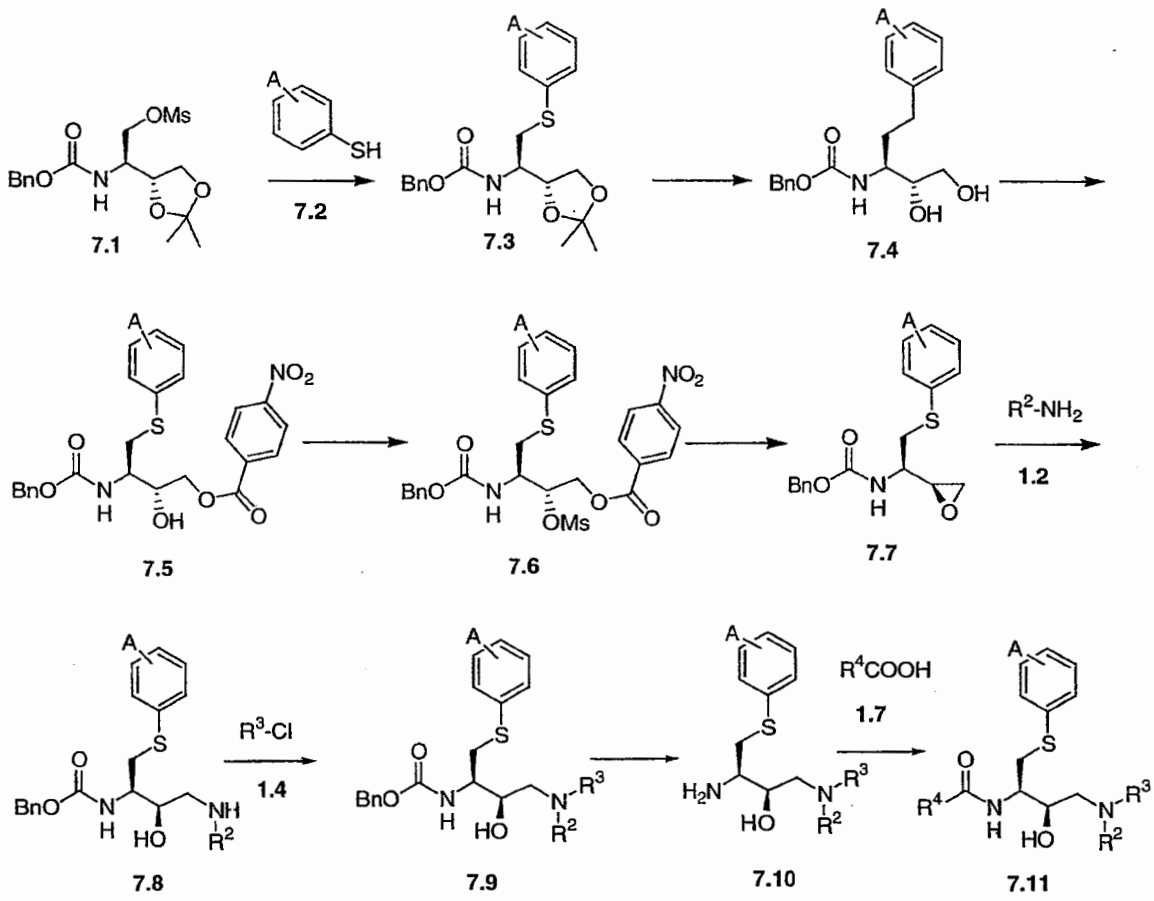
The intermediate phosphonate esters **1**, in which X is sulfur, the R_4COOH group does not contain a amine group, and in which substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, are prepared as shown in Schemes **7-9.**

Scheme 7 illustrates one method for the preparation of the compounds **1** in which the substituent X is S, and in which the group A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br etc. In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, **7.1**, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol **7.2** to afford the thioether **7.3**. The preparation of thiol **7.2** is described in Schemes **63-72**. The reaction is conducted in a suitable solvent such as, for example, pyridine, DMF and the like, in the presence of an inorganic or organic base, at from 0°C to 80°C, for from 1-12 hours, to afford the thioether **7.3**. Preferably the mesylate **7.1** is reacted with an equimolar amount of the thiol, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°C, to give the product **7.3**. The 1,3-dioxolane protecting group present in the compound **7.3** is then removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol **7.4**. Methods for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p191. For example, the 1,3-dioxolane compound **7.3** is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture. Preferably, the 1,3-dioxolane **7.3** is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°C, to yield the product **7.4**. The primary hydroxyl group of the diol **7.4** is then selectively acylated by reaction with an electron-withdrawing acyl halide such as, for example, pentafluorobenzoyl chloride or mono- or di-nitrobenzoyl chlorides. The reaction is conducted in an inert solvent such as dichloromethane and the like, in the presence of an inorganic or organic base. Preferably, equimolar amounts of the diol **7.4** and 4-nitrobenzoyl chloride are reacted in a solvent such as ethyl acetate, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, to afford the hydroxy ester **7.5**. The hydroxy ester is next reacted with a sulfonyl chloride such as methanesulfonyl chloride, 4-toluenesulfonyl chloride and the like, in the presence of a base, in an aprotic polar solvent at low temperature, to afford the corresponding sulfonyl ester **7.6**. Preferably, equimolar amounts of the carbinol **7.5** and methanesulfonyl chloride are reacted together in ethyl acetate containing triethylamine, at about 10°C, to yield the mesylate **7.6**. The compound **7.6** is then subjected to a hydrolysis-

cyclization reaction to afford the oxirane **7.7**. The mesylate or analogous leaving group present in **7.6** is displaced by hydroxide ion, and the carbinol thus produced, without isolation, spontaneously transforms into the oxirane **7.7** with elimination of 4-nitrobenzoate. To effect this transformation, the sulfonyl ester **7.6** is reacted with an alkali metal hydroxide or tetraalkylammonium hydroxide in an aqueous organic solvent. Preferably, the mesylate **7.6** is reacted with potassium hydroxide in aqueous dioxan at ambient temperature for about 1 hour, to afford the oxirane **7.7**.

The oxirane compound **7.7** is then subjected to regiospecific ring-opening reaction by treatment with a secondary amine **1.2**, to give the aminoalcohol **7.8**. The amine and the oxirane are reacted in a protic organic solvent, optionally in the additional presence of water, at 0°C to 100°C, and in the presence of an inorganic base, for 1 to 12 hours, to give the product **7.8**. Preferably, equimolar amounts of the reactants **7.7** and **1.2** are reacted in aqueous methanol at about 60°C in the presence of potassium carbonate, for about 6 hours, to afford the aminoalcohol **7.8**. The free amine is then substituted by treatment with an acid, chloroformate or sulfonyl chloride as described above in Scheme **1** to give the amine **7.9**. The carbobenzyloxy (cbz) protecting group in the product **7.9** is removed to afford the free amine **7.10**. Methods for removal of cbz groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition, p. 335. The methods include catalytic hydrogenation and acidic or basic hydrolysis. For example, the cbz-protected amine **7.9** is reacted with an alkali metal or alkaline earth hydroxide in an aqueous organic or alcoholic solvent, to yield the free amine **7.10**. Preferably, the cbz group is removed by the reaction of **7.9** with potassium hydroxide in an alcohol such as isopropanol at ca. 60°C to afford the amine **7.10**. The amine **7.10** so obtained is next acylated with a carboxylic acid or activated derivative **1.7**, using the conditions described above in Scheme **1** to afford the product **7.11**

Scheme 7



Scheme **8** illustrates an alternative preparation of the compounds **1** in which the substituent X is S, and in which the group A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br etc. In this sequence, 4-amino-tetrahydro-furan-3-ol, **8.1**, the preparation of which is described in Tet. Lett., 2000, 41, 7017, is reacted with a carboxylic acid or activated derivative thereof, R^4COOH, **1.7**, using the conditions described above for in Scheme **1** for the preparation of amides, to afford the amide **8.2**. The amide product **8.2** is then transformed, using the sequence of reactions shown in Scheme **8**, into the isoxazoline compound **8.5**. The hydroxyl group on the tetrahydrofuran moiety in **8.2** is converted into a leaving group such as p-toluenesulfonyl or the like, by reaction with a sulfonyl chloride in an aprotic solvent such as pyridine or dichloromethane. Preferably, the hydroxy amide **8.2** is reacted with an equimolar amount of methanesulfonyl chloride in pyridine, at ambient temperature, to afford the methanesulfonyl ester **8.3**. The product **8.3**, bearing a suitable sulfonyl ester leaving group, is then subjected to acid-catalyzed rearrangement to afford the isoxazoline **8.4**. The

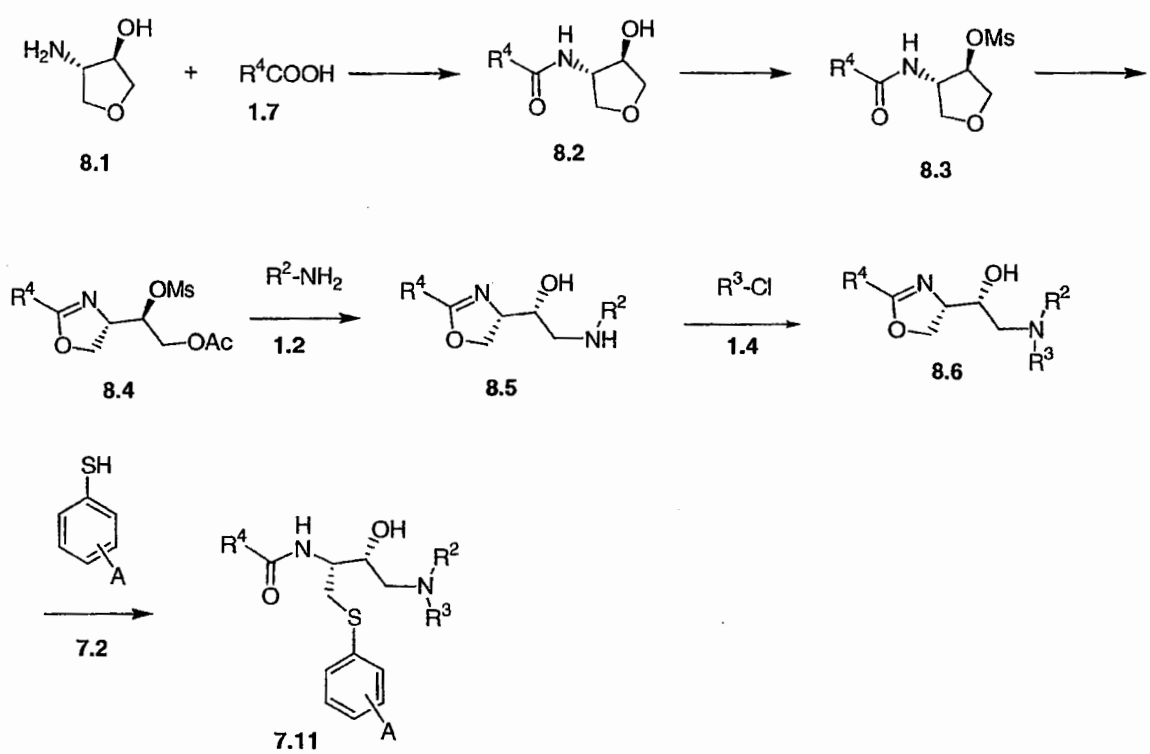
rearrangement reaction is conducted in the presence of an acylating agent such as a carboxylic anhydride, in the presence of a strong acid catalyst. Preferably, the mesylate **8.3** is dissolved in an acylating agent such as acetic anhydride at about 0°C, in the presence of about 5 mole % of a strong acid such as sulfuric acid, to afford the isoxazoline mesylate **8.4**. The leaving group, for example a mesylate group, is next subjected to a displacement reaction with an amine. The compound **8.4** is reacted with an amine **1.2**, as defined in Chart **3**, in a protic solvent such as an alcohol, in the presence of an organic or inorganic base, to yield the displacement product **8.5**. Preferably, the mesylate compound **8.4** is reacted with an equimolar amount of the amine **1.2**, in the presence of an excess of an inorganic base such as potassium carbonate, at ambient temperature, to afford the product **8.5**. The product **8.5** is then treated with R^3Cl, chart **6** as described above in Scheme **1** to afford the amine **8.6**. The compound **8.6** is then reacted with a thiol **7.2** to afford the thioether **7.11**. The reaction is conducted in a polar solvent such as DMF, pyridine or an alcohol, in the presence of a weak organic or inorganic base, to afford the product **7.11**. Preferably, the isoxazoline **8.6** is reacted, in methanol, with an equimolar amount of the thiol **7.2**, in the presence of an excess of a base such as potassium bicarbonate, at ambient temperature, to afford the thioether **7.11**.

The procedures illustrated in Scheme **7-8** depict the preparation of the compounds **7.11** in which X is S, and in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br etc, as described below. Scheme **9** illustrates the conversion of compounds **7.11** in which A is a precursor to the group link-$P(O)(OR^1)_2$ into the compounds **1** in which X=S. Procedures for the conversion of the substituent A into the group link-$P(O)(OR^1)_2$ are illustrated below, (Schemes **47 – 99**).

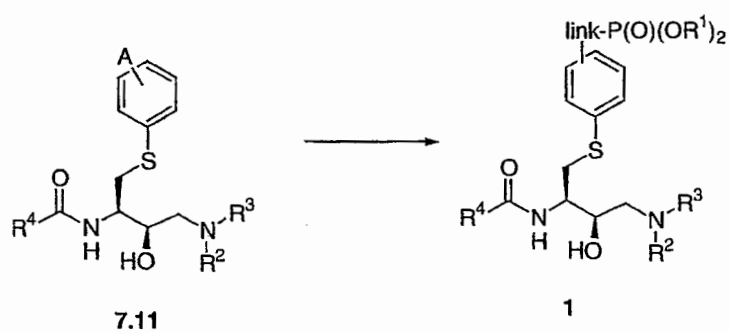
Scheme **9a-9b** depicts the preparation of phosphonate esters **1**, in which X is sulfur, the R_4COOH group does contain a amine group, and in which substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. The amine **7.10** prepared in Scheme **7** is treated with the CBZ protected amine **5.1** using the same conditions described in Scheme **5** for the preparation of **5.2** to give CBZ amine **9a.1.** Removal of the CBZ group as described in Scheme **5** to give **9a.2** followed by treatment with chloroacetyl chloride as described in Scheme **5** gives chloride **9a.3.** The chloride **9a.3** is then treated with the amine **5.7** to give the amine **9a.4** as described in Scheme **5.**

The reactions shown in Scheme **9a** illustrate the preparation of the compound **9a.4** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **9b** depicts the conversion of **9a.4** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **1** in which X is sulfur. In this procedure **9a.4** is converted, using the procedures described below, Schemes **47-99**, into the compound **1**.

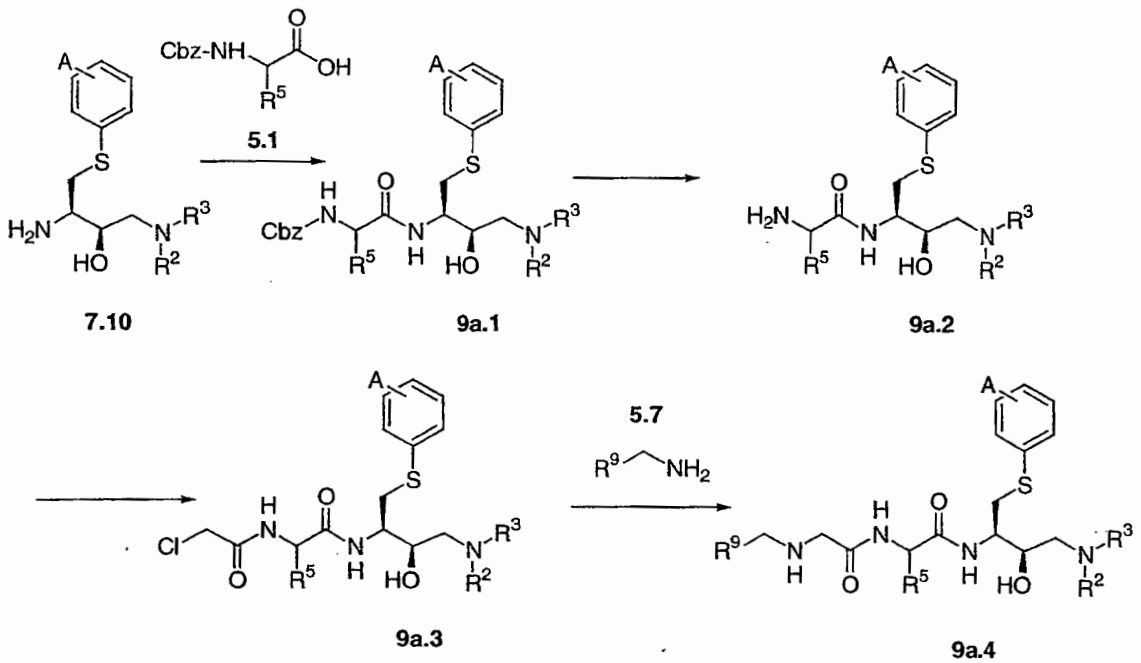
Scheme 8



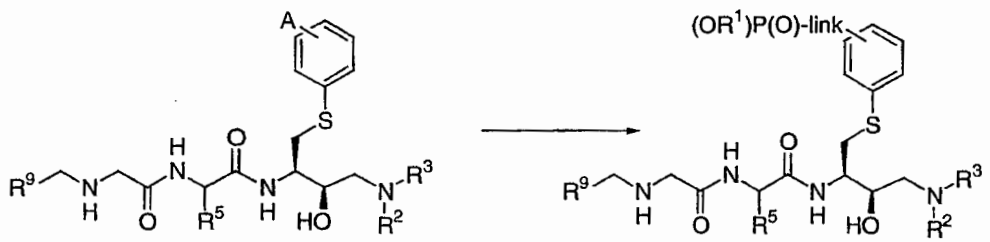
Scheme 9



Scheme 9a



Scheme 9b



Preparation of the phosphonate ester intermediates 2 and 3 in which X is a direct bond

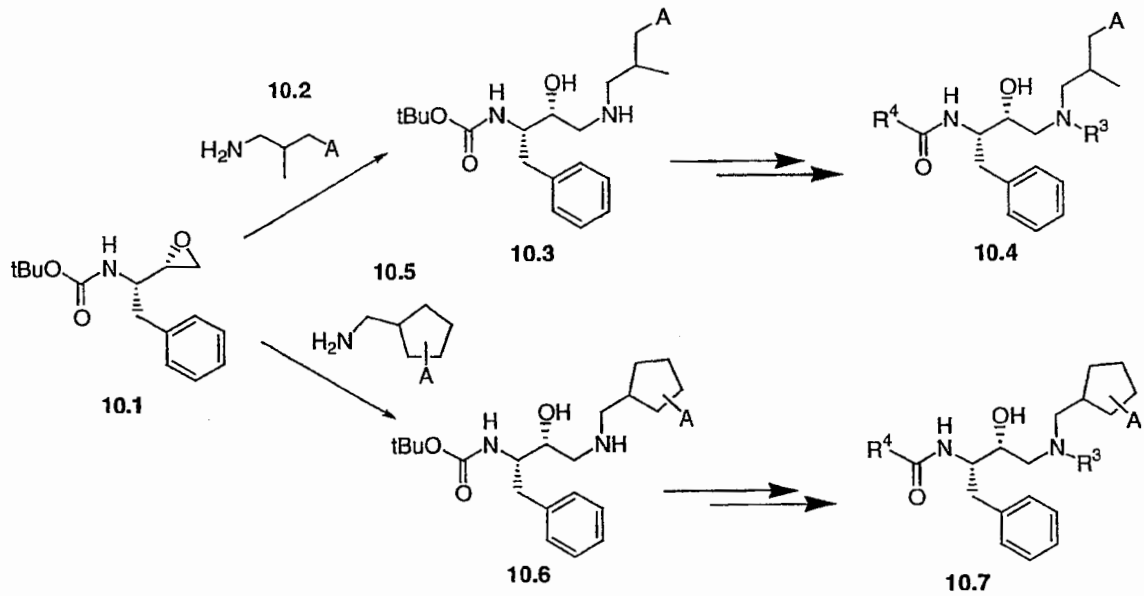
Schemes **10-12** illustrate the preparation of the phosphonate esters **2** and **3** in which X is a direct bond and the R_4COOH group does not contain a primary or secondary amine group. As shown in Scheme **10**, the epoxide **10.1,** prepared as described in J. Med. Chem 1994, 37, 1758 is reacted with the amine **10.2** or **10.5**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, to afford the amine **10.3** and **10.6** respectively. The reaction is performed under the same conditions as described

above, Scheme **1** for the preparation of the amine **1.3**. The preparation of the amines **10.2** is described in Schemes **73-75** and amines **10.5** in schemes **76-78**. The products **10.3** and **10.6** are then transformed, using the sequence of reactions described above, Scheme **1**, for the conversion of the amine **1.3** into the amide **1.8**, into the aminoamide **10.4** and **10.7** respectively.

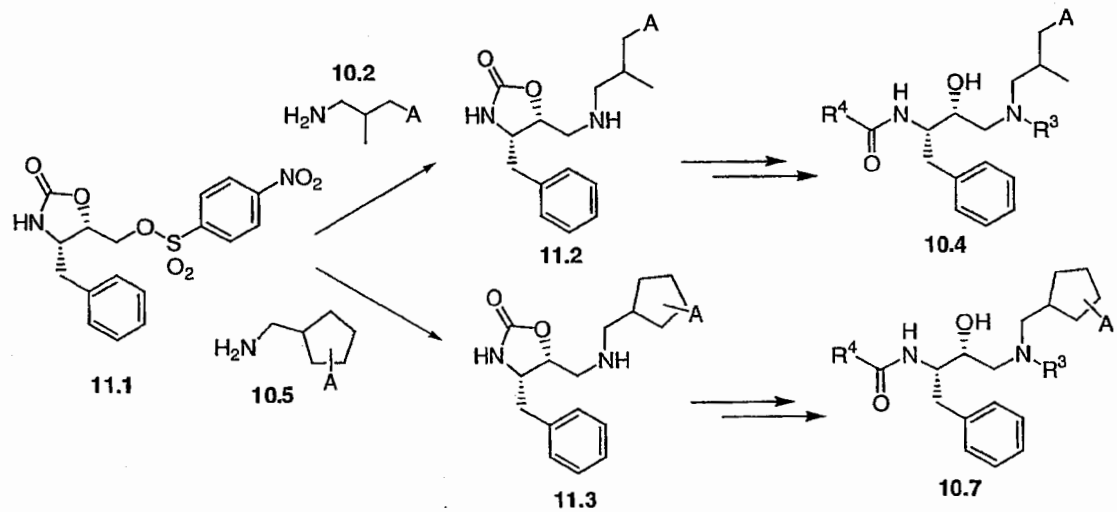
An alternative route to the amines **10.4** and **10.7** is shown in Scheme **11** in which sulfonyl ester **11.1** prepared according to Chimia 1996, 50, 532 is treated under conditions described in Scheme **2** with the amines **10.2** or **10.5** to give the amines **11.2** or **11.3** respectively. These amine products are then converted as described above, Scheme **2**, into the amides **10.4** and **10.7** respectively.

The reactions shown in Scheme **10** and **11** illustrate the preparation of the compounds **10.4** and **10.7** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **12** depicts the conversion of these compounds **10.4** and **10.7** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **2** and **3** respectively, in which X is a direct bond. In this procedure, the amines **10.4** and **10.7** are converted, using the procedures described below, Schemes **47-99**, into the compounds **2** and **3** respectively.

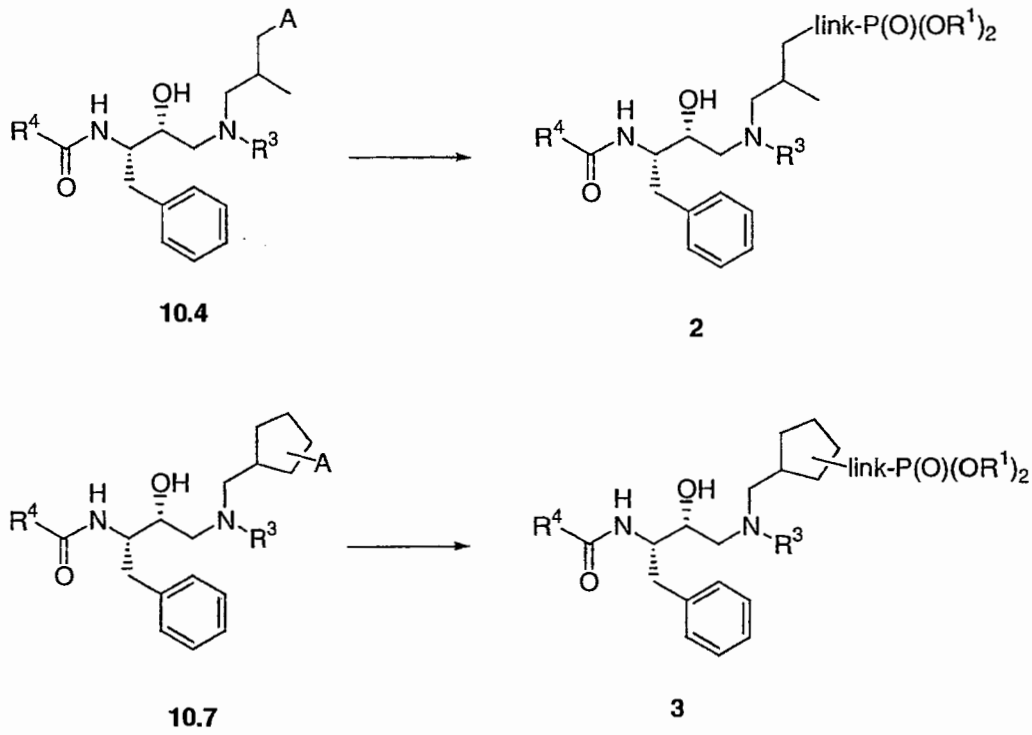
Scheme 10



Scheme 11



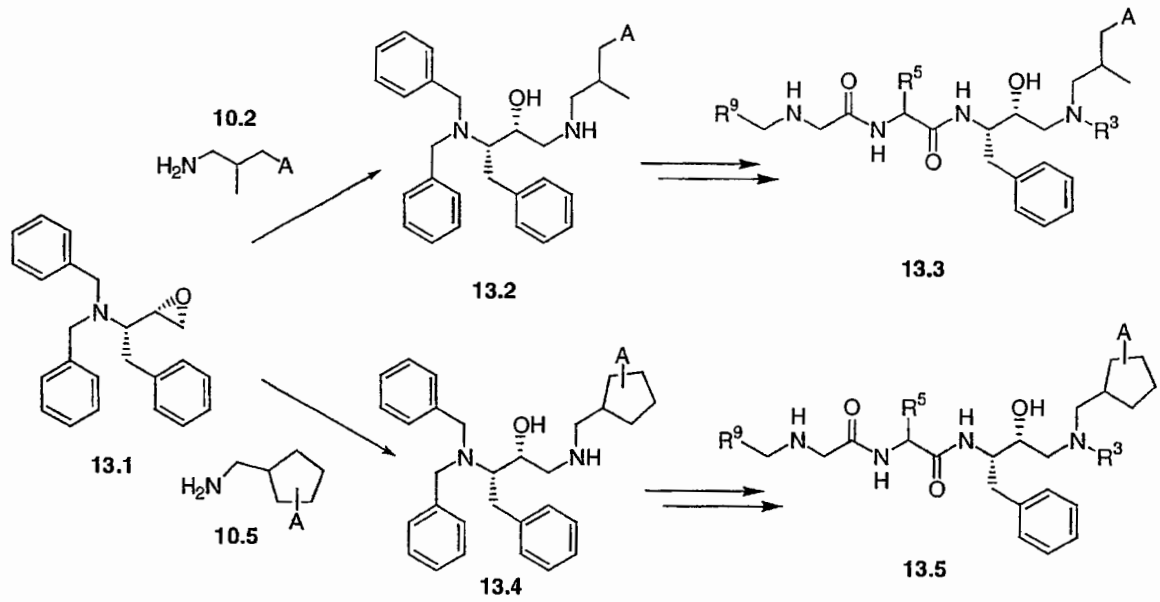
Scheme 12



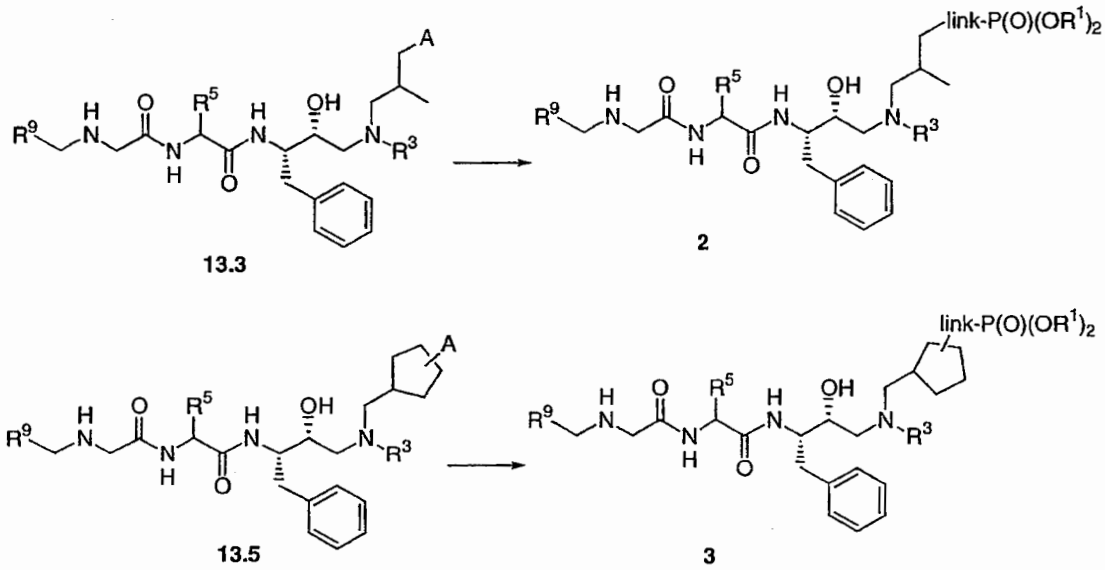
Schemes **13-14** illustrates the preparation of the phosphonate esters **2** and **3** in which X is a direct bond and the R_4COOH group contains an amine. The epoxide **13.1**, prepared as described in US 6391919B1, or J. Org. Chem. 1996, 61, 3635 is reacted, as described above, (Scheme **1**) with the amine **10.2** or **10.5**, in which substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, to give the amino alcohols **13.2** and **13.4,** respectively. These amines are then converted as described in Scheme **3** for the conversion of **3.2** into **3.4** and Scheme **5** for the conversion of **3.4** into **5.8,** into the amine products **13.3** and **13.5** respectively.

The reactions shown in Scheme **13** illustrate the preparation of the compounds **13.3** and **13.5** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **14** depicts the conversion of the compounds **13.3** and **13.5** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **2** and **3** in which X is a direct bond. In this procedure, the compounds **13.3** and **13.5** are converted, using the procedures described below, Schemes **47-99**, into the compounds **2** and **3** respectively.

Scheme 13



Scheme 14



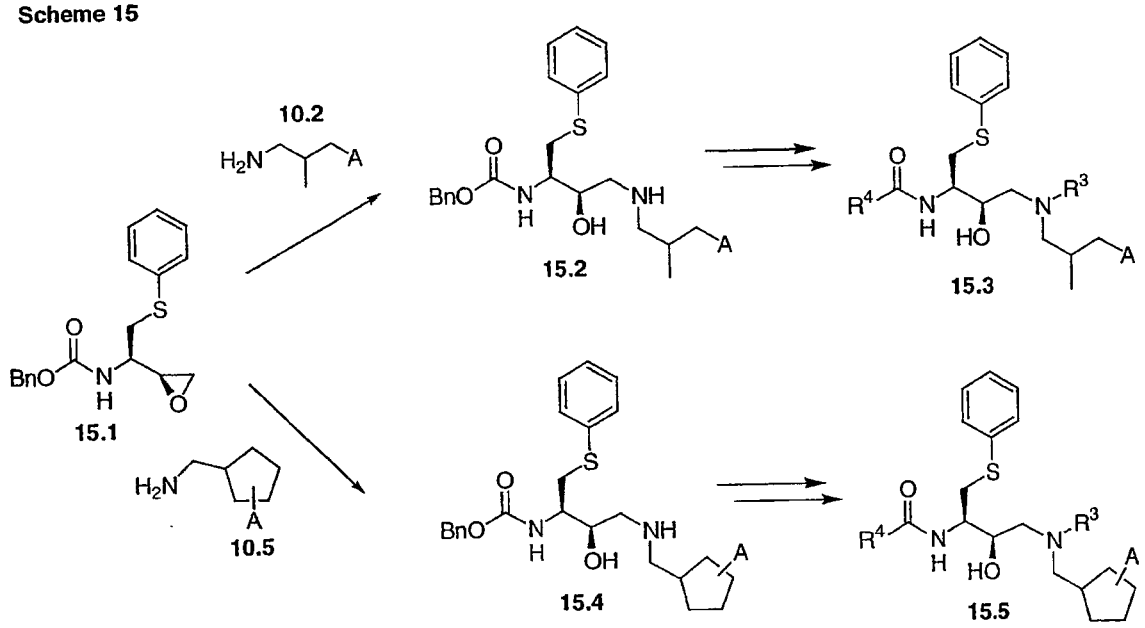
Preparation of the phosphonate ester intermediates 2 and 3 in which X is a sulfur

The intermediate phosphonate esters **2** and **3**, in which the group A is attached to a sulfur linked aryl moiety, and the R_4COOH group does not contain an amine group, are prepared as shown in Schemes **15-17**. In Scheme **15**, epoxide **15.1** is prepared from mesylate **7.1** using the conditions described in Scheme **7** for the preparation of **7.7** from **7.1**, except incorporating

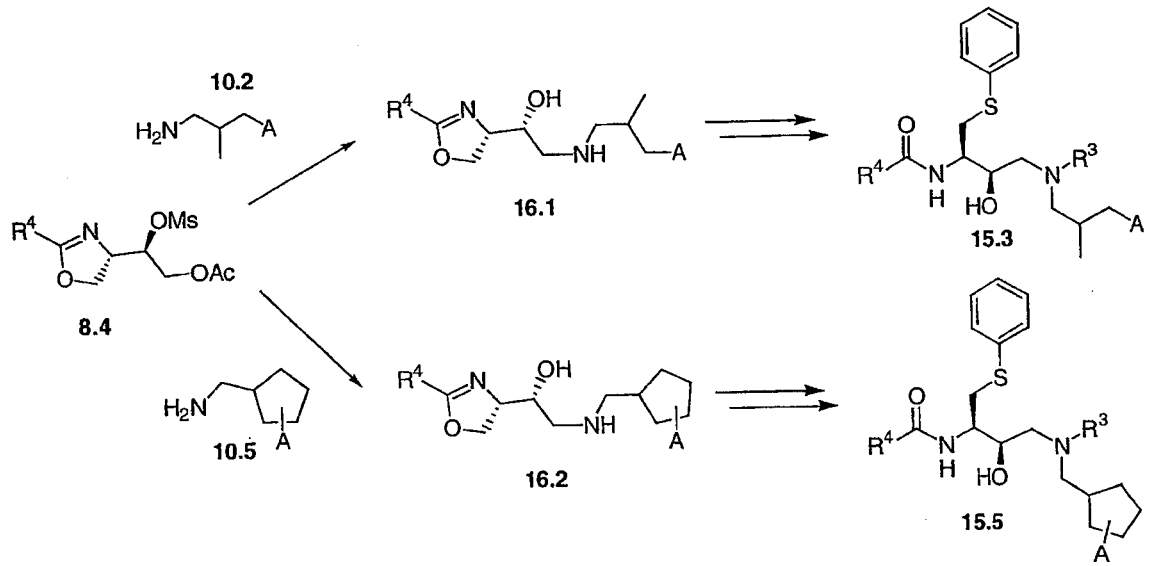
thiophenol for thiol **7.2.** The epoxide **15.1** is then treated with amine **10.2** or amine **10.5**, in which substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme **7**, to give the amines **15.2** and **15.4**. Further application of Scheme **7** on the amines **15.2** and **15.4** yields the alcohols **15.3** and **15.5** respectively. Alternatively, Scheme **16** depicts the preparation of **15.3** and **15.5** using the mesylate **8.4.** The amines **10.2** and **10.5** are reacted with mesylate **8.4** under conditions described in Scheme **8** to give amines **16.1** and **16.2** respectively. Further modification of **16.1** and **16.2** according to the conditions described in Scheme **8** then affords alcohols **15.3** and **15.5** respectively.

The reactions shown in Scheme **15-16** illustrate the preparation of the compounds **15.3** and **15.5** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **17** depicts the conversion of **15.3** and **15.5** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **2** and **3** in which X is sulfur. In this procedure **15.3** or **15.5** is converted, using the procedures described below, Schemes **47-99**, into the compound **2** and **3**.

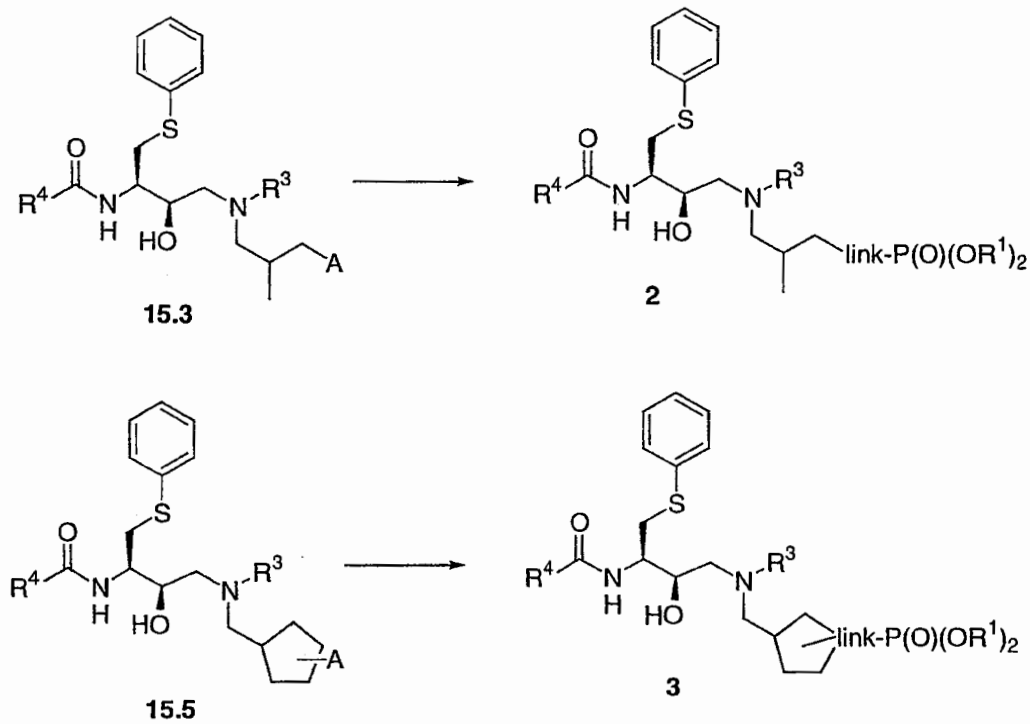
Scheme 15



Scheme 16



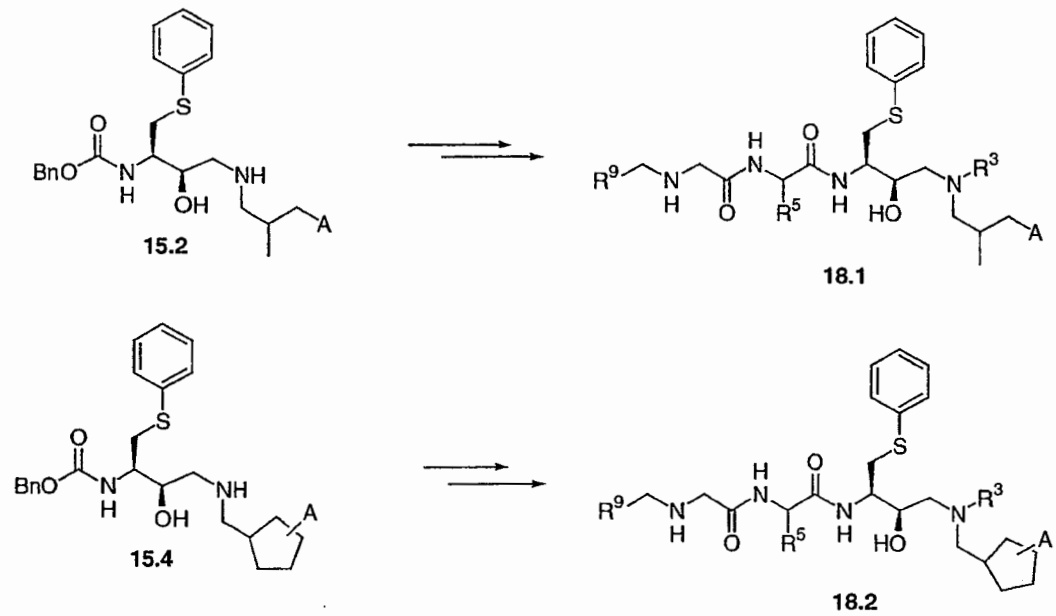
Scheme 17



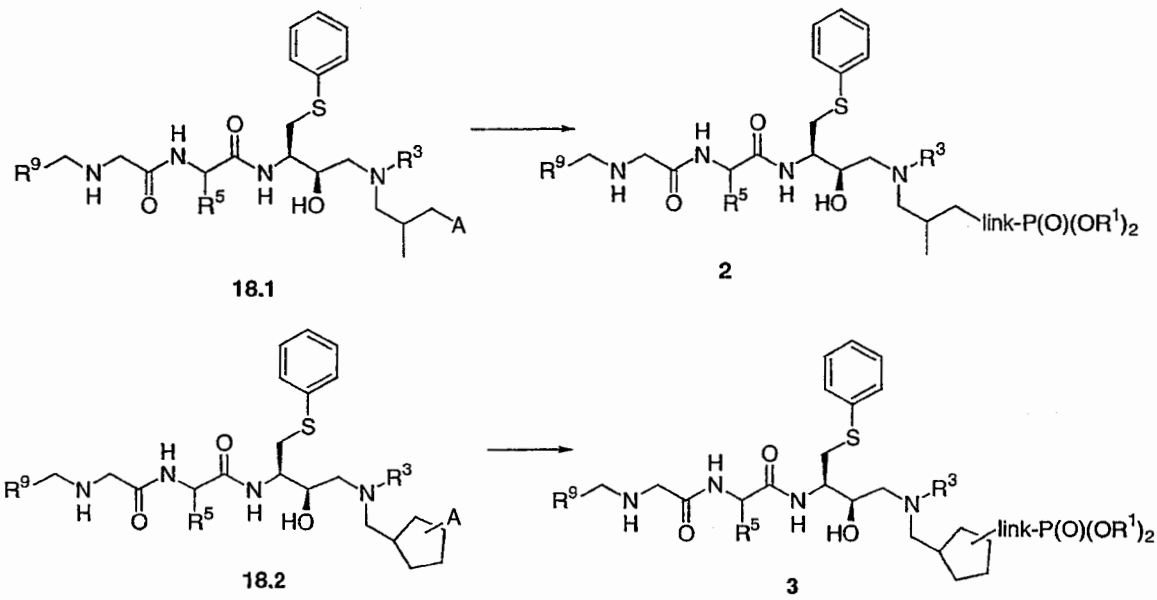
Scheme **18-19** depict the preparation of phosphonate esters **2** and **3**, in which the group A is attached to a sulfur linked aryl moiety, and the R_4COOH group contains a amine group. The amines **15.2** and **15.4,** in which substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, prepared in Scheme **15**, are converted using the same conditions described in Scheme **7** for the preparation of the amine **7.10** from **7.8** and Scheme **9a** for the preparation of **9a.4** from **7.10** to give **18.1** and **18.2** respectively.

The reactions shown in Scheme **18** illustrate the preparation of the compound **18.1** and **18.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **19** depicts the conversion of **18.1** and **18.2** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **2** and **3** respectively in which X is sulfur. In this procedure **18.1** and **18.2** are converted, using the procedures described below, Schemes **47-99**, into the compounds **2** and **3**

Scheme 18



Scheme 19



Preparation of the phosphonate ester intermediates 4 in which X is a direct bond

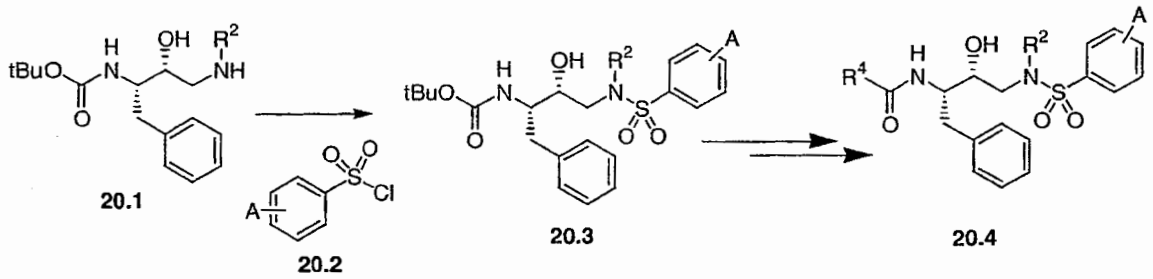
Schemes **20-22** illustrate the preparation of the phosphonate esters **4** in which X is a direct bond and the R group does not contain a primary or secondary amine group. As shown in Scheme **20**, the amine **20.1** is reacted with the sulfonyl chloride **20.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc, to

afford the product **20.3**. The reaction is performed under the same conditions as described above, Scheme **1** for the preparation of the sulfonamide **1.5**. Amine **20.1** is prepared by treatment of epoxide **10.1** with the amine **1.2** as described in Scheme **1** for the preparation of **1.3**. The preparation of sulfonyl chloride **20.2** is described in Schemes **92-97**. The product **20.3** is then transformed, using the sequence of reactions described above, Scheme **1,** for the conversion of the amide **1.5** into the amide **1.8**, into the product **20.4**.

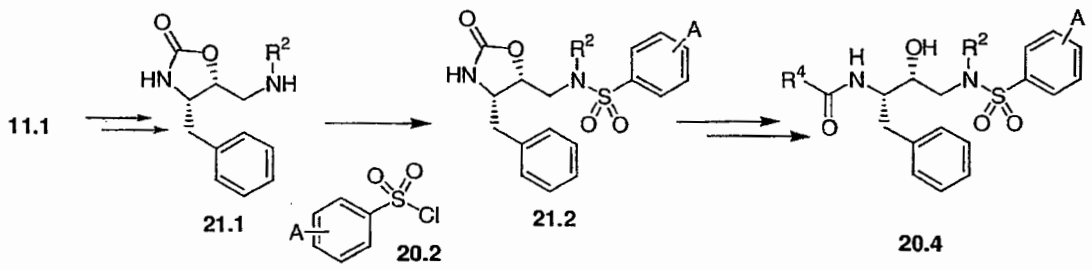
An alternative route to the product **20.4** is shown in Scheme **21** in which amine **11.1** is treated under conditions described in Scheme **2** with the amine **1.2** to give the amine **21.1.** The amine **21.1** is then sulfonylated with **20.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme **2,** to afford the product **21.2**. The product **21.2** is then converted as described above, Scheme **2,** into the sulfonamide **20.4**.

The reactions shown in Scheme **20** and **21** illustrate the preparation of the compound **20.4** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **22** depicts the conversion of this compounds **20.4** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **4** respectively, in which X is a direct bond. In this procedure, the amines **20.4** is converted, using the procedures described below, Schemes **47-99**, into the compounds **4**.

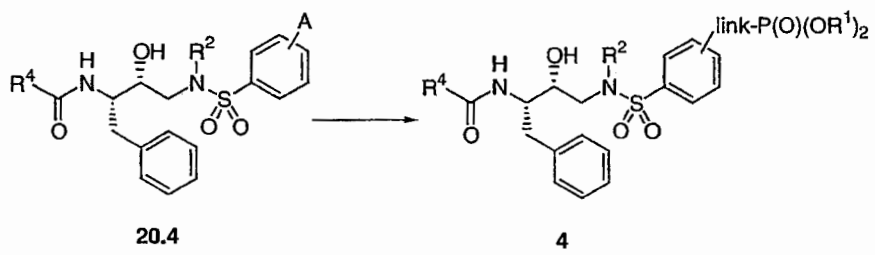
Scheme 20



Scheme 21



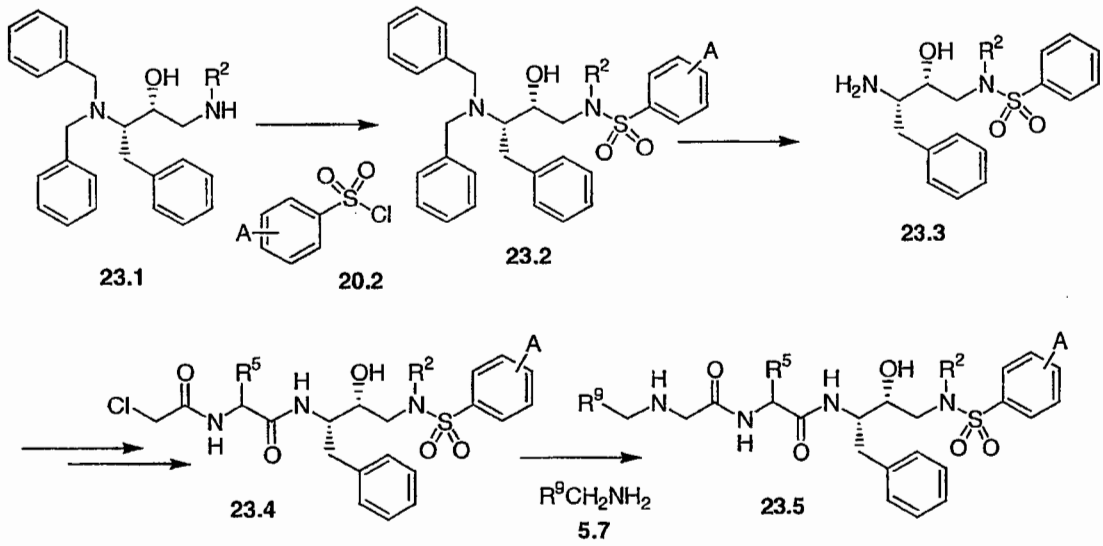
Scheme 22



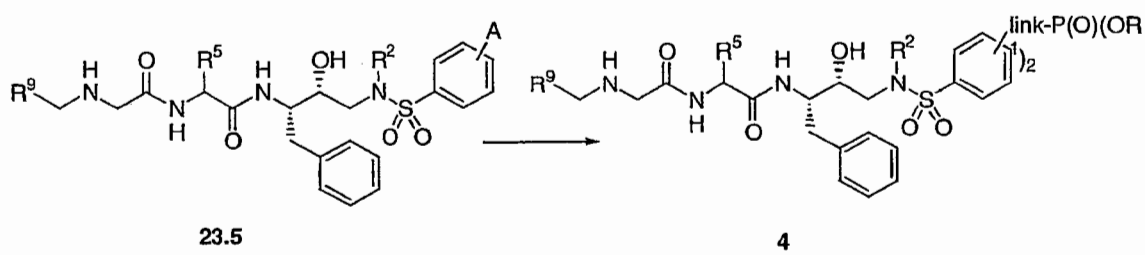
Schemes **23** illustrates the preparation of the phosphonate esters **4** in which X is a direct bond and the R_4COOH group contains an amine group. The amine **23.1**, prepared from the epoxide **13.1** and an amine **1.2** as described in Scheme **13** for the synthesis of **13.2** from **13.1,** is reacted with the sulfonyl chloride **20.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Schemes **1** for the synthesis of **1.5**, to give the product **23.2**. The product **23.2** is then reduced to amine **23.3** according to the conditions described in Scheme **3** for the preparation of **3.4** from **3.3**. The amine product is then converted as described in Scheme **5** into the chloride **23.4.** The chloride is treated with the amine **5.7** to afford the amine **23.5**, as described in Scheme **5** for the preparation of **5.8** from **5.7**.

The reactions shown in Scheme **23** illustrate the preparation of the compound **23.5** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **24** depicts the conversion of the compound **23.5** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **4** in which X is a direct bond. In this procedure, the compound **23.5** is converted, using the procedures described below, Schemes **47-99**, into the compound **4**.

Scheme 23



Scheme 24



Preparation of the phosphonate ester intermediates 4 in which X is a sulfur

The intermediate phosphonate ester **4**, in which the group A is attached to a sulfur linked aryl moiety, and the R_4COOH group does not contain an amine is prepared as shown in Schemes **25-27**. Amine **25.1** prepared from epoxide **15.1** and amine **1.2** as described in Scheme **15** is

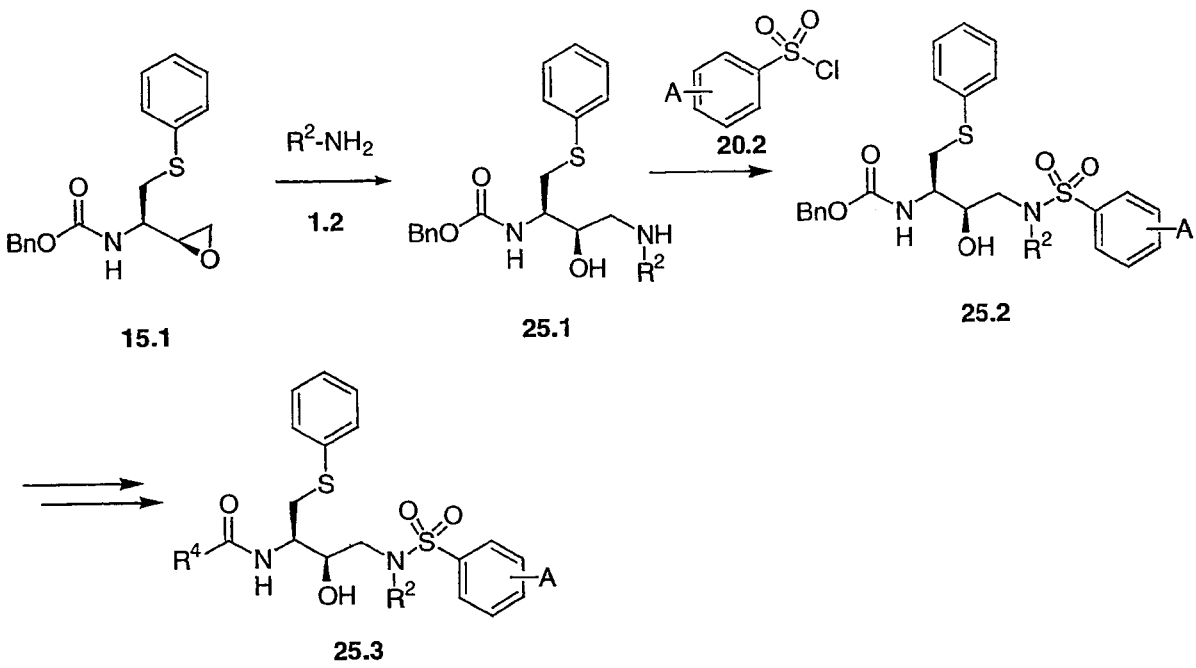
treated with sulfonamide **20.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, using the conditions described in Scheme **7**, to give the sulfonamide **25.2.** The sulfonamide **25.2** is then converted as described in Scheme **7** for the conversion of **7.9** to **7.10,** and Scheme **9a** for the conversion of **7.10** into **9a.4,** to the product **25.3**. Alternatively, Scheme **26**, illustrates how the amine **8.5** prepared according to Scheme **8** is reacted with **20.2** under conditions described in Scheme **8** for the preparation of **8.6** from **8.5**, to give the sulfonamide **26.1**. Further modification according to the conditions described in Scheme **8** for the preparation of **7.11**, affords sulfonamide **25.3**.

The reactions shown in Scheme **25-26** illustrate the preparation of the compounds sulfonamide **25.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **27** depicts the conversion of **25.3** in which A is [OH], [SH], [NH], Br etc, into the phosphonate **4** in which X is sulfur. In this procedure **25.3** is converted, using the procedures described below, Schemes **47-99**, into the compound **4**.

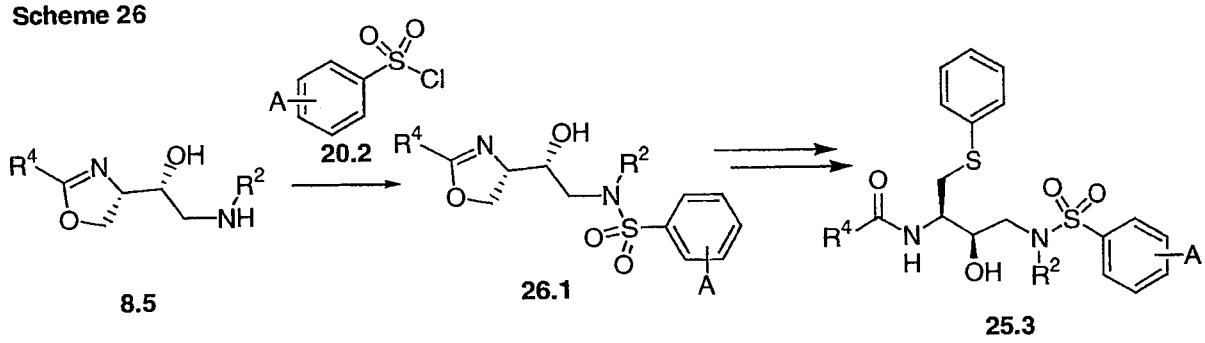
Preparation of the intermediate phosphonate ester **4**, in which the group A is attached to a sulfur linked aryl moiety, and the R_4COOH group contains an amine are prepared as shown in Schemes **28-29**. Amine **25.2** (Scheme **25**) in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, is converted to **28.1** as described in Scheme **7** for the preparation of the amine **7.10** from **7.9** and Scheme **9a** for the preparation of **9a.4** from **7.10.**

The reactions shown in Scheme **28** illustrate the preparation of the compounds sulfonamide **28.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **29** depicts the conversion of **28.1** in which A is [OH], [SH], [NH], Br etc, into the phosphonate **4** in which X is sulfur. In this procedure **28.1** is converted, using the procedures described below, Schemes **47-99**, into the compound **4**.

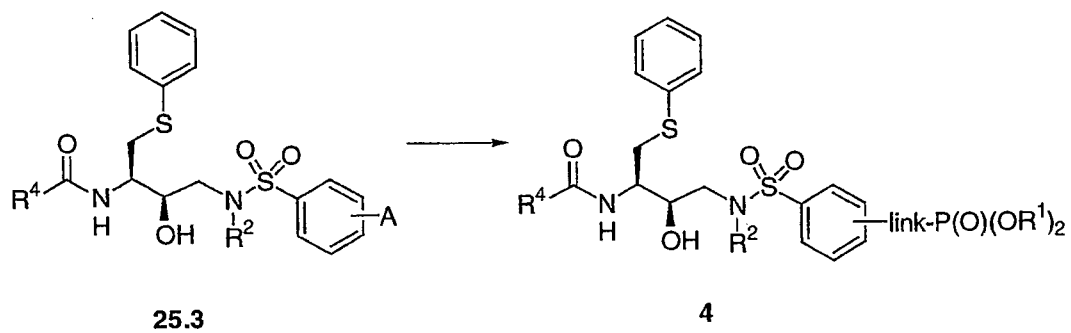
Scheme 25



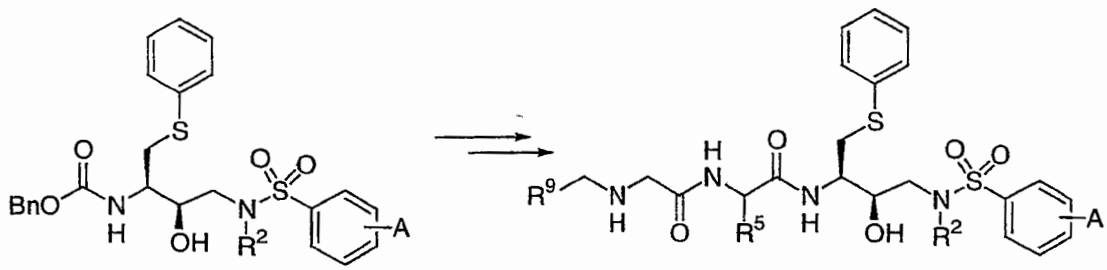
Scheme 26



Scheme 27

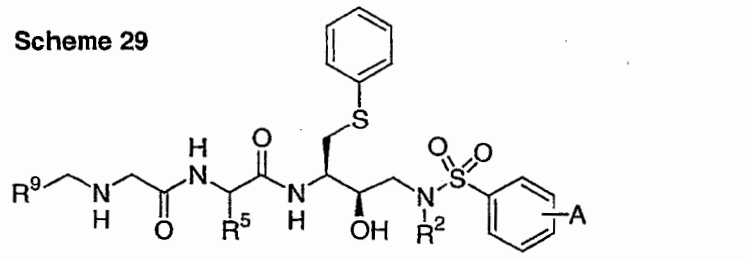


Scheme 28

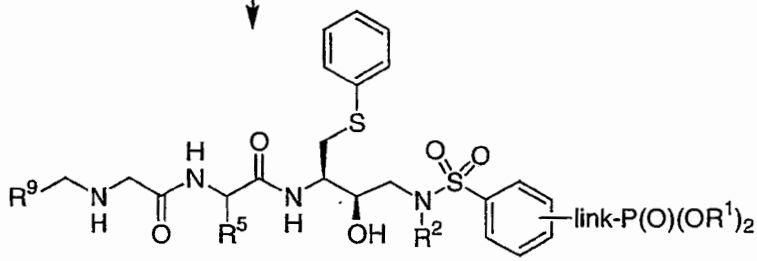


25.2 28.1

Scheme 29



28.1



4

Preparation of the phosphonate ester intermediates 5 in which X is a direct bond

Schemes **30** illustrates the preparation of the phosphonate esters **5** in which X is a direct bond and the R group does not contain a primary or secondary amine group. As shown in Scheme **30**, the amine **23.1** (Scheme **23**) is reacted with the alcohol **30.1** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, to afford the carbamate **30.2**. The reaction is performed under conditions described below, Scheme 98, for making carbamates from amines and alcohols. The preparation of the **30.1** is described in

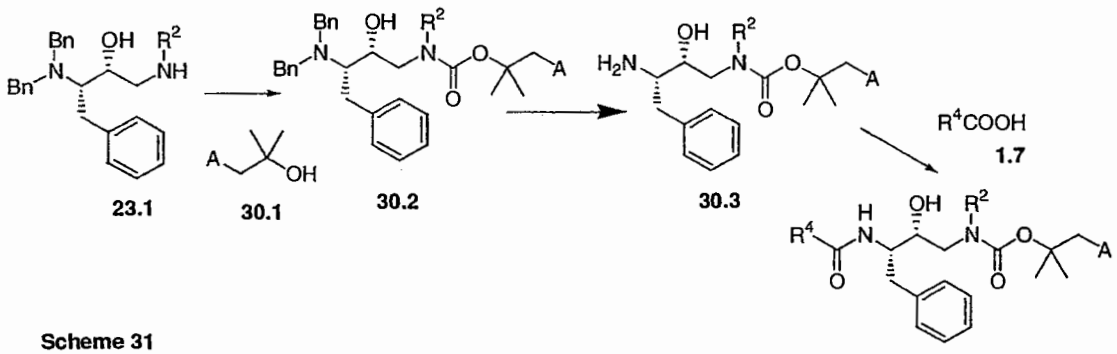
Schemes **83-86**. The carbamate **30.2** is then deprotected using conditions described in Scheme **3** for removal of the benzyl groups to give **30.3**. Treatment of **30.3** with the R^4COOH acid **1.7** using the conditions described in Scheme **1** then afford the amide **30.4**

The reactions shown in Scheme **30** illustrate the preparation of the compound **30.4** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **31** depicts the conversion of this compounds **30.4** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **5** respectively, in which X is a direct bond. In this procedure, the amines **30.4** is converted, using the procedures described below, Schemes **47-99**, into the compounds **5**.

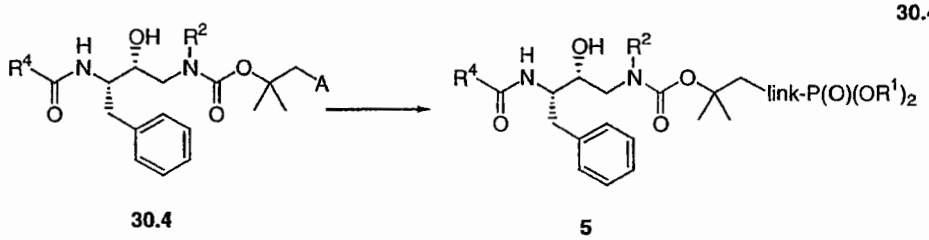
Schemes **32** illustrates the preparation of the phosphonate esters **5** in which X is a direct bond and the R_4COOH group contains an amine. The carbamate **30.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, is converted into the chloride **32.1** using conditions as described in Scheme **9a**. Chloride **32.1** is then treated with amine **5.7** to give the amine **32.2,** as described in Scheme **9a** for the conversion of **7.10** into **9a.3**.

The reactions shown in Scheme **32** illustrate the preparation of the compound **32.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **33** depicts the conversion of the compound **32.2** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **5** in which X is a direct bond. In this procedure, the compound **32.2** is converted, using the procedures described below, Schemes **47-99**, into the compound **5**.

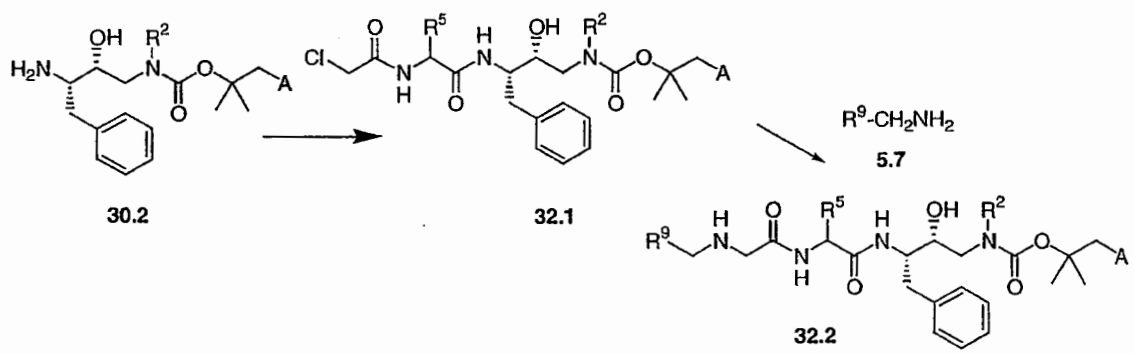
Scheme 30



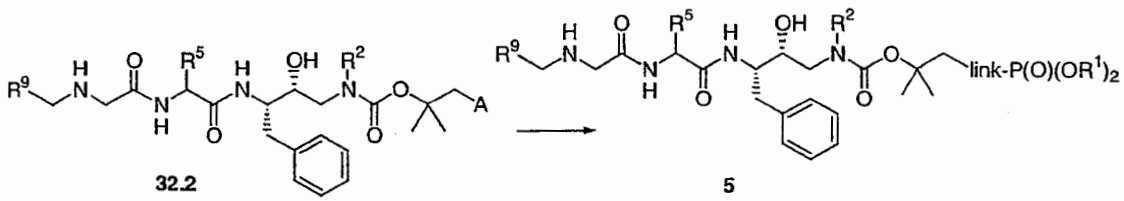
Scheme 31



Scheme 32



Scheme 33



Preparation of the phosphonate ester intermediates 5 in which X is a sulfur

The intermediate phosphonate ester **5**, in which the group A is attached to a sulfur linked aryl moiety, is prepared as shown in Schemes **34-36**. Amine **25.1** prepared according to Scheme **25,** is treated with alcohol **30.1** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, using the conditions described below ,

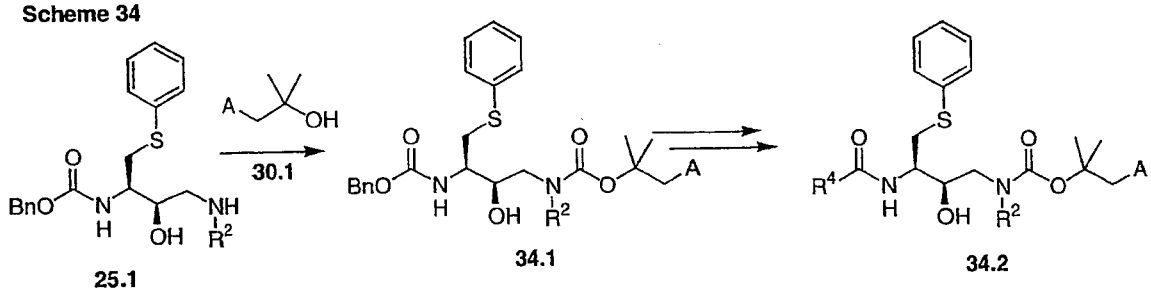
Scheme 98, to give the carbamate **34.1.** The carbamate **34.1** is then converted as described in Scheme **7**, for the conversion of **7.9** to **7.11**, to the product **34.2**. Alternatively the amine **8.5** prepared according to Scheme **8** can be reacted with alcohol **30.1** under conditions described in Scheme **98** to give the carbamate **35.1**. Further modification according to the conditions described in Scheme **8,** except incorporating thiophenol, then affords sulfonamide **34.2**.

The reactions shown in Scheme **34-35** illustrate the preparation of the compounds sulfonamide **34.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **36** depicts the conversion of **34.2** in which A is [OH], [SH], [NH], Br etc, into the phosphonate **5** in which X is sulfur. In this procedure **34.2** is converted, using the procedures described below, Schemes **47-99**, into the compound **5**.

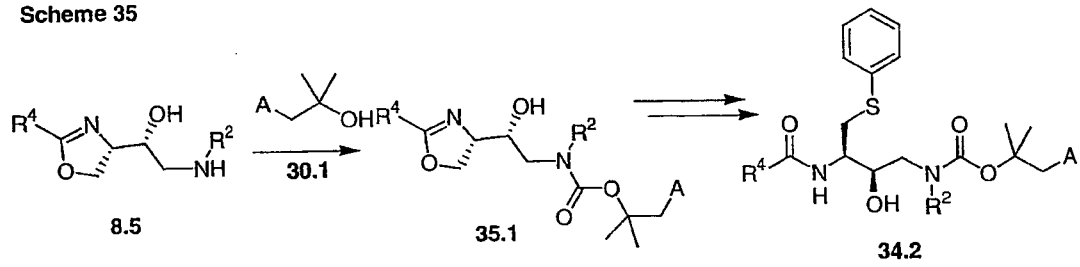
Preparation of the intermediate phosphonate ester **5**, in which the group A is attached to a sulfur linked aryl moiety, and the R_4COOH group contains an amine are prepared as shown in Schemes **37-38**. Carbamate **34.1** (Scheme **35**) in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, is converted to **37.1,** as described in Scheme **7** for the preparation of the amine **7.10** from **7.9** and Scheme **9a** for the preparation of **9a.4** from **7.10.**.

The reactions shown in Scheme **37** illustrate the preparation of the compounds sulfonamide **37.1** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **38** depicts the conversion of **37.1** in which A is [OH], [SH], [NH], Br etc, into the phosphonate **5** in which X is sulfur. In this procedure **37.1** is converted, using the procedures described below, Schemes **47-99**, into the compound **5**.

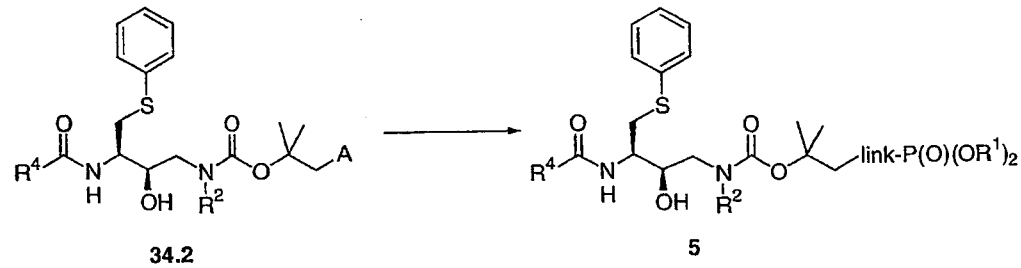
Scheme 34



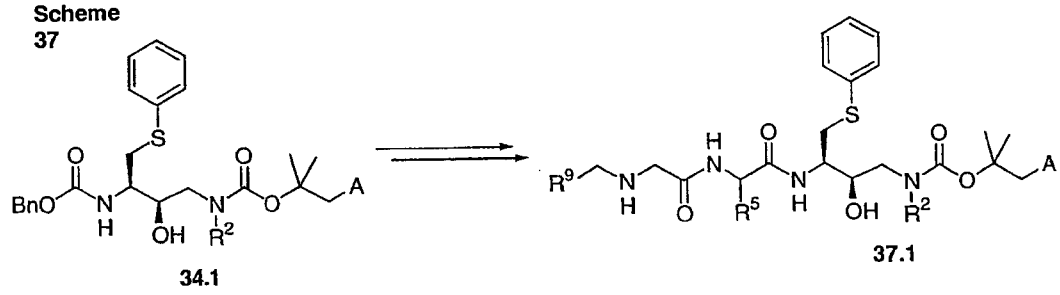
Scheme 35



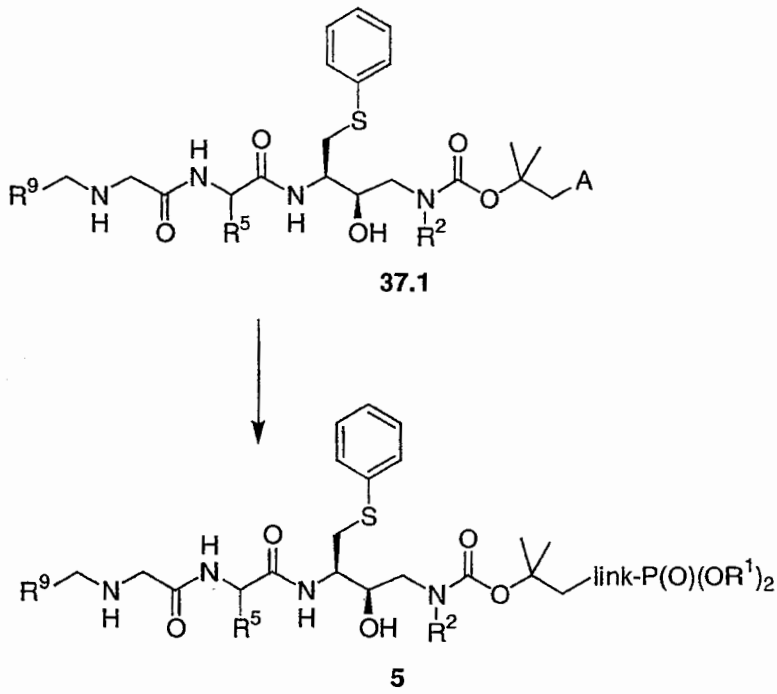
Scheme 36



Scheme 37



Scheme 38



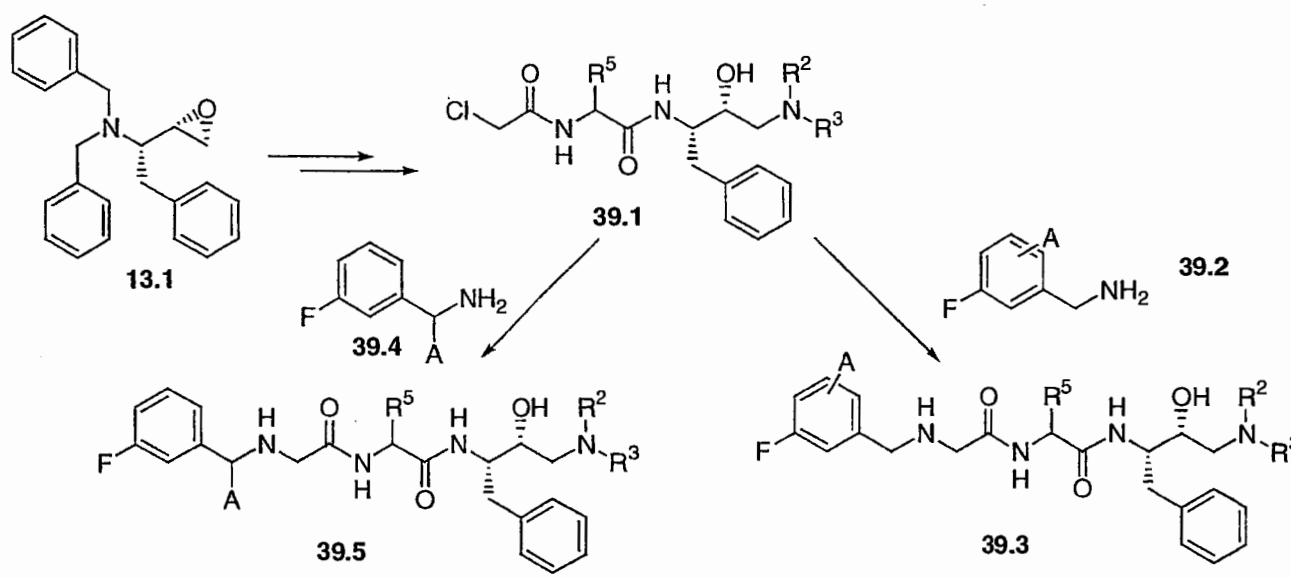
Preparation of the phosphonate ester intermediates 6 and 7 in which X is a direct bond

Schemes **39-40** illustrate the preparation of the phosphonate esters **6** and **7** in which X is a direct bond. As shown in Scheme **39**, the epoxide **13.1,** prepared as described in Scheme **13** is converted to the chloride **39.1**, as described in Scheme **3**, for the preparation of **3.4**, and Scheme **5,** for the conversion of **3.4** into **5.6**. The chloride **39.1** is then reacted with the amine **39.2** or **39.4**, in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, to afford the amine **39.3** and **39.5** respectively. The reaction is performed under the same conditions as described above, Scheme **5** for the preparation of the amine **5.8** from **5.6**. The prepartion of **39.2** and **39.4**, amines in which A is link-$P(O)(OR^1)_2$, are shown in Schemes **79-80** and Schemes **81-82** respectively.

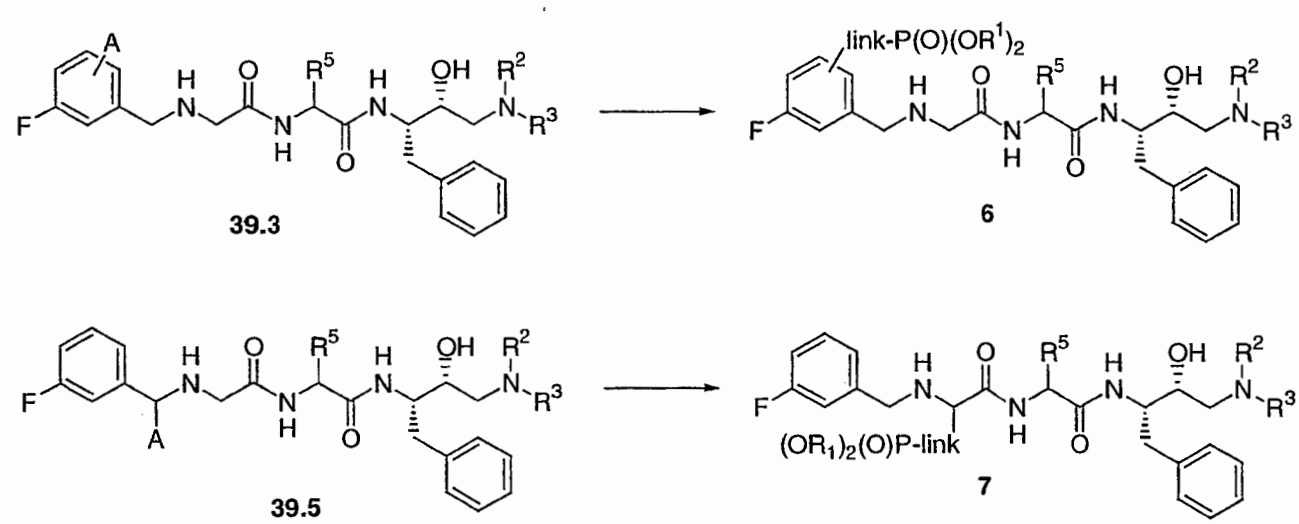
The reactions shown in Scheme **39** illustrate the preparation of the compounds **39.3** and **39.5** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **40** depicts the conversion of these compounds **39.3** and **39.5** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **6** and **7** respectively, in

which X is a direct bond. In this procedure, the amines **39.3** and **39.5** are converted, using the procedures described below, Schemes **47-99**, into the compounds **6** and **7** respectively.

Scheme 39



Scheme 40



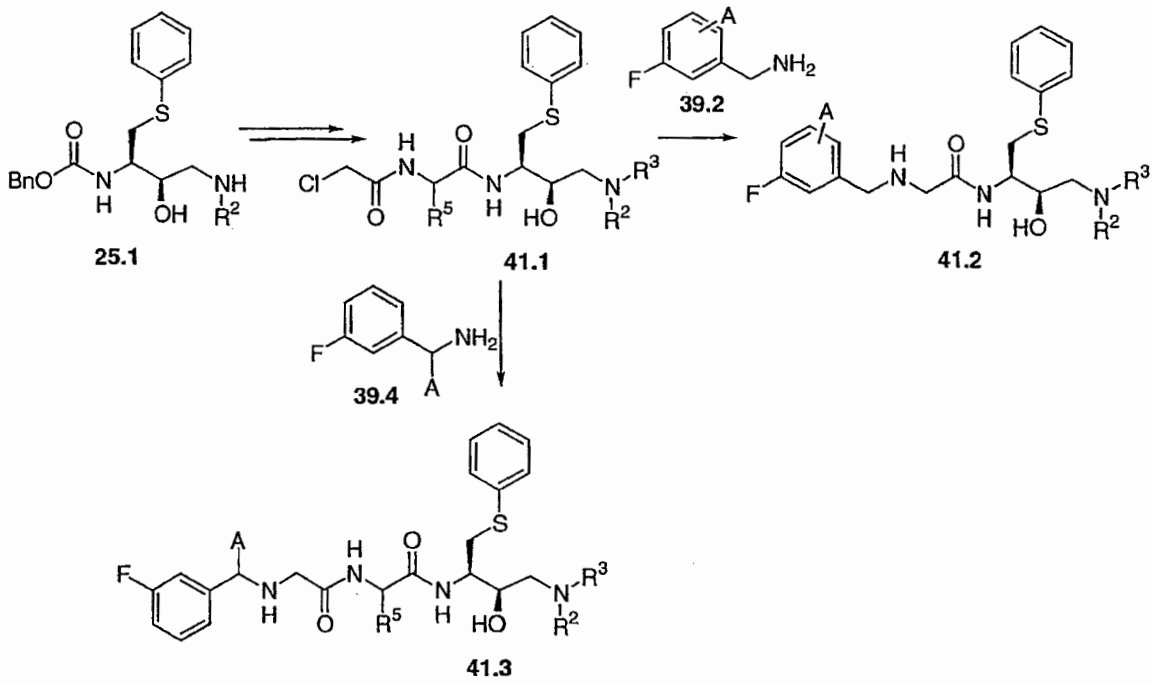
Preparation of the phosphonate ester intermediates 6 and 7 in which X is a sulfur

The intermediate phosphonate esters **6** and **7**, in which the group A is attached to a sulfur linked aryl moiety, are prepared as shown in Scheme **41-42**. The amine **25.1** (Scheme **25**) is

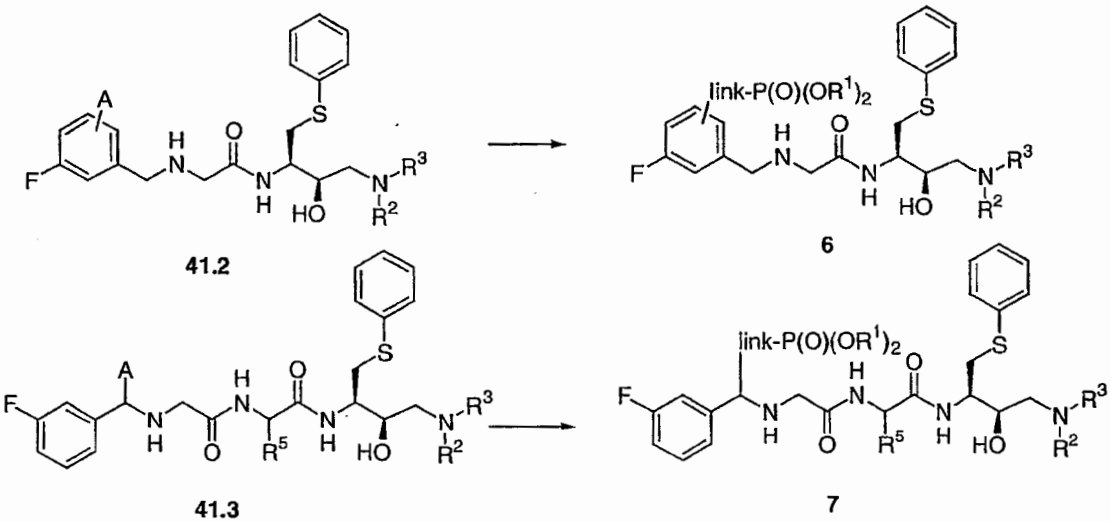
converted to the chloride **41.1** as described in Scheme **7** for the preparation of **7.10** from **7.8,** and Scheme **9a** for conversion of **7.10** to **9a3.** The chloride **41.1** is then treated with amine **39.2** or amine **39.4**, in which substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme **5**, to give the amines **41.2** and **41.3** respectively.

The reactions shown in Scheme **41** illustrate the preparation of the compounds **41.2** and **41.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **42** depicts the conversion of **41.2** and **41.3** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **6** and **7** in which X is sulfur. In this procedure **41.2** or **41.3** is converted, using the procedures described below, Schemes **47-99**, into the compound **6** and **7**.

Scheme 41



Scheme 42



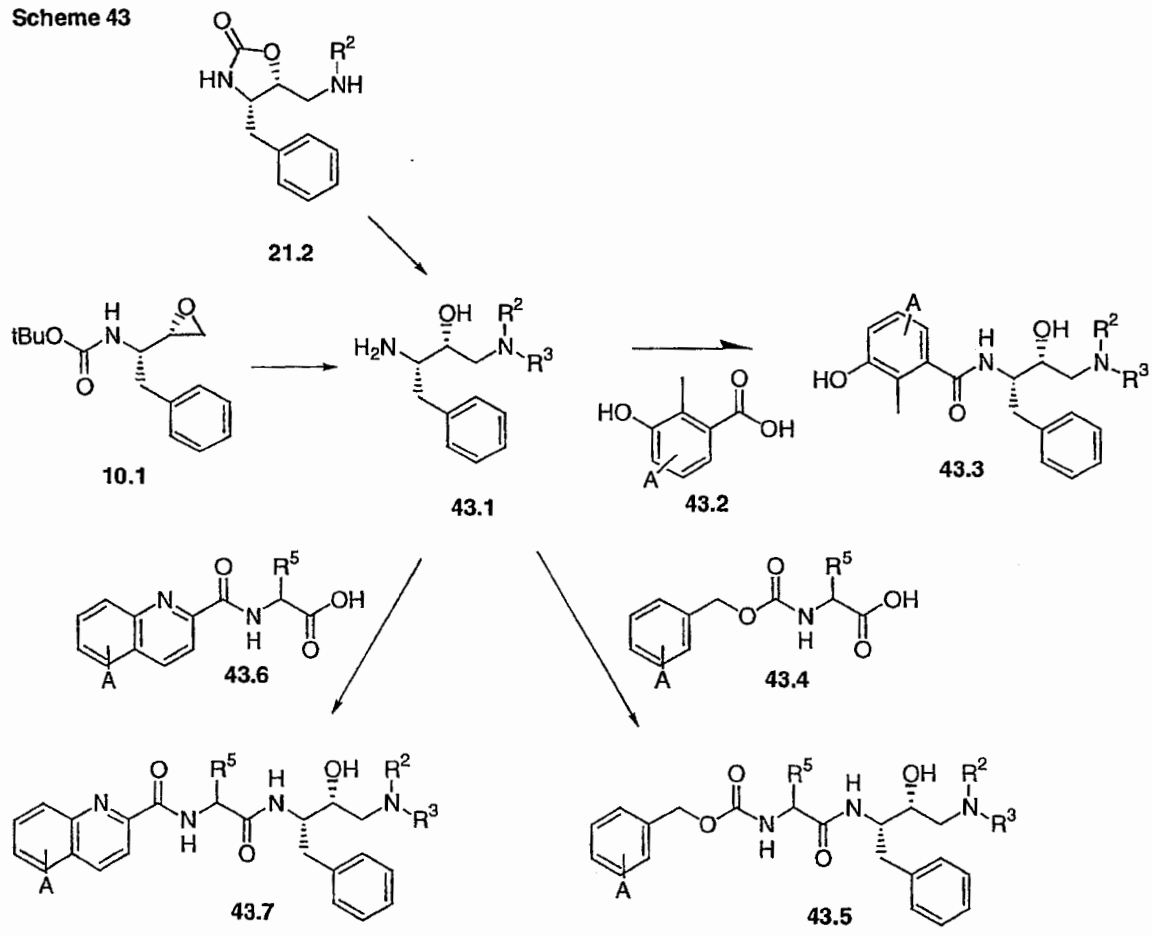
Preparation of the phosphonate ester intermediates 8-10 in which X is a direct bond

Schemes **43-44** illustrate the preparation of the phosphonate esters **8-10** in which X is a direct bond. As shown in Scheme **43**, the amine **43.1** prepared from **10.1** or **21.2** is reacted with the acid **43.2, 43.4** or **43.6**, in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, to afford the amide **43.3, 43.5** and **43.7** respectively. The reaction is performed under the same conditions as described above, Scheme

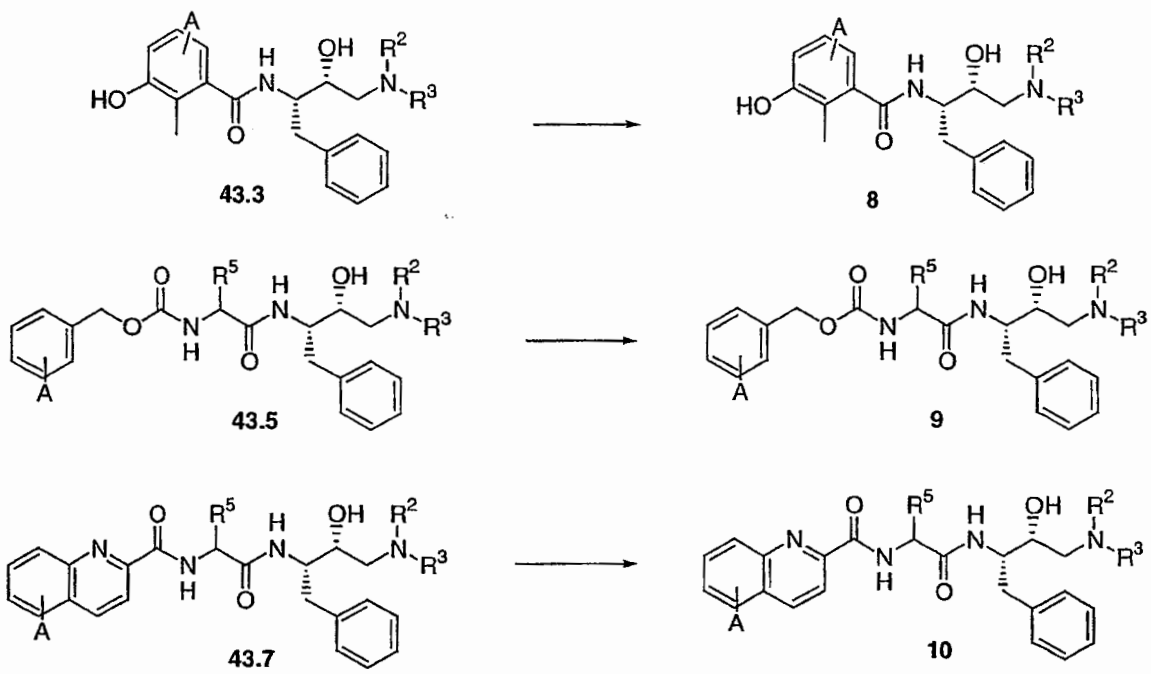
1 for the preparation of the amide **1.8**. Amine **43.1** is prepared from epoxide **10.1** using the conditions described in Scheme **1** except utilising **10.1** in place of **1.1**. Amine **43.1** is prepared from **21.2** according to the conditions described in Scheme **2** except utilizing **21.2** in place of **2.1**. The preparation of the acid **43.2** is described in Schemes **47-51**, acid **43.4** is described in Schemes **87-91**, and acid **43.6** is described in Schemes **52-55**.

The reactions shown in Scheme **43** illustrate the preparation of the compounds **43.3, 43.5** and **43.7** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **44** depicts the conversion of these compounds **43.3, 43.5,** and **43.7** in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters **8, 9** and **10** respectively, in which X is a direct bond. In this procedure, the amines **43.3, 43.5** and **43.7** are converted, using the procedures described below, Schemes **47-99**, into the compounds **8, 9,** and **10** respectively.

Scheme 43



Scheme 44

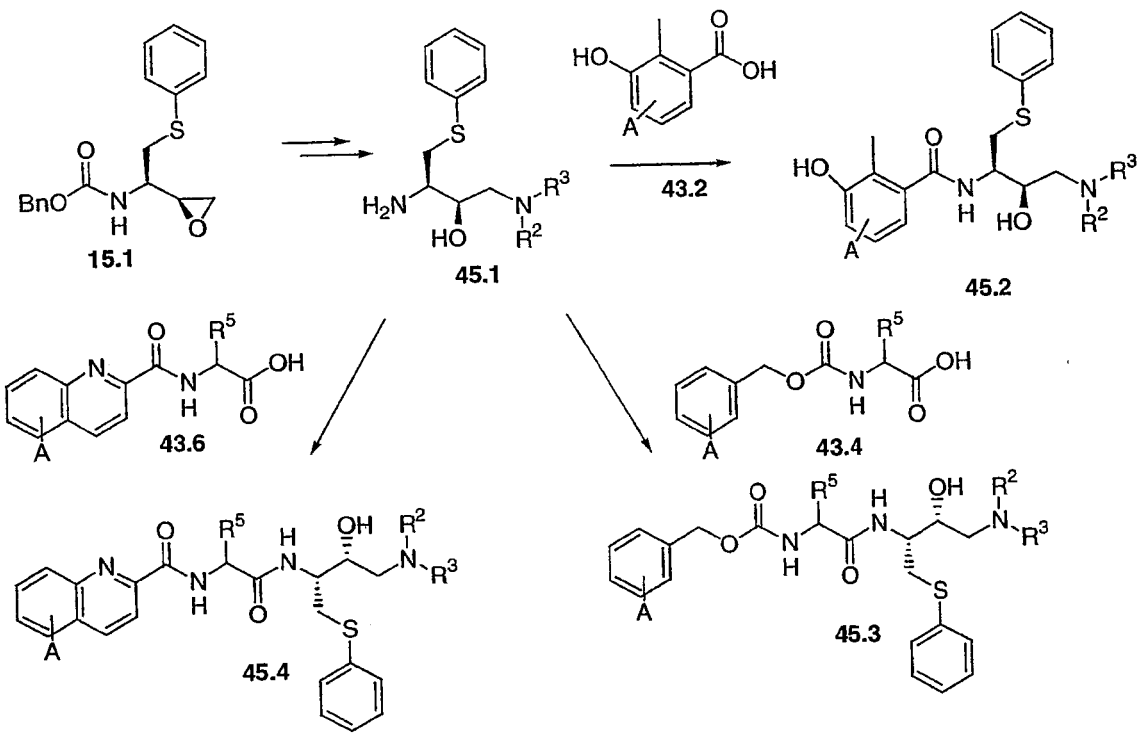


Preparation of the phosphonate ester intermediates 8-10 in which X is a sulfur

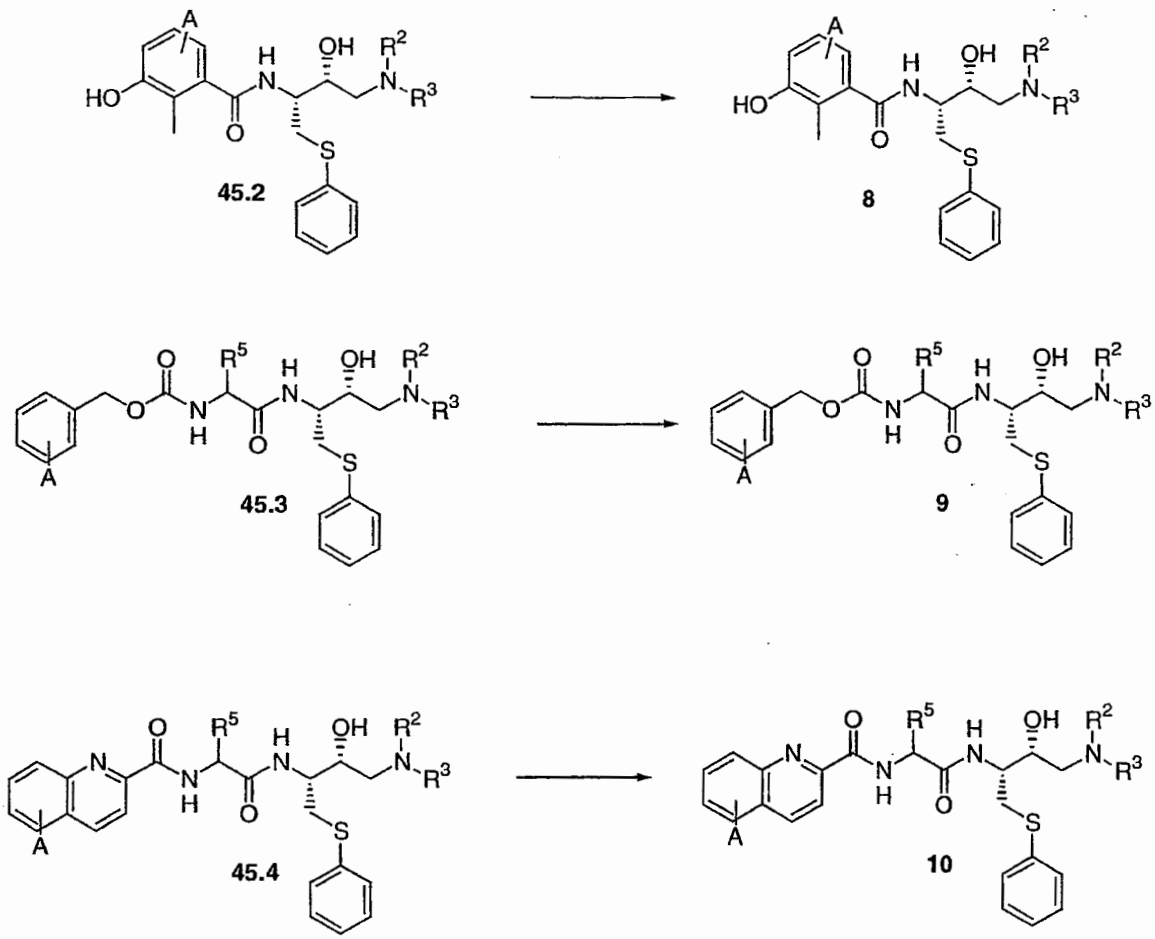
The intermediate phosphonate esters **8-10**, in which the group A is attached to a sulfur linked aryl moiety, are prepared as shown in Schemes **45-46**. In Scheme **45**, epoxide **15.1** is prepared from mesylate **7.1** using the conditions described in Scheme 7 except incorporating thiophenol for thiol **7.2.** The epoxide **15.1** is then converted to amine **45.1** according to the conditions described in Scheme 7 for the preparation of **7.10** from **7.7.** Amine **45.1** is then treated with acids **43.2, 43.4** or **43.6**, in which substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme **7**, to give the amides **45.2, 45.3,** and **45.4** respectively .

The reactions shown in Scheme **45** illustrate the preparation of the compounds **45.2, 45.3,** and **45.4** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme **46** depicts the conversion **45.2, 45.3,** and **45.4** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **8, 9** and **10** respectively in which X is sulfur. In this procedure **45.2, 45.3,** and **45.4** is converted, using the procedures described below, Schemes **47-99**, into the compounds **8, 9** and **10** respectively.

Scheme 45



Scheme 46



Preparation of phosphonate-containing hydroxymethyl benzoic acids 43.2.

Schemes **47** - **51** illustrate methods for the preparation of phosphonate-containing hydroxymethyl benzoic acids **43.2** which are employed in the preparation of the phosphonate esters **8**.

Scheme **47** illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid **47.1** is subjected to halogen-methyl exchange to afford the organometallic intermediate **47.2**. This compound is reacted with a chlorodialkyl phosphite **47.3** to yield the phenylphosphonate ester **47.4**, which upon deprotection affords the carboxylic acid **47.5**.

For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, **47.6**, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Am. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane **47.7**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester **47.8**. This compound is treated with boron trifluoride at 0^0 to effect rearrangement to the orthoester **47.9**, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether **47.10**. Halogen-metal exchange is performed by the reaction of the substrate **47.10** with butyllithium, and the lithiated intermediate is then coupled with a chlorodialkyl phosphite **47.3**, to produce the phosphonate **47.11**. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid **47.12**.

Using the above procedures, but employing, in place of the bromo compound **47.6**, different bromo compounds **47.1**, there are obtained the corresponding products **47.5**.

Scheme **48** illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

In this method, a suitably protected dimethyl hydroxybenzoic acid, **48.1**, is reacted with a brominating agent, so as to effect benzylic bromination. The product **48.2** is reacted with a sodium dialkyl phosphite, **48.3**, as described in J. Med. Chem., 1992, 35, 1371, to effect displacement of the benzylic bromide to afford the phosphonate **48.4**. Deprotection of the carboxyl function then yields the carboxylic acid **48.5**.

For example, 2,5-dimethyl-3-hydroxybenzoic acid, **48.6**, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p.17, to afford the ether ester **48.7**. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or diisopropylethylamine. The product **48.7** is then reacted with a brominating agent, for example N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product **48.8**. This compound is then reacted with a sodium dialkyl

phosphite **48.3** in tetrahydrofuran, as described above, to afford the phosphonate **48.9**. Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields the carboxylic acid **48.10**. Using the above procedures, but employing, in place of the methyl compound **48.6**, different methyl compounds **48.1**, there are obtained the corresponding products **48.5**.

Scheme **49** illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom. In this method, a suitably protected hydroxy- or mercapto-substituted hydroxy methyl benzoic acid **49.1** is reacted, under the conditions of the Mitsonobu reaction, with a dialkyl hydroxymethyl phosphonate **49.2**, to afford the coupled product **49.3**, which upon deprotection affords the carboxylic acid **49.4**.

For example, 3,6-dihydroxy-2-methylbenzoic acid, **49.5**, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester **49.6**, by treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 77, to afford the mono-silyl ether **49.7**. This compound is then reacted with a dialkyl hydroxymethylphosphonate **49.2**, under the conditions of the Mitsonobu reaction. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. The reaction affords the coupled product **49.8**. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic carboxylic acid **49.9**.

Using the above procedures, but employing, in place of the phenol **49.5**, different phenols or thiophenols **49.1**, there are obtained the corresponding products **49.4**.

Scheme **50** depicts the preparation of phosphonate esters attached to the hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains.

In this method, a dialkyl alkenylphosphonate **50.2** is coupled, by means of a palladium catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid **50.1**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. The product **50.3** is deprotected to afford the phosphonate **50.4;** the latter compound is subjected to catalytic hydrogenation to afford the saturated carboxylic acid **50.5**.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid **50.6,** prepared as described in WO 9218490, is converted as described above, into the silyl ether OBO ester **50.7** as described above. This compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate **50.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above to afford the product **50.9**. Deprotection, or hydrogenation/deprotection, of this compound, as described above, then affords respectively the unsaturated and saturated products **50.10** and **50.11**.

Using the above procedures, but employing, in place of the bromo compound **50.6**, different bromo compounds **50.1**, and/or different phosphonates **50.2**, there are obtained the corresponding products **50.4** and **50.5**.

Scheme **51** illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

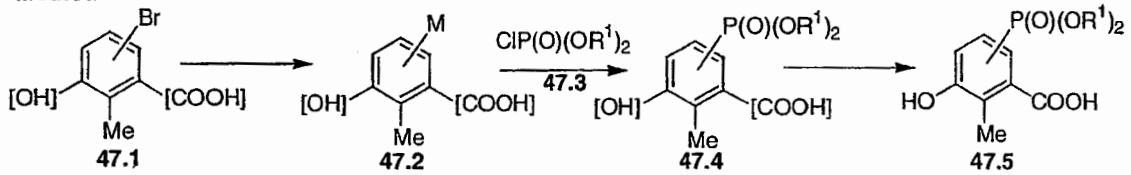
In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid **51.1** is converted to the corresponding boronic acid **51.2**, by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82. The product is subjected to a Suzuki coupling reaction with a dialkyl bromophenyl phosphonate **51.3**. The product **51.4** is then deprotected to afford the diaryl phosphonate product **51.5**.

For example, the silylated OBO ester **51.6**, prepared as described above, (Scheme **47**), from 5-bromo-3-hydroxybenzoic acid, the preparation of which is described in J. Labelled. Comp. Radiopharm., 1992, 31, 175, is converted into the boronic acid **51.7**, as described above. This material is coupled with a dialkyl 4-bromophenyl phosphonate **51.8**, prepared as described in J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, in the presence of sodium bicarbonate, as described, for example, in Palladium reagents and catalysts J. Tsuji, Wiley 1995, p 218, to afford the diaryl phosphonate **51.9**. Deprotection, as described above, then affords the benzoic acid **51.10**.

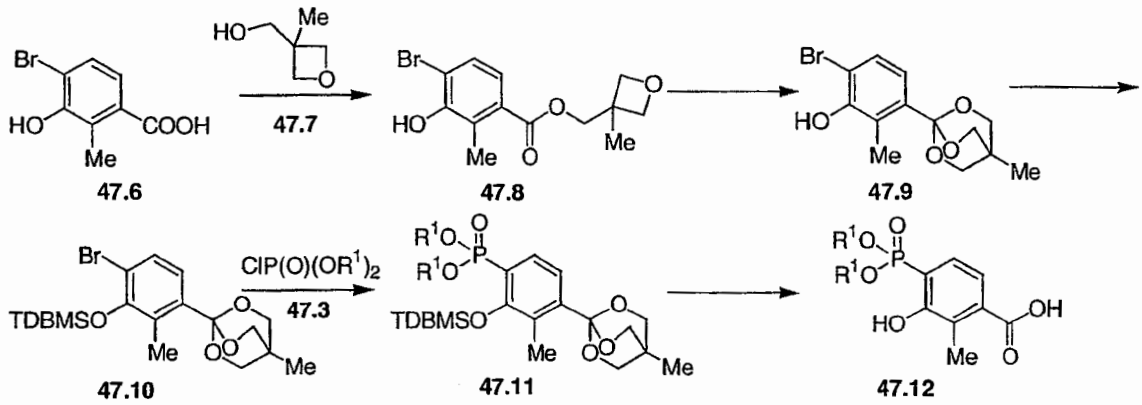
Using the above procedures, but employing, in place of the bromo compound **51.6**, different bromo compounds **51.1**, and/or different phosphonates **51.3**, there are obtained the corresponding carboxylic acid products **51.5**.

Scheme 47

Method

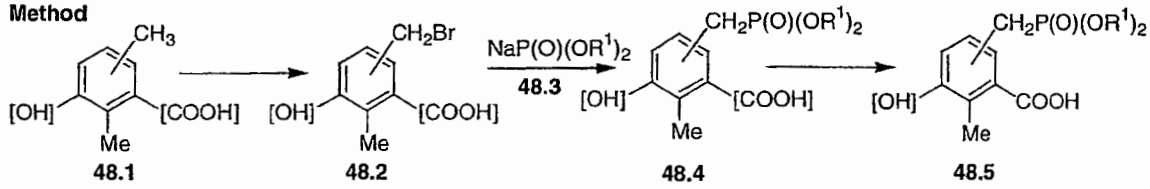


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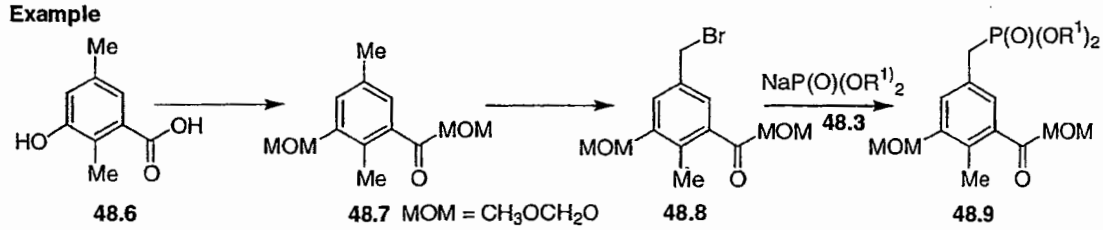


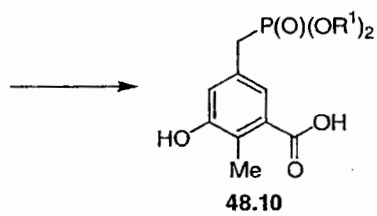
Scheme 48

Method



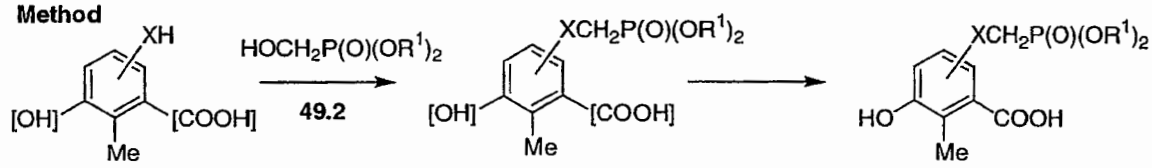
Example



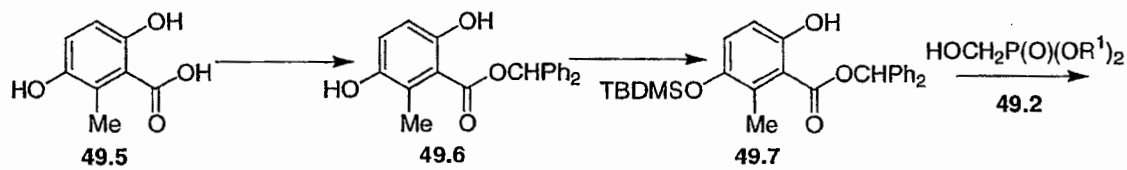


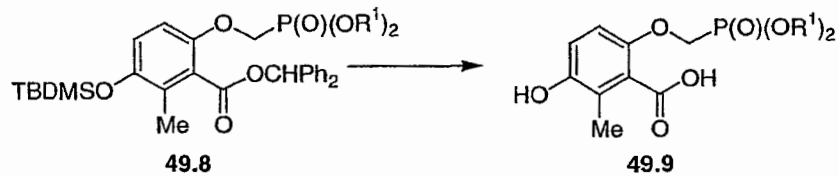
Scheme 49

Method

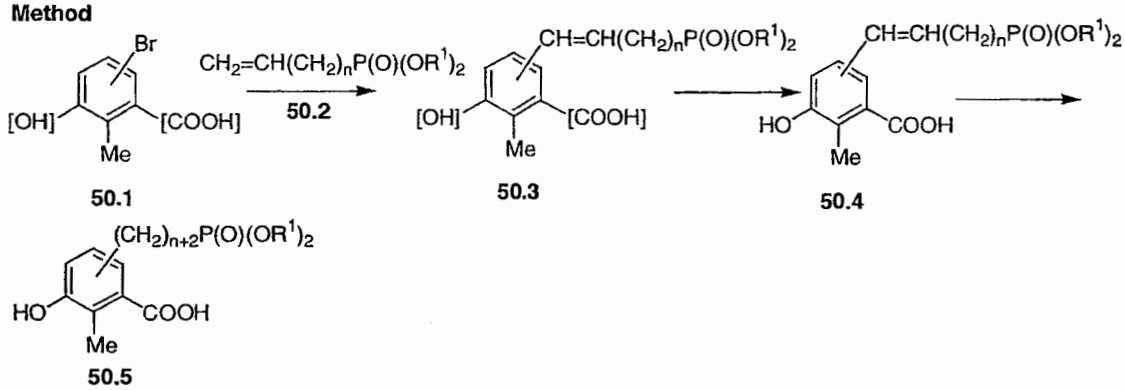


Example

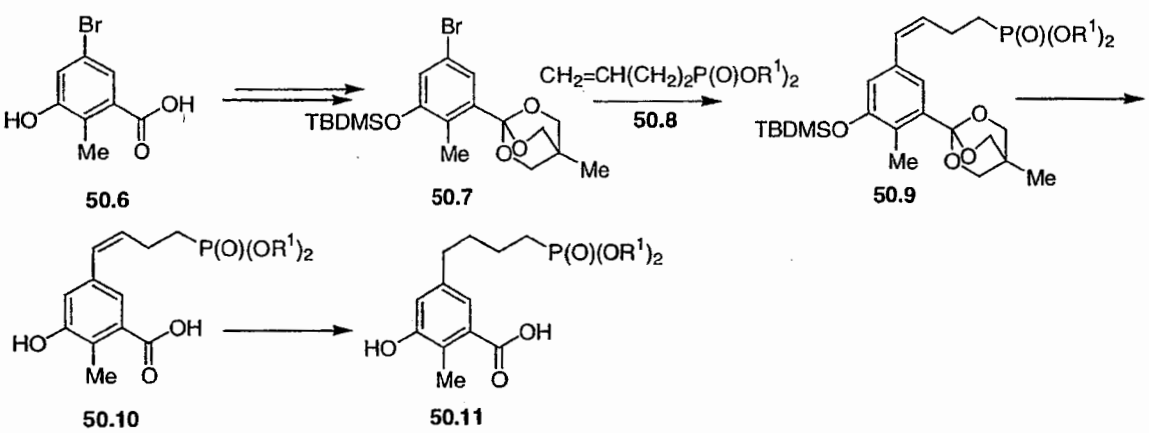




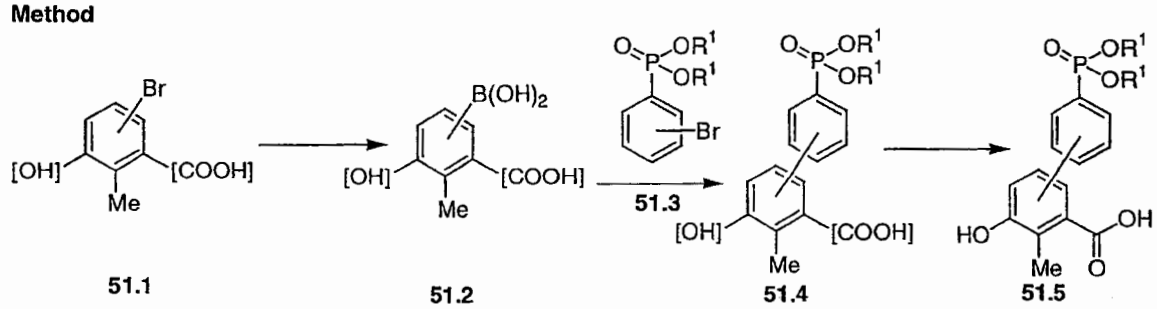
Scheme 50
Method



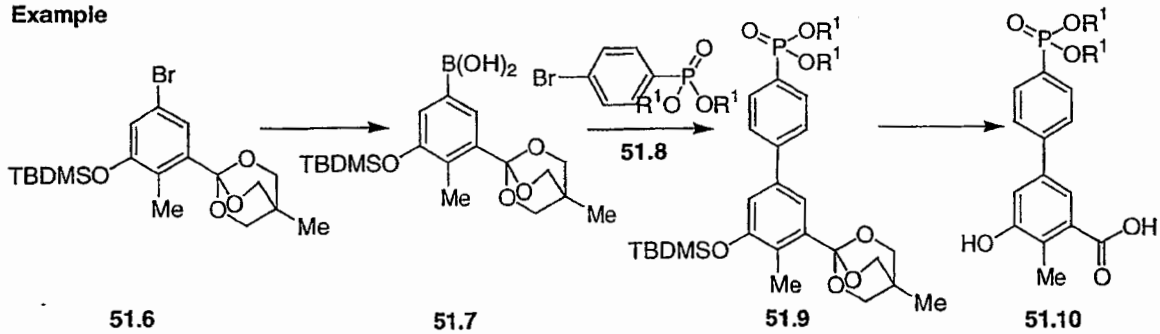
Example



Scheme 51
Method



Example



Preparation of quinoline 2-carboxylic acids 43.6 incorporating phosphonate moieties.

The reaction sequences depicted in Schemes **43** - **46** for the preparation of the phosphonate esters **10** employ a quinoline-2-carboxylic acid reactant **43.6** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br etc. A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het. Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines is described, for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.

Scheme **52** illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde **52.1** is reacted with an alkyl pyruvate ester **52.2**, in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester **52.3**. Hydrolysis of the ester, for example by the use of aqueous base, then afford the corresponding carboxylic acid **52.4**. The carboxylic acid product **52.4** in which X is NH_2 can be further transformed into the corresponding compounds **52.6** in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoborate, is then heated in aqueous solution, for example as described in Organic

Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol **52.6**, Y = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, **52.6**, Y = Br. Alternatively, the diazonium tetrafluoborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to afford the thiol **52.6**, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters **52.3** instead of the carboxylic acids **52.5**.

For example, 2,4-diaminobenzaldehyde **52.7** (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate **52.2** in methanol, in the presence of a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate **52.8**. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **52.9**. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoborate **52.10** by reaction with sodium nitrite and tetrafluoboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, **52.11**, Z = OH. Alternatively, the diazonium tetrafluoborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-bromoquinoline-2-carboxylic acid **52.11**, Z = Br. Alternatively, the diazonium tetrafluoborate **52.10** is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid **52.11**, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde **52.7**, different aminobenzaldehydes **52.1**, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids **52.6** are obtained. The variously substituted quinoline carboxylic acids and esters can then be transformed, as described herein, (Schemes **53** – **55**) into phosphonate-containing derivatives.

Scheme **53** depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester **53.1** is transformed, via a diazotization procedure as described above (Scheme **52**) into the corresponding phenol or

thiol **53.2**. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate **53.3**, under the conditions of the Mitsonobu reaction, to afford the phosphonate ester **53.4**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **53.4**. Basic hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **53.5**. The product is then coupled with a suitably protected aminoacid derivative **53.6** to afford the amide **53.7**. The reaction is performed under similar conditions to those described above, Scheme **1**. The ester protecting group is then removed to yield the carboxylic acid **53.8**.

For example, methyl 6-amino-2-quinoline carboxylate **53.9**, prepared as described in J. Het. Chem., 1989, 26, 929, is converted, by means of the diazotization procedure described above, into methyl 6-mercaptoquinoline-2-carboxylate **53.10**. This material is reacted with a dialkyl hydroxymethylphosphonate **53.11** (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether **53.12**. Basic hydrolysis then afford the carboxylic acid **53.13**. The latter compound is then converted, as described above, into the aminoacid derivative **53.16**.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline carboxylate **53.9**, different aminoquinoline carboxylic esters **53.1**, and/or different dialkyl hydroxymethylphosphonates **53.3** the corresponding phosphonate ester products **53.8** are obtained.

Scheme **54** illustrates the preparation of quinoline-2-carboxylic acids incorporating phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester **54.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate **54.2**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as

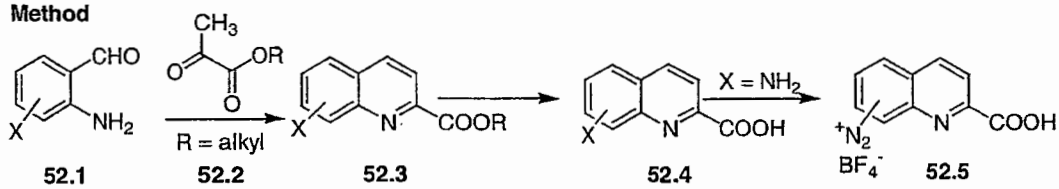
dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Thus, Heck coupling of the bromo compound **54.1** and the olefin **54.2** affords the olefinic ester **54.3**. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid **54.4**. The latter compound is then transformed, as described above, into the homolog **54.5**. Optionally, the unsaturated carboxylic acid **54.4** can be reduced to afford the saturated analog **54.6**. The reduction reaction can be effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5, or catalytically. The product **54.6** is then converted, as described above (Scheme **53**) into the aminoacid derivative **54.7**.

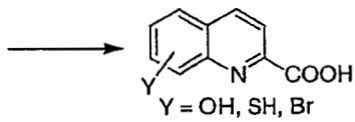
For example, methyl 7-bromoquinoline-2-carboxylate, **54.8**, prepared as described in J. Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60° with a dialkyl vinylphosphonate **54.9** (Aldrich) in the presence of 2 mol% of tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product **54.10** The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid **54.11**. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product **54.12**. The latter compound is then converted, as described above, into the aminoacid derivative **54.13**. The unsaturated product **54.11** is similarly converted into the analog **54.14**.

Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate **54.8**, different bromoquinoline carboxylic esters **54.1**, and/or different dialkyl alkenylphosphonates **54.2**, the corresponding phosphonate ester products **54.5** and **54.7** are obtained.

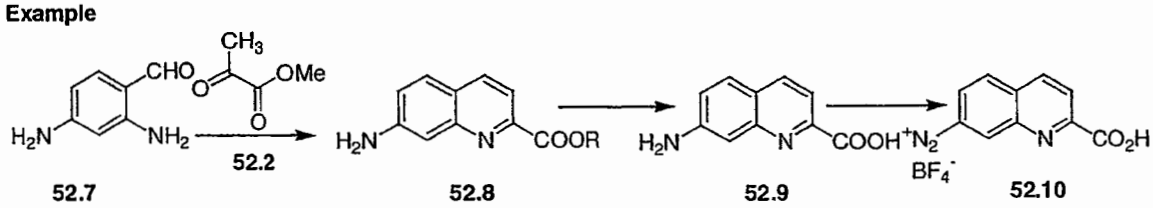
Scheme 52

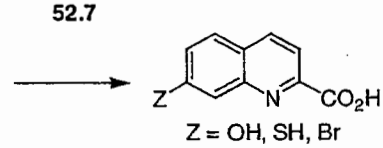
Method





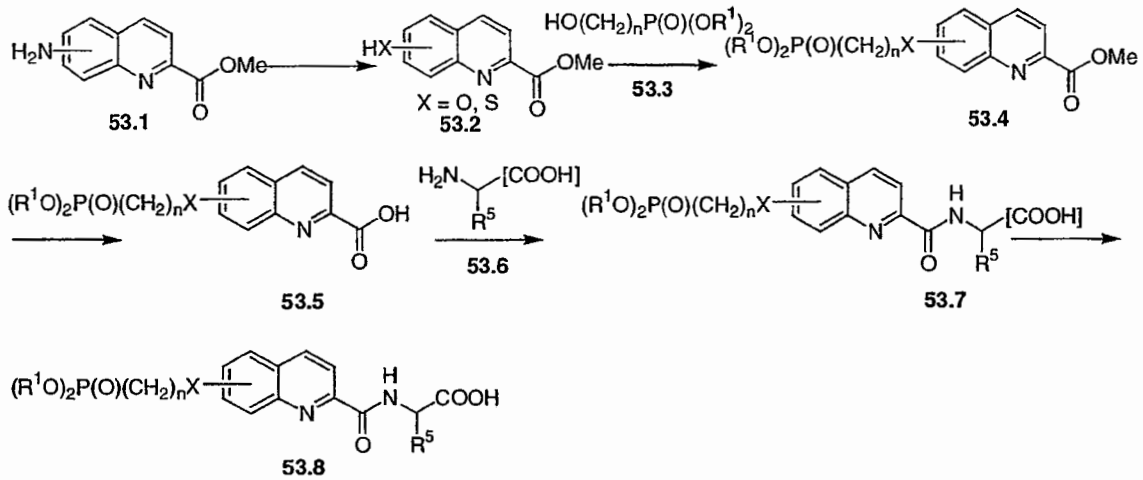
Example



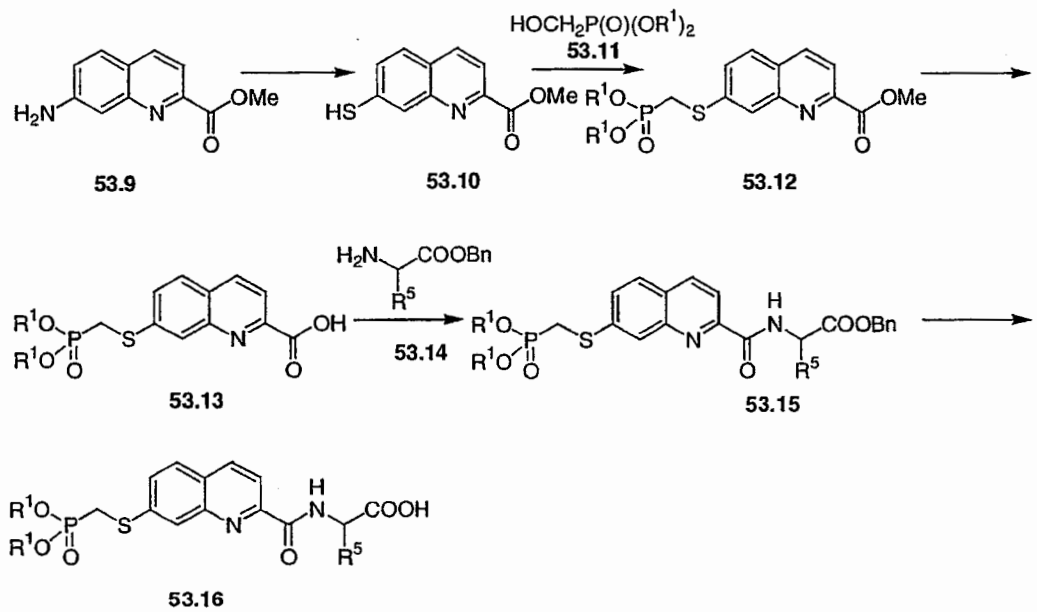


Scheme 53

Method

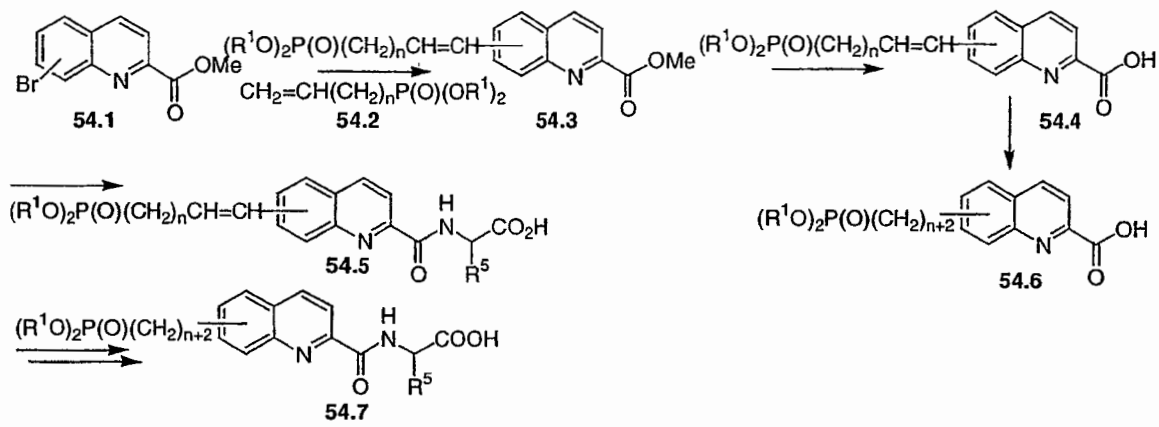


Example

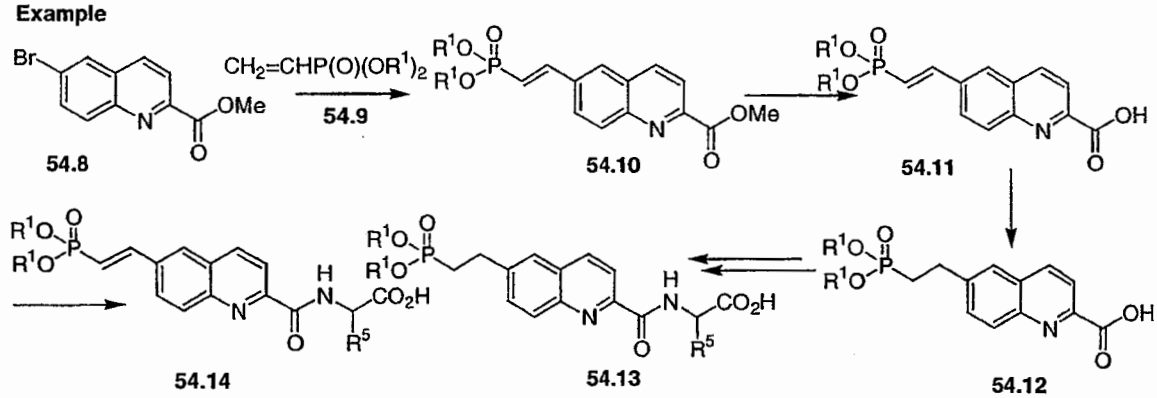


Scheme 54

Method



Example

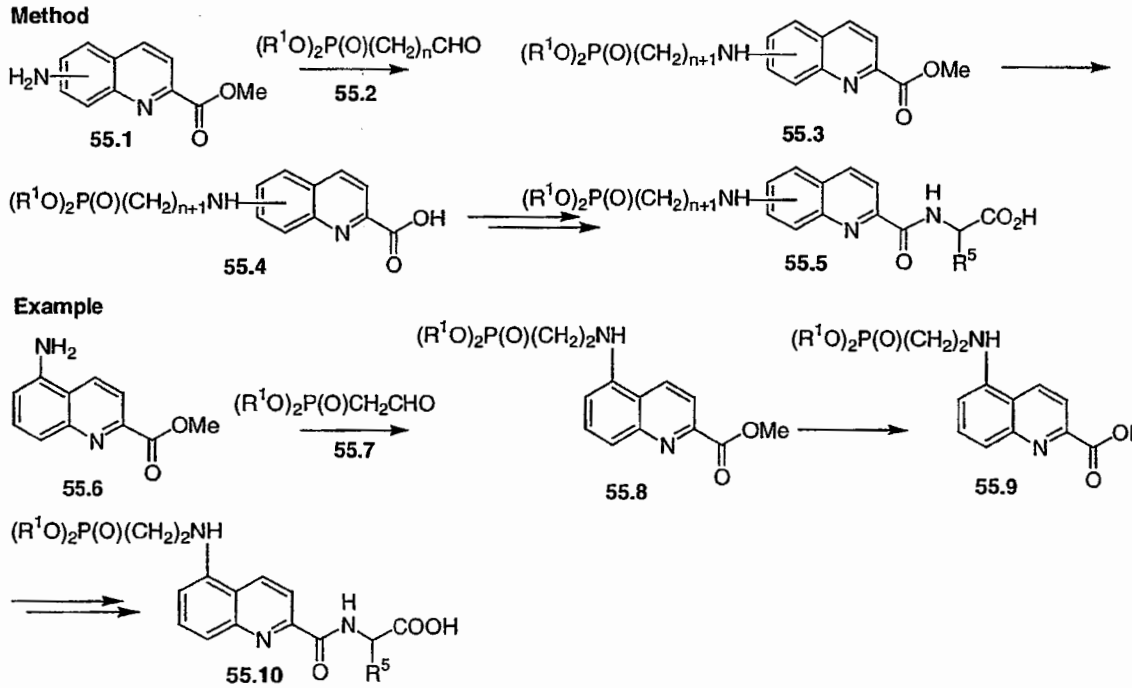


Scheme **55** depicts the preparation of quinoline-2-carboxylic acid derivatives **55.5** in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate **55.1** is reacted with a phosphonate aldehyde **55.2** under reductive amination conditions, to afford the aminoalkyl product **55.3**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product **55.3** is then hydrolyzed to yield the free carboxylic acid **55.4**. The latter compound is then converted, as described above, into the aminoacid derivative **55.5**.

For example, methyl 7-aminoquinoline-2-carboxylate **55.6**, prepared as described in J. Am. Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **55.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **55.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **55.9**. The latter compound is then converted, as described above, into the aminoacid derivative **55.10**. Using the above procedures, but employing, in place of the formylmethyl phosphonate **55.7**, different formylalkyl phosphonates **55.2**, and/or different aminoquinolines **55.1**, the corresponding products **55.5** are obtained.

Scheme 55

Method



Example

Preparation of phenylalanine derivatives 1.1 incorporating phosphonate moieties.

Scheme **56** illustrates the conversion of variously substituted phenylalanine derivatives **56.1** into epoxides **1.1**, the incorporation of which into the compounds **1** is depicted in Schemes **1** and **3**.

A number of compounds **56.1** or **56.2**, for example those in which X is 2, 3, or 4-OH, or X is 4-NH_2 are commercially available. The preparations of different compounds **56.1** or **56.2** are described in the literature. For example, the preparation of compounds **56.1** or **56.2** in which

X is 3-SH, 4-SH, 3-NH_2, 3-CH_2OH or 4-CH_2OH, are described respectively in WO0036136, J. Am. Chem. Soc., 1997, 119, 7173, Helv. Chim. Acta, 1978, 58, 1465, Acta Chem. Scand., 1977, B31, 109 and Syn. Com., 1998, 28, 4279. Resolution of compounds **56.1**, if required, can be accomplished by conventional methods, for example as described in Recent Dev. Synth. Org. Chem., 1992, 2, 35.

The variously substituted aminoacids **56.2** are protected, for example by conversion to the BOC derivative **56.3**, by treatment with BOC anhydride, as described in J. Med. Chem., 1998, 41, 1034. The product **56.3** is then converted into the methyl ester **56.4**, for example by treatment with ethereal diazomethane. The substituent X in **56.4** is then transformed, using the methods described below, Schemes **57-59**, into the group A. The products **56.5** are then converted, via the intermediates **56.6** - **56.9**, into the epoxides **1.1**. The methyl ester **56.5** is first hydrolyzed, for example by treatment with one molar equivalent of aqueous methanolic lithium hydroxide, or by enzymatic hydrolysis, using, for example, porcine liver esterase, to afford the carboxylic acid **56.6**. The conversion of the carboxylic acid **56.6** into the epoxide **1.1**, for example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, is then effected. The carboxylic acid is first converted into the acid chloride, for example by treatment with oxalyl chloride, or into a mixed anhydride, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone **56.7**. The diazoketone is converted into the chloroketone **56.8** by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether. The latter compound is then reduced, for example by the use of sodium borohydride, to produce a mixture of chlorohydrins from which the desired 2S, 3S diastereomer **56.9** is separated by chromatography. This material is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide **1.1**. Optionally, the above described series of reactions can be performed on the methyl ester **56.4**, so as to yield the epoxide **1.1** in which A is OH, SH, NH, Nalkyl or CH_2OH.

Methods for the transformation of the compounds **56.4**, in which X is a precursor group to the substituent link-$P(O)(OR^1)_2$, are illustrated in Schemes **57-59**.

Scheme **56a** illustrates the conversion of variously substituted phenylalanine derivatives **56a.1** into epoxides **3.1**, the incorporation of which into the compounds **1** is depicted in Schemes **3**. Starting from the same reagents described above, Scheme **56**, the compound **56.2** is converted

into the epoxide **56a.6** as described in J. Org. Chem 1996,61, 3635. The amino acid **56.2** is converted to the tribenzyl ester **56a.3** by treatment with benzyl bromide in ethanol in the presence of potassium carbonate. The substituent X in **56a.3** is then transformed, using the methods described below, Schemes **57-59**, into the group A, compound **56a.4**. These methods describe procedures in which the amine is BOC protected. However the same procedures are applicable to other amine protecting groups such as dibenzyl. The products **56a.4** are then converted, via the intermediates **56a.5** into the epoxides **3.1.** The ester **56a.4** is reduced with lithium aluminum hydride to the alcohol which is then oxidized to the aldehyde **56a.4** by treatment with pyridine sulfur trioxide in DMSO and triethylamine. The aldehyde **56a.4** is then converted to the epoxide **3.1** by treatment with chloromethylbromide and excess lithium in THF at –65 °C. A mixture of isomers are produced which are separated by chromatography.

Scheme **57** depicts the preparation of epoxides **57.4** incorporating a phosphonate group linked to the phenyl ring by means of a heteroatom O, S or N. In this procedure, the phenol, thiol, amine or carbinol **57.1** is reacted with a derivative of a dialkyl hydroxymethyl phosphonate **57.2**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is OH, SH, NH_2 or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is CH_2OH, a base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **57.3**, which, employing the sequence of reactions shown in Scheme **56** or **56a**, is transformed into the epoxide **57.4**.

For example, 2-tert.-butoxycarbonylamino-3-(4-hydroxy-phenyl)-propionic acid methyl ester, **57.5** (Fluka) is reacted with a dialkyl trifluoromethanesulfonyloxy phosphonate **57.6**, prepared as described in Tet. Lett., 1986, 27, 1477, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the ether product **57.5**. The latter compound is then converted, using the sequence of reactions shown in Scheme **56**, into the epoxide **57.8**.

Using the above procedures, but employing different phenols, thiols, amines and carbinols **57.1** in place of **57.5**, and/or different phosphonates **57.2**, the corresponding products **57.4** are obtained.

Scheme **58** illustrates the preparation of a phosphonate moiety is attached to the phenylalanine scaffold by means of a heteroatom and a multi-carbon chain.

In this procedure, a substituted phenylalanine derivative **58.1** is reacted with a dialkyl bromoalkyl phosphonate **58.2** to afford the product **58.3**. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a suitable base such as sodium hydride or cesium carbonate. The product is then transformed, using the sequence of reactions shown in Scheme **56**, into the epoxide **58.4**.

For example, the protected aminoacid **58.5**, prepared as described above (Scheme **56**) from 3-mercaptophenylalanine, the preparation of which is described in WO 0036136, is reacted with a dialkyl 2-bromoethyl phosphonate **58.6**, prepared as described in Synthesis, 1994, 9, 909, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the thioether product **58.7**. The latter compound is then converted, using the sequence of reactions shown in Scheme **56**, into the epoxide **58.8**.

Using the above procedures, but employing different phenols, thiols, and amines **58.1** in place of **58.5**, and/or different phosphonates **58.2**, the corresponding products **58.4** are obtained.

Scheme **59** depicts the preparation of phosphonate-substituted phenylalanine derivatives in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom.

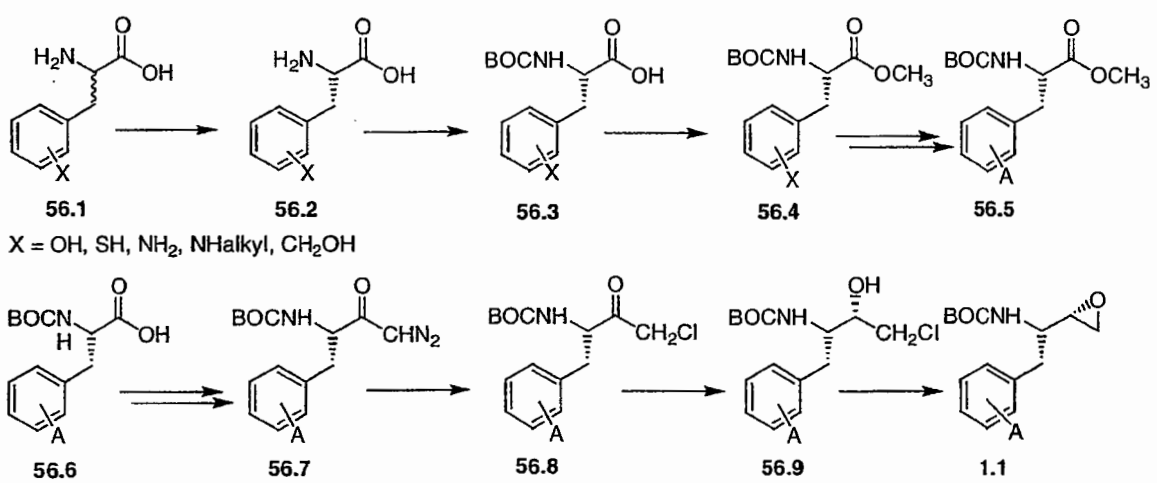
In this procedure, a protected hydroxymethyl-substituted phenylalanine **59.1** is converted into the halomethyl-substituted compound **59.2**. For example, the carbinol **59.1** is treated with triphenylphosphine and carbon tetrabromide, as described in J. Am. Chem. Soc., 108, 1035, 1986 to afford the product **59.2** in which Z is Br. The bromo compound is then reacted with a dialkyl terminally hetero-substituted alkylphosphonate **59.3**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is SH, NH_2 or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is OH, a strong base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **59.4**, which, employing the sequence of reactions shown in Scheme **56**, is transformed into the epoxide **59.5**.

For example, the protected 4-hydroxymethyl-substituted phenylalanine derivative **59.6**, obtained from the 4-hydroxymethyl phenylalanine, the preparation of which is described in

Syn. Comm., 1998, 28, 4279, is converted into the bromo derivative **59.7**, as described above. The product is then reacted with a dialkyl 2-aminoethyl phosphonate **59.8**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the amine product **59.9**. The latter compound is then converted, using the sequence of reactions shown in Scheme **56**, into the epoxide **59.10**.

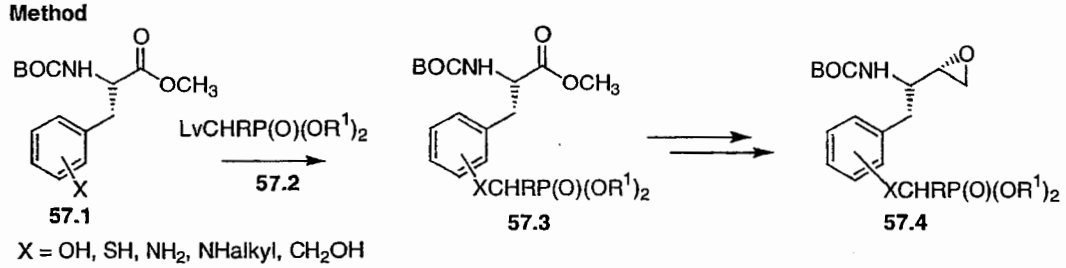
Using the above procedures, but employing different carbinols **59.1** in place of **59.6**, and/or different phosphonates **59.3**, the corresponding products **59.5** are obtained.

Scheme 56

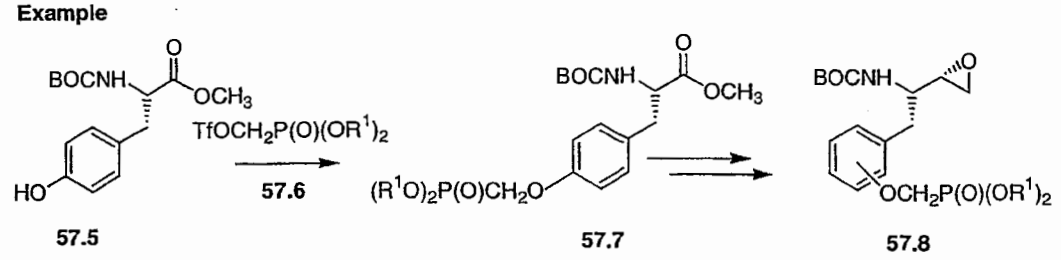


Scheme 57

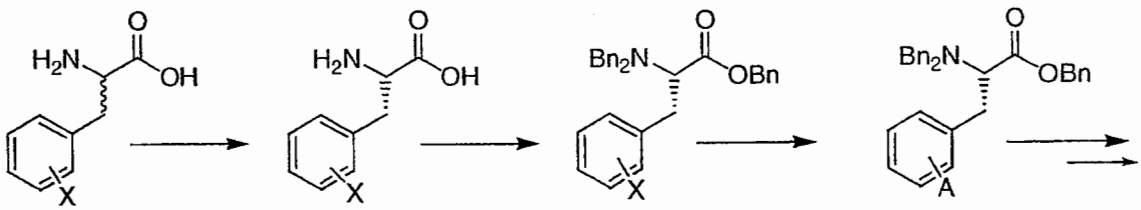
Method



Example

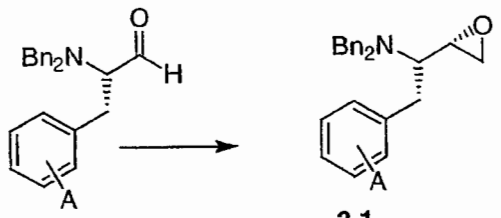


Scheme 56a



56.1 **56.2** **56a.3** **56a.4**

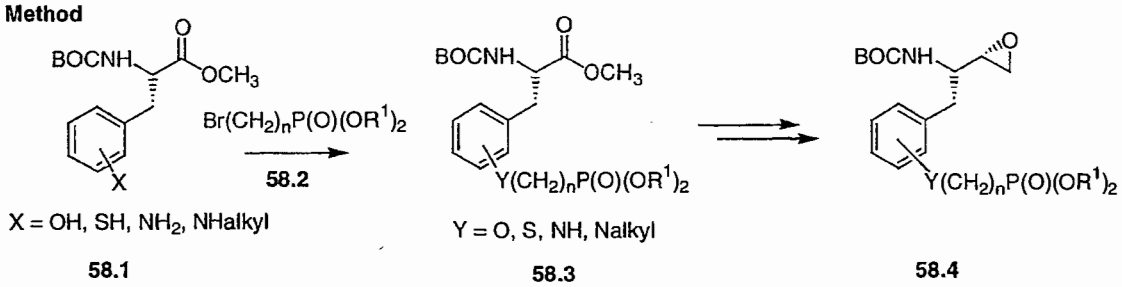
X = OH, SH, NH_2, NHalkyl, CH_2OH



56a.5 **3.1**

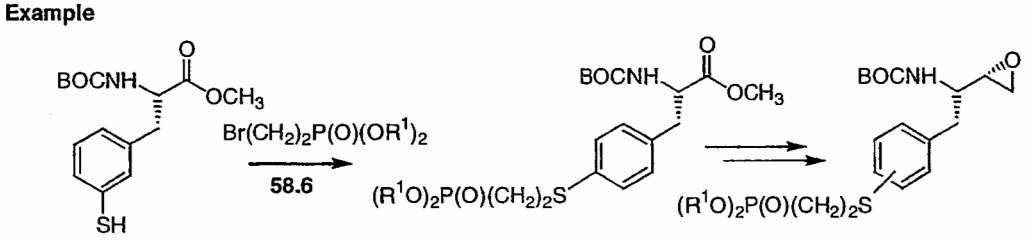
Scheme 58

Method



58.1 58.3 58.4

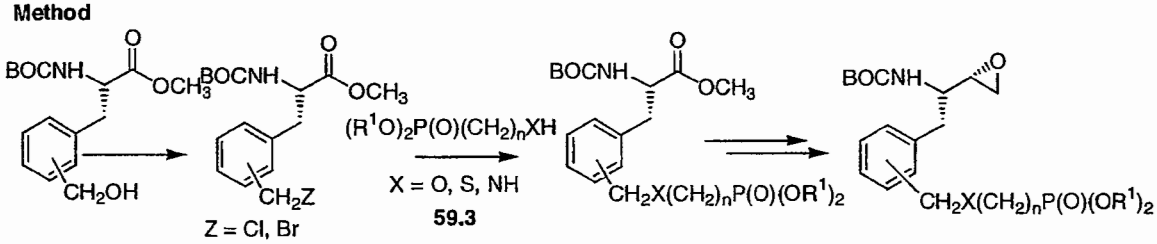
Example



58.5 58.7 58.8

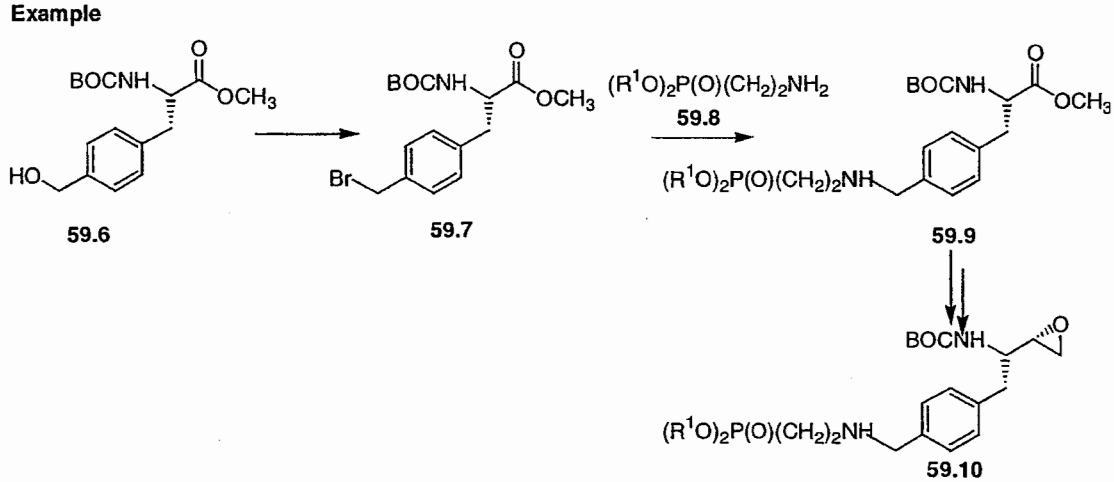
Scheme 59

Method



59.1 59.2 59.4 59.5

Example



59.6 59.7 59.9

59.10

Preparation of phenylalanine derivatives 2.1 incorporating phosphonate moieties or precursors thereto.

Scheme **60** illustrates the preparation of the hydroxymethyl oxazolidine derivative **2.1**, in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor thereto, such as [OH], [SH] Br etc. In this reaction sequence, the substituted phenylalanine **60.1**, in which A is as defined above, is transformed, via the intermediates **60.2** - **60.9**, into the hydroxymethyl product **2.1**. In this procedure, phenylalanine, or a substituted derivative thereof, **60.1**, is converted into the phthalimido derivative **60.2**. The conversion of amines into phthalimido derivatives is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 358. The amine is reacted with phthalic anhydride, 2-carboethoxybenzoyl chloride or N-carboethoxyphthalimide, optionally in the presence of a base such as triethylamine or sodium carbonate, to afford the protected amine **60.2**. Preferably, the aminoacid is reacted with phthalic anhydride in toluene at reflux, to yield the phthalimido product. The carboxylic acid is then transformed into an activated derivative such as the acid chloride **60.3**, in which X is Cl. The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of a tertiary amide such as dimethylformamide. Preferably, the carboxylic acid is transformed into the acid chloride by reaction with oxalyl chloride and a catalytic amount of dimethylformamide, in toluene solution at ambient temperature, as described in WO 9607642. The acid chloride **60.3**, X = Cl, is then converted into the aldehyde **60.4** by means of a reduction reaction. This procedure is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 620. The transformation can be effected by means of catalytic hydrogenation, a procedure which is referred to as the Rosenmund reaction, or by chemical reduction employing, for example, sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride or triethylsilane. Preferably, the acid chloride **60.3** X = Cl, is hydrogenated in toluene solution over a 5% palladium on carbon catalyst, in the presence of butylene oxide, as described in WO 9607642, to afford the aldehyde **60.4**. The aldehyde **60.4** is then transformed into the cyanohydrin derivative **60.5**. The conversion of aldehydes into cyanohydrins is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 211. For example, the aldehyde **60.4** is converted into the cyanohydrin **60.5** by reaction with trimethylsilyl cyanide in an inert solvent such as dichloromethane, followed by treatment with an organic acid such as citric acid, as described

in WO 9607642, or by alternative methods described therein. The cyanohydrin is then subjected to acidic hydrolysis, to effect conversion of the cyano group into the corresponding carboxy group, with concomitant hydrolysis of the phthalimido substituent to afford the aminoacid **60.6** The hydrolysis reactions are effected by the use of aqueous mineral acid. For example, the substrate **60.5** is reacted with aqueous hydrochloric acid at reflux, as described in WO 9607642, to afford the carboxylic acid product **60.6**. The aminoacid is then converted into a carbamate, for example the ethyl carbamate **60.7**. The conversion of amines into carbamates is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 317. The amine is reacted with a chloroformate, for example ethyl chloroformate, in the presence of a base such as potassium carbonate, to afford the carbamate **60.7**. For example, the aminoacid **60.6** is reacted, in aqueous solution, with ethyl chloroformate and sufficient aqueous sodium hydroxide to maintain a neutral pH, as described in WO 9607642, to afford the carbamate **60.7**. The latter compound is then transformed into the oxazolidinone **60.8**, for example by treatment with aqueous sodium hydroxide at ambient temperature, as described in WO 9607642. The resultant carboxylic acid is transformed into the methyl ester **60.9** by means of a conventional esterification reaction. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and an alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and an alkyl halide, for example an alkyl bromide. For example, the carboxylic acid **60.8** is converted into the methyl ester **60.9** by treatment with methanol at reflux temperature, in the presence of a catalytic amount of sulfuric acid, as described in WO 9607642. The carbomethoxyl group present in the compound **60.9** is then reduced to yield the corresponding carbinol **2.1**. The reduction of carboxylic esters to the carbinols is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 550. The transformation can be effected by the use of reducing agents such as borane-dimethylsulfide, lithium borohydride, diisobutyl aluminum hydride, lithium aluminum hydride and the like. For example, the ester **60.9** is reduced to the carbinol **2.1** by reaction with sodium borohydride in ethanol at ambient temperature, as described in WO 9607642.

The conversion of the substituent A into the group link-P(O)$(OR^1)_2$ may be effected at any convenient step in the reaction sequence, or after the reactant **2.1** has been incorporated into

the intermediates **1**. Specific examples of the preparation of the hydroxymethyl oxazolidinone reactant **2.1** are shown below, (Schemes **61-62**)

Scheme **61** depicts the preparation of hydroxymethyloxazolidinones **61.9** in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **61.1** is converted, using the series of reactions illustrated in Scheme **60**, into the bromophenyloxazolidinone **61.2**. The bromophenyl compound is then coupled, in the presence of a palladium (0) catalyst, with a dialkyl phosphite **61.3**, to afford the phosphonate product **61.4**. The reaction between aryl bromide and dialkyl phosphites to yield aryl phosphonates is described in Synthesis, 56, 1981, and in J. Med. Chem., 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The carbomethoxy substituent in the resultant phosphonate ester **61.4** is then reduced with sodium borohydride to the corresponding hydroxymethyl derivative **61.5**, using the procedure described above (Scheme **60**)
For example, 3-bromophenylalanine **61.6**, prepared as described in Pept. Res., 1990, 3, 176, is converted, using the sequence of reactions shown in Scheme **60**, into 4-(3-bromo-benzyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester **61.7**. This compound is then coupled with a dialkyl phosphite **61.3**, in toluene solution at reflux, in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to afford the phosphonate ester **61.8**. The carbomethoxy substituent is then reduced with sodium borohydride, as described above, to afford the hydroxymethyl product **61.9**.
Using the above procedures, but employing, in place of 3-bromophenylalanine **61.6** different bromophenylalanines **61.1** and/or different dialkyl phosphites **61.3**, the corresponding products **61.5** are obtained.

Scheme **62** illustrates the preparation of phosphonate-containing hydroxymethyl oxazolidinones **62.9** and **62.12** in which the phosphonate group is attached by means of a heteroatom and a carbon chain. In this sequence of reactions, a hydroxy or thio-substituted phenylalanine **62.1** is converted into the benzyl ester **62.2** by means of a conventional acid catalyzed esterification reaction. The hydroxyl or mercapto group is then protected. The protection of phenyl hydroxyl and thiol groups are described, respectively, in Protective

Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, and p. 277. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The protected ester **62.3** is then reacted with phthalic anhydride, as described above (Scheme **60**) to afford the phthalimide **62.4**. The benzyl ester is then removed, for example by catalytic hydrogenation or by treatment with aqueous base, to afford the carboxylic acid **62.5**. This compound is transformed, by means of the series of reactions shown in Scheme **60**, into the carbomethoxy oxazolidinone **62.6**, using in each step the same conditions as are described above (Scheme **60**). The protected OH or SH group is then deprotected. Deprotection of phenols and thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978. The resultant phenol or thiol **62.7** is then reacted with a hydroxyalkyl phosphonate **62.20** under the conditions of the Mitsonobu reaction, as described above (Scheme **49**), to afford the ether or thioether **62.8**. The latter compound is then reduced with sodium borohydride, as described above (Scheme **60**) to afford the hydroxymethyl analog **62.9**.

Alternatively, the phenol or thiophenol **62.7** is reacted with a dialkyl bromoalkyl phosphonate **62.10** to afford the alkylation product **62.11**. The alkylation reaction is performed in a polar organic solvent such as dimethylformamide, acetonitrile and the like, optionally in the presence of potassium iodide, and in the presence of an inorganic base such as potassium or cesium carbonate, or an organic base such as diazabicyclononene or dimethylaminopyridine. The ether or thioether product is then reduced with sodium borohydride to afford the hydroxymethyl compound **62.12**.

For example, 3-hydroxyphenylalanine **62.13** (Fluka) is converted in to the benzyl ester **62.14** by means of a conventional acid-catalyzed esterification reaction. The ester is then reacted with tert-butylchlorodimethylsilane and imidazole in dimethylformamide, to afford the silyl ether **62.15**. The protected ether is then reacted with phthalic anhydride, as described above (Scheme **60**) to yield the phthalimido-protected compound **62.16**. Basic hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, then affords the carboxylic acid **62.17**. This compound is then transformed, by means of the series of reactions shown in Scheme **60**, into the carbomethoxy-substituted oxazolidinone **62.18**. The silyl protecting group is then removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, to produce the phenol **62.19**. The latter compound is reacted with a dialkyl hydroxymethyl phosphonate **62.20** diethylazodicarboxylate and triphenylphosphine, by means of the Mitsonobu reaction. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4 and in Org. React., 1992, 42, 335. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. The reaction yields the phenolic ether **62.21**. The carbomethoxy group is then reduced by reaction with sodium borohydride, as described above, to afford the carbinol **62.22**.

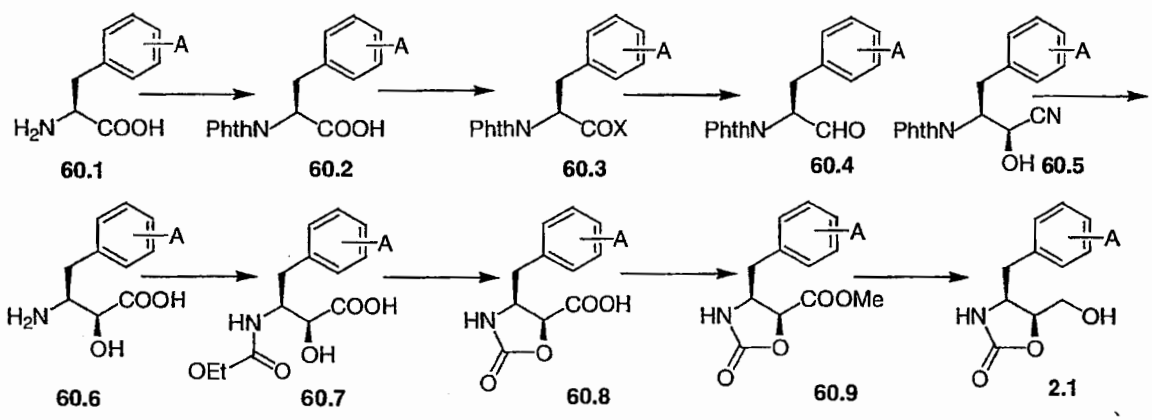
Using the above procedures, but employing, in place of 3-hydroxyphenylalanine **62.13**, different hydroxy or mercapto-substituted phenylalanines **62.1**, and/or different dialkyl hydroxyalkyl phosphonates **62.20**, the corresponding products **62.9** are obtained.

As a further example of the methods illustrated in Scheme **62**, 4-mercaptophenylalanine **62.23**, prepared as described in J. Am. Chem. Soc., 1997, 119, 7173, is converted into the benzyl ester **62.24** by means of a conventional acid-catalyzed esterification reaction. The mercapto group is then protected by conversion to the S-adamantyl group, by reaction with 1-adamantanol and trifluoroacetic acid at ambient temperature as described in Chem. Pharm. Bull., 26, 1576, 1978. The amino group is then converted into the phthalimido group as described above, and the ester moiety is hydrolyzed with aqueous base to afford the carboxylic acid **62.27**. The latter compound is then transformed, by means of the series of reactions

shown in Scheme **60**, into the carbomethoxy oxazolidinone **62.28**. The adamantyl protecting group is then removed by treatment of the thioether **62.28** with mercuric acetate in trifluoroacetic acid at 0°, as described in Chem. Pharm. Bull., 26, 1576, 1978, to produce the thiol **62.29**. The thiol is then reacted with one molar equivalent of a dialkyl bromoethylphosphonate **62.30**, (Aldrich) and cesium carbonate in dimethylformamide at 70°, to afford the thioether product **62.31**. The carbomethoxy group is then reduced with sodium borohydride, as described above, to prepare the carbinol **62.32**.

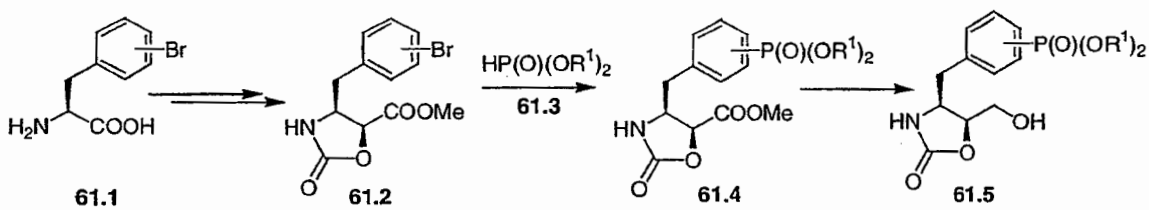
Using the above procedures, but employing, in place of 4-mercaptophenylalanine **62.23**, different hydroxy or mercapto-substituted phenylalanines **62.1**, and/or different dialkyl bromoalkyl phosphonates **62.10**, the corresponding products **62.12** are obtained.

Scheme 60

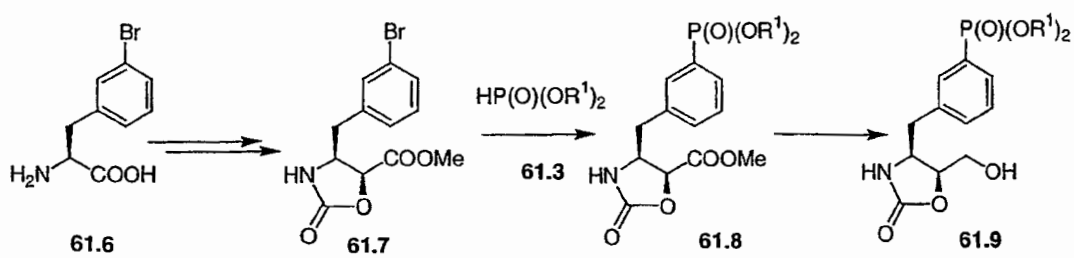


Scheme61

Method

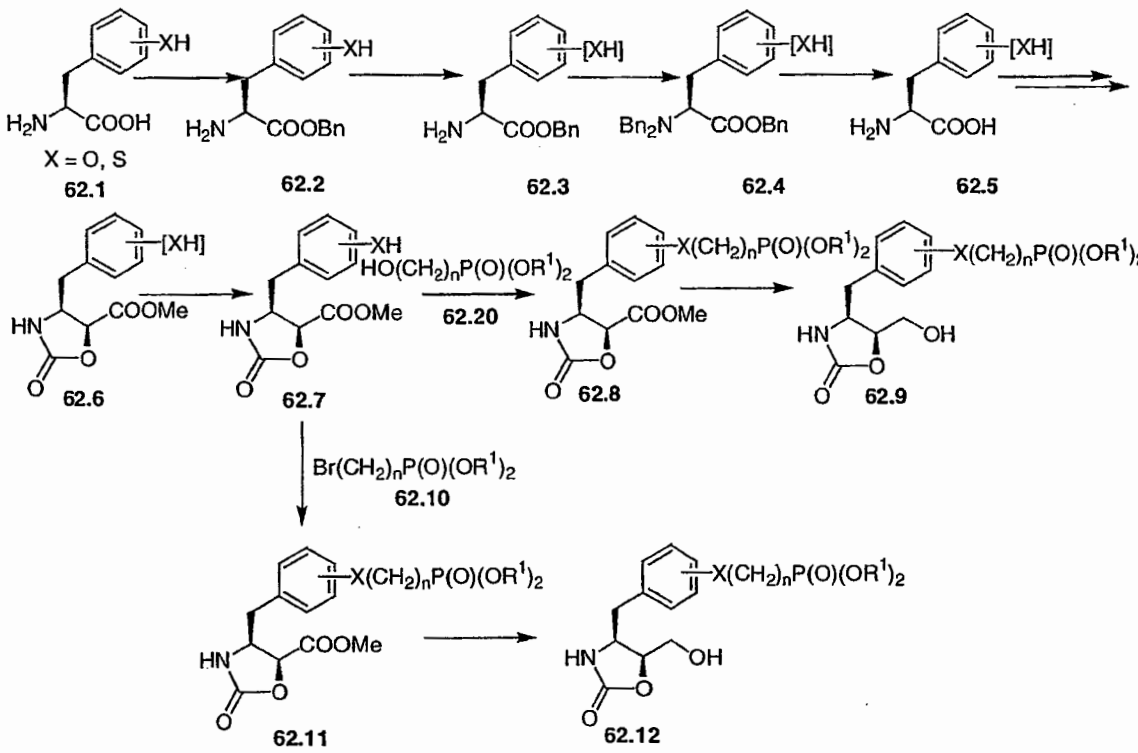


Example

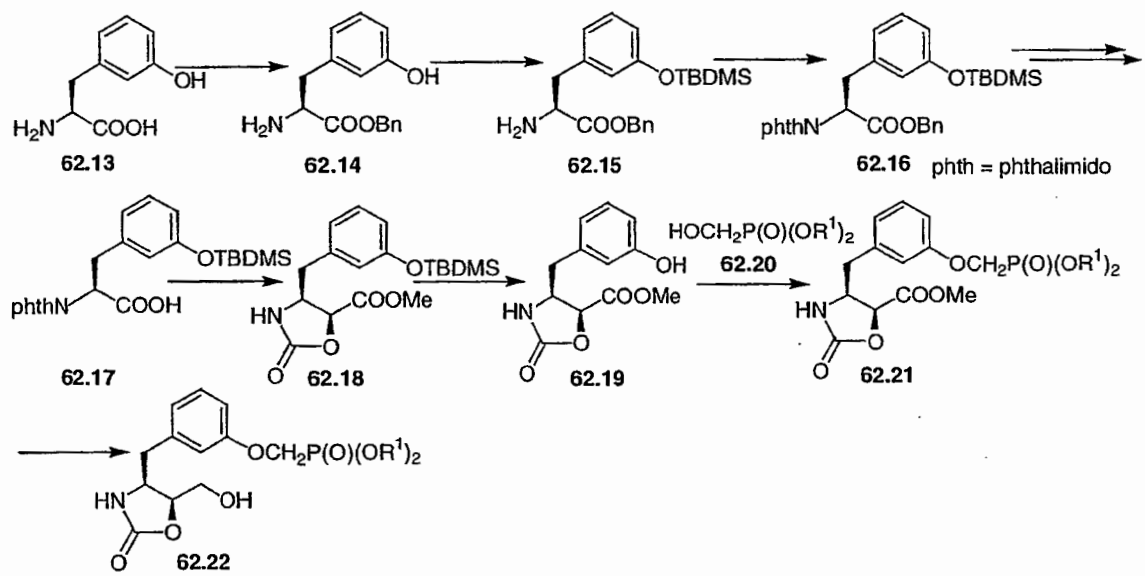


Scheme 62

Method

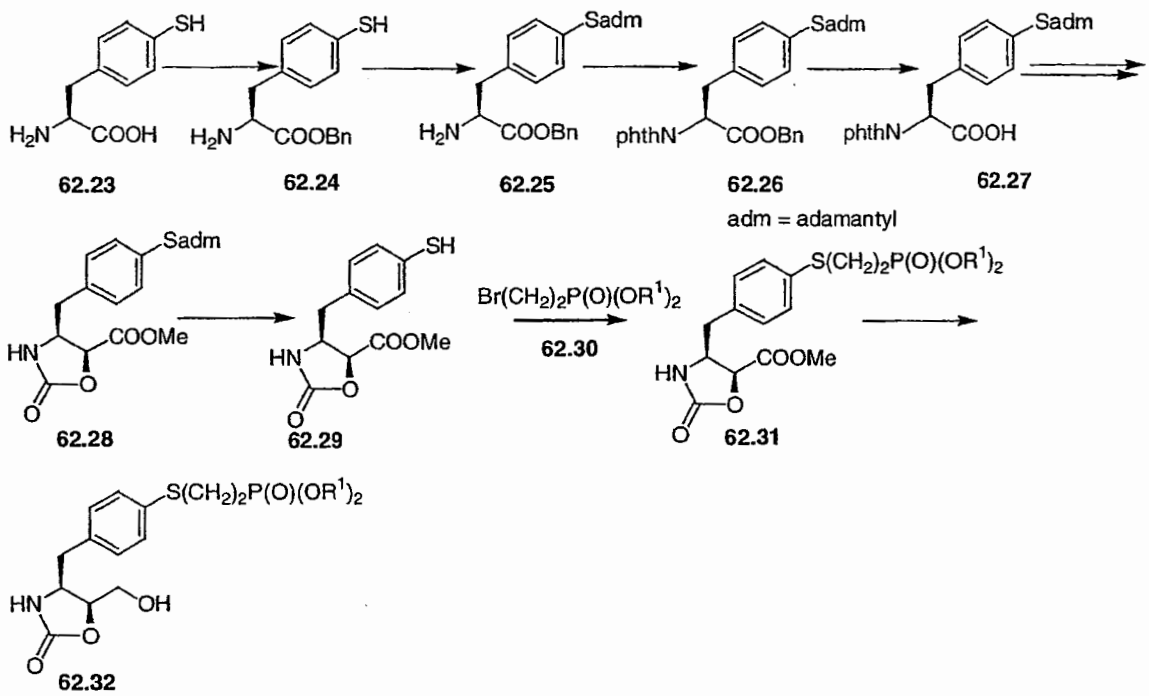


Scheme 62 Example 1



5

Scheme 62 Example 2



Preparation of the phosphonate-containing thiophenol derivatives 7.2.

Schemes **63** - **83** describe the preparation of phosphonate-containing thiophenol derivatives **7.2** which are employed as described above (Schemes **7** - **9**) in the preparation of the phosphonate ester intermediates **1** in which X is sulfur.

Scheme **63** depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol **63.1** is protected to afford the product **63.2**. The protection of phenyl thiol groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277. For example, thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in

Bull. Chem. Soc. Jpn., 37, 433, 1974. The product is then coupled, in the presence of triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, with a dialkyl phosphite **63.3**, to afford the phosphonate ester **63.4**. The thiol protecting group is then removed, as described above, to afford the thiol **63.5**.

For example, 3-bromothiophenol **63.6** is converted into the 9-fluorenylmethyl (Fm) derivative **63.7** by reaction with 9-fluorenylmethyl chloride and diisopropylethylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite **63.3**, as described above, to afford the phosphonate ester **63.8**. The Fm protecting group is then removed by treatment of the product with piperidine in dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol **63.9**.

Using the above procedures, but employing, in place of 3-bromothiophenol **63.6**, different thiophenols **63.1**, and/or different dialkyl phosphites **63.3**, the corresponding products **63.5** are obtained.

Scheme **64** illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol **64.2** is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative **64.3**. The latter compound is reacted with a halodialkyl phosphite **64.4** to afford the product **64.5;** deprotection then affords the thiophenol **64.6**

For example, 4-bromothiophenol **64.7** is converted into the S-triphenylmethyl (trityl) derivative **64.8**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **64.9** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorophosphite **64.10** to afford the phosphonate **64.11**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **64.12**.

Using the above procedures, but employing, in place of the bromo compound **64.7**, different halo compounds **64.1**, and/or different halo dialkyl phosphites **64.4**, there are obtained the corresponding thiols **64.6**.

Scheme **65** illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol **65.1** is subjected to free-radical bromination to afford a bromomethyl product **65.2**. This compound is reacted with a sodium dialkyl phosphite **65.3** or a trialkyl phosphite, to give the displacement or rearrangement product **65.4**, which upon deprotection affords the thiophenol **65.5**.

For example, 2-methylthiophenol **65.6** is protected by conversion to the benzoyl derivative **65.7**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **65.8.** This material is reacted with a sodium dialkyl phosphite **65.3**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **65.9**. Alternatively, the bromomethyl compound **65.8** is converted into the phosphonate **65.9** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **65.8** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100^0 to produce the phosphonate **65.9**. Deprotection of the phosphonate **65.9**, for example by treatment with aqueous ammonia, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiol **65.10**.

Using the above procedures, but employing, in place of the bromomethyl compound **65.8**, different bromomethyl compounds **65.2**, there are obtained the corresponding thiols **65.5**.

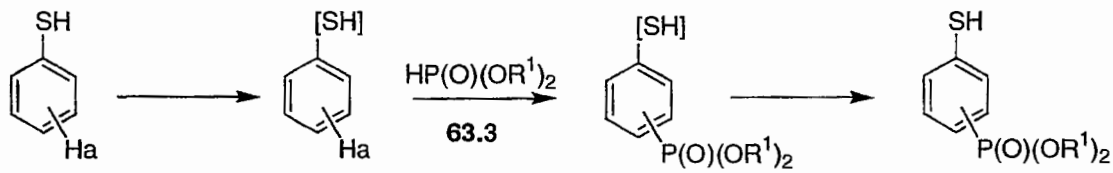
Scheme **66** illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **66.1** is reacted with a dialkyl hydroxyalkylphosphonate **66.2** under the conditions of the Mitsonobu reaction, for example as described in Org. React., 1992, 42, 335, to afford the coupled product **66.3**. Deprotection then yields the O- or S-linked products **66.4**.

For example, the substrate 3-hydroxythiophenol, **66.5**, is converted into the monotrityl ether **66.6**, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **66.7** in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound **66.8**. Removal of the trityl protecting group, as described above, then affords the thiophenol **66.9**.

Using the above procedures, but employing, in place of the phenol **66.5**, different phenols or thiophenols **66.1**, there are obtained the corresponding thiols **66.4**.

Scheme 63

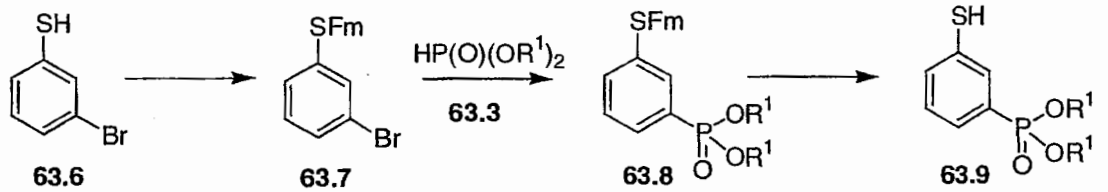
Method



63.1 **63.2** **63.4** **63.5**

Ha = halogen

Example

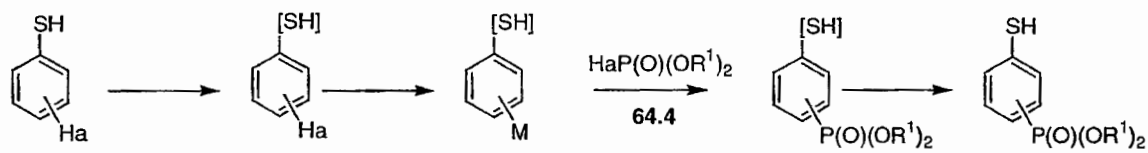


63.6 **63.7** **63.8** **63.9**

Fm = 9-fluorenylmethyl

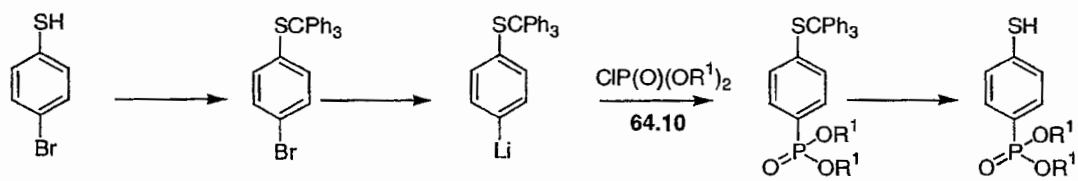
Scheme 64

Method



64.1 **64.2** **64.3** **64.5** **64.6**

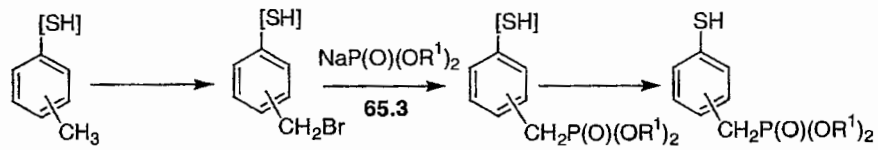
Example



64.7 **64.8** **64.9** **64.11** **64.12**

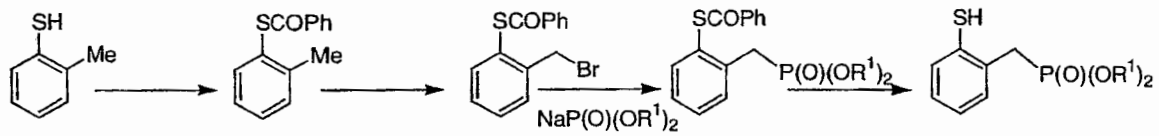
Scheme 65

Method



65.1 65.2 65.4 65.5

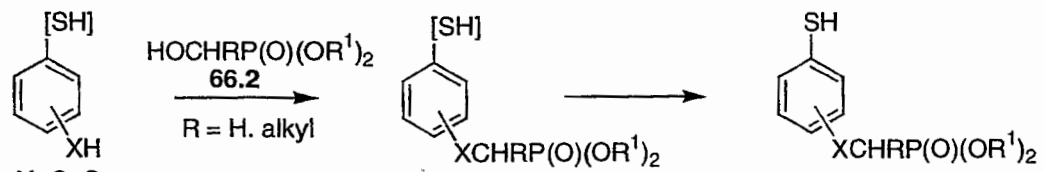
Example



65.6 65.7 65.8 65.3 65.9 65.10

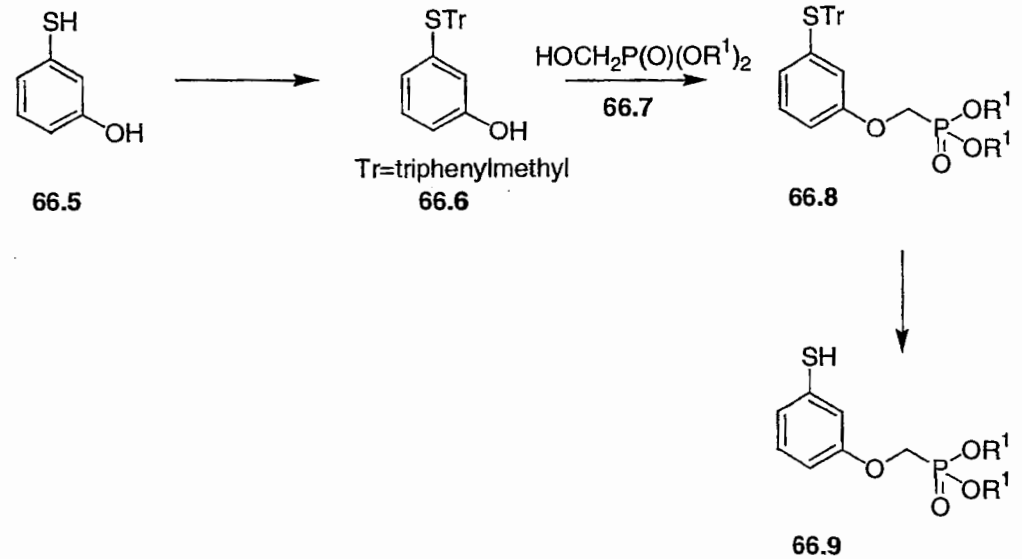
Scheme 66

Method



66.1 66.3 66.4

Example



66.5 Tr=triphenylmethyl 66.6 66.8 66.9

5

Scheme **67** illustrates the preparation of thiophenols **67.4** bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **67.1** is reacted with an activated ester, for example the trifluoromethanesulfonate **67.2**, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product **67.3**. Deprotection then affords the thiol **67.4**.

For example, 4-methylaminothiophenol **67.5** is reacted in dichloromethane solution with one equivalent of acetyl chloride and a base such as pyridine, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the S-acetyl product **67.6**. This material is then reacted with a dialkyl trifluoromethanesulfonylmethyl phosphonate **67.7**, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product **67.8**. Preferably, equimolar amounts of the phosphonate **67.7** and the amine **67.6** are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product **67.8**. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiophenol **67.9**.

Using the above procedures, but employing, in place of the thioamine **67.5**, different phenols, thiophenols or amines **67.1**, and/or different phosphonates **67.2**, there are obtained the corresponding products **67.4**.

Scheme **68** illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate **68.2**. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol **68.1** is reacted with a dialkyl bromoalkyl phosphonate **68.2** to afford the product **68.3**. Deprotection then affords the free thiophenol **68.4.**

For example, 3-hydroxythiophenol **68.5** is converted into the S-trityl compound **68.6**, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate **68.7**, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of

potassium iodide, at about 50°, to yield the ether product **68.8**. Deprotection, as described above, then affords the thiol **68.9**.

Using the above procedures, but employing, in place of the phenol **68.5**, different phenols, thiophenols or amines **68.1**, and/or different phosphonates **68.2**, there are obtained the corresponding products **68.4**.

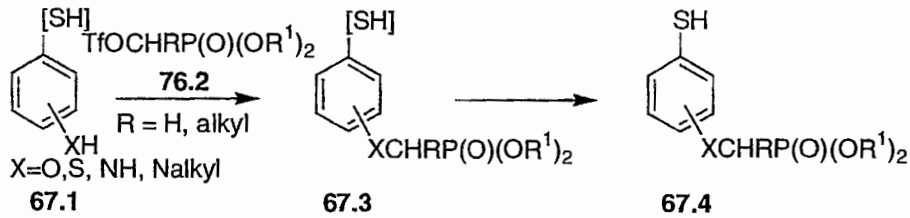
Scheme **69** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **69.2** is coupled with an aromatic bromo compound **69.1**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **69.3**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **69.4**, or the saturated analog **69.6**.

For example, 3-bromothiophenol is converted into the S-Fm derivative **69.7**, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate **69.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product **69.9**. Deprotection, as described above, then affords the thiol **69.10**. Optionally, the initially formed unsaturated phosphonate **69.9** is subjected to reduction, for example using diimide, as described above, to yield the saturated product **69.11**, which upon deprotection affords the thiol **69.12**.

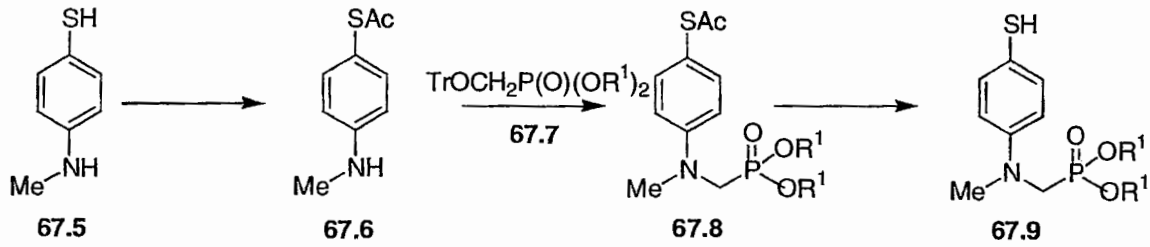
Using the above procedures, but employing, in place of the bromo compound **69.7**, different bromo compounds **69.1**, and/or different phosphonates **69.2**, there are obtained the corresponding products **69.4** and **69.6**

Scheme 67

Method

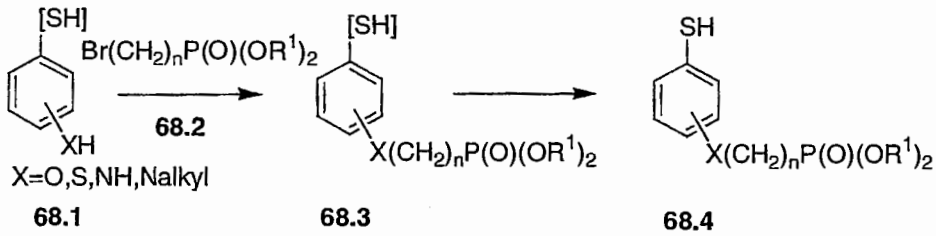


Example

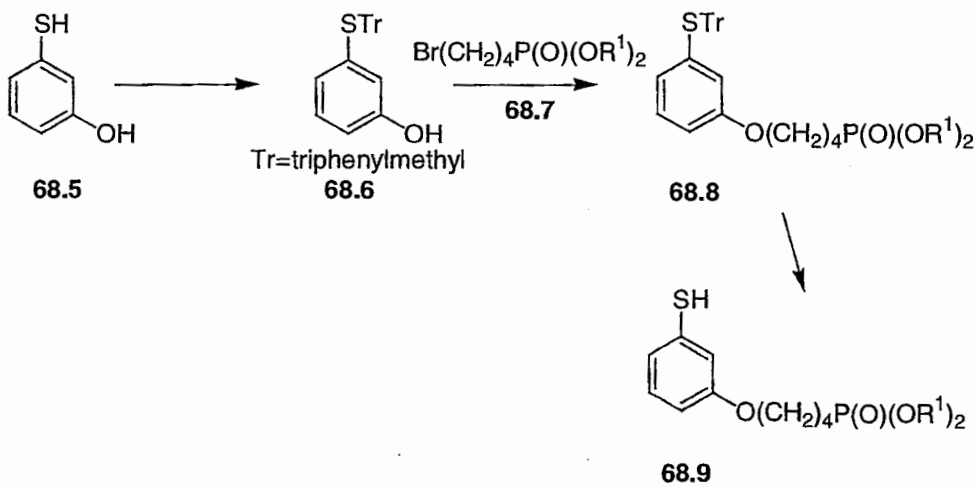


Scheme 68

Method

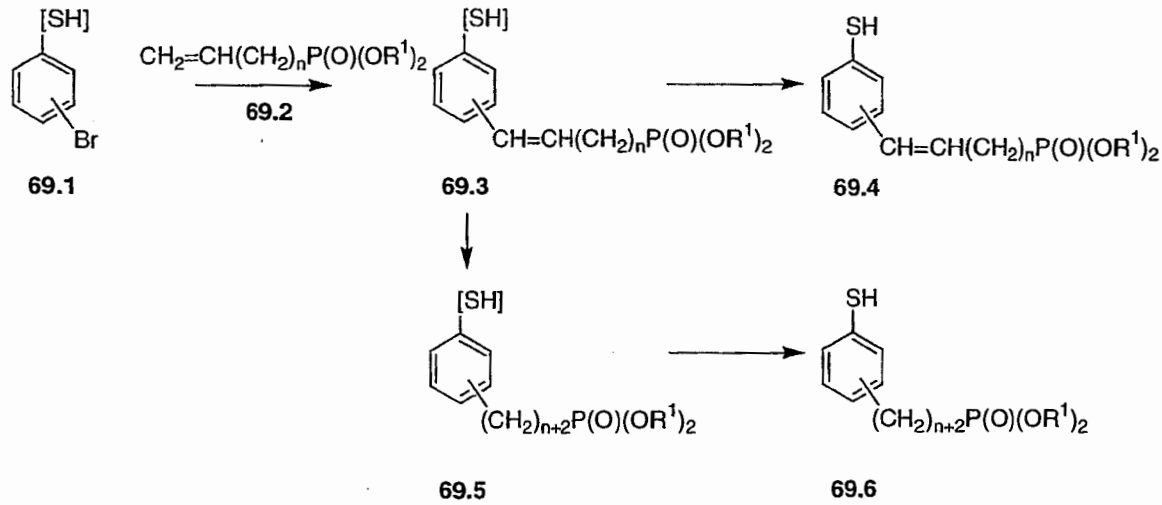


Example



Scheme 69

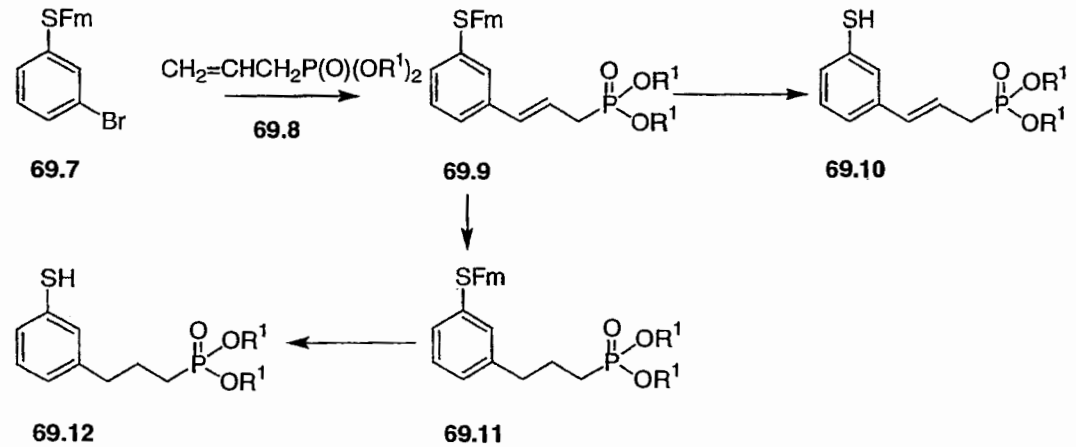
Method



69.1 69.3 69.4

69.5 69.6

Example



69.7 69.9 69.10

69.12 69.11

Scheme **70** illustrates the preparation of an aryl-linked phosphonate ester **70.4** by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **70.1** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product **70.3** which is deprotected to yield the thiol **70.4**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic

Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **70.5**. This material is reacted with a dialkyl 4-bromophenylphosphonate **70.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **70.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **70.8**.
Using the above procedures, but employing, in place of the boronate **70.5**, different boronates **70.1**, and/or different phosphonates **70.2**, there are obtained the corresponding products **70.4**.

Scheme **71** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **71.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **71.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **71.3** is then deprotected to afford the thiol **71.4**. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **71.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **71.5** is then reacted with a dialkyl 4-(bromomethyl)phenylphosphonate, **71.6**, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The thioether product **71.7** thus obtained is deprotected, as described above, to afford the thiol **71.8**.
Using the above procedures, but employing, in place of the thiophenol **71.5**, different phenols, thiophenols or amines **71.1**, and/or different phosphonates **71.2**, there are obtained the corresponding products **71.4**.

Scheme **72** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.
In this procedure, a suitably protected thiophenol **72.1**, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **72.2**, in the presence of an

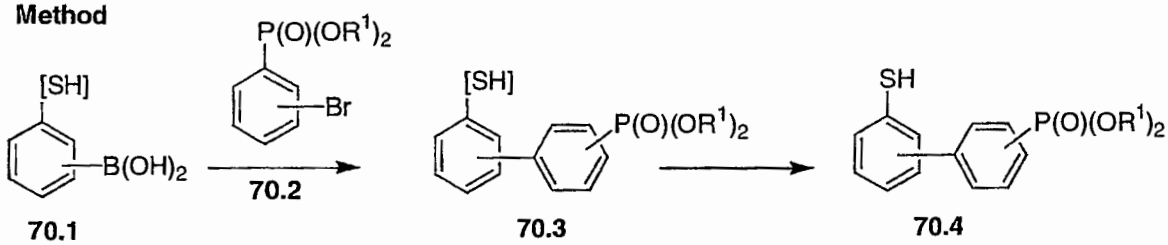
organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **72.3**. Deprotection, as described above, then affords the thiol **72.4**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p 707.

For example, 2,3-dihydro-1H-indole-5-thiol, **72.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **72.6**, as described above, and the ester is then reacted with the trifluoromethanesulfonate **72.7**, in a polar organic solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, to yield the phosphonate **72.8**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **72.9**.

Using the above procedures, but employing, in place of the thiol **72.5**, different thiols **72.1**, and/or different triflates **72.2**, there are obtained the corresponding products **72.4**.

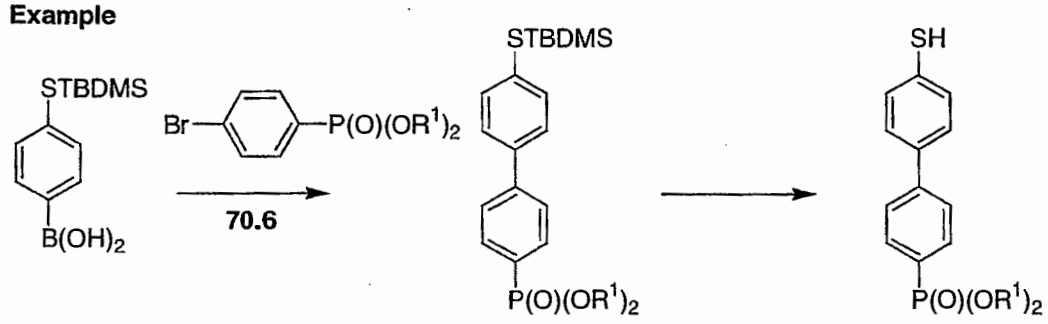
Scheme 70

Method



70.1 **70.3** **70.4**

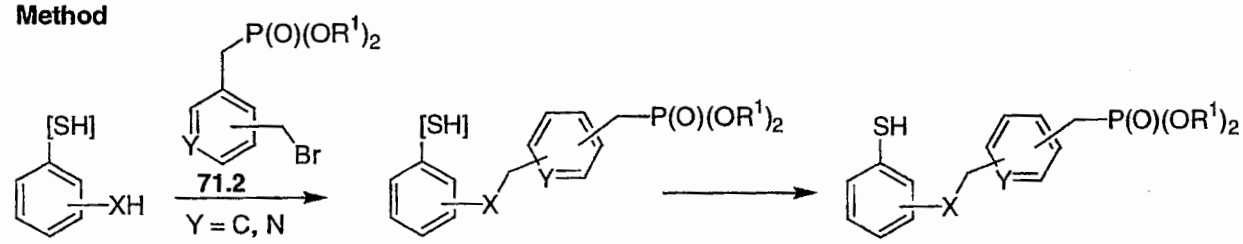
Example



70.5 **70.7** **70.8**

Scheme 71

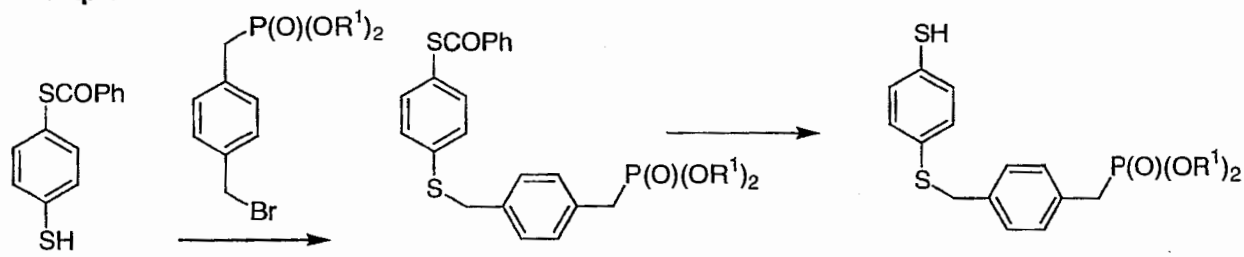
Method



X =O, S, NH, Nalkyl

71.1 **71.3** **71.4**

Example



71.5 **71.7** **71.8**

5 **Preparation of phosphonate-containing analogs of isobutylamine 10.2.**

Schemes **73 - 75** illustrate the preparation of the phosphonate-containing analogs of isobutylamine which are employed in the preparation of the phosphonate esters **2**.

Scheme **73** depicts the preparation of phosphonates which are attached to the isobutylamine by means of an amide linkage. In this procedure, an aminoacid **73.1** is protected to afford the product **73.2**. The protection of amino groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, 309. Amino groups are protected, for example, by conversion into carbamates such as the tert. butoxycarbamate (BOC) derivative, or by reaction with phthalic anhydride to afford the phthalimido (phth) derivative. The amine-protected aminoacid **73.2** is then coupled with a dialkyl aminoalkyl phosphonate **73.3**, to yield the amide **73.4**. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide. Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide. The protecting group is then removed to afford the amine **73.5**. Deprotection of amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 309ff. For example, BOC groups are removed by treatment with acids such as trifluoroacetic acid, and phthalimido groups are removed by reaction with hydrazine hydrate.

For example, 2-methyl-4-aminobutyric acid **73.6** (Acros) is reacted with phthalic anhydride in refluxing toluene, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 358, to give the phthalimido derivative **73.7**. The product is coupled with a dialkyl aminoethyl phosphonate **73.8**, the preparation of which is described in J. Org. Chem., 2000, 65, 676,

in the presence of dicyclohexyl carbodiimide, to give the amide **73.9**. The protecting group is removed by reaction of the product with ethanolic hydrazine at ambient temperature, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 358, to afford the amine **73.10**.

Using the above procedures, but employing, in place of the acid **73.6**, different acids **73.1**, and/or different amines **73.3**, the corresponding amides **73.5** are obtained.

Scheme **74** depicts the preparation of isobutylamine phosphonates in which the phosphonate is attached by means of an aromatic ring. In this procedure, 2-methyl-but-3-enylamine **74.1**, prepared as described in Org. Prep. Proc. Int. 1976, 8, 75, is coupled, in the presence of a palladium catalyst, as described above (Scheme **50**) with a dialkyl bromophenyl phosphonate **74.2** to afford the olefinic product **74.3**. Optionally, the product is reduced to afford the saturated analog **74.4**. The reduction is effected catalytically, for example by the use of a palladium catalyst, or chemically, for example by the use of diimide.

For example, the amine **74.1** is coupled with a dialkyl 4-bromophenyl phosphonate **74.5**, prepared as described in J. Organomet. Chem., 1999, 581, 62, to yield the product **74.6**. Catalytic hydrogenation in ethanol, using a 5% palladium catalyst, then affords the saturated compound **74.7**.

Using the above procedures, but employing, in place of the phosphonate **74.5**, different phosphonates **74.2** the corresponding products **74.3** and **74.4** are obtained.

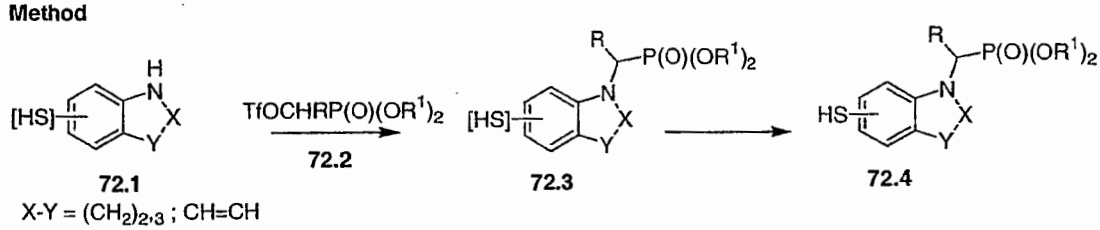
Scheme **75** illustrates the preparation of isobutylamine phosphonates in which the phosphonate group is attached by means of an alkylene chain. In this procedure, a bromoamine **75.1** is protected, as described in Scheme **73**, to afford the derivative **75.2**. The product is then reacted with a trialkyl phosphite **75.3**, in an Arbuzov reaction, as described in Scheme **65**, to give the phosphonate **75.4**. Deprotection then affords the amine **75.5**.

For example, 4-bromo-2-methyl-butylamine **75.6**, prepared as described in Tet., 1998, 54, 2365, is converted, as described above, into the phthalimido derivative **75.7**. The product is then heated at 110° with a trialkyl phosphite **75.3** to yield the phosphonate **75.8**, which upon reaction with ethanolic hydrazine affords the amine **75.9**.

Using the above procedures, but employing, in place of the bromide **75.6**, different bromides **75.1**, and/or different phosphites **75.3**, the corresponding products **75.5** are obtained.

Scheme 72

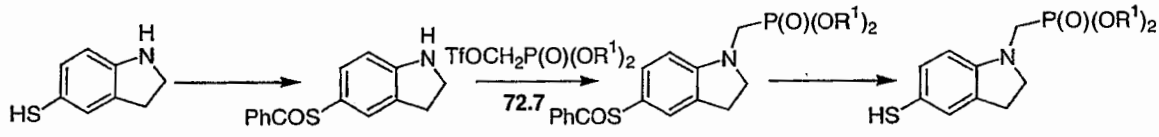
Method



72.1 72.3 72.4

X-Y = $(CH_2)_{2,3}$; CH=CH

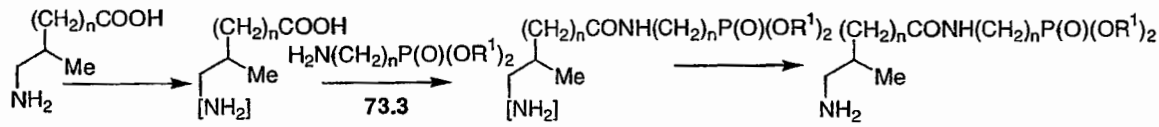
Example



72.5 72.6 72.8 72.9

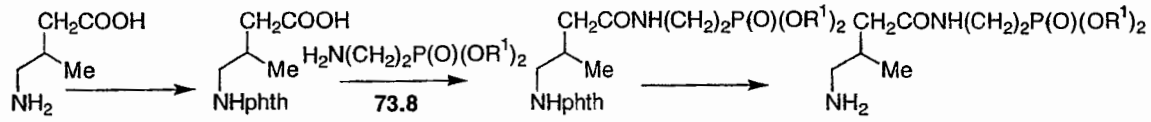
Scheme 73

Method



73.1 73.2 73.4 73.5

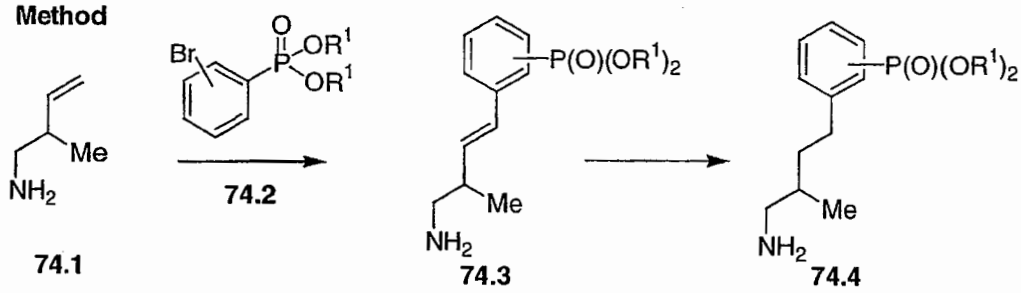
Example



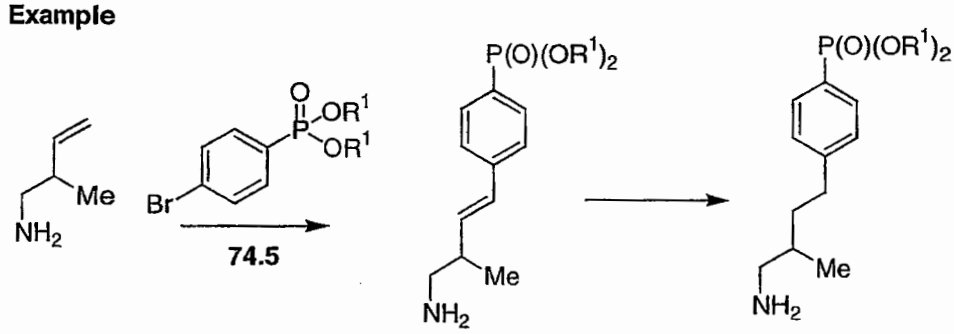
73.6 73.7 73.9 73.10

Scheme 74

Method

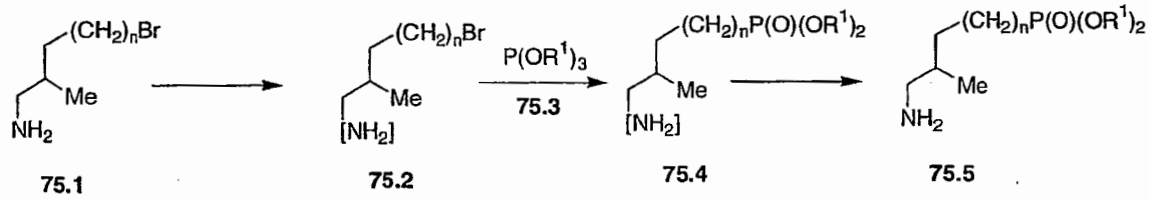


Example

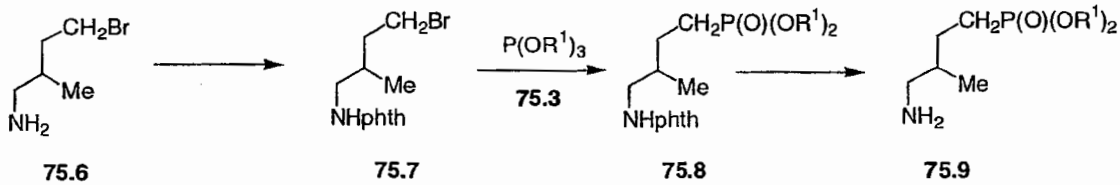


Scheme 75

Method



Example



Preparation of cyclopentylmethylamine phosphonates.

Schemes **76 - 78** illustrate the preparation of cyclopentylmethylamine phosphonates which are employed, as shown in Schemes **10 - 12**, in the preparation of the phosphonate esters **3**.

Scheme **76** depicts the preparation of phosphonates attached to the cyclopentyl ring either directly or by means of an alkoxy link. In this procedure, a hydroxy-substituted

cyclopentylmethylamine **76.1** is protected, and the protected derivative **76.2** is converted into the corresponding bromide **76.3**, for example by treatment with carbon tetrabromide and triphenyl phosphine as described in Scheme **59**. The bromo compound is then reacted with a trialkyl phosphite **76.4** in an Arbuzov reaction, as described above, to afford the phosphonate **76.5** which is then deprotected to give the amine **76.6**. Alternatively, the protected amine **76.2** is reacted with a dialkyl bromoalkyl phosphonate **76.7** to give the ether **76.8**. The alkylation reaction is conducted at ca 100° in a polar organic solvent such as dimethylformamide in the presence of a base such as sodium hydride or lithium hexamethyl disilylazide. The product is then deprotected to give the amine **76.9**.

For example, 3-aminomethyl-cyclopentanol **76.10**, prepared as described in Tet., 1999, 55, 10815, is converted, as described above, into the phthalimido derivative **76.11**. The product is then converted, as described above, into the bromo analog **76.12**. The latter compound is reacted at ca 120° with a trialkyl phosphite **76.4** to afford the phosphonate **76.13**, which upon deprotection by reaction with hydrazine yields the amine **76.14**.

Using the above procedures, but employing, in place of the bromide **76.12**, different bromides **76.3**, and/or different phosphites **76.4**, the corresponding products **76.6** are obtained. Alternatively, 2-aminomethyl-cyclopentanol **76.15**, prepared as described in Tet., 1999, 55, 10815, is converted into the phthalimido derivative **76.16**. The product is then reacted in dimethylformamide solution with an equimolar amount of a dialkyl bromopropyl phosphonate **76.17**, prepared as described in J. Am. Chem. Soc., 2000, 122, 1554, and sodium hydride, to give the ether **76.18**. Deprotection, as described above, then affords the amine **76.19**.
Using the above procedures, but employing, in place of the carbinol **76.15**, different carbinols **76.1**, and/or different phosphonates **76.7**, the corresponding products **76.9** are obtained.

Scheme **77** illustrates the preparation of cyclopentylmethylamines in which the phosphonate group is attached by means of an amide group. In this procedure, a carboxyalkyl-substituted cyclopentylmethylamine **77.1** is protected to afford the derivative **77.2**. The product is then coupled, as described above, (Scheme **1**) with a dialkyl aminoalkyl phosphonate **77.3** to yield the amide **77.4**. Deprotection then affords the amine **77.5**.

For example, 3-aminomethyl-cyclopentanecarboxylic acid **77.6** prepared as described in J. Chem. Soc. Perkin 2, 1995, 1381, is converted into the BOC derivative **77.7**, by reaction with BOC anhydride in aqueous sodium hydroxide, as described in Proc. Nat. Acad. Sci., 69, 730,

1972. The product is then coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminopropyl phosphonate **77.8** to produce the amide **77.9**. Removal of the BOC group, for example by treatment with hydrogen chloride in ethyl acetate, then affords the amine **77.10**. Using the above procedures, but employing, in place of the carboxylic acid **77.6**, different carboxylic acids **77.1**, and/or different phosphonates **77.3**, the corresponding products **77.5** are obtained.

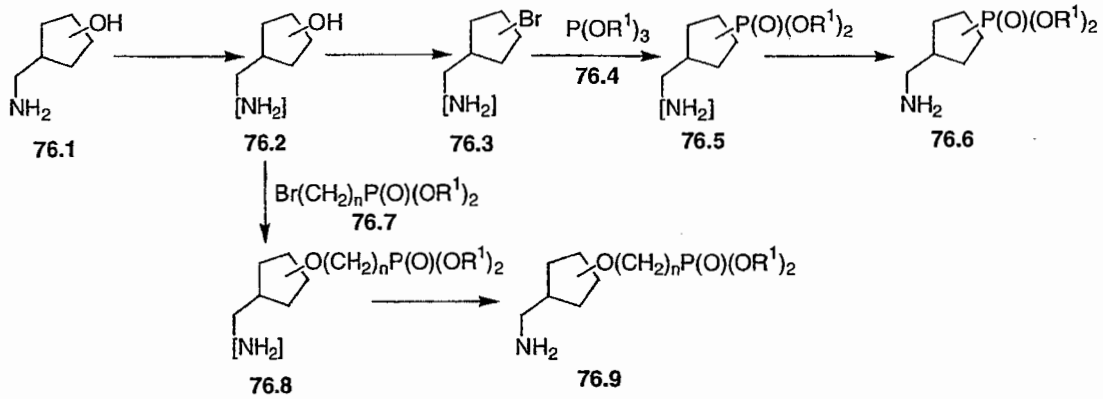
Scheme **78** illustrates the preparation of cyclopentylmethylamines in which the phosphonate group is attached by means of an aminoalkyl group. In this procedure, the more reactive amino group of an amino-substituted cyclopentylmethylamine **78.1** is protected, to give the derivative **78.2**. The product is then coupled, by means of a reductive amination reaction, as described in Scheme **55**, with a dialkyl formylalkyl phosphonate **78.3** to give the amine product **78.4**, which upon deprotection affords the amine **78.5**.

For example, 2-aminomethyl-cyclopentylamine **78.6** prepared as described in WO 9811052, is reacted with one molar equivalent of phthalic anhydride in refluxing tetrahydrofuran, to yield the phthalimido derivative **78.7**. The latter compound is reacted, in the presence of sodium cyanoborohydride, with a dialkyl formylmethyl phosphonate **78.8**, prepared as described in Zh. Obschei. Khim., 1987, 57, 2793, to afford the product **78.9**. Deprotection, as described above, then yields the amine **78.10**.

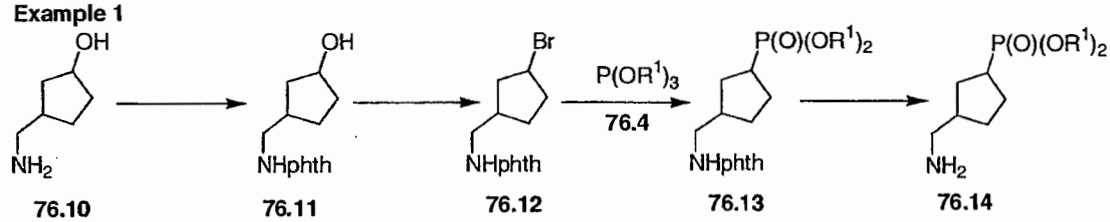
Using the above procedures, but employing, in place of the diamine **78.6**, different diamines **78.1**, and/or different phosphonates **78.3**, the corresponding products **78.5** are obtained.

Scheme 76

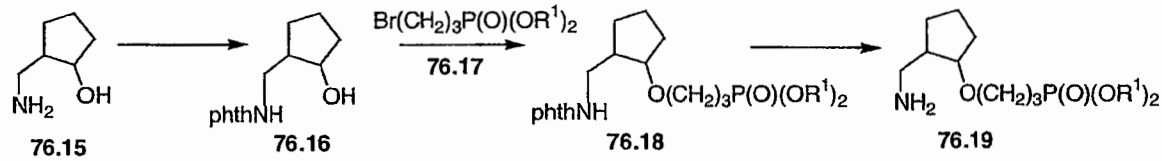
Method



Example 1

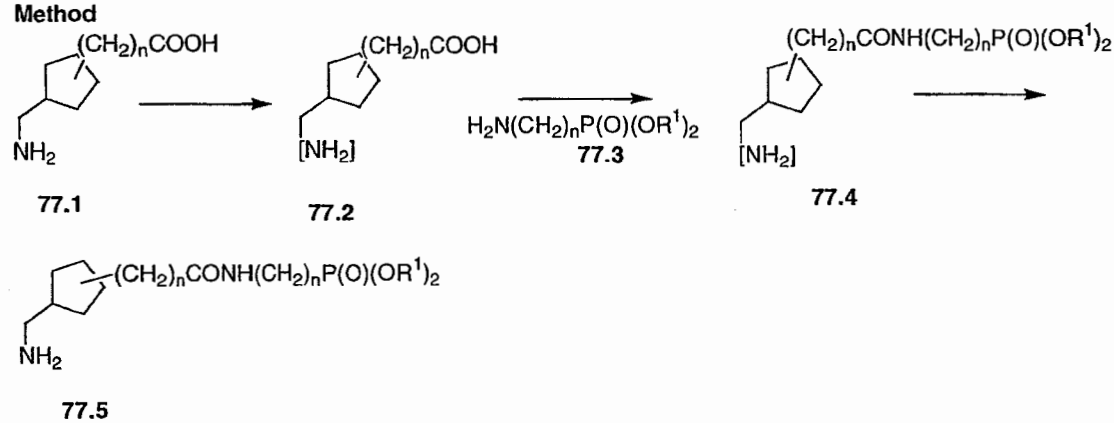


Example 2

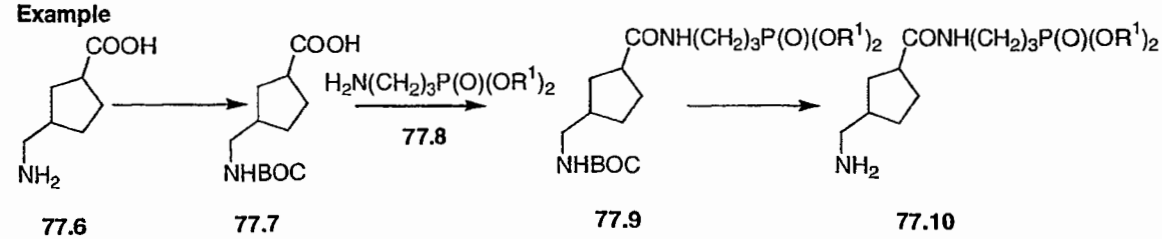


Scheme 77

Method

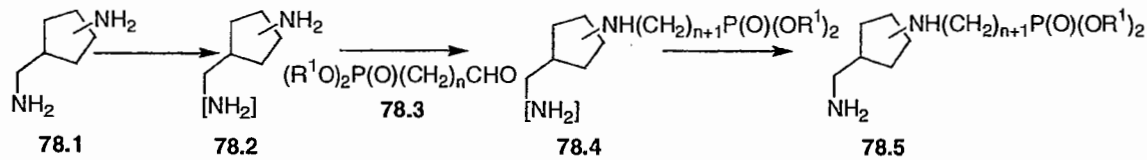


Example



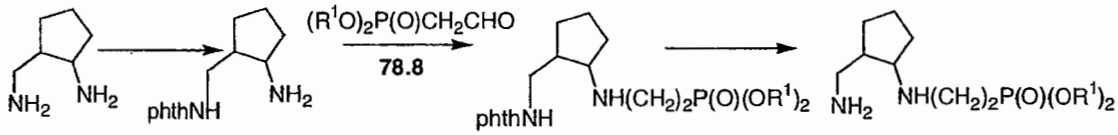
Scheme 78

Method



78.1 78.2 78.3 78.4 78.5

Example



78.6 78.7 78.8 78.9 78.10

Preparation of phosphonate-substituted fluorobenzylamines 39.2.

Schemes **79** and **80** illustrate the preparation of phosphonate-substituted 3-fluorobenzylamines **39.2** which are used in the preparation of the phosphonate esters **6**.

Scheme **79** depicts the preparation of fluorobenzylamines in which the phosphonate is attached by means of an amide or aminoalkyl linkage. In this procedure, the more reactive amino group in an amino-substituted 3-fluorobenzylamine **79.1** is protected. The product **79.2** is then coupled with a dialkyl carboxyalkyl phosphonate **79.3** to give the amide **79.4**, which upon deprotection yields the free amine **79.5**. Alternatively, the mono-protected diamine **79.2** is coupled, under reductive amination conditions, with a dialkyl formylalkyl phosphonate **79.6**, to produce the amine **79.7**, which upon deprotection affords the benzylamine **79.8**.

For example, 4-amino-3-fluorobenzylamine **79.9**, prepared as described in WO 9417035, is reacted in pyridine solution with one molar equivalent of acetic anhydride, to give the acetylamino product **79.10**. The product is reacted with a dialkyl carboxyethyl phosphonate **79.11**, (Epsilon) and dicyclohexyl carbodiimide, to afford the amide **79.12**. Deprotection, for example by reaction with 85% hydrazine, as described in J. Org. Chem., 43, 4593, 1978, then gives the amine **79.13**.

Using the above procedures, but employing, in place of the diamine **79.9**, different diamines **79.1**, and/or different phosphonates **79.3**, the corresponding products **79.5** are obtained.

As a further example, the mono-protected diamine **79.10** is reacted, as described above, with a dialkyl formyl phosphonate **79.13**, (Aurora) and sodium cyanoborohydride, to give the amination product **79.14**. Deprotection then affords the amine **79.15**.

Using the above procedures, but employing, in place of the diamine **79.10** different diamines **79.2**, and/or different phosphonates **79.6**, the corresponding products **79.8** are obtained.

Scheme **80** depicts the preparation of fluorobenzylamines in which the phosphonate is attached either directly or by means of a saturated or unsaturated alkylene linkage. In this procedure, a bromo-substituted 3-fluorobenzylamine **80.1** is protected. The product **80.2** is coupled, by means of a palladium-catalyzed Heck reaction, as described in Scheme **50**, with a dialkyl alkenyl phosphonate **80.3**, to give the olefinic product **80.4** which upon deprotection affords the amine **80.5**. Optionally, the double bond is reduced, for example by catalytic hydrogenation over a palladium catalyst, to yield the saturated analog **80.9**. Alternatively, the protected bromobenzylamine **80.6** is coupled, as described in Scheme **61**, in the presence of a palladium catalyst, with a dialkyl phosphite **80.6** to produce the phosphonate **80.7**. Deprotection then affords the amine **80.8**.

For example, 2-bromo-5-fluorobenzylamine **80.10**, (Esprix Fine Chemicals) is converted, as described above, into the N-acetyl derivative **80.11**. The product is the coupled in dimethylformamide solution with a dialkyl vinyl phosphonate **80.12**, (Fluka) in the presence of palladium (II) acetate and triethylamine, to give the coupled product **80.13**. Deprotection then affords the amine **80.14** and hydrogenation of the latter compound yields the saturated analog **80.15**.

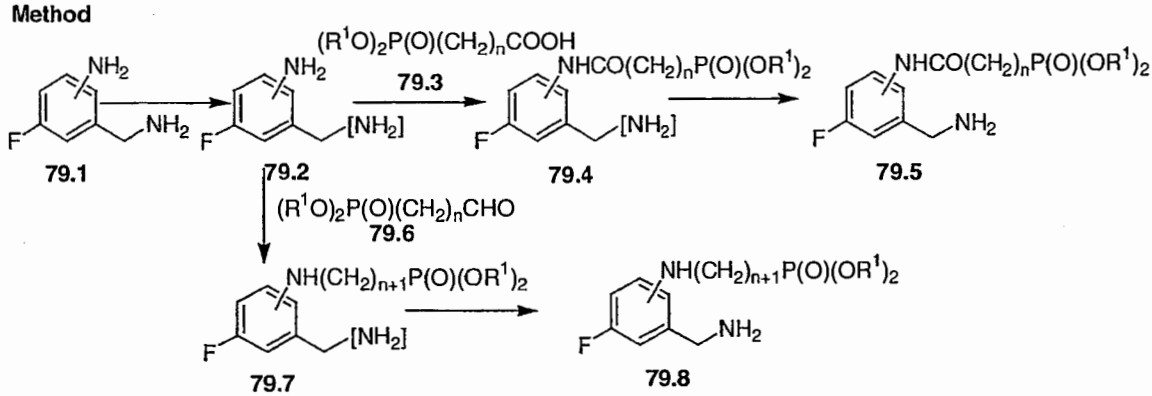
Using the above procedures, but employing, in place of the bromo compound **80.10** different bromo compounds **80.1**, and/or different phosphonates **80.3**, the corresponding products **80.5** and **80.9** are obtained.

As a further example, the protected amine **80.11** is coupled, in toluene at 100°, with a dialkyl phosphite **80.6**, in the presence of tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine, to give the phosphonate **80.16**. Deprotection then affords the amine **80.17**.

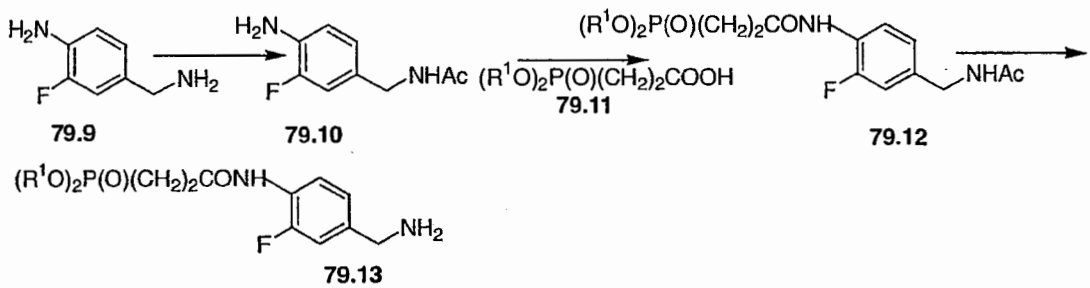
Using the above procedures, but employing, in place of the bromo compound **80.11** different bromo compounds **80.2**, and/or different phosphites **80.6**, the corresponding products **80.8** are obtained.

Scheme 79

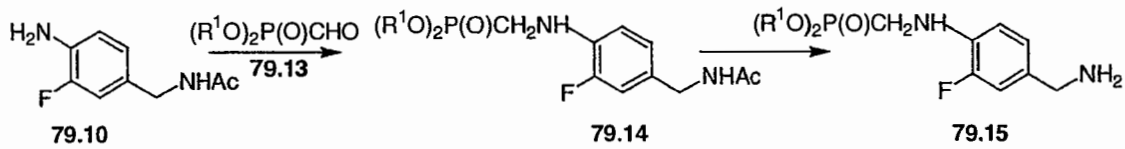
Method



Example 1

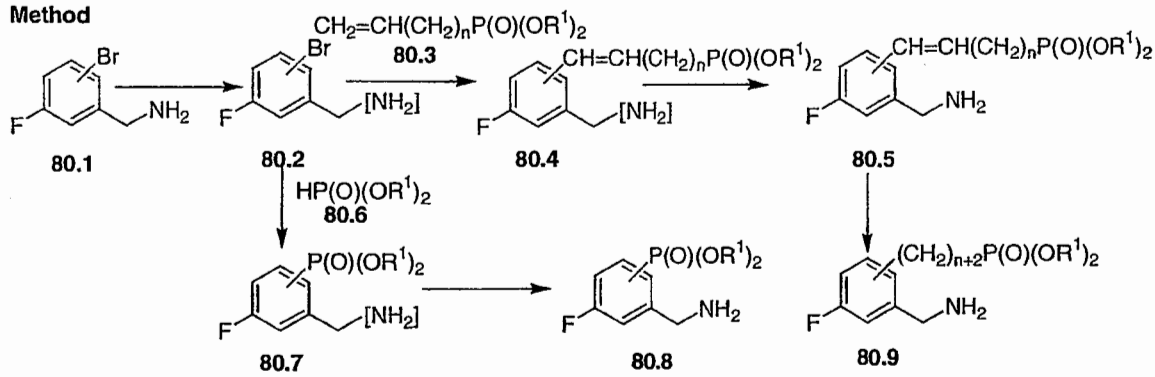


Example 2

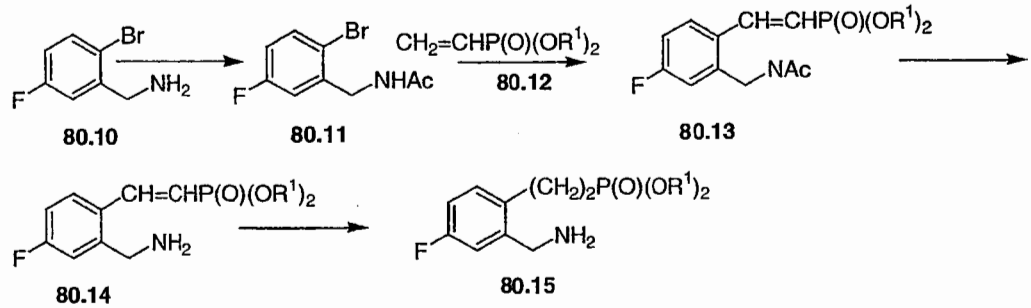


Scheme 80

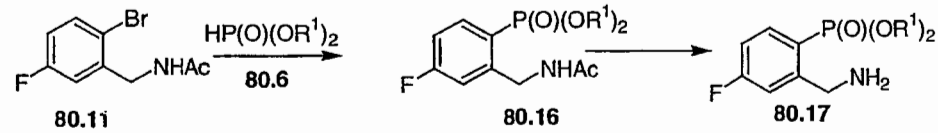
Method



Example 1



Example 2



Preparation of phosphonate-substituted fluorobenzylamines 39.4.

Schemes **81** and **82** illustrate the preparation of phosphonate-substituted 3-fluorobenzylamines **39.4** which are used in the preparation of the phosphonate esters **7**.

Scheme **81** depicts the preparation of 3-fluorobenzylamines in which the phosphonate group is attached by means of an amide linkage. In this procedure, 3-fluorophenylalanine **81.1**, (Alfa Aesar) is converted into the BOC derivative **81.2**. The product is then coupled with a dialkyl aminoalkyl phosphonate **81.3** to afford the amide **81.4**, which upon deprotection gives the amine **81.5**.

For example, the BOC-protected aminoacid **81.2** is coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminomethyl phosphonate **81.6** (Interchim), to prepare the amide **81.7**. Deprotection then affords the amine **81.8**.

Using the above procedures, but employing, in place of the amine **81.6** different amines **81.3**, the corresponding products **81.5** are obtained.

Scheme **82** illustrates the preparation of fluorobenzylamine derivatives in which the phosphonate group is attached by means of an alkyl or alkoxy chain. In this procedure, a hydroxyalkyl-substituted 3-fluorobenzylamine **82.1** is converted into the BOC derivative **82.2**. This compound is then reacted with a dialkyl bromoalkyl phosphonate **82.3** to give the ether **82.4**. The alkylation reaction is conducted in a polar organic solvent such as N-methylpyrrolidinone in the presence of a strong base such as sodium bis(trimethylsilyl)amide. Deprotection of the product then affords the amine **82.5**. Alternatively, the N-protected carbinol **82.2** is converted into the corresponding bromide **82.6**, for example by reaction with N-bromoacetamide and triphenyl phosphine. The bromo compound is then reacted with a trialkyl phosphite in an Arbuzov reaction, as described above, to give the phosphonate **82.8**, which upon deprotection affords the amine **82.9**.

For example, 2-amino-2-(3-fluoro-phenyl)-ethanol **82.10**, prepared as described in DE 4443892, is converted into the BOC derivative **82.11**. The latter compound is then reacted in dimethylformamide at 100° with a dialkyl bromoethyl phosphonate **82.12** (Aldrich) and sodium hydride, to give the ether product **82.13**. Removal of the BOC group then yields the amine **82.14**.

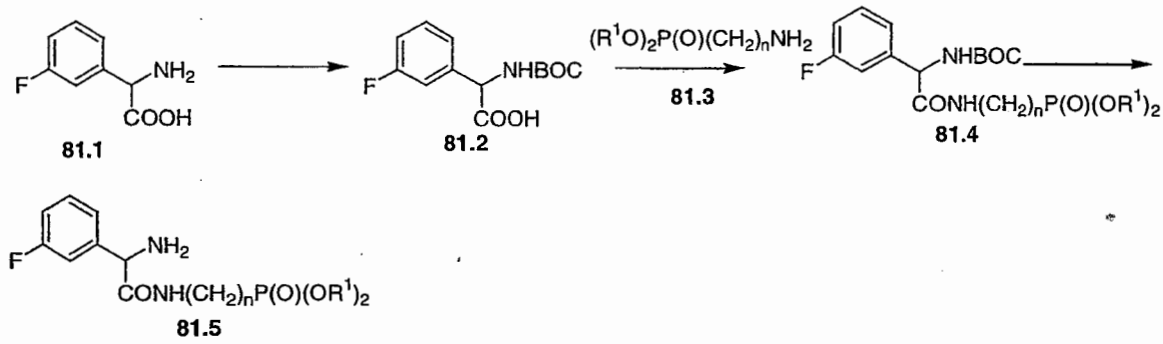
Using the above procedures, but employing, in place of the carbinol **82.10** different carbinols **82.1**, and/or different phosphonates **82.3** the corresponding products **82.5** are obtained.

As a further example, the BOC-protected carbinol **82.11** is reacted with carbon tetrabromide and triphenylphosphine to produce the bromo compound **82.15**. This material is heated at 120° with an excess of a trialkyl phosphite **82.7** to give the phosphonate **82.16**. Deprotection then yields the amine **82.17**.

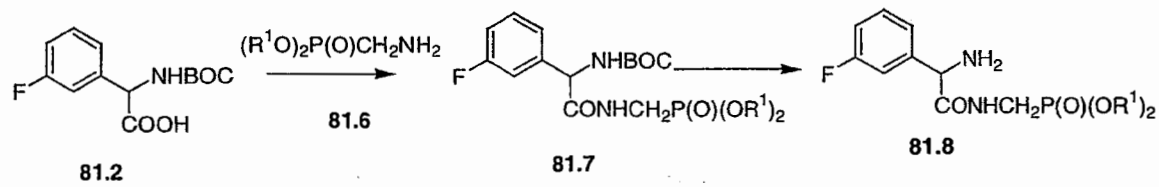
Using the above procedures, but employing, in place of the carbinol **82.11** different carbinols **82.2**, and/or different phosphonates **82.7** the corresponding products **82.9** are obtained.

Scheme 81

Method

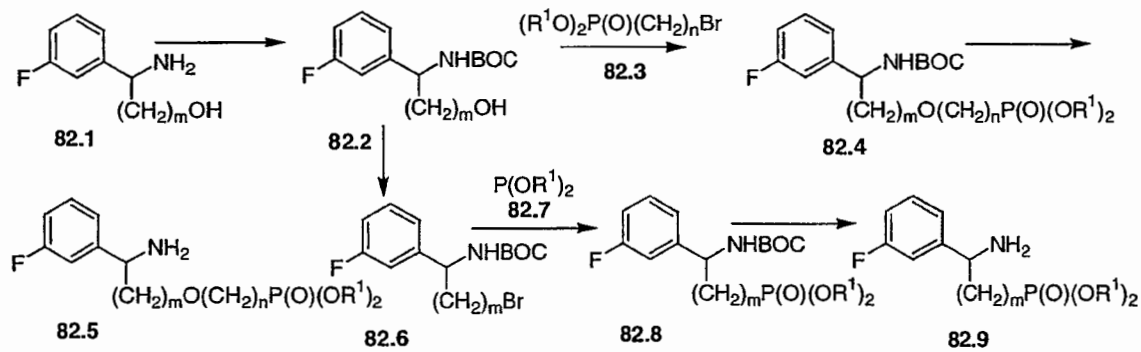


Example

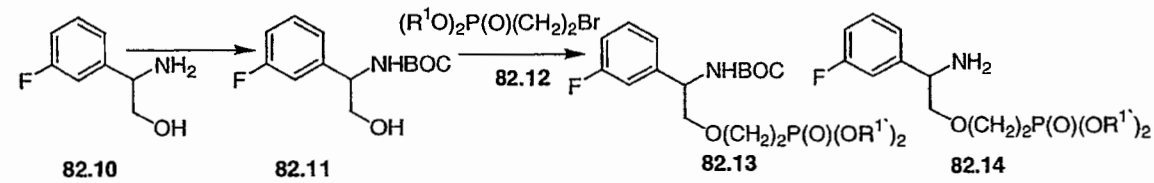


Scheme 82

Method



Example 1



Preparation of the phosphonate-containing tert. butanol derivatives 30.1.

Schemes **83** - **86** illustrate the preparation of the tert. butanol derivatives **30.1** which are employed in the preparation of the phosphonate esters **5**.

Scheme **83** depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of an alkylene chain. In this procedure, a bromoalkyl carbinol **83.1** is reacted with a trialkyl phosphite **83.2** in an Arbuzov reaction, to afford the phosphonate **83.3**. For example, 4-bromo-2-methyl-butan-2-ol **83.4** prepared as described in Bioorg. Med. Chem. Lett., 2001, 9, 525, and a trialkyl phosphite **83.2** are heated at ca. 120° to produce the phosphonate **83.5**.

Using the above procedures, but employing, in place of the bromo compound **83.4** different bromo compounds **83.1**, and/or different phosphites **83.2** the corresponding products **83.3** are obtained.

Scheme **84** depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of an amide linkage. In this procedure, a carboxylic acid **84.1** is coupled with a dialkyl aminoalkyl phosphonate **84.2** to afford the amide **84.3**. The reaction is conducted under the conditions previously described (Scheme **1**) for the preparation of amides.

For example, equimolar amounts of 3-hydroxy-3-methyl-butyric acid **84.4**, (Fluka) and a dialkyl aminoethyl phosphonate **84.5**, the preparation of which is described in J. Org. Chem., 2000, 65, 676 are reacted in tetrahydrofuran in the presence of dicyclohexylcarbodiimide to yield the amide **84.6**.

Using the above procedures, but employing, in place of the carboxylic acid **84.4** different acids **84.1**, and/or different amines **84.2** the corresponding products **84.3** are obtained.

Scheme **85** depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of a heteroatom and an alkylene chain. In this procedure, a hydroxy, mercapto or amino-substituted carbinol **85.1** is reacted with a dialkyl bromoalkyl phosphonate **85.2** to afford the ether, thioether or amine products **85.3**. The reaction is conducted in a polar organic solvent in the presence of suitable base such as sodium hydride or cesium carbonate. For example, 4-mercapto-2-methyl-butan-2-ol **85.4** prepared as described in Bioorg. Med. Chem. Lett., 1999, 9, 1715, is reacted in tetrahydrofuran containing cesium carbonate with a dialkyl bromobutyl phosphonate **85.5**, the preparation of which is described in Synthesis, 1994, 9, 909, to yield the thioether **85.6**.

Using the above procedures, but employing, in place of the thiol **85.4** different alcohols, thiol or amines **85.1**, and/or different bromides **85.2** the corresponding products **85.3** are obtained.

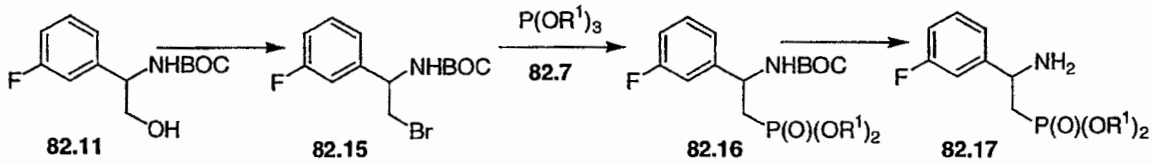
Scheme **86** depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of a nitrogen and an alkylene chain. In this procedure, a hydroxyaldehyde **86.1** is reacted with a dialkyl aminoalkyl phosphonate **86.2** under reductive amination conditions, as described above, (Scheme **55**) to afford the amine **86.3**.

For example, 3-hydroxy-3-methyl-butyraldehyde **86.4** and a dialkyl aminoethyl phosphonate **86.5** the preparation of which is described in J. Org. Chem., 2000, 65, 676 are reacted together in the presence of sodium triacetoxyborohydride, to yield the amine **86.6**.

Using the above procedures, but employing, in place of the aldehyde **86.4** different aldehydes **86.1**, and/or different amines **86.2** the corresponding products **86.3** are obtained.

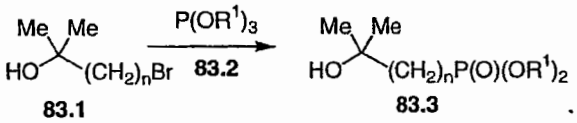
Scheme 82

Example 2

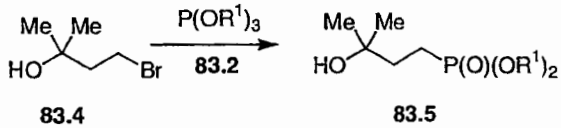


Scheme 83

Method

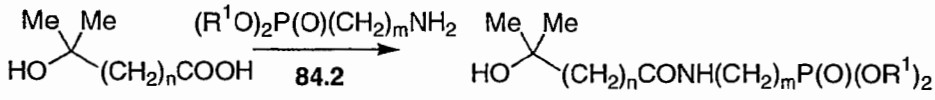


Example



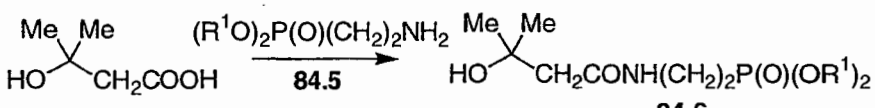
Scheme 84

Method



84.1 **84.3**

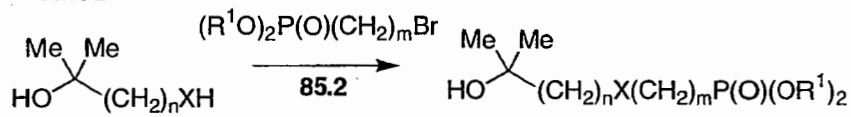
Example



84.4 **84.6**

Scheme 85

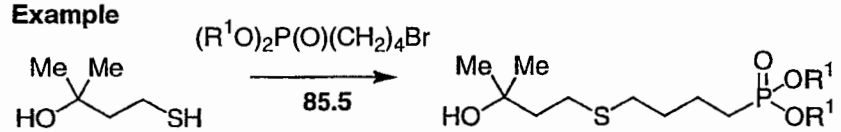
Method



85.1 **85.3**

X = O, S, NH

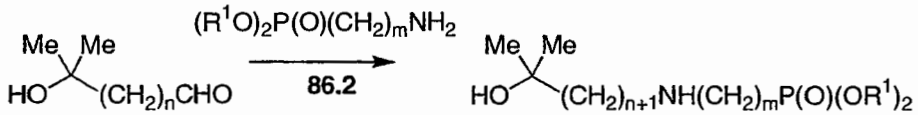
Example



85.4 **85.6**

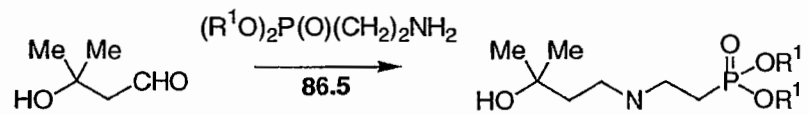
Scheme 86

Method



86.1 **86.3**

Example



86.4 **86.6**

Preparation of the phosphonate-containing benzyl carbamates 43.4.

Schemes **87 - 91** illustrate methods for the preparation of the benzyl carbamates **43.4** which are employed in the preparation of the phosphonate esters **9.** The benzyl alcohols are obtained

by reduction of the corresponding benzaldehydes, the preparation of which is described in Schemes **87** - **90**.

Scheme **87** illustrates the preparation of benzaldehyde phosphonates **87.3** in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde **87.1** is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate **87.2**, under reductive amination conditions, as described above in Scheme **55**, to yield the phosphonate product **87.3**.

For example, benzene-1,3-dialdehyde **87.4** is reacted with a dialkyl aminopropyl phosphonate **87.5**, (Acros) and sodium triacetoxyborohydride, to afford the product **87.6**.

Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde **87.4**, different benzene dialdehydes **87.1**, and/or different phosphonates **87.2**, the corresponding products **87.3** are obtained.

Scheme **88** illustrates the preparation of benzaldehyde phosphonates either directly attached to the benzene ring or attached by means of a saturated or unsaturated carbon chain. In this procedure, a bromobenzaldehyde **88.1** is coupled, as described above, with a dialkyl alkenylphosphonate **88.2**, to afford the alkenyl phosphonate **88.3**. Optionally, the product is reduced to afford the saturated phosphonate ester **88.4**. Alternatively, the bromobenzaldehyde is coupled, as described above, with a dialkyl phosphite **88.5** to afford the formylphenylphosphonate **88.6**.

For example, as shown in Example **1**, 3-bromobenzaldehyde **88.7** is coupled with a dialkyl propenylphosphonate **88.8** (Aldrich) to afford the propenyl product **88.9**. Optionally, the product is reduced, for example by the use of diimide, to yield the propyl phosphonate **88.10**.

Using the above procedures, but employing, in place of 3-bromobenzaldehyde **88.7**, different bromobenzaldehydes **88.1**, and/or different alkenyl phosphonates **88.2**, the corresponding products **88.3** and **88.4** are obtained.

Alternatively, as shown in Example **2**, 4-bromobenzaldehyde is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite **88.5** to afford the 4-formylphenyl phosphonate product **88.12**.

Using the above procedures, but employing, in place of 4-bromobenzaldehyde **88.11**, different bromobenzaldehydes **88.1**, the corresponding products **88.6** are obtained.

Scheme **89** illustrates the preparation of formylphenyl phosphonates in which the phosphonate moiety is attached by means of alkylene chains incorporating two heteroatoms O, S or N. In this procedure, a formyl phenoxy, phenylthio or phenylamino alkanol, alkanethiol or alkylamine **89.1** is reacted with a an equimolar amount of a dialkyl haloalkyl phosphonate **89.2**, to afford the phenoxy, phenylthio or phenylamino phosphonate product **89.3**. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile **89.1**. In cases in which Y is O, a strong base such as sodium hydride or lithium hexamethyldisilazide is employed. In cases in which Y is S or N, a base such as cesium carbonate or dimethylaminopyridine is employed.

For example, 2-(4-formylphenylthio)ethanol **89.4**, prepared as described in Macromolecules, 1991, 24, 1710, is reacted in acetonitrile at 60° with one molar equivalent of a dialkyl iodomethyl phosphonate **89.5**, (Lancaster) to give the ether product **89.6**.

Using the above procedures, but employing, in place of the carbinol **89.4**, different carbinols, thiols or amines **89.1**, and/or different haloalkyl phosphonates **89.2**, the corresponding products **89.3** are obtained.

Scheme **90** illustrates the preparation of formylphenyl phosphonates in which the phosphonate group is linked to the benzene ring by means of an aromatic or heteroaromatic ring. In this procedure, a formylbenzeneboronic acid **90.1** is coupled, in the presence of a palladium catalyst, with one molar equivalent of a dibromoarene, **90.2**, in which the group Ar is an aromatic or heteroaromatic group. The coupling of aryl boronates with aryl bromides to afford diaryl compounds is described in Palladium Reagents and Catalysts, by J. Tsuji, Wiley 1995, p. 218. The components are reacted in a polar solvent such as dimethylformamide in the presence of a palladium(0) catalyst and sodium bicarbonate. The product **90.3** is then coupled, as described above (Scheme **50**) with a dialkyl phosphite **90.4** to afford the phosphonate **90.5**.

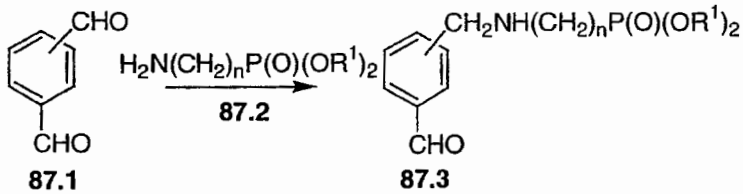
For example, 4-formylbenzeneboronic acid **90.6** is coupled with 2,5-dibromothiophene **90.7** to yield the phenylthiophene product **90.8**. This compound is then coupled with the dialkyl phosphite **90.4** to afford the thienyl phosphonate **90.9**.

Using the above procedures, but employing, in place of dibromothiophene **90.7**, different dibromoarenes **90.2**, and/or different formylphenyl boronates **90.1**, the corresponding products **90.5** are obtained.

Scheme **91** illustrates the preparation of the benzyl carbamates **43.4** which are employed in the preparation of the phosphonate esters **9**. In this procedure, the substituted benzaldehydes **91.1**, prepared as shown in Schemes **87** – **90**, are converted into the corresponding benzyl alcohols **91.2**. The reduction of aldehydes to afford alcohols is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 527ff. The transformation is effected by the use of reducing agents such as sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride, diisobutyl aluminum hydride and the like. The resultant benzyl alcohol is then reacted with the aminoester **91.3** to afford the carbamate **91.4**. The reaction is performed under the conditions described below, Scheme **98**. For example, the benzyl alcohol is reacted with carbonyldiimidazole to produce an intermediate benzyloxycarbonyl imidazole, and the intermediate is reacted with the aminoester **91.3** to afford the carbamate **91.4**. The methyl ester is then hydrolyzed to yield the carboxylic acid **43.4**.

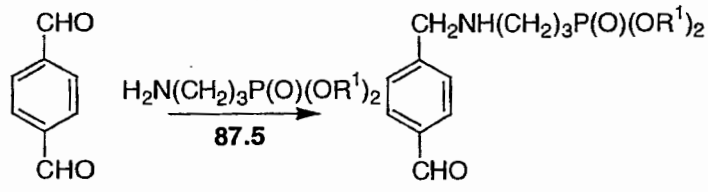
Scheme 87

Method



87.1 **87.3**

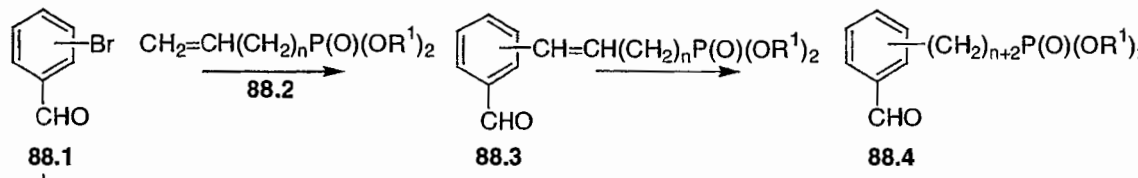
Example

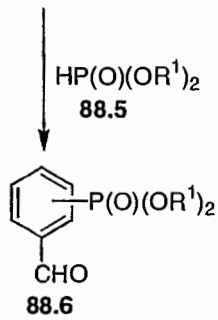


87.4 **87.6**

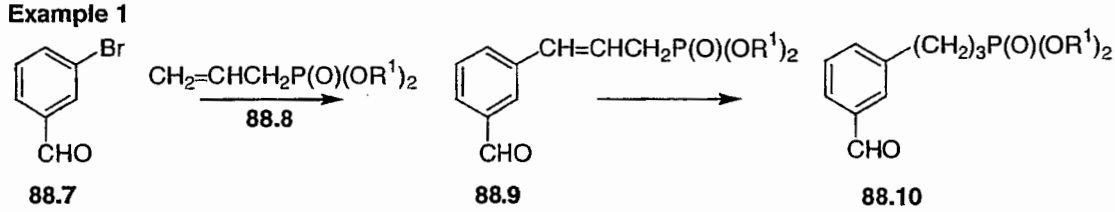
Scheme 88

Method

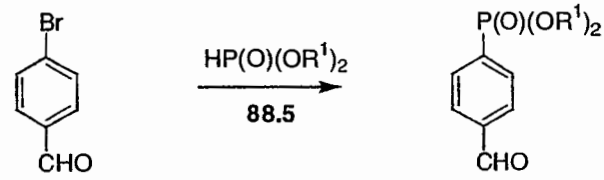




Example 1

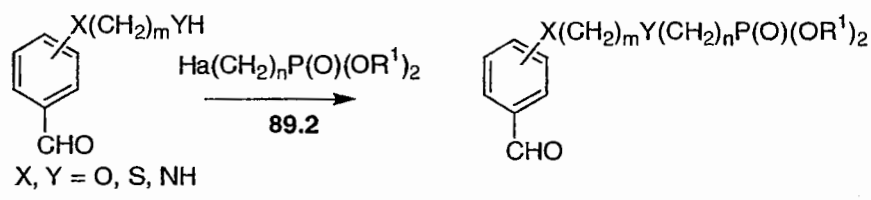


Example 2

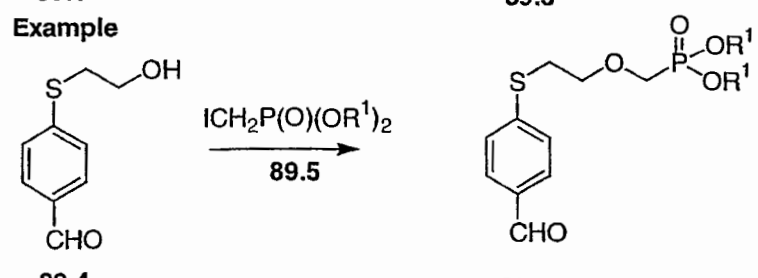


Scheme 89

Method

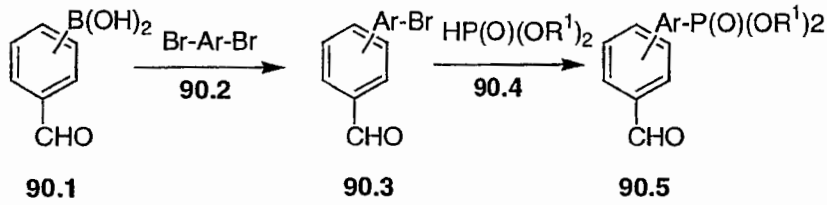


Example



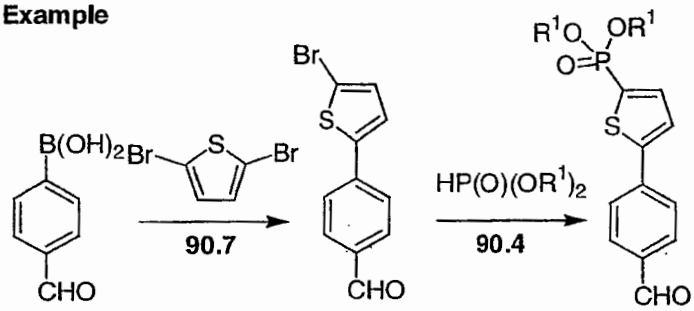
Scheme 90

Method



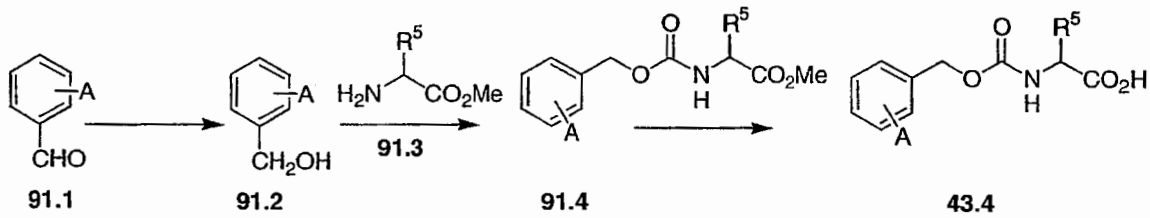
90.1 **90.3** **90.5**

Example



90.6 **90.8** **90.9**

Scheme 91



91.1 **91.2** **91.4** **43.4**

Preparation of phosphonate-containing benzenesulfonyl chlorides 20.2.

Schemes **92** - **97** illustrate methods for the preparation of the sulfonyl chlorides **20.2** which are employed in the preparation of the phosphonate esters **4**. Sulfonic acids and/or sulfonyl halides are obtained by oxidation of the corresponding thiols, as described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 813, and in Tet. 1965, 21, 2271. For example, the phosphonate-containing thiols which are prepared according to Schemes **63** - **72** are transformed into the corresponding sulfonic acids by oxidation with bromine in aqueous organic solution, as described in J. Am. Chem. Soc., 59, 811, 1937, or by oxidation with hydrogen peroxide, as described in Rec. Trav. Chim., 54, 205, 1935, or by reaction with

oxygen in alkaline solution, as described in Tet. Let., 1963, 1131, or by the use of potassium superoxide, as described in Aust. J. Chem., 1984, 37, 2231. Schemes **92- 96** describe the preparation of phosphonate-substituted benzenesulfonic acids; Scheme **97** describes the conversion of the sulfonic acids into the corresponding sulfonyl chlorides. Alternatively, the intermediate thiols, when propduced, can be directly converted to the sulfonyl chloride as described in Scheme **97a**

Scheme **92** depicts the preparation of variously substituted benzenesulfonic acids in which the phosphonate group is directly attached to the benzene ring. In this procedure, a bromo-substituted benzenethiol **92.1** is protected, as previously described. The protected product **92.2** is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **92.3**, to give the corresponding phosphonate **92.4**. The thiol group is then deprotected to afford the thiol **92.5**, and this compound is oxidized to afford the sulfonic acid **92.6**.
For example, 4-bromobenzenethiol **92.7** is converted into the S-adamantyl derivative **92.8**, by reaction with 1-adamantanol in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978. The product is then reacted with a dialkyl phosphite and a palladium catalyst, as described previously, to yield the phosphonate **92.9**. The adamantyl group is then removed by reaction with mercuric acetate in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978, to give the thiol **92.10**. The product is then reacted with bromine in aqueous solution to prepare the sulfonic acid **92.11**.
Using the above procedures, but employing, in place of the thiol **92.7**, different thiols **92.1**, and/or different dialkyl phosphites **92.3**, the corresponding products **92.6** are obtained.

Scheme **93** illustrates the preparation of amino-substituted benzenesulfonic acids in which the phosphonate group is attached by means of an alkoxy group. In this procedure, a hydroxy amino-substituted benzenesulfonic acid **93.1** is reacted with a dialkyl bromoalkyl phosphonate **93.2** to afford the ether **93.3**. The reaction is performed in a polar solvent such as dimethylformamide in the presence of a base such as potassium carbonate. The yield of the product **93.3** is increased by treatment of the crude reaction product with dilute aqueous base, so as to hydrolyze any sulfonic esters which are produced.
For example, 3-amino-4-hydroxybenzenesulfonic acid **93.4** (Fluka) is reacted with a dialkyl bromopropyl phosphonate **93.5** prepared as described in J. Am. Chem. Soc., 2000, 122, 1554,

in dimethylformamide containing potassium carbonate, followed by the addition of water, to produce the ether **93.6**.

Using the above procedures, but employing, in place of the phenol **93.4**, different phenols **93.1**, and/or different phosphonates **93.2**, the corresponding products **93.3** are obtained.

Scheme **94** illustrates the preparation of methoxyl-substituted benzenesulfonic acids in which the phosphonate group is attached by means of an amide group. In this procedure, a methoxy amino-substituted benzenesulfonic acid **94.1** is reacted, as described previously for the preparation of amides, with a dialkyl carboxyalkyl phosphonate **94.2** to produce the amide **94.3**.

For example, 3-amino-4-methoxybenzenesulfonic acid **94.4**, (Acros) is reacted in dimethylformamide solution with a dialkyl phosphonoacetic acid **94.2** (Aldrich) and dicyclohexyl carbodiimide, to produce the amide **94.6**.

Using the above procedures, but employing, in place of the amine **94.4**, different amines **94.1**, and/or different phosphonates **94.2**, the corresponding products **94.3** are obtained.

Scheme **95** illustrates the preparation of substituted benzenesulfonic acids in which the phosphonate group is attached by means of a saturated or unsaturated alkylene group. In this procedure, a halo-substituted benzenesulfonic acid **95.1** is coupled, in a palladium catalyzed Heck reaction with a dialkyl alkenyl phosphonate **95.2** to afford the phosphonate **95.3**. Optionally, the product is reduced, for example by catalytic hydrogenation over a palladium catalyst, to give the saturated analog **95.4**.

For example, 4-amino-3-chlorobenzenesulfonic aid **95.5** (Acros) is reacted in N-methylpyrrolidinone solution at 80° with a dialkyl vinylphosphonate **95.6** (Aldrich), palladium (II) chloride bis(acetonitrile), sodium acetate and tetraphenylphosphonium chloride, as described in Ang. Chem. Int. Ed. Engl., 37, 481, 1998, to produce the olefinic product **95.7**. Catalytic hydrogenation using a 5% palladium on carbon catalyst then affords the saturated analog **95.8**.

Using the above procedures, but employing, in place of the chloro compound **95.5**, different chlorides **95.1**, and/or different phosphonates **95.2**, the corresponding products **95.3** and **95.4** are obtained.

Scheme **96** depicts the preparation of benzenesulfonic acids in which the phosphonate group is attached by means of an amide linkage. In this procedure, an amino carboxy substituted benzene thiol **96.1** is coupled with a dialkyl aminoalkyl phosphonate **96.2** to produce the amide **96.3**. The product is then oxidized, as described above, to afford the corresponding sulfonic acid **96.4**.

For example, 2-amino-5-mercaptobenzoic acid **96.5**, prepared as described in Pharmazie, 1973, 28, 433, is reacted with a dialkyl aminoethyl phosphonate **96.6** and dicyclohexyl carbodiimide, to prepare the amide **96.7**. The product is then oxidized with aqueous hydrogen peroxide to yield the sulfonic acid **96.8**.

Using the above procedures, but employing, in place of the carboxylic acid **96.5**, different acids **96.1**, and/or different phosphonates **96.2**, the corresponding products **96.4** are obtained.

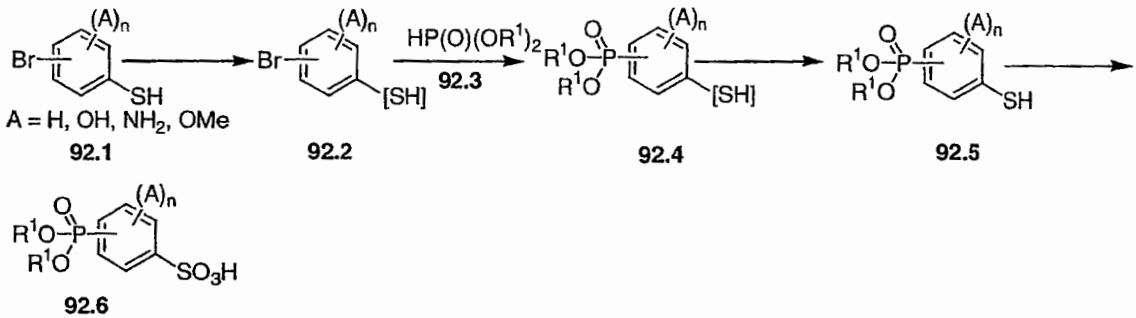
Scheme **97** illustrates the conversion of benzenesulfonic acids into the corresponding sulfonyl chlorides. The conversion of sulfonic acids into sulfonyl chlorides is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 821. The transformation is effected by the use of reagents such as thionyl chloride or phosphorus pentachloride.

For example, as shown in Scheme **97**, the variously substituted phosphonate-containing benzenesulfonic acids **97.1**, prepared as described above, are treated with thionyl chloride, oxalyl chloride, phosphorus pentachloride, phosphorus oxychloride and the like to prepare the corresponding sulfonyl chlorides **97.2**.

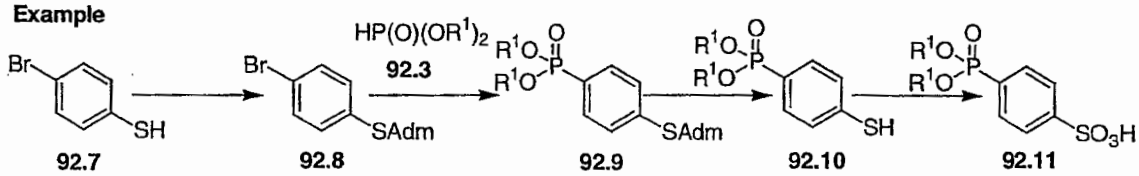
Scheme **97a** illustrates the conversion of thiols into the corresponding sulfonyl chlorides which can be applied to any of the thiol intermediates in Schemes **92-96**. The thiol is oxidized as described in Synthesis 1987, 4, 409 or J. Med. Chem. 1980, 12, 1376 to afford the sulfonyl chloride directly. For example, treatment of protected thiol **97a.1**, prepared from **96.7** using standard protecting groups for amines as described in Greene and Wuts, third edition, ch 7, with HCl and chlorine affords the sulfonyl chloride **97a.2**. Alternatively treatment of **92.10** with the same conditions gives the sulfonyl chloride **97a.3**.

Scheme 92

Method

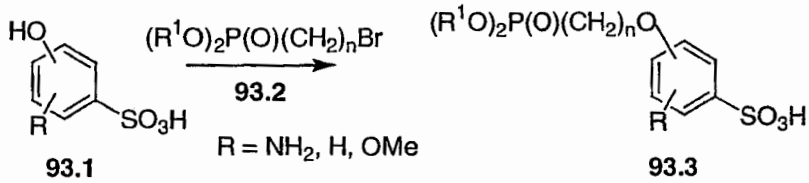


Example

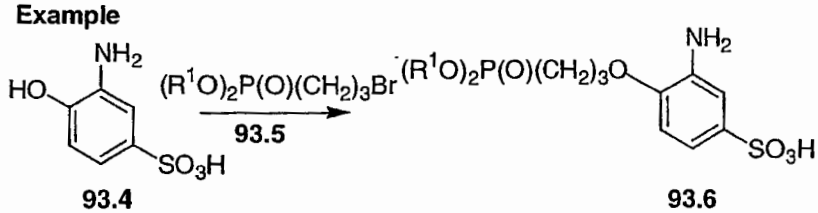


Scheme 93

Method

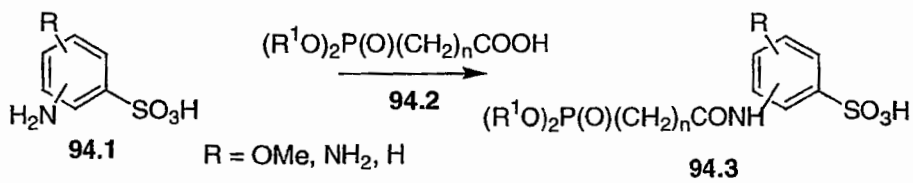


Example

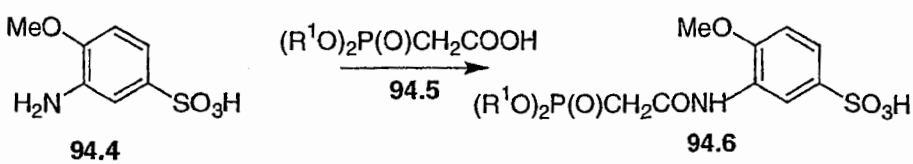


Scheme 94

Method

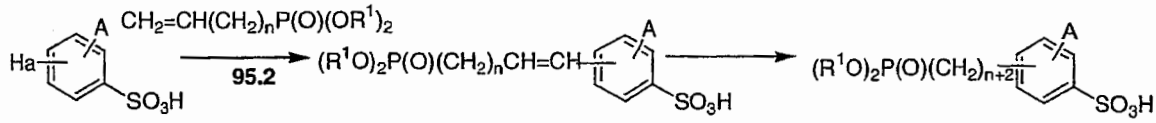


Example



Scheme 95

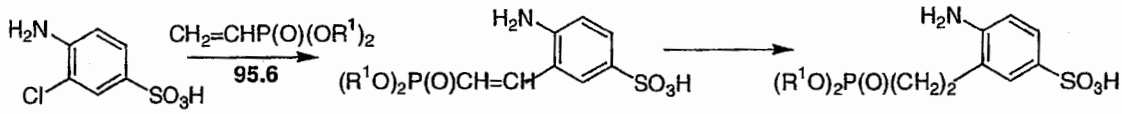
Method



A = H, OMe, NH_2

95.1 **95.3** **95.4**

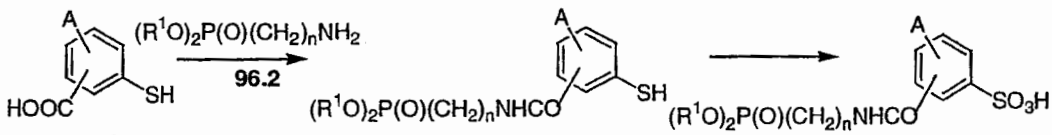
Example



95.5 **95.7** **95.8**

Scheme 96

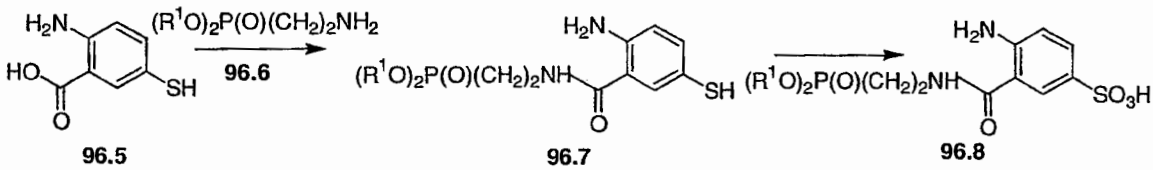
Method



A = H, OMe, Ha

96.1 **96.3** **96.4**

Example



96.5 **96.7** **96.8**

Scheme 97



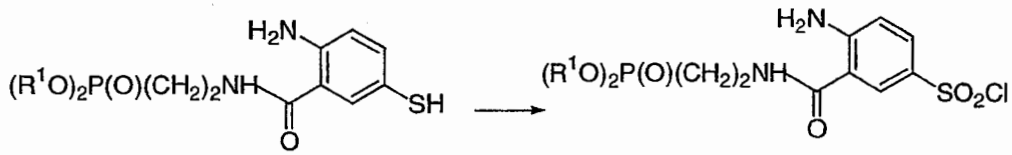
97.1 **97.2**

Scheme 97a



97a.1 **97.2**

Example



97a.1 **97.2**



92.10 **97a.3**

Preparation of carbamates.

The phosphonate esters **1** - **4** in which R^4 is formally derived from the carboxylic acids shown in Chart **5c**, and the phosphonate esters **5** and **9** contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme **98** illustrates various methods by which the carbamate linkage is synthesized. As shown in Scheme **98**, in the general reaction generating carbamates, a carbinol **98.1**, is converted into the activated derivative **98.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **98.2** is then reacted with an amine **98.3**, to afford the carbamate product **98.4**. Examples **1 – 7** in Scheme **98** depict methods by which the general reaction is effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.

Scheme **98**, Example **1** illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **98.1**. In this procedure, the carbinol is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **98.6**. The latter compound is then reacted with the amine component **98.3**, in the presence of an organic or inorganic base, to afford the carbamate **98.7**. For example, the chloroformyl compound **98.6** is reacted with the amine **98.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **98.7**. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme **98**, Example **2** depicts the reaction of the chloroformate compound **98.6** with imidazole to produce the imidazolide **98.8**. The imidazolide product is then reacted with the amine **98.3** to yield the carbamate **98.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme **98** Example **3**, depicts the reaction of the chloroformate **98.6** with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester **98.10**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **98.19 - 98.24** shown in Scheme **98**, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **98.19**, N-hydroxysuccinimide **98.20**, or pentachlorophenol, **98.21**, the mixed carbonate **98.10** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of

dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **98.22** or 2-hydroxypyridine **98.23** is performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme **98** Example **4** illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **98.8** is employed. In this procedure, a carbinol **98.5** is reacted with an equimolar amount of carbonyl diimidazole **98.11** to prepare the intermediate **98.8**. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **98.8** is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **98.7**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate **98.7**.

Scheme **98**, Example **5** illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **98.13**. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **98.12**, to afford the alkoxycarbonyl product **98.13**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. The product is then reacted with the amine $R'NH_2$ to afford the carbamate **98.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80° as described in Syn., 1977, 704.

Scheme **98**, Example **6** illustrates the preparation of carbamates in which a carbonate $(R"O)_2CO$, **98.14**, is reacted with a carbinol **98.5** to afford the intermediate alkyloxycarbonyl intermediate **98.15**. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate **98.7**. The procedure in which the reagent **98.15** is derived from hydroxybenztriazole **98.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **98.15** is derived from N-hydroxysuccinimide **98.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **98.15** is derived from 2-hydroxypyridine **98.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **98.15** is derived from 4-nitrophenol **98.24** is described in Syn. 1993, 199. The reaction between equimolar amounts of the carbinol ROH and the carbonate **98.14** is conducted in an inert organic solvent at ambient temperature.

Scheme **98**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides **98.16**. In this procedure, an alkyl chloroformate **98.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **98.16**. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **98.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

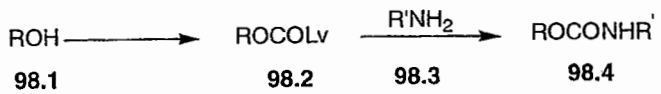
Scheme **98**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine **98.17**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **98.7**.

Scheme **98**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **98.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **98.7**.

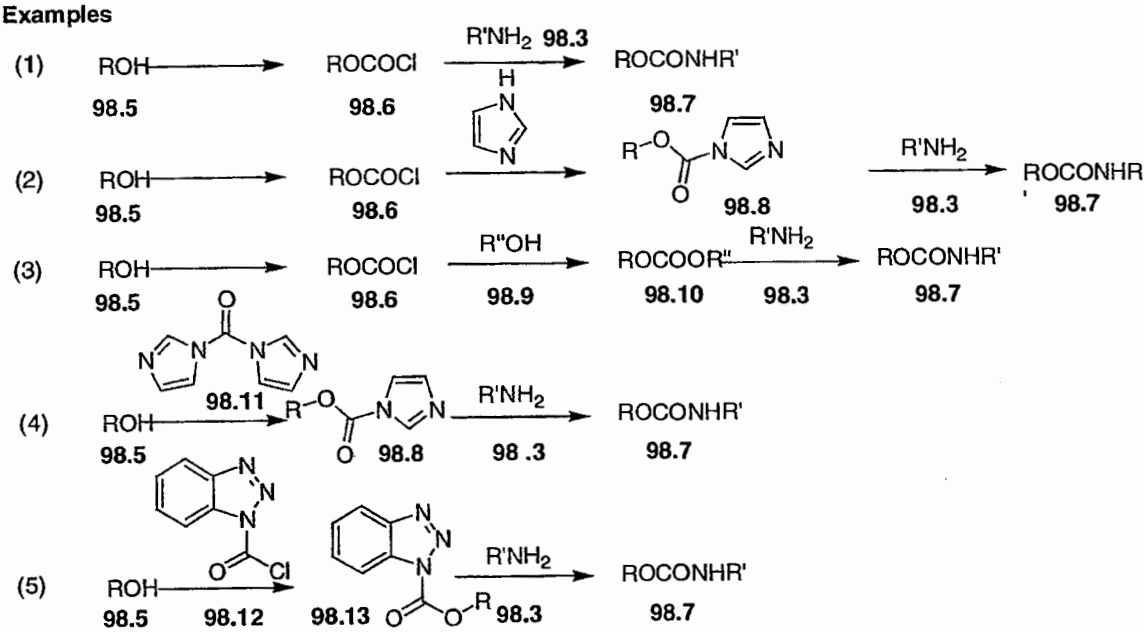
Scheme **98**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **98.7**.

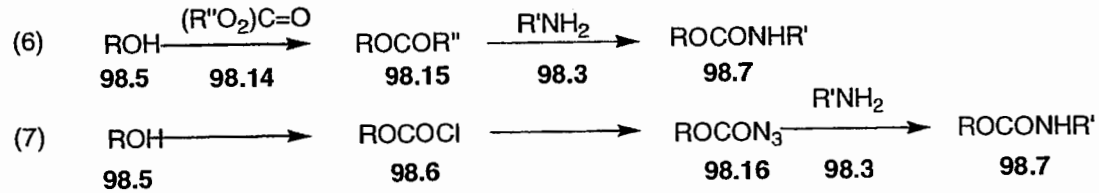
Scheme 98

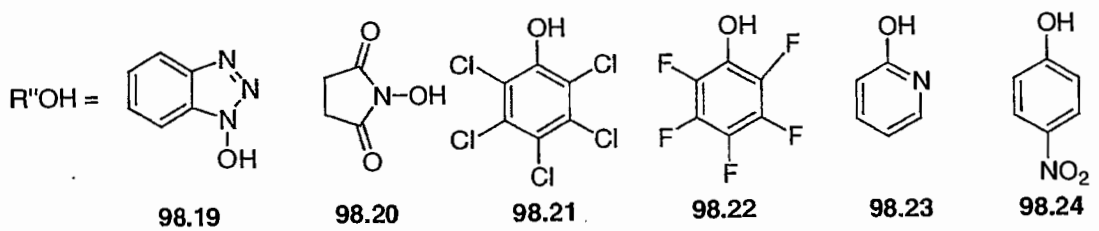
General reaction



Examples







Interconversions of the phosphonates R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH) and R-link-P(O)(OH)$_2$.

Schemes **1** - **97** described the preparations of phosphonate esters of the general structure R-link-P(O)(OR^1)$_2$, in which the groups R^1, the structures of which are defined in Charts **1** and **2**, may be the same or different. The R^1 groups attached to the phosphonate esters **1** - **13**, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme **99**. The group R in Scheme **99** represents the substructure to which the substituent link-P(O)(OR^1)$_2$ is attached, either in the compounds **1** - **13** or in precursors thereto. The R^1 group may be changed, using the procedures described below, either in the precursor compounds, or in the esters **1** - **13**. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **99.1** into the corresponding phosphonate monoester **99.2** (Scheme **99**, Reaction **1**) is accomplished by a number of methods. For example, the ester **99.1** in which R^1 is an aralkyl group such as benzyl, is converted into the monoester compound **99.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester **99.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **99.2** is effected by treatment of the ester **99.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **99.1** in which one of the groups R^1 is aralkyl, such as benzyl, and the other is alkyl, are converted into the monoesters **99.2** in which R^1 is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, are converted into the monoester **99.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **99.1** or a phosphonate monoester **99.2** into the corresponding phosphonic acid **99.3** (Scheme **99**, Reactions **2** and **3**) is effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **99.2** in which R^1 is aralkyl such as benzyl, is converted into the corresponding phosphonic acid **99.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **99.2** in which R^1 is alkenyl such as, for example, allyl, is converted into the phosphonic acid **99.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **99.1** in which R^1 is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **99.1** in which R^1 is phenyl is described in J. Am. Chem. Soc., 78, 2336, 1956.

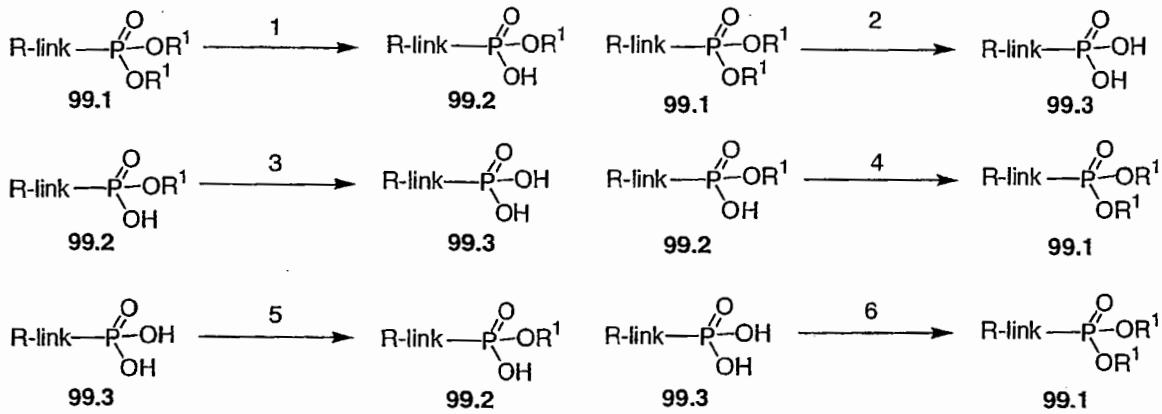
The conversion of a phosphonate monoester **99.2** into a phosphonate diester **99.1** (Scheme **99**, Reaction **4**) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl is effected by a number of reactions in which the substrate **99.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **99.2** to the diester **99.1** is effected by the use of the Mitsonobu reaction, as described above, Scheme **49**. The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **99.2** is transformed into the phosphonate diester **99.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in

which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester is transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **99.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **99.1**.

A phosphonic acid R-link-$P(O)(OH)_2$ is transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **99**, Reaction **5**) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ **99.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid R-link-$P(O)(OH)_2$ **99.3** is transformed into a phosphonate diester R-link-$P(O)(OR^1)_2$ **99.1** (Scheme **99**, Reaction **6**) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **99.3** are transformed into phosphonic esters **99.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°. Alternatively, phosphonic acids **99.3** are transformed into phosphonic esters **99.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **99.1**.

Scheme 99



General applicability of methods for introduction of phosphonate substituents.

The procedures described for the introduction of phosphonate moieties (Schemes **47** - **97**) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into hydroxymethyl benzoic acids, (Schemes **47** - **51**) are applicable to the introduction of phosphonate moieties into quinolines, thiophenols, isobutylamines, cyclopentylamines, tert. butanols, benzyl alcohols, phenylalanines, benzylamines and benzenesulfonic acids, and the methods described for the introduction of phosphonate moieties into the above-named substrates (Schemes **52** - **97**) are applicable to the introduction of phosphonate moieties into hydroxymethyl benzoic acid substrates.

Preparation of phosphonate intermediates 11 - 13 with phosphonate moieties incorporated into the R^2, R^3 or R^4 groups.

The chemical transformations described in Schemes **1** - **99** illustrate the preparation of compounds **1** - **10** in which the phosphonate ester moiety is attached to the substructures listed above. The various chemical methods employed for the introduction of phosphonate ester groups into the above-named moieties can, with appropriate modifications known to those skilled in the art, be applied to the introduction of a phosphonate ester group into the compounds R^4COOH, R^3Cl, R^2NH_2. The resultant phosphonate-containing analogs, designated as $R^{4a}COOH$, $R^{3a}Cl$ and NH_2R^{2a} are then, using the procedures described above, employed in the preparation of the compounds **11**, **12** and **13**. The procedures required for the

utilization of the phosphonate-containing analogs are the same as those described above for the utilization of the compounds R^2NH_2 , R^3Cl and R^4COOH.

KNI-like phosphonate protease inhibitors (KNILPPI)

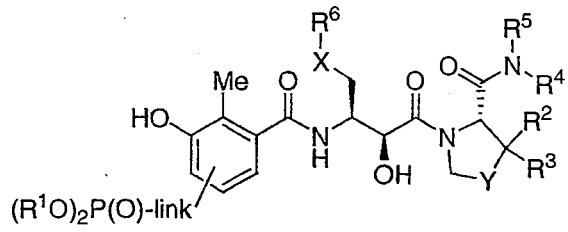
Preparation of the intermediate phosphonate esters 1-12.

The structures of the intermediate phosphonate esters **1** to **12** and the structures for the component groups R^1, R^2, R^3, R^7, R^9, X and Y of this invention are shown in Charts **1** and **2**. The structures of the R^8COOH components are shown in Charts **3a**, **3b** and **3c**. The structures of the $R^{10}R^{11}NH$ and R^4R^5NH components are shown in Charts **4a**, and **4b** respectively. The structures of the R^6XCH_2 groups are shown in Chart **5**. Specific stereoisomers of some of the structures are shown in Charts **1** - **5**; however, all stereoisomers are utilized in the syntheses of the compounds **1** to **12**. Subsequent chemical modifications to the compounds **1** to **12**, as described herein, permit the synthesis of the final compounds of this invention.

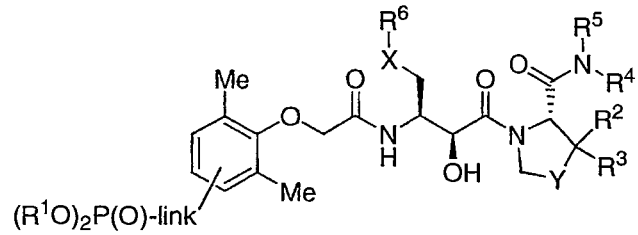
The intermediate compounds **1** to **12** incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **6** and **7** illustrate examples of the linking groups present in the structures **1** - **12**.

Schemes **1** - **103** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1** - **10**, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters **11** and **12**, in which the phosphonate moiety is incorporated into the groups R^8COOH and $R^{10}R^{11}NH$, is also described below.

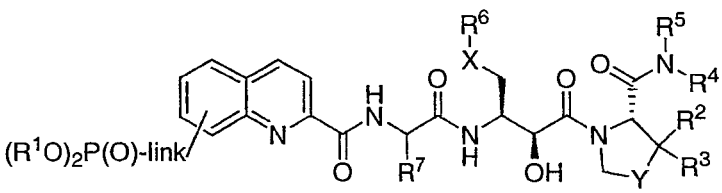
Chart 1



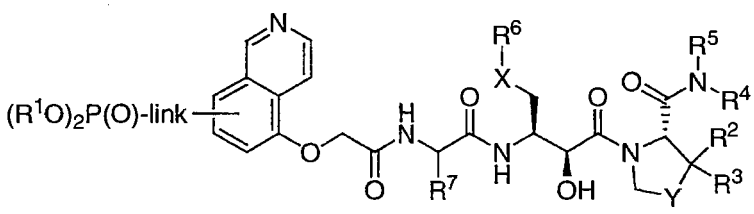
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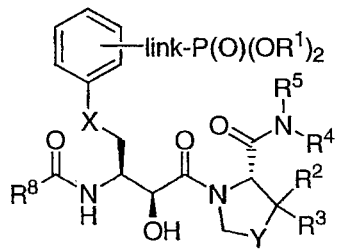
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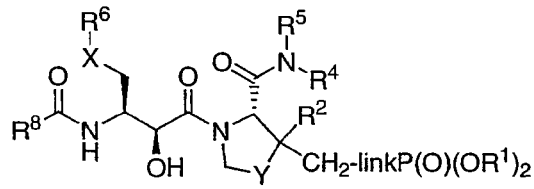
3



4



5



6

R^1 = H, alkyl, haloalkyl,alkenyl, aralkyl, aryl

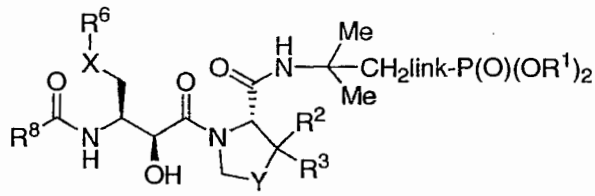
R^2, R^3 = H,H; H, methyl; methyl, methyl;H, Cl

R^7 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

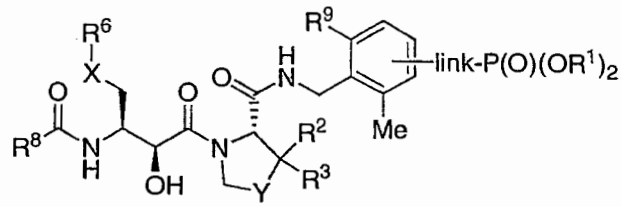
X = S or direct bond

Y = S, CH_2

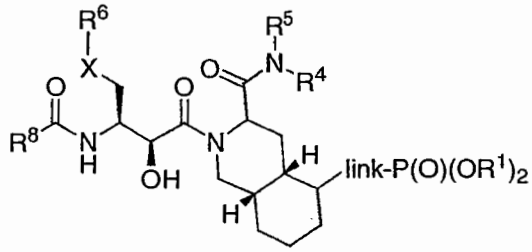
Chart 2



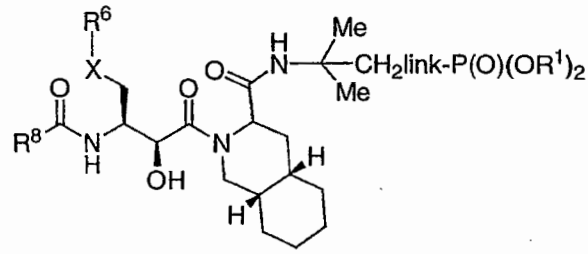
7



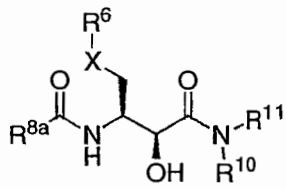
8



9

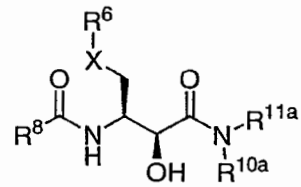


10



11

R^{8a} = phosphonate-containing R^8



12

R^{10a}, R^{11a} = phosphonate-containing R^{10} or R^{11}

R^1 = H, alkyl, haloalkyl,alkenyl, aralkyl, aryl

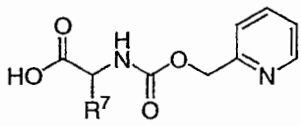
R^2, R^3 = H,H; H, methyl; methyl, methyl;H, Cl.

R^9 = H, methyl

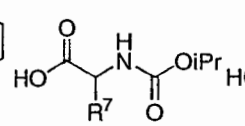
X = S or direct bond

Y = S, CH_2

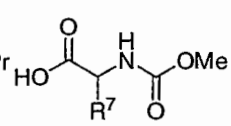
Chart 3a Structures of the R^8COOH components



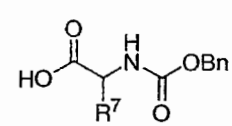
C1



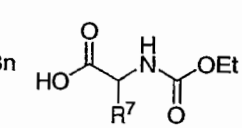
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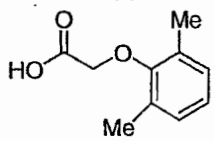
C3



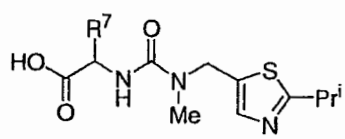
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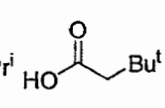
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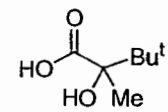
C6



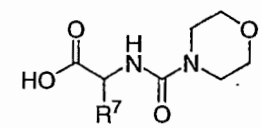
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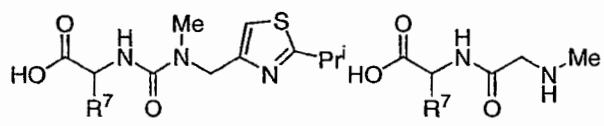
C8



C9

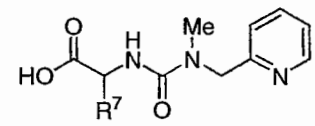


C10

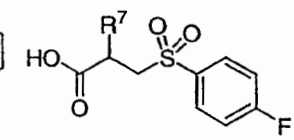


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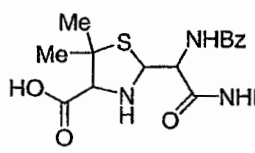
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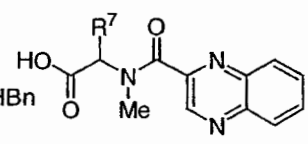
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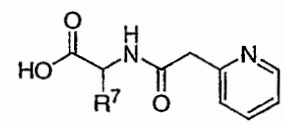
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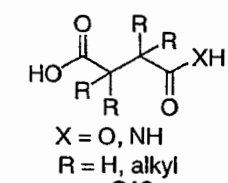
C15



C16

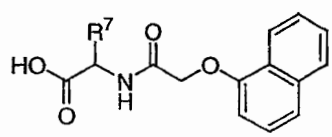


C17

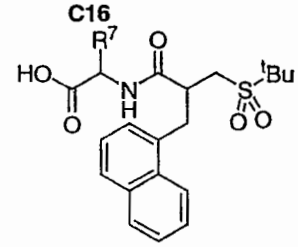


X = O, NH
R = H, alkyl

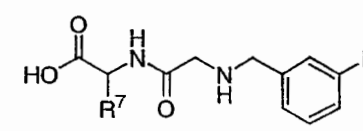
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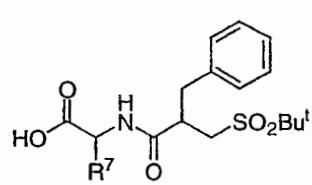
C19



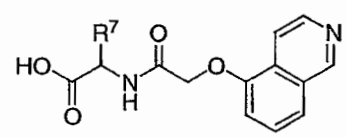
C20



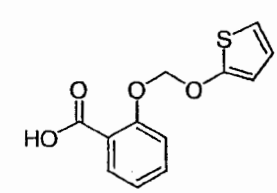
C21



C22



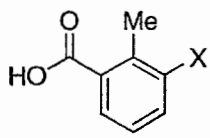
C23



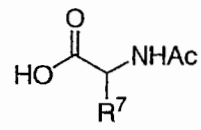
C24

R^7 = alkyl, $CH_2SO_2CH_3$, $C(CH_3)_2SO_2CH_3$, CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

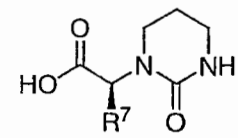
Chart 3b Structures of the R^8COOH components



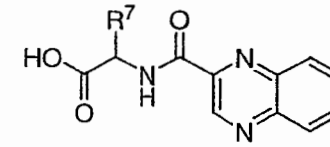
C25
X = OH, NH_2



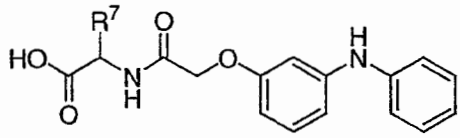
C26



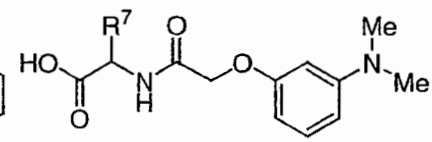
C27



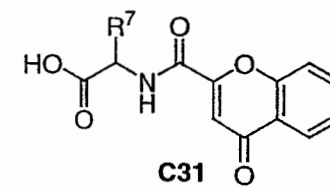
C28



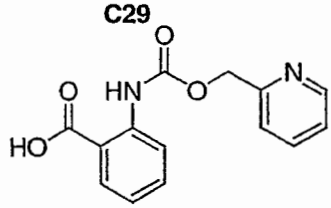
C29



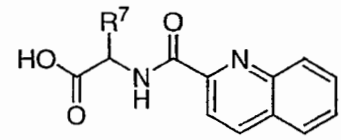
C30



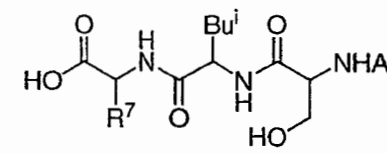
C31



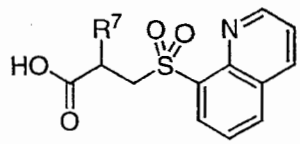
C32



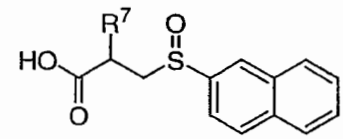
C33



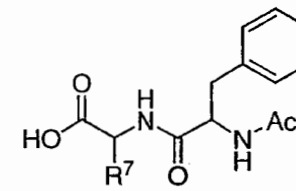
C34



C35



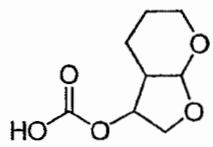
C36



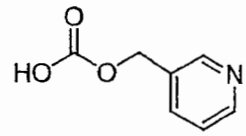
C37

R^7 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

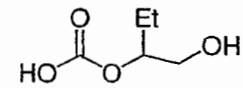
Chart 3c Structures of the R^8COOH components



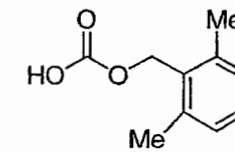
C38



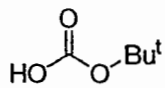
C39



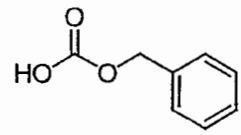
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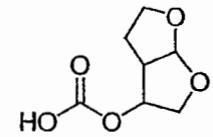
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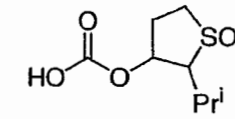
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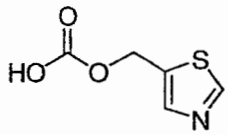
C43



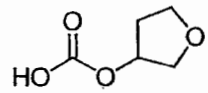
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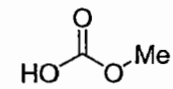
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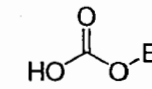
C46



C47



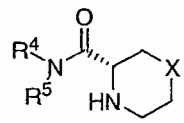
C48



C49

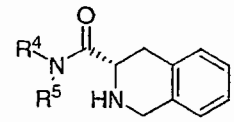
Chart 4a Structures of the $R^{10}R^{11}NH$ components

$R^{10}R^{11}NH$ =

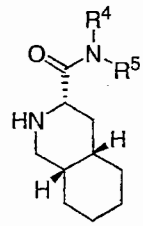


X = N,C

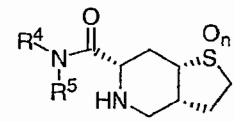
1.2



A1



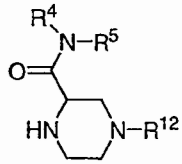
A2



A3

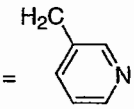
n=0,2

A4

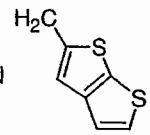


A5

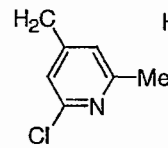
R^{12} =



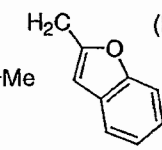
A6



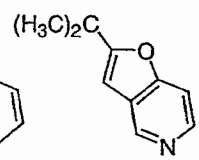
A7



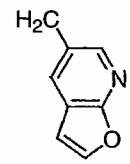
A8



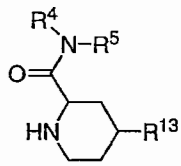
A9



A10

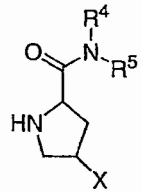


A11



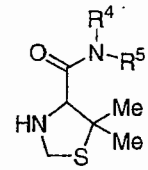
A12

R^{13}=OCH_2Ph
S-3-pyridyl
S-4-pyridyl
OCH_2-4-pyridyl

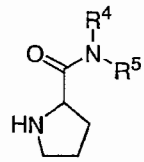


A13

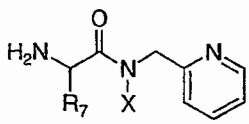
X = Cl, OMe



A14

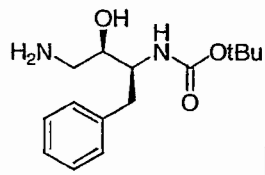


A15

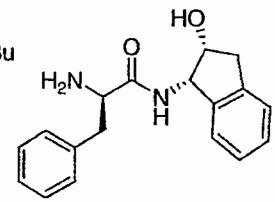


X=H or Me

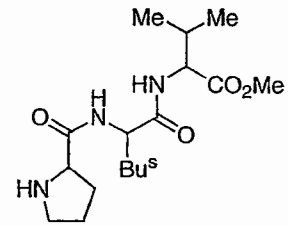
A16



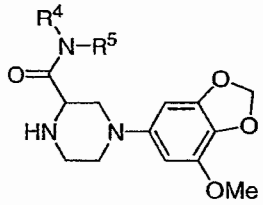
A17



A18



A19

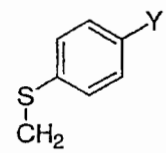


A20

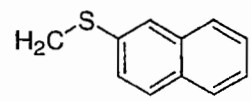
R^7 = alkyl, $CH_2SO_2CH_3$,$C(CH_3)_2SO_2CH_3$,CH_2CONH_2, CH_2SCH_3, imidaz-4-ylmethyl, CH_2NHAc, $CH_2NHCOCF_3$

Chart 5 Structures of the R^6XCH_2 groups.

R^6SCH_2 =



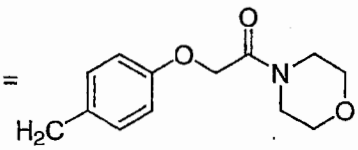
13



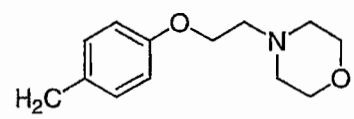
14

Y = H, F

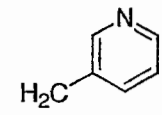
R^6CH_2 =



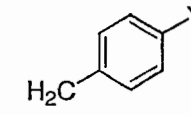
15



16



17



18

Y = H, OC_2H_5, $OCH_2C_6H_5$

Chart 6 Examples of the linking groups between the scaffold and the phosphonate moiety.

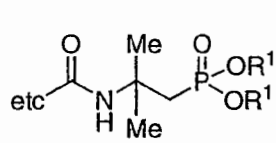
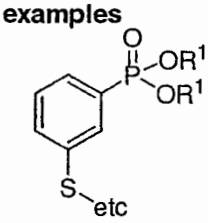
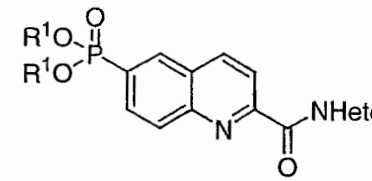
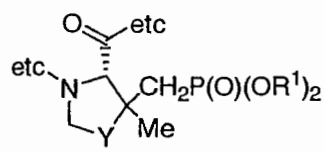
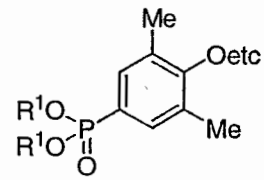
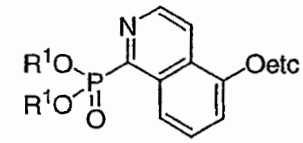
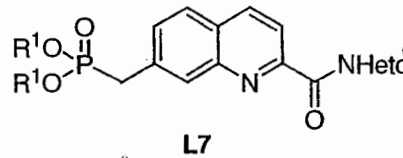
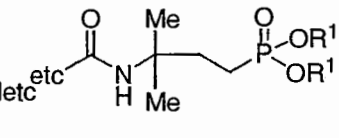
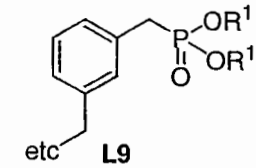
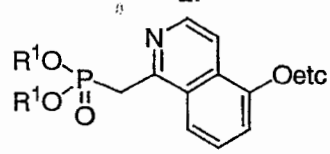
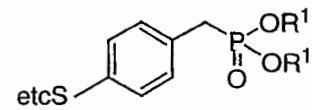
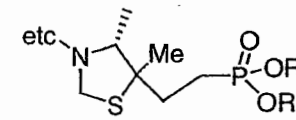
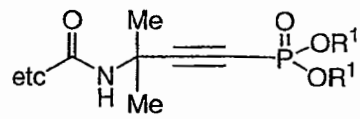
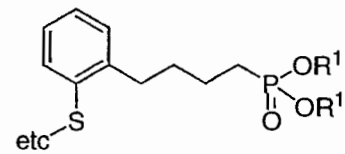
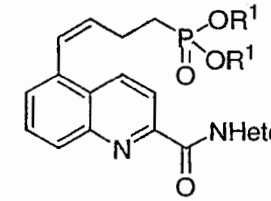
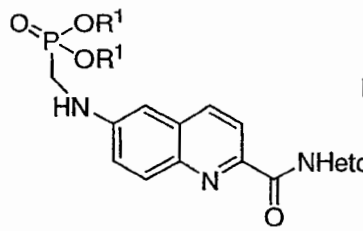
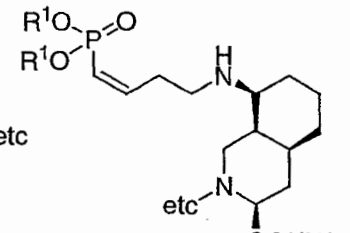
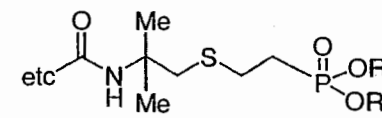
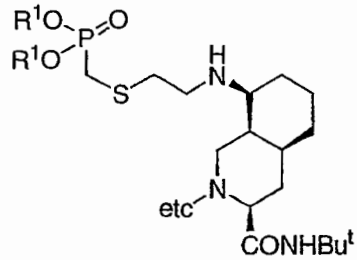
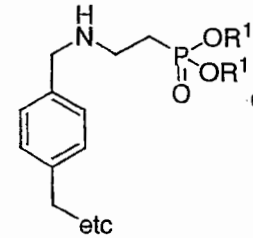
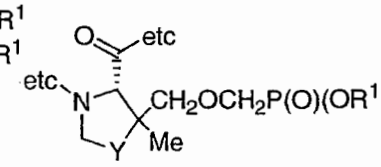
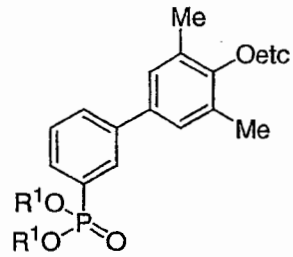
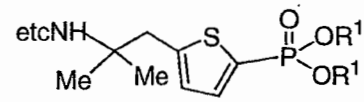
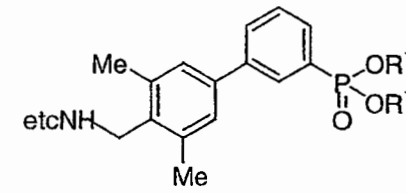
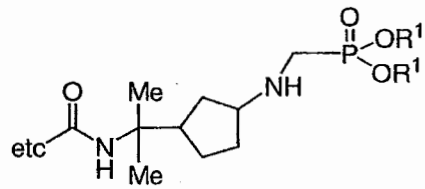
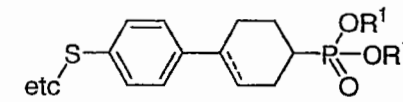
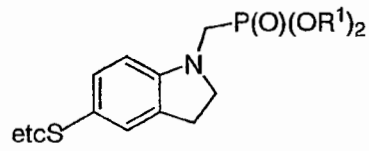
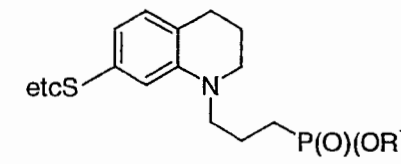
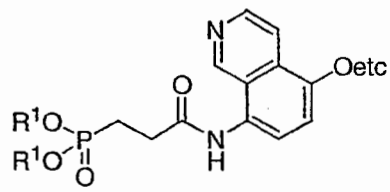
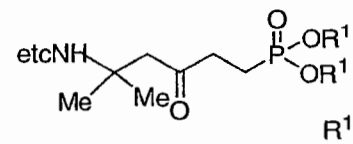
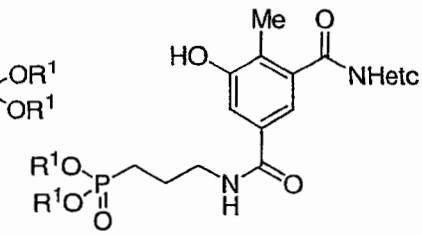
link	examples
direct bond	 L1  L2  L3  L4  L5  L6
single carbon	 L7  L8  L9  L10  L11  L12
multiple carbon	 L13  L14  L15
hetero atoms	 L16  L17  L18  L19  L20  L21

Chart 7 Examples of the linking groups between the scaffold and the phosphonate moiety.

link	examples		
aryl, heteroaryl			
	L22	**L23**	**L24**
cycloalkyl			
	L25	**L26**	
cyclized			
	L27	**L28**	
amide			
	L29	**L30**	**L31**

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the

art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], etc.

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

Schemes **1** and **2** illustrate the preparation of the phosphonate esters **1** in which X is a direct bond. As shown in Scheme **1**, a BOC-protected cyclic aminoacid **1.1** is reacted with an amine **1.2** to afford the amide **1.3**. The carboxylic acid **1.1** in which Y is CH_2 and R^2 and R^3 are H is commercially available (Bachem). The preparation of the carboxylic acid **1.1** in which Y is S and R^2 and R^3 are CH_3 is described in Tet. Asym., 13, 2002, 1201; the preparation of the carboxylic acid **1.1** in which Y is S and R^2 is H and R^3 is CH_3 is described in JP 60190795; the preparation of the carboxylic acid **1.1** in which Y is S and R^2 and R^3 are H is described in EP 0574135; the preparation of the carboxylic acid **1.1** in which Y is CH_2, R^2 is H and R^3 is Cl is described in EP 587311.

The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide. Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide. Preferably, equimolar amounts of the carboxylic acid **1.1** and the amine **1.2** are reacted together in tetrahydrofuran solution in the presence of

dicyclohexylcarbodiimide and N-hydroxysuccinimide, for example as described in EP 574135, to yield the amide product **1.3**. The BOC protecting group is then removed to give the free amine **1.4**. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC protecting group is removed by treatment of the compound **1.3** with 8M methanesulfonic acid in acetonitrile, as described in Tet. Asym., 13, 2000, 1201, to afford the amine **1.4**. The latter compound is then reacted with a carboxylic acid **1.5**, to afford the amide **1.6**. The preparation of the carboxylic acid reactants **1.5** is described below, (Schemes **41**, **42**). The reaction is performed under similar conditions to those described above for the preparation of the amide **1.3**. Preferably, equimolar amounts of the amine **1.4** and the carboxylic acid **1.6** are reacted in tetrahydrofuran solution at ambient temperature in the presence of dicyclohexylcarbodiimide and hydroxybenztriazole, for example as described in EP 574135, to yield the amide **1.6**. The BOC protecting group is then removed from the product **1.6** to afford the amine **1.7**, using similar conditions to those described above for the removal of BOC protecting group from the compound **1.3**. Preferably, the BOC group is removed by treatment of the substrate **1.6** with a 4M solution of hydrogen chloride in dioxan at 0°, for example as described in EP 574135, to give the amine product **1.7**.

The amine is then reacted with a carboxylic acid **1.8**, or an activated derivative thereof, in which the substituent A is the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], NH_2, Br, etc, as described herein, to afford the amide **1.9**. The preparation of the carboxylic acids **1.8** is described below in Schemes **45** - **49**. The reaction between the amine **1.7** and the carboxylic acid **1.8** is conducted under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**.

The procedures illustrated in Scheme **1** describe the preparation of the compounds **1.9** in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

Scheme **2** depicts the conversion of the compounds **1.9** in which the A is a precursor to the substituent link-P(O)$(OR^1)_2$ into the compounds **1**. Procedures for the conversion of the

substituents [OH], [SH], [NH_2], Br etc into the substituent link-P(O)(OR^1)$_2$ are described below in Schemes **45 - 101.**

In the preceding and following schemes, the conversion of various substituents into the group link-P(O)(OR^1)$_2$ can be effected at any convenient stage of the synthetic sequence, as well as at the end. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures.

The phosphonate esters **5 - 12** in which the substituent R^8CO is derived from one of the carboxylic acids **C38 - C49**, as shown in Chart **3c**, incorporate a carbamate linkage. Various methods for the preparation of carbamate groups are described below in Scheme **102.**

In the above and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme **103**)

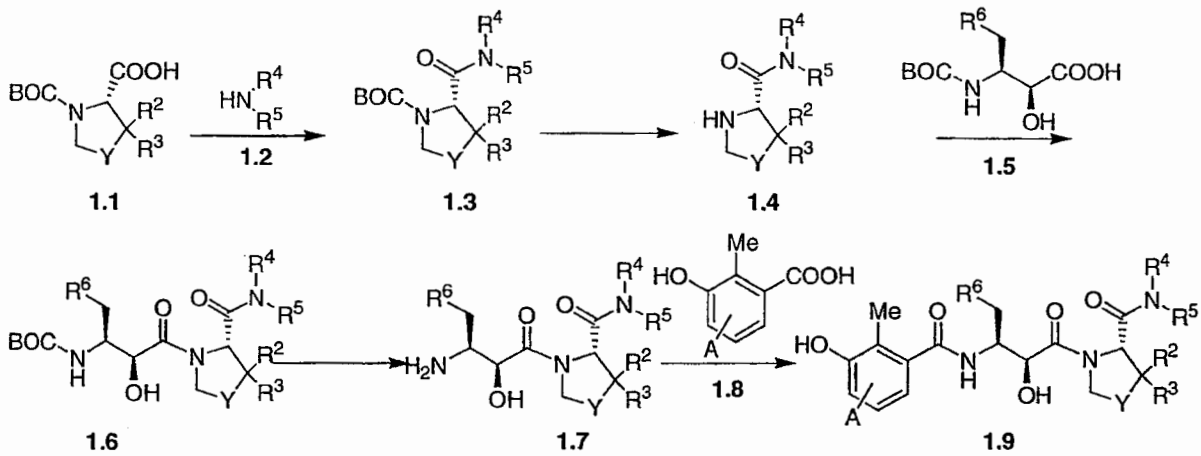
Preparation of the phosphonate ester intermediates 1 in which X is sulfur.

Schemes **3** and **4** illustrate the preparation of the phosphonate ester intermediates **1** in which X is sulfur. Scheme **3** illustrates the reaction of the amine **1.3**, prepared as described in Scheme **1**, with a carboxylic acid reagent **3.1**, to give the amide product **3.2**. The preparation of the carboxylic acid reagents **3.1** is described below in Schemes **43** and **44**. The reaction between the carboxylic acid **3.1** and the amine **1.3** is performed under similar conditions to those described above for the preparation of the amide **1.6**. The amide product **3.2** is then subjected to a deprotection reaction to remove the BOC substituent and afford the amine **3.3**. The reaction is performed under similar conditions to those described in Scheme **1** for the removal of BOC protecting groups. The amine product **3.3** is then reacted with a carboxylic acid **1.8**, or an activated derivative thereof, in which the substituent A is the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], NH_2, Br, etc, as described herein, to afford the amide product **3.4**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.9**.

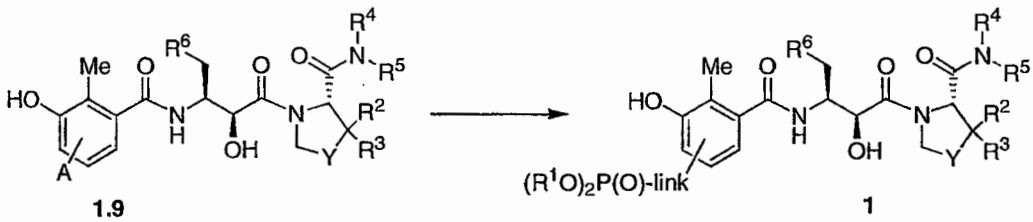
The procedures illustrated in Scheme **3** describe the preparation of the compounds **3.4** in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

Scheme **4** depicts the conversion of the compounds **3.4** in which the A is a precursor to the substituent link-P(O)$(OR^1)_2$ into the compounds **1**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-P(O)$(OR^1)_2$ are described below in Schemes **45** - **101**.

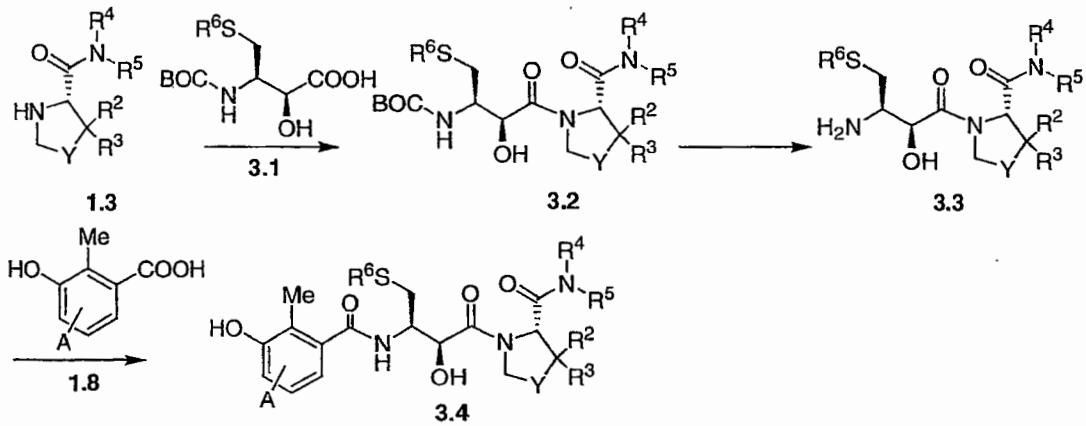
Scheme 1



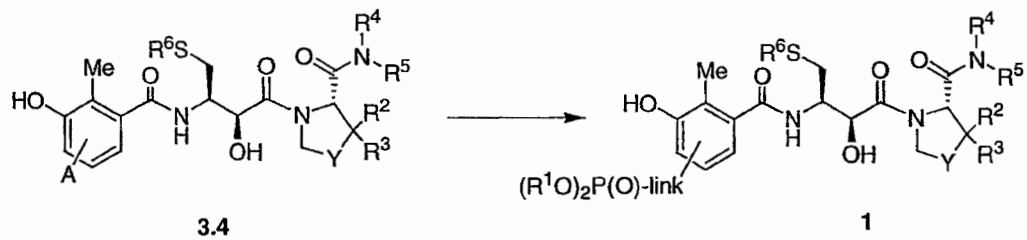
Scheme 2



Scheme 3



Scheme 4



Preparation of the phosphonate ester intermediates 2 in which X is a direct bond.

Schemes **5** and **6** depict the preparation of the intermediate phosphonate esters **2** in which X is direct bond. As shown in Scheme **5**, the amine **1.7**, prepared as described in Scheme **1**, is reacted with a carboxylic acid **5.1**, or an activated derivative thereof, in which the substituent A is the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], NH_2, Br, etc, as described herein, to afford the amide product **5.2**. The preparation of the carboxylic acids **5.1** is described below in Schemes **50** - **56**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.9**.

The procedures illustrated in Scheme **5** describe the preparation of the compounds **5.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.
Scheme **6** depicts the conversion of the compounds **5.2** in which the A is a precursor to the substituent link-$P(O)(OR^1)_2$ into the compounds **2**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-$P(O)(OR^1)_2$ are described below in Schemes **45** - **101**.

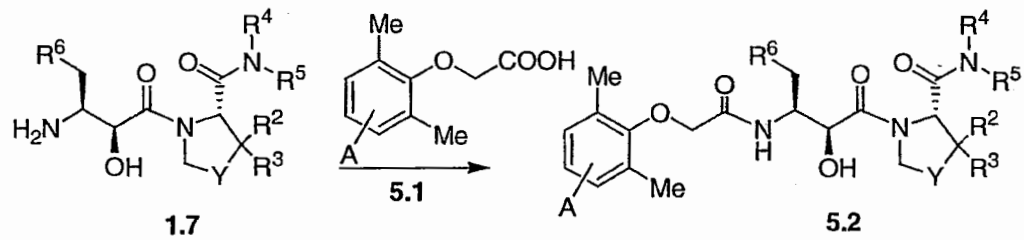
Preparation of the phosphonate ester intermediates 2 in which X is sulfur.

Schemes **7** and **8** depict the preparation of the intermediate phosphonate esters **2** in which X is sulfur. As shown in Scheme **7**, the amine **3.3**, prepared as described in Scheme **3**, is reacted with a carboxylic acid **5.1**, or an activated derivative thereof, in which the substituent A is the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], NH_2, Br, etc, as described herein, to afford the amide product **7.1**. The preparation of the carboxylic acids **5.1** is described below in Schemes **50** - **56**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.9**.

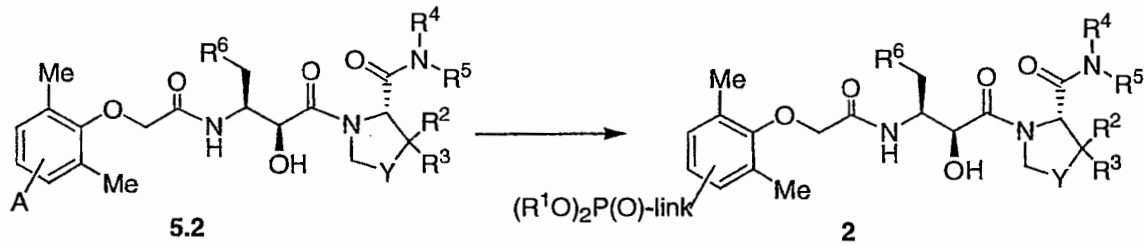
The procedures illustrated in Scheme **7** describe the preparation of the compounds **7.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.
Scheme **8** depicts the conversion of the compounds **7.1** in which the A is a precursor to the substituent link-$P(O)(OR^1)_2$ into the compounds **2**. Procedures for the conversion of the

substituents [OH], [SH], [NH_2], Br etc into the substituent link-P(O)(OR^1)$_2$ are described below in Schemes **45** - **101**.

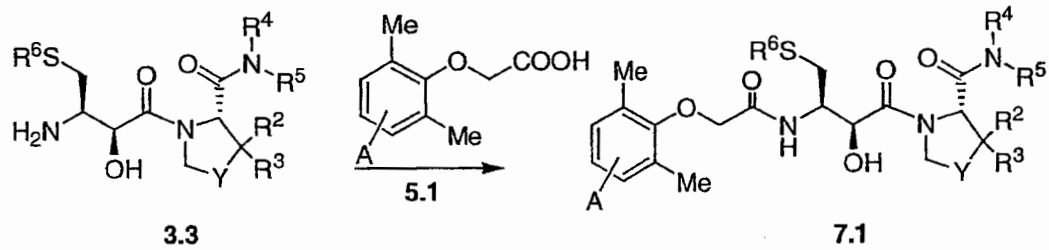
Scheme 5



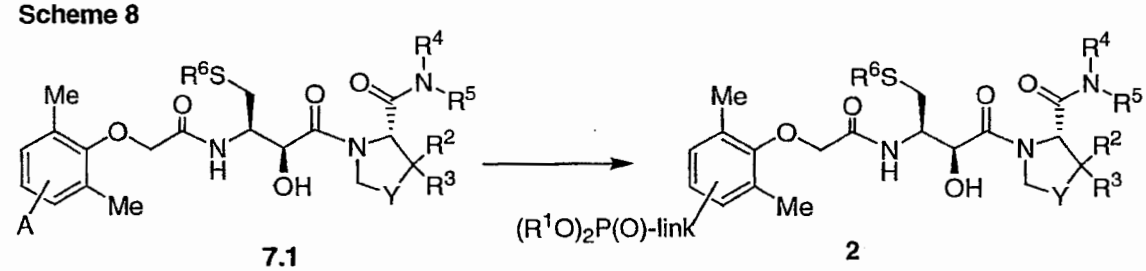
Scheme 6



Scheme 7



Scheme 8



Preparation of the phosphonate ester intermediates 3 in which X is a direct bond.

Schemes **9** and **10** depict the preparation of the intermediate phosphonate esters **3** in which X is direct bond. As shown in Scheme **9**, the amine **1.7**, prepared as described in Scheme **1**, is reacted with a carboxylic acid **9.1**, or an activated derivative thereof, in which the substituent A is the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], NH_2, Br,

etc, as described herein, to afford the amide product **9.2**. The preparation of the carboxylic acids **9.1** is described below in Schemes **57** - **60**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.9**.

The procedures illustrated in Scheme **9** describe the preparation of the compounds **9.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

Scheme **10** depicts the conversion of the compounds **9.2** in which the group A is a precursor to the substituent link-P(O)$(OR^1)_2$ into the compounds **3**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-P(O)$(OR^1)_2$ are described below in Schemes **45** - **101**.

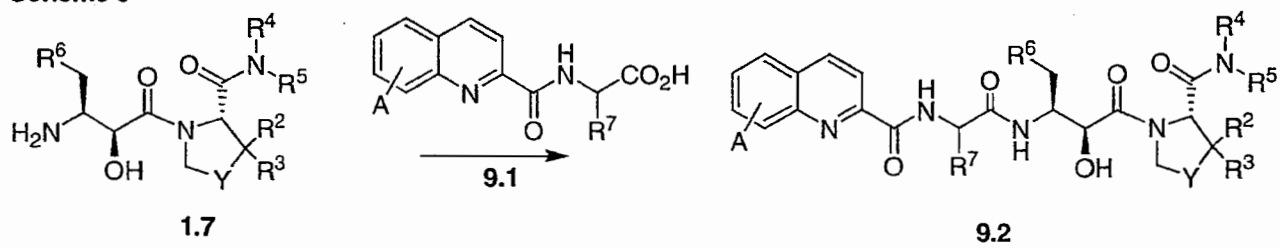
Preparation of the phosphonate ester intermediates 3 in which X is sulfur.

Schemes **11** and **12** depict the preparation of the intermediate phosphonate esters **3** in which X is sulfur. As shown in Scheme **11**, the amine **3.3**, prepared as described in Scheme **3**, is reacted with a carboxylic acid **9.1**, or an activated derivative thereof, in which the substituent A is the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], NH_2, Br, etc, as described herein, to afford the amide product **11.1**. The preparation of the carboxylic acids **9.1** is described below in Schemes **57** - **60**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.9**.

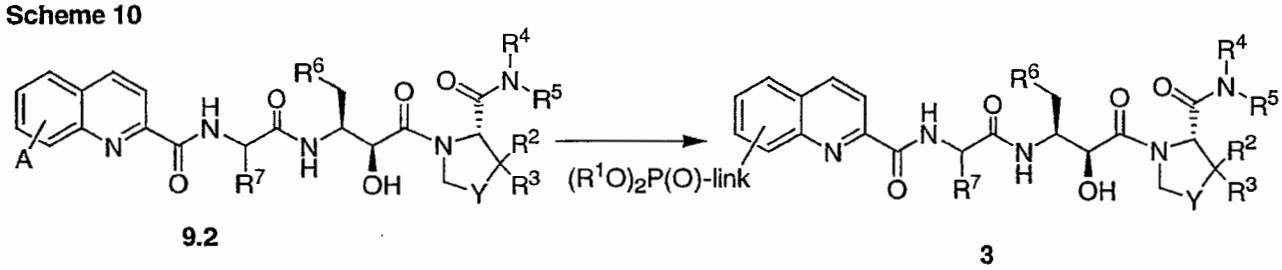
The procedures illustrated in Scheme **11** describe the preparation of the compounds **11.1** in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

Scheme **12** depicts the conversion of the compounds **11.1** in which the A is a precursor to the substituent link-P(O)$(OR^1)_2$ into the compounds **3**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-P(O)$(OR^1)_2$ are described below in Schemes **45** - **101**.

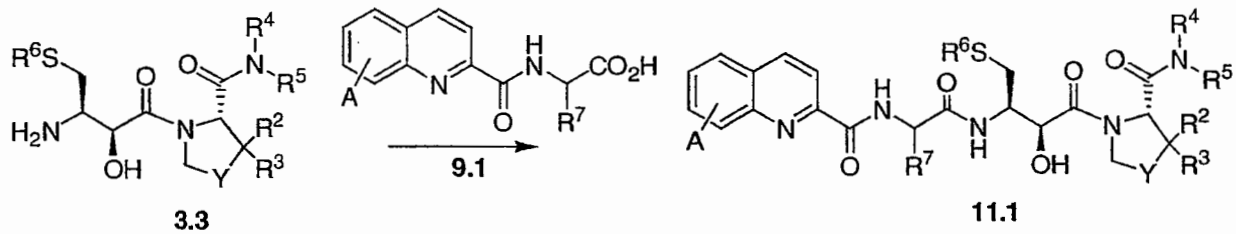
Scheme 9



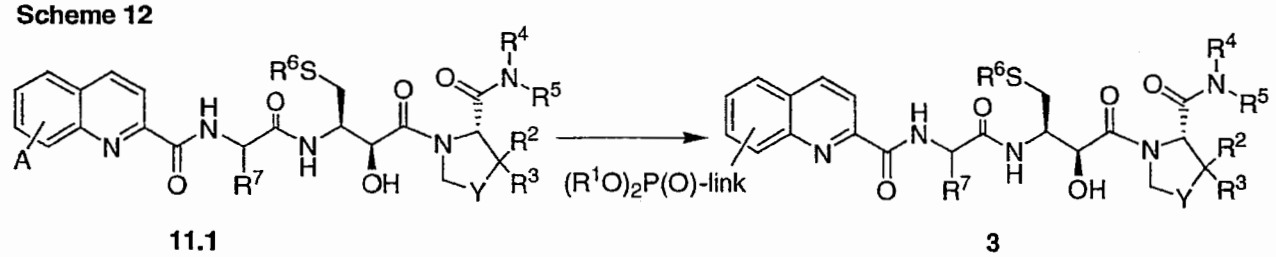
Scheme 10



Scheme 11



Scheme 12



Preparation of the phosphonate ester intermediates 4 in which X is a direct bond.

Schemes **13** and **14** depict the preparation of the intermediate phosphonate esters **4** in which X is direct bond. As shown in Scheme **13**, the amine **1.7**, prepared as described in Scheme **1**, is reacted with a carboxylic acid **13.1**, or an activated derivative thereof, in which the substituent A is the group link-P(O)(OR^1)$_2$, or a precursor group thereto, such as [OH], [SH], NH_2, Br, etc, as described herein, to afford the amide product **13.2**. The preparation of the carboxylic acids **13.1** is described below in Schemes **61** - **66**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.9**.

The procedures illustrated in Scheme **13** describe the preparation of the compounds **13.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

Scheme **14** depicts the conversion of the compounds **13.2** in which the A is a precursor to the substituent link-P(O)$(OR^1)_2$ into the compounds **4**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-P(O)$(OR^1)_2$ are described below in Schemes **45** - **101**.

Preparation of the phosphonate ester intermediates 4 in which X is sulfur.

Schemes **15** and **16** depict the preparation of the intermediate phosphonate esters **4** in which X is sulfur. As shown in Scheme **15**, the amine **3.3**, prepared as described in Scheme **3**, is reacted with a carboxylic acid **13.1**, or an activated derivative thereof, in which the substituent A is the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], NH_2, Br, etc, as described herein, to afford the amide product **15.1**. The preparation of the carboxylic acids **13.1** is described below in Schemes **61** - **66**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.9**.

The procedures illustrated in Scheme **15** describe the preparation of the compounds **15.1** in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

Scheme **16** depicts the conversion of the compounds **15.1** in which the A is a precursor to the substituent link-P(O)$(OR^1)_2$ into the compounds **4**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-P(O)$(OR^1)_2$ are described below in Schemes **45** - **101**.

Preparation of the phosphonate ester intermediates 5 in which X is a direct bond.

Schemes **17** and **18** show the preparation of the intermediate phosphonate esters **5** in which X is a direct bond. As depicted in Scheme **17**, the amine **1.4**, prepared as described in Scheme **1**, is reacted with the carboxylic acid **17.1**, or an activated derivative thereof, to yield the amide product **17.2**. The preparation of the carboxylic acids **17.1** in which the group A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, is

described in Schemes **67 – 71**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.6**. The BOC protecting group is then removed from the product **17.2** to afford the amine **17.3**. The deprotection reaction is performed using similar conditions to those described above in Scheme **1**. The resultant amine **17.3** is then reacted with a carboxylic acid R^8COOH or activated derivative thereof, **17.4** to give the amide **17.5**. For those carboxylic acids R^8COOH listed in Charts **3a** and **3b**, the reaction is performed using similar conditions to those described above for the preparation of the amide **1.9**, (Scheme **1**); for those carboxylic acids R^8COOH listed in Chart **3c**, the reaction is performed using conditions described below (Scheme **102**) for the preparation of carbamates.

The procedures illustrated in Scheme **17** describe the preparation of the compounds **17.5** in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

Scheme **18** depicts the conversion of the compounds **17.5** in which the A is a precursor to the substituent link-$P(O)(OR^1)_2$ into the compounds **5**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-$P(O)(OR^1)_2$ are described below in Schemes **45** - **101**.

Preparation of the phosphonate ester intermediates 5 in which X is sulfur.

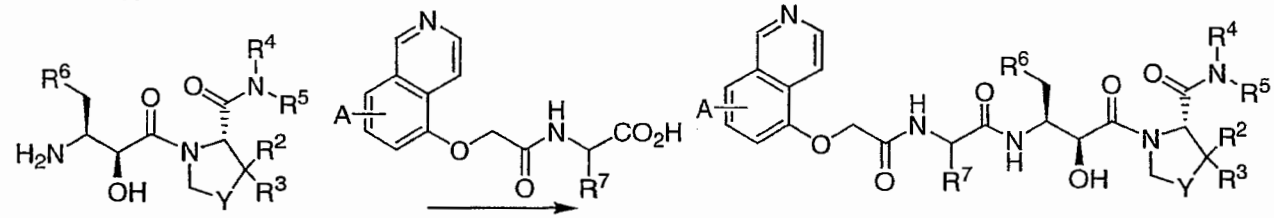
Schemes **19** and **20** show the preparation of the intermediate phosphonate esters **5** in which X is sulfur. As depicted in Scheme **19**, the amine **1.4**, prepared as described in Scheme **1**, is reacted with the carboxylic acid **19.1**, or an activated derivative thereof, to yield the amide product **19.2**. The preparation of the carboxylic acids **19.1** in which the group A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, is described in Schemes **72** - **83**. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide **1.6**. The BOC protecting group is then removed from the product **19.2** to afford the amine **19.3**. The deprotection reaction is performed using similar conditions to those described above in Scheme **1**. The resultant amine **19.3** is then reacted with a carboxylic acid R^8COOH or activated derivative thereof, **19.4** to give the amide **19.4**. For those carboxylic acids R^8COOH listed in Charts **3a**

and **3b**, the reaction is performed using similar conditions to those described above for the preparation of the amide **1.9**, (Scheme **1**); for those carboxylic acids R^8COOH listed in Chart **3c**, the reaction is performed using conditions described below (Scheme **102**) for the preparation of carbamates.

The procedures illustrated in Scheme **19** describe the preparation of the compounds **19.4** in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

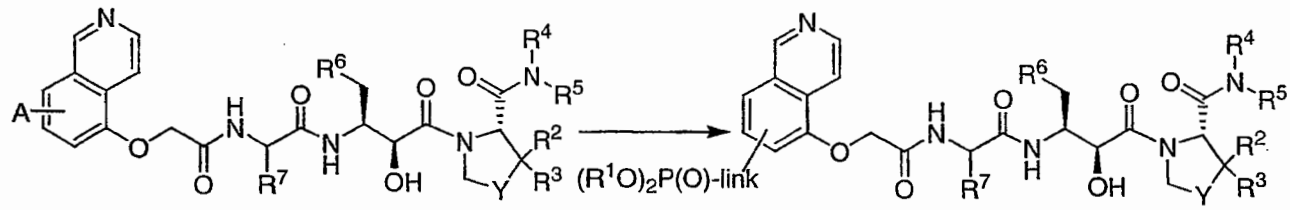
Scheme **20** depicts the conversion of the compounds **19.4** in which the A is a precursor to the substituent link-$P(O)(OR^1)_2$ into the compounds **5**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-$P(O)(OR^1)_2$ are described below in Schemes **45** - **101**.

Scheme 13



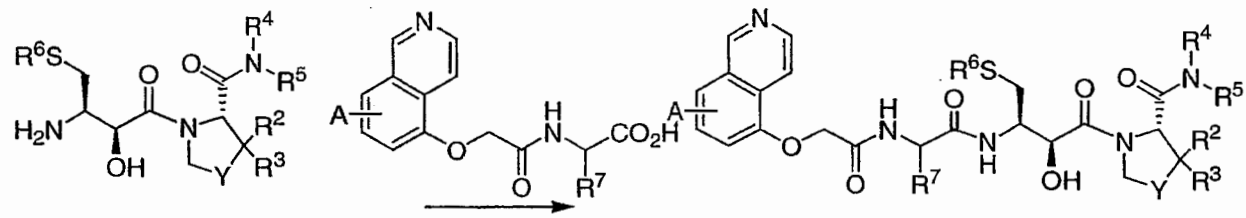
1.7 13.1 13.2

Scheme 14



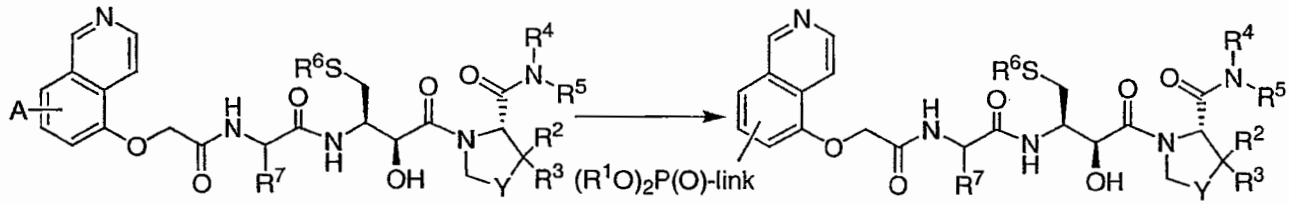
13.2 4

Scheme 15



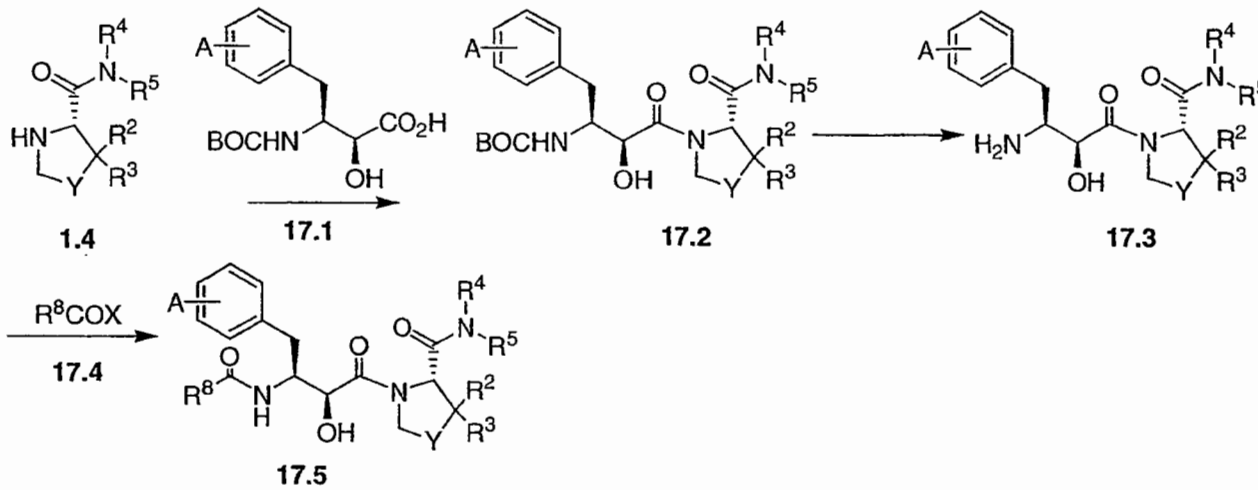
3.3 13.1 15.1

Scheme 16

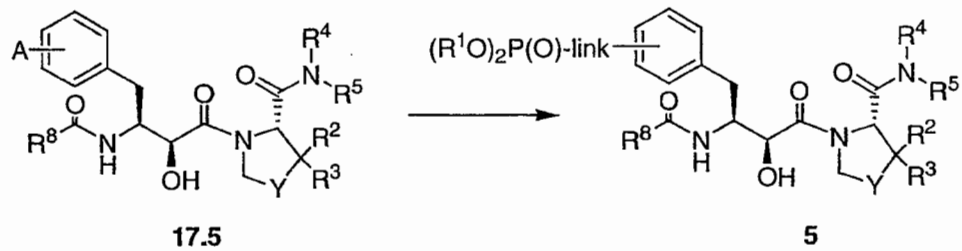


15.1 4

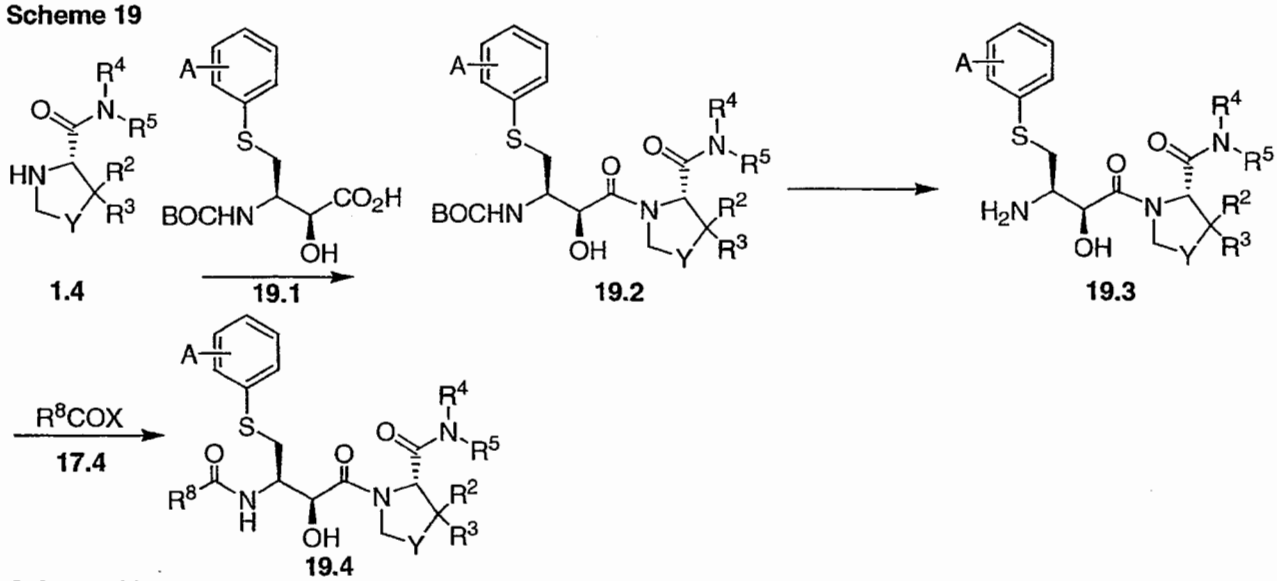
Scheme 17



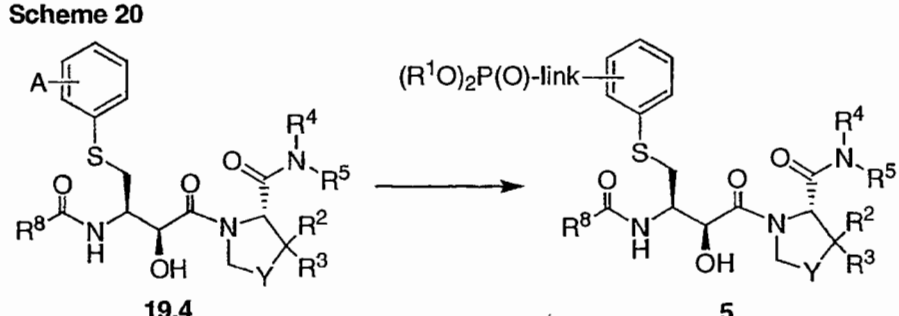
Scheme 18



Scheme 19



Scheme 20



Preparation of the phosphonate ester intermediates 6 in which X is a direct bond.

Schemes **21** and **22** illustrate the preparation of the phosphonate esters **6** in which X is a direct bond. In this procedure, the carboxylic acid **21.1**, in which the group A is the substituent link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein, is reacted with the amine **1.2** to afford the amide **21.2**. The preparation of the carboxylic acids **21.1** is described below in Schemes **98** - **101**. The reaction is performed under similar conditions to those described in Scheme **1** for the preparation of the amide **1.3**. The product **21.2** is then deprotected to yield the free amine **21.3**, using the procedures described above for the removal of BOC groups. The amine **21.3** is then converted, by reaction with the carboxylic acid **1.5**, into the amide **21.4**, using the conditions described above for the preparation of the amide **1.6**. The amide **21.4** is then deprotected to afford the amine **21.5**, and the latter compound is acylated with the carboxylic acid **17.4** to give the amide **21.6**.

The procedures illustrated in Scheme **21** describe the preparation of the compounds **21.6** in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

Scheme **22** depicts the conversion of the compounds **21.6** in which the A is a precursor to the substituent link-$P(O)(OR^1)_2$ into the compounds **6**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-$P(O)(OR^1)_2$ are described below in Schemes **45** - **101**.

Preparation of the phosphonate ester intermediates 6 in which X is sulfur.

Schemes **23** and **24** illustrate the preparation of the phosphonate esters **6** in which X is sulfur. In the procedure shown in Scheme **23**, the amine **21.3**, prepared as described in Scheme **21**, is reacted with the carboxylic acid **3.1** to afford the amide **23.1**. The reaction is performed under similar conditions to those described in Scheme **1** for the preparation of the amide **1.3**. The product **23.1** is then converted, by means of deprotection and acylation, as shown in Scheme **21** for the conversion of the compound **21.4** into the compound **21.6**, into the amide product **23.2**.

The procedures illustrated in Scheme **23** describe the preparation of the compounds **23.2** in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

Scheme **24** depicts the conversion of the compounds **23.2** in which the A is a precursor to the substituent link-P(O)$(OR^1)_2$ into the compounds **6**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-P(O)$(OR^1)_2$ are described below in Schemes **45** - **101**.

Preparation of the phosphonate ester intermediates 7 in which X is a direct bond.

Schemes **25** and **26** illustrate the preparation of the phosphonate esters **7** in which X is a direct bond. As shown in Scheme **25**, the carboxylic acid **1.1** is reacted with the amine **25.1**, in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein, to produce the amide **25.2**. The reaction is performed using similar conditions to those described above for the preparation of the amide **1.3**. The preparation of the amines **25.1** is described below, in Schemes **84** - **87**. The amide product **25.2** is then transformed, using the sequence of reactions shown in Scheme **21** for the conversion of the amide **21.2** into the compound **21.6**, into the compound **25.3**.

The procedures illustrated in Scheme **25** describe the preparation of the compounds **25.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

Scheme **25** depicts the conversion of the compounds **25.3** in which the A is a precursor to the substituent link-P(O)$(OR^1)_2$ into the compounds **7**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-P(O)$(OR^1)_2$ are described below in Schemes **45** - **101**.

Preparation of the phosphonate ester intermediates 7 in which X is sulfur.

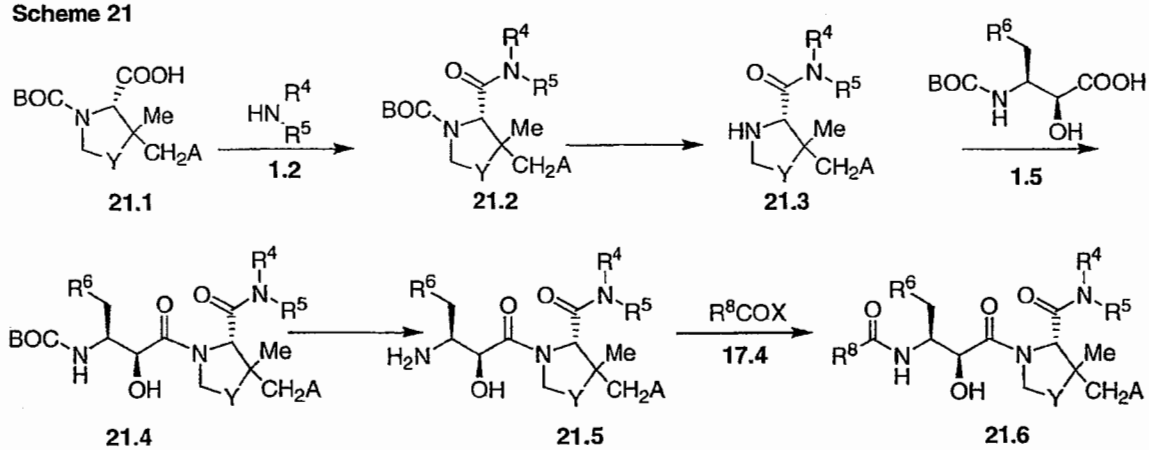
Schemes **27** and **28** illustrate the preparation of the phosphonate esters **7** in which X is sulfur. As shown in Scheme **27**, the BOC-protected amine **25.2** is deprotected to yield the free amine

27.1, using the conditions previously described. The amine **27.1** is then reacted, as described above, with the carboxylic acid **3.1** to afford the amide **27.2**. The latter compound is then transformed, as described above, (Scheme **23**) into the product **27.3**.

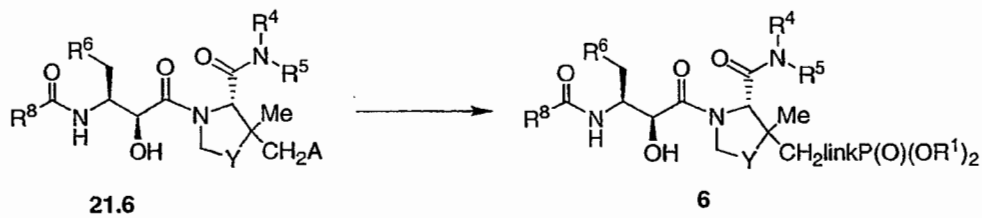
The procedures illustrated in Scheme **27** describe the preparation of the compounds **27.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

Scheme **28** depicts the conversion of the compounds **27.3** in which the A is a precursor to the substituent link-$P(O)(OR^1)_2$ into the compounds **7**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-$P(O)(OR^1)_2$ are described below in Schemes **45** - **101**.

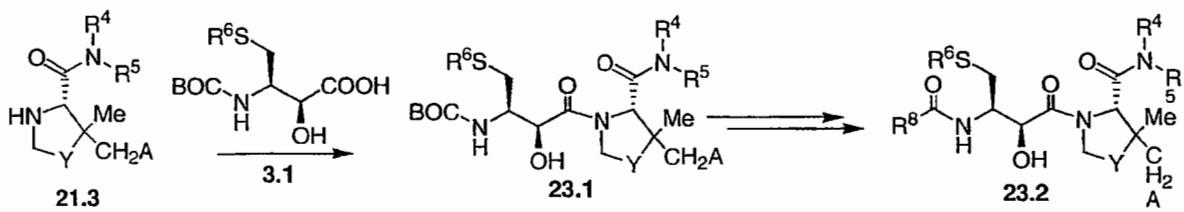
Scheme 21



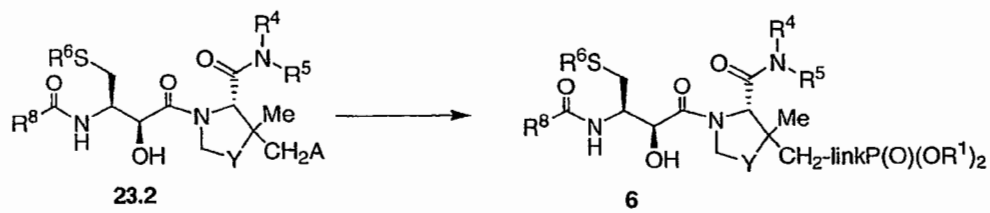
Scheme 22



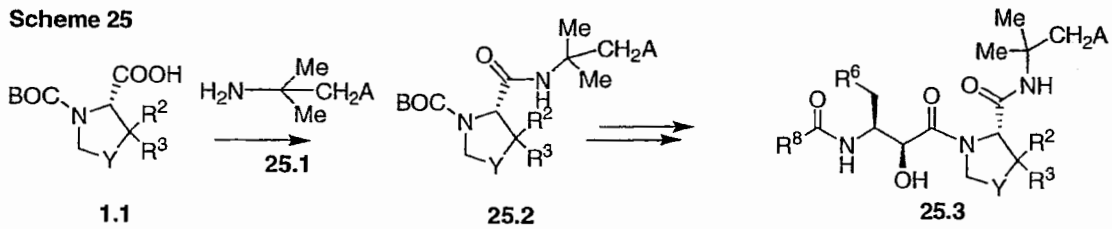
Scheme 23



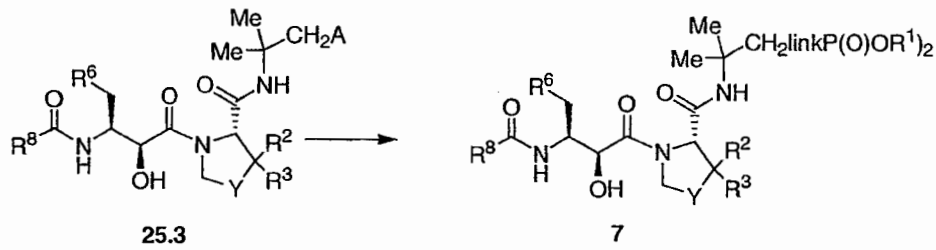
Scheme 24



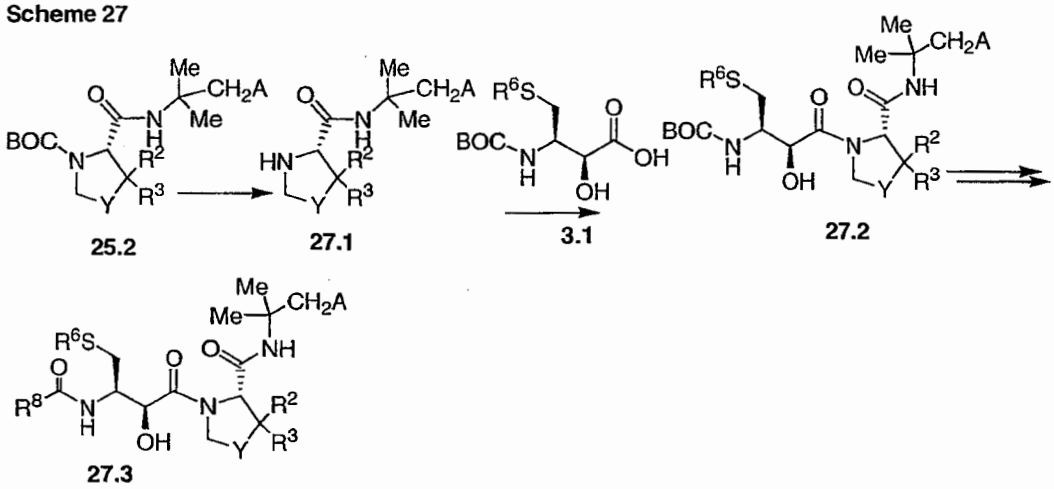
Scheme 25



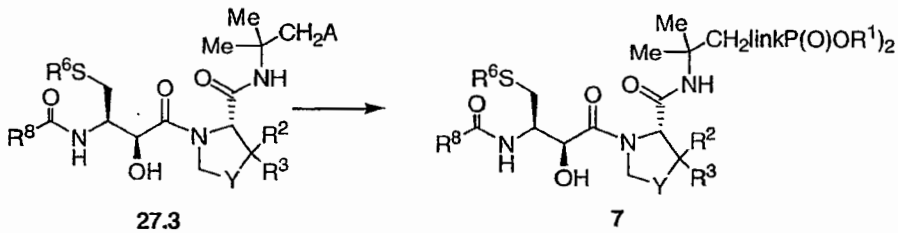
Scheme 26



Scheme 27



Scheme 28



Preparation of the phosphonate ester intermediates 8 in which X is a direct bond.

Schemes **29** and **30** illustrate the preparation of the phosphonate esters **8** in which X is a direct bond. As shown in Scheme **29**, the carboxylic acid **1.1** is reacted with the amine **29.1**, in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein, to produce the amide **29.2**. The reaction is

performed using similar conditions to those described above for the preparation of the amide **1.3**. The preparation of the amines **29.1** is described below, in Schemes **86** - **88**. The amide product **29.2** is then transformed, using the sequence of reactions shown in Scheme **21** for the conversion of the amide **21.2** into the compound **21.6**, into the compound **29.3**.

The procedures illustrated in Scheme **29** describe the preparation of the compounds **29.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

Scheme **30** depicts the conversion of the compounds **29.3** in which the A is a precursor to the substituent link-$P(O)(OR^1)_2$ into the compounds **8**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-$P(O)(OR^1)_2$ are described below in Schemes **45** - **101**.

Preparation of the phosphonate ester intermediates 8 in which X is sulfur.

Schemes **31** and **32** illustrate the preparation of the phosphonate esters **8** in which X is sulfur. As shown in Scheme **31**, the BOC-protected amine **29.2** is deprotected to yield the free amine **31.1**, using the conditions previously described. The amine **31.1** is then reacted, as described above, with the carboxylic acid **3.1** to afford the amide **31.2**. The latter compound is then transformed, as described above, (Scheme **23**) into the product **31.3**.

The procedures illustrated in Scheme **31** describe the preparation of the compounds **31.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.

Scheme **32** depicts the conversion of the compounds **31.3** in which the A is a precursor to the substituent link-$P(O)(OR^1)_2$ into the compounds **8**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-$P(O)(OR^1)_2$ are described below in Schemes **45** - **101**.

Preparation of the phosphonate ester intermediates 9 in which X is a direct bond.

Schemes **33** and **34** illustrate the preparation of the phosphonate esters **9** in which X is a direct bond. As shown in Scheme **33**, the carboxylic acid **1.5** is reacted with the amine **33.1**, in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], $[NH_2]$, Br, etc, as described herein, to produce the amide **33.2**. The reaction is performed using similar conditions to those described above for the preparation of the amide **1.6** in Scheme 1. The preparation of the amines **33.1** is described below, in Schemes **91** - **97**. The amide product **33.2** is then transformed into the compound **33.3**, using the sequence of reactions shown in Scheme **21** for the conversion of the amide **21.4** into the compound **21.6**.

The procedures illustrated in Scheme **33** describe the preparation of the compounds **33.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], $[NH_2]$, Br, etc, as described herein.
Scheme **34** depicts the conversion of the compounds **33.3** in which the A is a precursor to the substituent link-P(O)$(OR^1)_2$ into the compounds **9**. Procedures for the conversion of the substituents [OH], [SH], $[NH_2]$, Br etc into the substituent link-P(O)$(OR^1)_2$ are described below in Schemes **45** - **101**.

Preparation of the phosphonate ester intermediates 9 in which X is sulfur.

Schemes **35** and **36** illustrate the preparation of the phosphonate esters **9** in which X is sulfur. As shown in Scheme **35** the amine **33.2** is transformed into **35.1** by similar means described above (Scheme **23**) for converting **21.3** into **23.2**.

The procedures illustrated in Scheme **35** describe the preparation of the compounds **35.1** in which the substituent A is either the group link-P(O)$(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], $[NH_2]$, Br, etc, as described herein.
Scheme **36** depicts the conversion of the compounds **35.1** in which the A is a precursor to the substituent link-P(O)$(OR^1)_2$ into the compounds **9**. Procedures for the conversion of the substituents [OH], [SH], $[NH_2]$, Br etc into the substituent link-P(O)$(OR^1)_2$ are described below in Schemes **45** - **101**.

Preparation of the phosphonate ester intermediates 10 in which X is a direct bond.

Schemes **37** and **38** illustrate the preparation of the phosphonate esters **10** in which X is a direct bond. As shown in Scheme **37**, the carboxylic acid **1.5** is reacted with the amine **37.1**, in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein, to produce the amide **37.2**. The reaction is performed using similar conditions to those described above for the preparation of the amide **1.6**. The preparation of the amines **37.1** is described below, in Scheme **91-97**. The amide product **37.2** is then transformed into the compound **37.3**, using the sequence of reactions shown in Scheme **21** for the conversion of the amide **21.4** into the compound **21.6**.

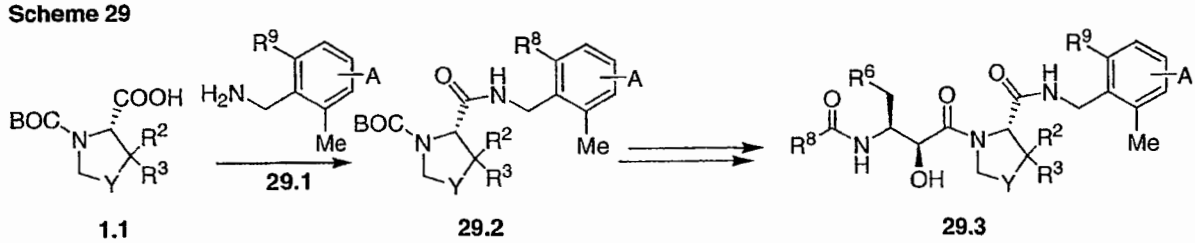
The procedures illustrated in Scheme **37** describe the preparation of the compounds **37.3** in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.
Scheme **38** depicts the conversion of the compounds **37.3** in which the A is a precursor to the substituent link-$P(O)(OR^1)_2$ into the compounds **10**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-$P(O)(OR^1)_2$ are described below in Schemes **45** - **101**.

Preparation of the phosphonate ester intermediates 10 in which X is sulfur.

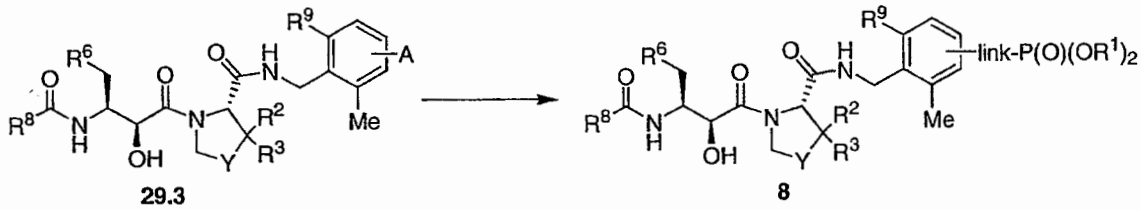
Schemes **39** and **40** illustrate the preparation of the phosphonate esters **10** in which X is sulfur. As shown in Scheme **39** the amine **37.1** is transformed into the product **39.1**, as described above, (Scheme **23**) for the conversion of **21.3** into **23.2**.

The procedures illustrated in Scheme **39** describe the preparation of the compounds **39.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein.
Scheme **40** depicts the conversion of the compounds **39.1** in which the A is a precursor to the substituent link-$P(O)(OR^1)_2$ into the compounds **10**. Procedures for the conversion of the substituents [OH], [SH], [NH_2], Br etc into the substituent link-$P(O)(OR^1)_2$ are described below in Schemes **45** - **101**.

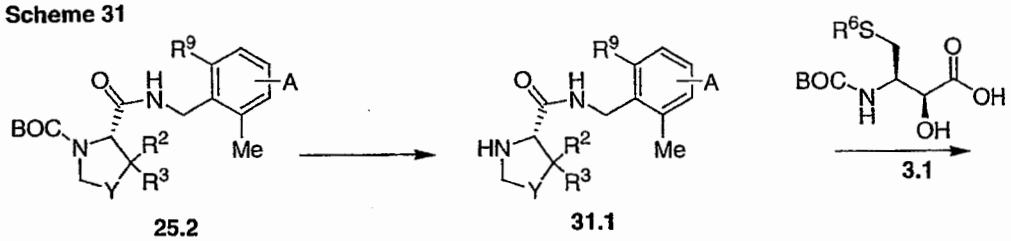
Scheme 29



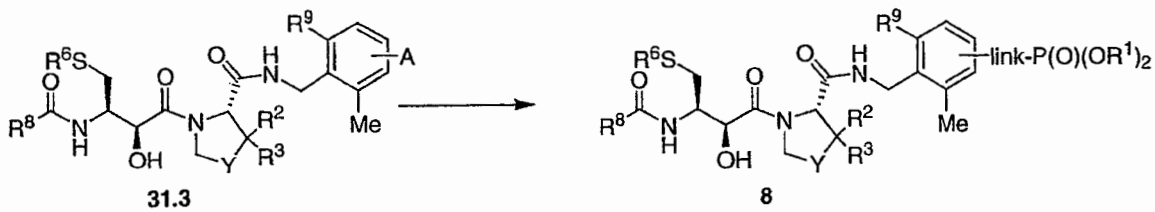
Scheme 30



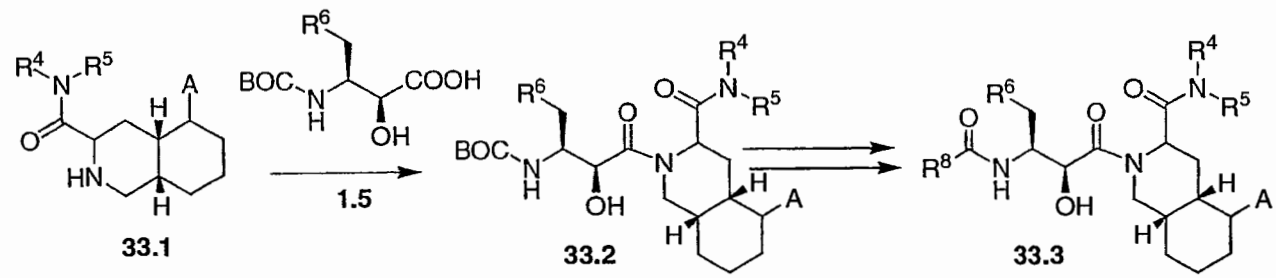
Scheme 31



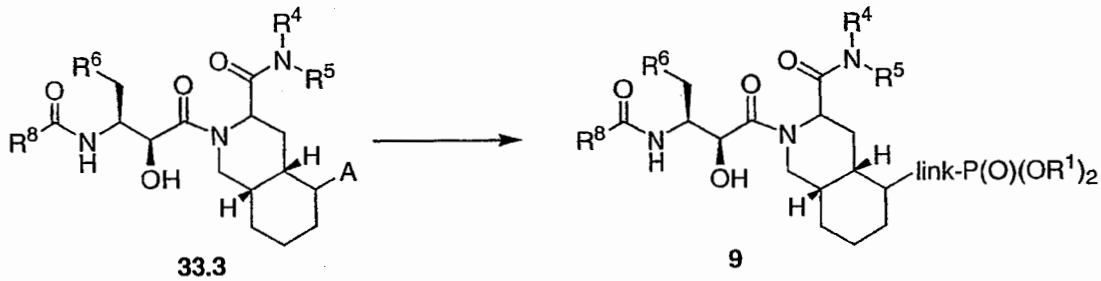
Scheme 32



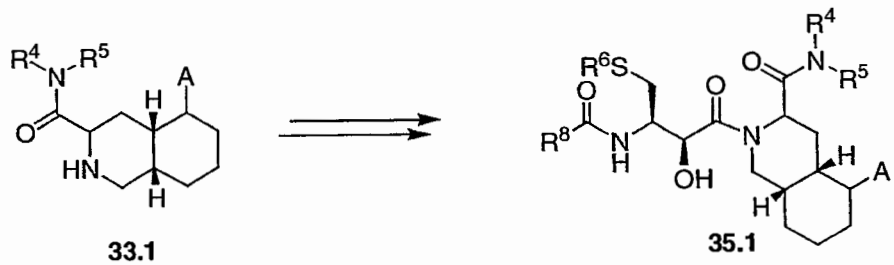
Scheme 33



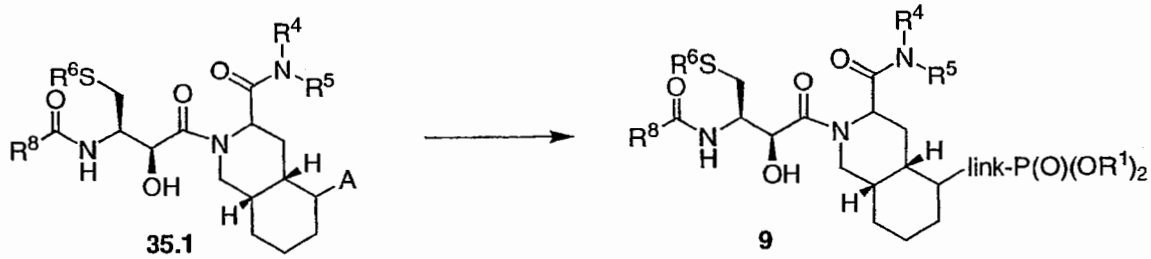
Scheme 34



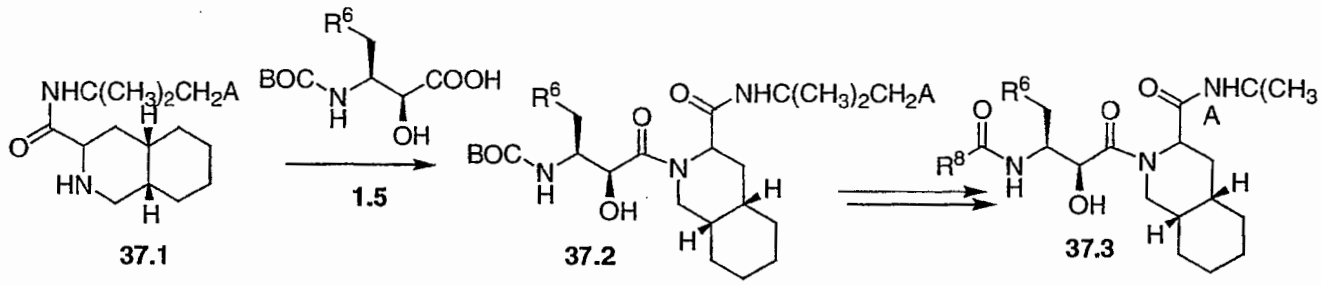
Scheme 35



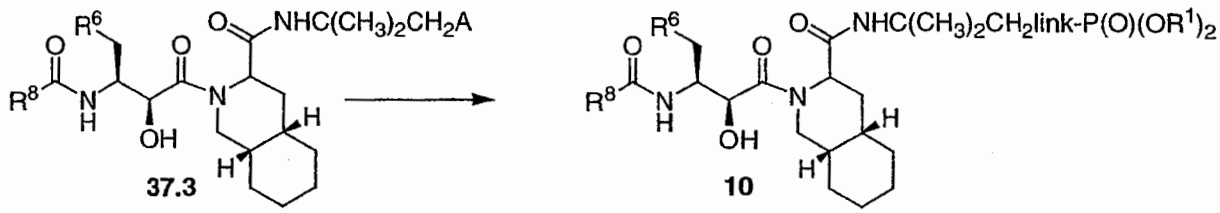
Scheme 36



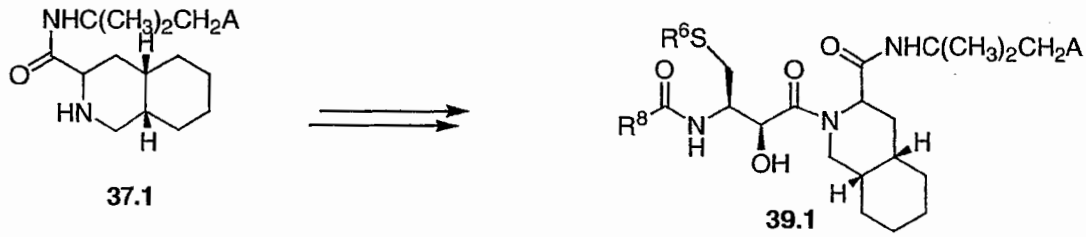
Scheme 37



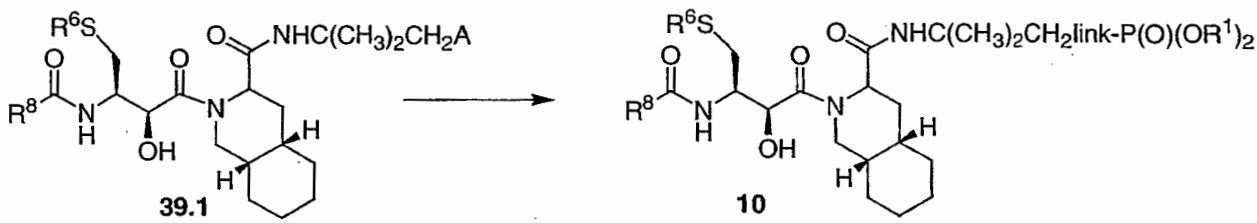
Scheme 38



Scheme 39



Scheme 40



Preparation of the BOC-protected aminohydroxy phenylbutanoic acids 1.5.

The preparation of the butanoic acid derivatives **1.5** in which R^6 is phenyl is described, for example, in Tet. Asym., 2002, 13, 1201, Eur. J. Med. Chem., 2000, 35, 887, Chem. Pharm. Bull., 2000, 48, 1310, J. Med. Chem., 1994, 37, 2918, J. Chem. Res., 1999, 282 and J. Med.

Chem., 1993, 36, 211. The analogs **1.5** in which the substituent R^6 is as described in Chart **5** are prepared by analogous reaction sequences.

Schemes **41** and **42** illustrate two alternative procedures for the preparation of the reactants **1.5**. As shown in Scheme **41**, the BOC-protected aminoacid **41.1** is converted into the corresponding aldehyde **41.3**. Numerous methods are known for the conversion of carboxylic acids and derivatives into the corresponding aldehydes, for example as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 619-627. The conversion is effected by direct reduction of the carboxylic acid, for example employing diisobutyl aluminum hydride, as described in J. Gen. Chem. USSR., 34, 1021, 1964, or alkyl borane reagents, for example as described in J. Org. Chem., 37, 2942, 1972. Alternatively, the carboxylic acid is converted into an amide, such as the N-methoxy N-methyl amide, and the latter compound is reduced with lithium aluminum hydride, for example as described in J. Med. Chem., 1994, 37, 2918, to afford the aldehyde **41.3**. Alternatively, the carboxylic acid is reduced to the corresponding carbinol **41.2**. The reduction of carboxylic acids to carbinols is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 548ff. The reduction reaction is performed by the use of reducing agents such as borane, as described in J. Am. Chem. Soc., 92, 1637, 1970, or by lithium aluminum hydride, as described in Org. Reac., 6, 649, 1951. The resultant carbinol **41.2** is then converted into the aldehyde **41.3** by means of an oxidation reaction. The oxidation of a carbinol to the corresponding aldehyde is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. The conversion is effected by the use of oxidizing agents such as pyridinium chlorochromate, as described in J.Org. Chem., 50, 262, 1985, or silver carbonate, as described in Compt. Rend. Ser. C., 267, 900, 1968, or dimethyl sulfoxide/acetic anhydride, as described in J. Am. Chem. Soc., 87, 4214, 1965. Preferably, the carbinol **41.2** is converted into the aldehyde **41.3** by oxidation with pyridine-sulfur trioxide in dimethyl sulfoxide, as described in Eur. J. Med. Chem., 35, 2000, 887. The aldehyde **41.3** is then transformed into the cyanohydrin **1.4**. The transformation of an aldehyde into the corresponding cyanohydrin is effected by reaction with an alkali metal cyanide such as potassium cyanide, in an aqueous organic solvent mixture. Preferably, a solution of the aldehyde in ethyl acetate is reacted with an aqueous solution of potassium cyanide, as described in Eur. J. Med. Chem., 35, 2000, 887, to yield the cyanohydrin **41.4**. Optionally, a

methanolic solution of the aldehyde is first treated with an aqueous solution of sodium bisulfite, and the bisulfite adduct which is formed in situ is then reacted with an aqueous solution of sodium cyanide, as described in J. Med. Chem., 37, 1994, 2918, to give the cyanohydrin **41.4**. The latter compound is then hydrolyzed to afford the hydroxyacid product **41.5**. The hydrolysis is effected under acidic conditions; for example, the cyanohydrin **41.4** is heated in a mixture of concentrated hydrochloric acid and dioxan, as described in Eur. J. Med. Chem., 35, 2000, 887, optionally in the presence of anisole, as described in J. Med. Chem., 37, 1994, 2918, to afford the hydroxyacid product, from which the (2S), (3S) isomer **41.5** is isolated. The BOC protecting group is then attached, for example by reaction of the aminoacid **41.5** with BOC anhydride in aqueous tetrahydrofuran containing triethylamine, as described in Eur. J. Med. Chem., 35, 2000, 887.

Alternatively, the BOC-protected aminohydroxy phenylbutanoic acids **1.5** are obtained by means of the reaction sequence shown in Scheme **42**. In this sequence, the N, N-dibenzyl aminoacid ester **42.1**, prepared as described in Tet., 1995, 51, 6397, is converted, using the procedures described above in Scheme **41**, into the corresponding aldehyde **42.2**. The latter compound is then reacted with a silylmethyl Grignard reagent, for example isopropoxydimethylsilylmethylmagnesium chloride **42.3**, to give the carbinol product **42.4**. Preferably, the aldehyde and ca. two molar equivalents of the Grignard reagent are reacted in tetrahydrofuran solution at 0°, as described in Tet. Asym., 2002, 13, 1201. The silyl carbinol **42.4** is then reacted with aqueous ammonium chloride, as described in Tet. Asym., 2002, 13, 1201, to give the diol **42.5**. The N-benzyl groups are then removed to afford the free amine **42.6**. The removal of N-benzyl groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 365. Benzyl groups are removed by catalytic hydrogenation in the presence of hydrogen or a hydrogen donor, by reduction with sodium in ammonia, by treatment with trichloroethyl chloroformate, or by oxidation, for example by the use of ruthenium tetroxide or 3-chloroperoxybenzoic acid and ferrous chloride. Preferably, the debenzylation is effected by hydrogenation of the substrate **42.5** in ethanol at ca 50° in the presence of 5% palladium on carbon catalyst, as described in Tet. Asym., 2002, 13, 1201, to produce the amine **42.6**. The BOC protecting group is then attached using the procedures described above, and the resultant product **42.7** is oxidized to give the carboxylic acid **1.5**. The oxidation of carbinols to

afford the corresponding carboxylic acid is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 835. The conversion can be effected by the sue of oxidizing agents such as chromium trioxide in acetic acid, potassium permanganate, ruthenium tetroxide or silver oxide. Preferably, the transformation is effected by the use of sodium chlorite and sodium hypochlorite in aqueous acetonitrile in the presence of a pH 6.7 phosphate buffer and a catalytic amount of 2,2,6,6,-tetramethylpiperidin-1-oxyl, as described in Tet. Asym., 2002, 13, 1201, to afford the carboxylic acid **1.5**.

Preparation of the BOC-protected aminohydroxy arylthiobutanoic acids 3.1.

Schemes **43** and **44** illustrate two alternative methods for the preparation of the BOC-protected aminohydroxy arylthiobutanoic acids **3.1**. As shown in Scheme **43**, N, N-dibenzyl serine methyl ester **43.1**, prepared as described in J. Org. Chem., 1986, 63, 1709, is converted into the methanesulfonate ester **43.2**. The carbinol is reacted with methanesulfonyl chloride and triethylamine in toluene, as described in J. Org. Chem., 65, 2000, 1623, to produce the mesylate **43.2**. The latter compound is then reacted with a thiophenol R^6SH, in the presence of a base, to give the thioether **43.4**. The displacement reaction is performed in an organic solvent such as dimethylformamide, or in an aqueous organic solvent mixture, in the presence of an organic base such as triethylamine or dimethylaminopyridine, or an inorganic base such as potassium carbonate and the like. Preferably, the reactants are combined in toluene solution in the presence of aqueous sodium hydroxide and a phase transfer catalyst such as tetrabutyl ammonium bromide, as described in J. Org. Chem., 65, 2000, 1623, to afford the product **43.4**. The ester product is then transformed into the corresponding aldehyde **43.5**, using the procedures described above (Scheme **41**). The aldehyde is then converted, using the sequence of reactions shown in Scheme **41**, into the BOC-protected aminohydroxy arylthiobutanoic acids **3.1**.

Alternatively, as shown in Scheme **44**, the aldehyde **43.5** is converted, using the sequence of reactions shown in Scheme **42**, into the product **3.1**. The component reactions of this sequence are performed under similar conditions to those described for the analogous reactions in Scheme **42**.

Preparation of phosphonate-containing hydroxymethyl benzoic acids 1.8.

Schemes **45** - **49** illustrate methods for the preparation of phosphonate-containing hydroxymethyl benzoic acids **1.8** which are employed in the preparation of the phosphonate esters **1**.

Scheme **45** illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid **45.1** is subjected to halogen-methyl exchange to afford the organometallic intermediate **45.2**. This compound is reacted with a chlorodialkyl phosphite **45.3** to yield the phenylphosphonate ester **45.4**, which upon deprotection affords the carboxylic acid **45.5**.

For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, **45.6**, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Am. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane **45.7**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester **45.8**. This compound is treated with boron trifluoride at 0^0 to effect rearrangement to the orthoester **45.9**, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether **45.10**. Halogen-metal exchange is performed by the reaction of the substrate **45.10** with butyllithium, and the lithiated intermediate is then coupled with a chlorodialkyl phosphite **45.3**, to produce the phosphonate **45.11**. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid **45.12**.

Using the above procedures, but employing, in place of the bromo compound **45.6**, different bromo compounds **45.1**, there are obtained the corresponding products **45.5**.

Scheme **46** illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

In this method, a suitably protected dimethyl hydroxybenzoic acid, **46.1**, is reacted with a brominating agent, so as to effect benzylic bromination. The product **46.2** is reacted with a sodium dialkyl phosphite, **46.3**, as described in J. Med. Chem., 1992, 35, 1371, to effect

displacement of the benzylic bromide to afford the phosphonate **46.4**. Deprotection of the carboxyl function then yields the carboxylic acid **46.5**.

For example, 2,5-dimethyl-3-hydroxybenzoic acid, **46.6**, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p.17, to afford the ether ester **46.7**. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or diisopropylethylamine. The product **46.7** is then reacted with a brominating agent, for example N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product **46.8**. This compound is then reacted with a sodium dialkyl phosphite **46.3** in tetrahydrofuran, as described above, to afford the phosphonate **46.9**. Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields the carboxylic acid **46.10**. Using the above procedures, but employing, in place of the methyl compound **46.6**, different methyl compounds **46.1**, there are obtained the corresponding products **46.5**.

Scheme **47** illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom.

In this method, a suitably protected hydroxy- or mercapto-substituted hydroxy methyl benzoic acid **47.1** is reacted, under the conditions of the Mitsonobu reaction, with a dialkyl hydroxymethyl phosphonate **47.2**, to afford the coupled product **47.3**, which upon deprotection affords the carboxylic acid **47.4**.

For example, 3,6-dihydroxy-2-methylbenzoic acid, **47.5**, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester **47.6**, by treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 77, to afford the mono-silyl ether **47.7**. This compound is then reacted with a dialkyl hydroxymethylphosphonate **47.2**, under the conditions of the Mitsonobu reaction. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p.

448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4 and in Org. React., 1992, 42, 335. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. The reaction affords the coupled product **47.9**. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic carboxylic acid **47.9**.

Using the above procedures, but employing, in place of the phenol **47.5**, different phenols or thiophenols **47.1**, there are obtained the corresponding products **47.4**.

Scheme **48** depicts the preparation of phosphonate esters attached to the hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains. In this method, a dialkyl alkenylphosphonate **48.2** is coupled, by means of a palladium catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid **48.1**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. The product **48.3** is deprotected to afford the phosphonate **48.4;** the latter compound is subjected to catalytic hydrogenation to afford the saturated carboxylic acid **48.5**.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid **48.6,** prepared as described in WO 9218490, is converted as described above, into the silyl ether OBO ester **48.7**. This compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate **48.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above to afford the product **48.9**. Deprotection, or hydrogenation/deprotection, of this compound, as described above, then affords respectively the unsaturated and saturated products **48.10** and **48.11**.

Using the above procedures, but employing, in place of the bromo compound **48.6**, different bromo compounds **48.1**, and/or different phosphonates **48.2**, there are obtained the corresponding products **48.4** and **48.5**.

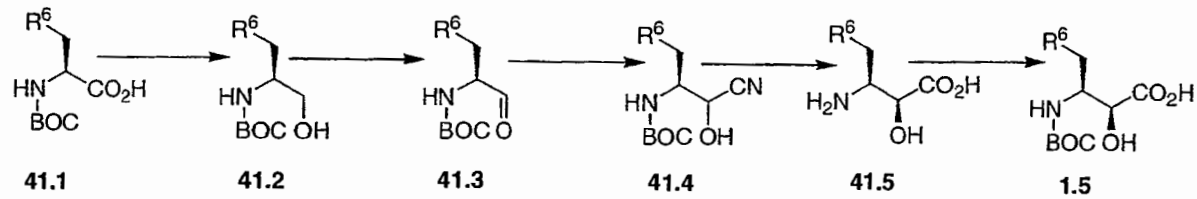
Scheme **49** illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid **49.1** is converted to the corresponding boronic acid **49.2**, by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82. The product is subjected to a Suzuki coupling reaction with a dialkyl bromophenyl phosphonate **49.3**. The product **49.4** is then deprotected to afford the diaryl phosphonate product **49.5**.

For example, the silylated OBO ester **49.6**, prepared as described above, (Scheme **45**), from 5-bromo-3-hydroxybenzoic acid, the preparation of which is described in J. Labelled. Comp. Radiopharm., 1992, 31, 175, is converted into the boronic acid **49.7**, as described above. This material is coupled with a dialkyl 4-bromophenyl phosphonate **49.8**, prepared as described in J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, in the presence of sodium bicarbonate, as described, for example, in Palladium reagents and catalysts J. Tsuji, Wiley 1995, p 218, to afford the diaryl phosphonate **49.9**. Deprotection, as described above, then affords the benzoic acid **49.10**.

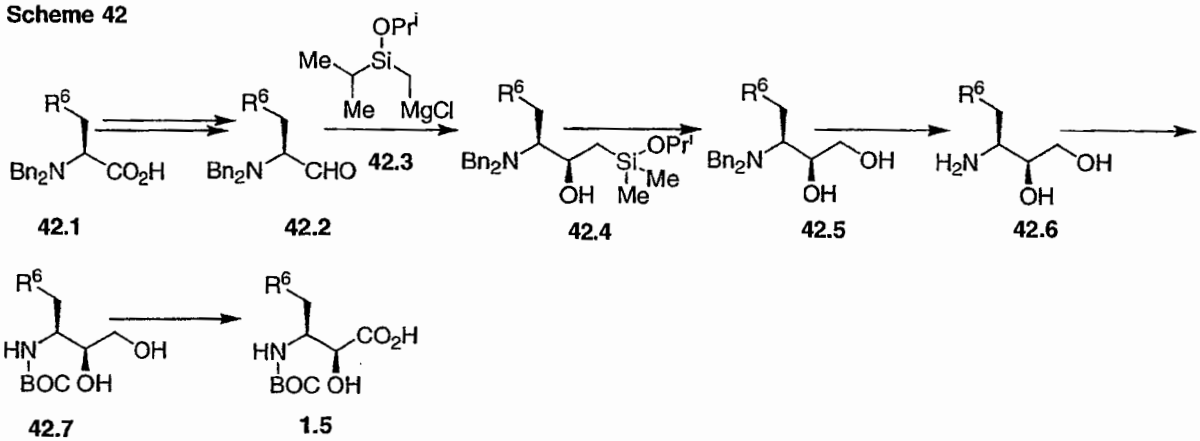
Using the above procedures, but employing, in place of the bromo compound **49.6**, different bromo compounds **49.1**, and/or different phosphonates **49.3**, there are obtained the corresponding carboxylic acid products **49.5**.

Scheme 41



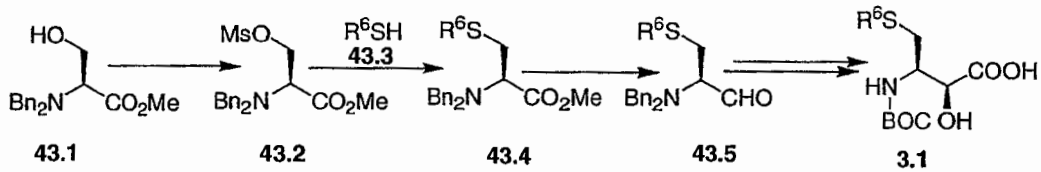
41.1 41.2 41.3 41.4 41.5 1.5

Scheme 42



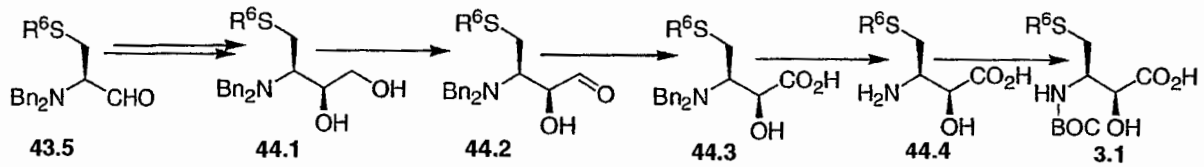
42.1 42.2 42.3 42.4 42.5 42.6 42.7 1.5

Scheme 43



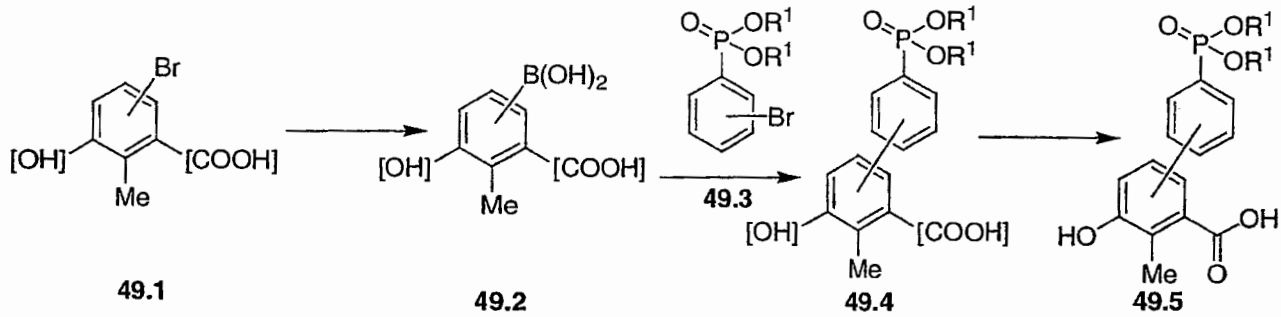
43.1 43.2 43.4 43.5 3.1

Scheme 44

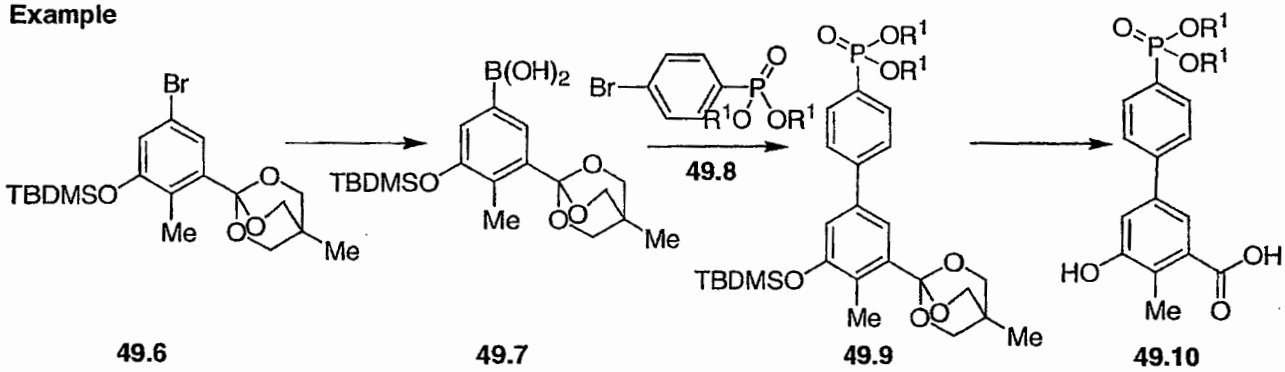


43.5 44.1 44.2 44.3 44.4 3.1

Scheme 49
Method



Example



Preparation of dimethylphenoxyacetic acids 5.1 incorporating phosphonate moieties.

The preparation of the dimethylphenoxyacetic acids **5.1** incorporating phosphonate moieties which are used in the preparation of the phosphonate esters **2** is described in Schemes **50** - **56**.

Scheme **50** illustrates two alternative methods by means of which 2,6-dimethylphenoxyacetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the 2,6-dimethylphenol moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed 2,6-dimethylphenoxyacetic acid intermediate. In the first sequence, a substituted 2,6-dimethylphenol **50.1**, in which the substituent B is a precursor to the group link-P(O)$(OR^1)_2$, and in which the phenolic hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound **50.2**. Methods for the conversion of the substituent B into the group link-P(O)$(OR^1)_2$ are described in Schemes **46** - **101**.

The protected phenolic hydroxyl group present in the phosphonate-containing product **50.2** is then deprotected, using methods described below, to afford the phenol **50.3**.

The phenolic product **50.3** is then transformed into the corresponding phenoxyacetic acid **50.4**, in a two step procedure. In the first step, the phenol **50.3** is reacted with an ester of bromoacetic acid **50.4**, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of phenols to afford phenolic ethers is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the phenol and the alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol **50.3** and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described in US Patent 5914332, to afford the ester **50.5**.

The thus-obtained ester **50.5** is then hydrolyzed to afford the carboxylic acid **50.6**. The methods used for this reaction depend on the nature of the group R. If R is an alkyl group such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group, methods for hydrolysis are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

Preferably, the ester product **50.5** which R is ethyl is hydrolyzed to the carboxylic acid **50.6** by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in US Patent 5914332.

Alternatively, an appropriately substituted 2,6-dimethylphenol **50.8**, in which the substituent B is a precursor to the group link-$P(O)(OR^1)_2$, is transformed into the corresponding phenoxyacetic ester **50.7**. The conditions employed for the alkylation reaction are similar to those described above for the conversion of the phenol **50.3** into the ester **50.5**.

The phenolic ester **50.7** is then converted, by transformation of the group B into the group link-$P(O)(OR^1)_2$ followed by ester hydrolysis, into the carboxylic acid **50.6**. The group B which is present in the ester **50.6** may be transformed into the group link-$P(O)(OR^1)_2$ either before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes **51** - **56** illustrate the preparation of 2,6-dimethylphenoxyacetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of phenoxyacetic esters acids **50.7**, with, if appropriate, modifications made according to the knowledge of one skilled in the art.

Scheme **51** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester which is attached to the phenolic group by means of a carbon chain incorporating a nitrogen atom. The compounds **51.4** are obtained by means of a reductive alkylation reaction between a 2,6-dimethylphenol aldehyde **51.1** and an aminoalkyl phosphonate ester **51.2.** The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component **51.2** and the aldehyde component **51.1** are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product **51.3**. The amination product **51.3** is then converted into the phenoxyacetic acid compound **51.4**, using the alkylation and ester hydrolysis procedures described above, (Scheme **50**) For example, equimolar amounts of 4-hydroxy-3,5-dimethylbenzaldehyde **51.5** (Aldrich) and a dialkyl aminoethyl phosphonate **51.6**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in J. Am. Chem. Soc., 91, 3996, 1969, to afford the amine product **51.7**. The product is then converted into the acetic acid **51.8**, as described above. Using the above procedures, but employing, in place of the aldehyde **51.5**, different aldehydes **51.1**, and/or different aminoalkyl phosphonates **51.2**, the corresponding products **51.4** are obtained.

Scheme **52** depicts the preparation of 2,6-dimethylphenols incorporating a phosphonate group linked to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, an optionally protected bromo-substituted 2,6-dimethylphenol **52.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate **52.2**. The coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl bromide and the olefin are coupled in a polar solvent such as

dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst. Following the coupling reaction, the product **52.3** is converted, using the procedures described above, (Scheme **50**) into the corresponding phenoxyacetic acid **52.4**. Alternatively, the olefinic product **52.3** is reduced to afford the saturated 2,6-dimethylphenol derivative **52.5**. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or diimide. Following the reduction reaction, the product **52.5** is converted, as described above, (Scheme **50**) into the corresponding phenoxyacetic acid **52.6**.

For example, 3-bromo-2,6-dimethylphenol **52.7**, prepared as described in Can. J. Chem., 1983, 61, 1045, is converted into the tert-butyldimethylsilyl ether **52.8**, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 p. 77. The product **52.8** is reacted with an equimolar amount of a dialkyl allyl phosphonate **52.9**, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°, to produce the coupled product **52.10**. The silyl group is removed, for example by the treatment of the ether **52.10** with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Am. Chem., Soc., 94, 6190, 1972, to afford the phenol **52.11**. This compound is converted, employing the procedures described above, (Scheme **50**) into the corresponding phenoxyacetic acid **52.12**. Alternatively, the unsaturated compound **52.11** is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog **52.13**. This compound is converted, employing the procedures described above, (Scheme **50**) into the corresponding phenoxyacetic acid **52.14**.

Using the above procedures, but employing, in place of 3-bromo-2,6-dimethylphenol **52.7**, different bromophenols **52.1**, and/or different dialkyl alkenyl phosphonates **52.2**, the corresponding products **52.4** and **52.6** are obtained.

Scheme **53** illustrates the preparation of phosphonate-containing 2,6-dimethylphenoxyacetic acids **53.1** in which the phosphonate group is attached to the 2,6-dimethylphenoxy moiety by

means of a carbocyclic ring. In this procedure, a bromo-substituted 2,6-dimethylphenol **53.2** is converted, using the procedures illustrated in Scheme **50**, into the corresponding 2,6-dimethylphenoxyacetic ester **53.3**. The latter compound is then reacted, by means of a palladium-catalyzed Heck reaction, with a cycloalkenone **53.4**, in which n is 1 or 2. The coupling reaction is conducted under the same conditions as those described above for the preparation of the unsaturated phosphonate **52.3**. (Scheme **52**). The product **53.5** is then reduced catalytically, as described above for the reduction of the phosphonate **52.3**, (Scheme **52**), to afford the substituted cycloalkanone **53.6**. The ketone is then subjected to a reductive amination procedure, by reaction with a dialkyl 2-aminoalkylphosphonate **53.7** and sodium triacetoxyborohydride, as described in J. Org. Chem., 61, 3849, 1996, to yield the amine phosphonate **53.8**. The reductive amination reaction is conducted under the same conditions as those described above for the preparation of the amine **51.3** (Scheme **51**). The resultant ester **53.8** is then hydrolyzed, as described above, to afford the phenoxyacetic acid **53.1**.

For example, 4-bromo-2,6-dimethylphenol **53.9** (Aldrich) is converted, as described above, into the phenoxy ester **53.10**. The latter compound is then coupled, in dimethylformamide solution at ca. 60°, with cyclohexenone **53.11**, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to yield the cyclohexenone **53.12**. The enone is then reduced to the saturated ketone **53.13**, by means of catalytic hydrogenation employing 5% palladium on carbon as catalyst. The saturated ketone is then reacted with an equimolar amount of a dialkyl aminoethylphosphonate **53.14**, prepared as described in J. Org. Chem., 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the amine **53.15**. Hydrolysis, employing lithium hydroxide in aqueous methanol at ambient temperature, then yields the acetic acid **53.16**.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylphenol **53.9**, different bromo-substituted 2,6-dimethylphenols **53.2**, and/or different cycloalkenones **53.4**, and/or different dialkyl aminoalkylphosphonates **53.7**, the corresponding products **53.1** are obtained.

Scheme **54** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate group attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an optionally protected hydroxy, thio or amino-substituted 2,6-dimethylphenol **54.1** is reacted, in the

presence of a base such as, for example, potassium carbonate, and optionally in the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl phosphonate **54.2**. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°. The product of the alkylation reaction, **54.3** is then converted, as described above (Scheme **50**) into the phenoxyacetic acid **54.4**.

For example, 2,6-dimethyl-4-mercaptophenol **54.5**, prepared as described in EP 482342, is reacted in dimethylformamide at ca. 60° with an equimolar amount of a dialkyl bromobutyl phosphonate **54.6**, the preparation of which is described in Synthesis, 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the thioether product **54.7**. This compound is converted, employing the procedures described above, (Scheme **50**) into the corresponding phenoxyacetic acid **54.8**.

Using the above procedures, but employing, in place of 2,6-dimethyl-4-mercaptophenol **54.5**, different hydroxy, thio or aminophenols **54.1**, and/or different dialkyl bromoalkyl phosphonates **54.2**, the corresponding products **54.4** are obtained.

Scheme **55** illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester group attached by means of an aromatic or heteroaromatic group. In this procedure, an optionally protected hydroxy, mercapto or amino-substituted 2.6-dimethylphenol **55.1** is reacted, under basic conditions, with a bis(halomethyl)aryl or heteroaryl compound **55.2**. Equimolar amounts of the phenol and the halomethyl compound are reacted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium or cesium carbonate, or dimethylaminopyridine, to afford the ether, thioether or amino product **55.3**. The product **55.3** is then converted, using the procedures described above, (Scheme **50**) into the phenoxyacetic ester **55.4**. The latter compound is then subjected to an Arbuzov reaction by reaction with a trialkylphosphite **55.5** at ca. 100° to afford the phosphonate ester **55.6**. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in Handb. Organophosphorus Chem., 1992, 115. The resultant product **55.6** is then converted into the acetic acid **55.7** by hydrolysis of the ester moiety, using the procedures described above, (Scheme **50**).

For example, 4-hydroxy-2,6-dimethylphenol **55.8** (Aldrich) is reacted with one molar equivalent of 3,5-bis(chloromethyl)pyridine, the preparation of which is described in Eur. J.

Inorg. Chem., 1998, 2, 163, to afford the ether **55.10**. The reaction is conducted in acetonitrile at ambient temperature in the presence of five molar equivalents of potassium carbonate. The product **55.10** is then reacted with ethyl bromoacetate, using the procedures described above, (Scheme **50**) to afford the phenoxyacetic ester **55.11**. This product is heated at 100° for 3 hours with three molar equivalents of triethyl phosphite **55.12**, to afford the phosphonate ester **55.13**. Hydrolysis of the acetic ester moiety, as described above, for example by reaction with lithium hydroxide in aqueous ethanol, then affords the phenoxyacetic acid **55.14**.

Using the above procedures, but employing, in place of the bis(chloromethyl) pyridine **55.9**, different bis(halomethyl) aromatic or heteroaromatic compounds **55.2**, and/or different hydroxy, mercapto or amino-substituted 2,6-dimethylphenols **55.1** and/or different trialkyl phosphites **55.5**, the corresponding products **55.7** are obtained.

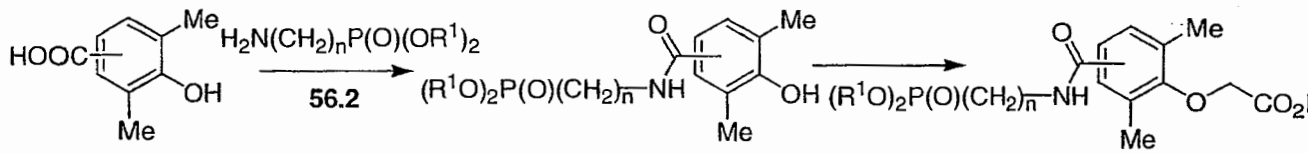
Scheme **56** illustrates the preparation of dimethylphenoxyacetic acids incorporating a phosphonate group attached by mans of an amide group. In this procedure, a carboxy-substituted 2,6-dimethylphenol **56.1** is reacted with a dialkyl aminoalkyl phosphonate **56.2** to afford the amide product **56.3**. The amide-forming reaction is performed under similar conditions to those described above for the preparation of the amides **1.3** and **1.6**. The product **56.3** is then transformed, as described above (Scheme **50**) into the phenoxyacetic acid **56.4**.

For example, 3,5-dimethyl-4-hydroxybenzoic acid **56.5** (Aldrich) is reacted with a dialkyl aminoethylphosphonate **56.6**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in tetrahydrofuran solution in the presence of dicyclohexylcarbodiimide to produce the amide **56.7**. The product is then transformed, as described above, (Scheme **50**) into the corresponding phenoxyacetic acid **56.8**.

Using the above procedures, but employing, in place of 3,5-dimethyl-4-hydroxybenzoic acid **56.5**, different carboxy-substituted 2,6-dimethylphenols **56.1**, and/or different dialkyl aminoalkyl phosphonates **56.2**, the corresponding products **56.4** are obtained.

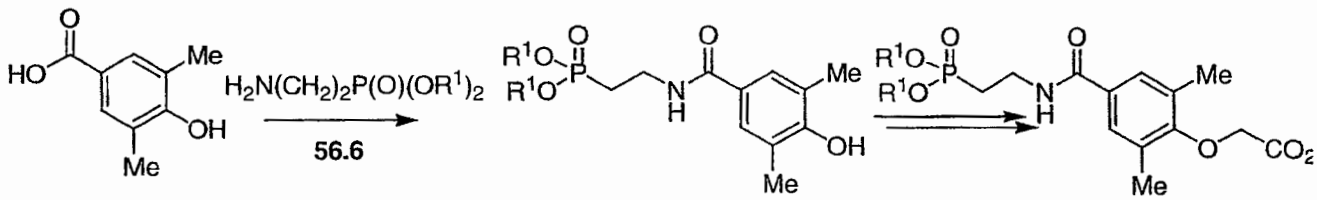
Scheme 56

Method



56.1 56.3 56.4

Example



56.5 56.7 56.8

Preparation of quinoline 2-carboxylic acids 9.1 incorporating phosphonate moieties.

The reaction sequences depicted in Schemes **9** - **12** for the preparation of the phosphonate esters **3** employ a quinoline-2-carboxylic acid reactant **9.1** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br etc.

A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het. Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines is described, for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.

Scheme **57** illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde **57.1** is reacted with an alkyl pyruvate ester **57.2**,

in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester **57.3**. Hydrolysis of the ester, for example by the use of aqueous base, then afford the corresponding carboxylic acid **57.4**. The carboxylic acid product **57.4** in which X is NH_2 can be further transformed into the corresponding compounds **57.6** in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoborate, is then heated in aqueous solution, for example as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol **57.6**, Y = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, **57.6**, Y = Br. Alternatively, the diazonium tetrafluoborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to afford the thiol **57.6**, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters **57.3** instead of the carboxylic acids **57.5**.

For example, 2,4-diaminobenzaldehyde **57.7** (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate **57.2** in methanol, in the presence of a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate **57.8**. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **57.9**. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoborate **57.10** by reaction with sodium nitrite and tetrafluoboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, **57.11**, Z = OH. Alternatively, the diazonium tetrafluoborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-bromoquinoline-2-carboxylic acid **57.11**, Z = Br. Alternatively, the diazonium tetrafluoborate **57.10** is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as

described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid **57.11**, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde **57.7**, different aminobenzaldehydes **57.1**, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids **57.6** are obtained. The variously substituted quinoline carboxylic acids and esters can then be transformed, as described herein, (Schemes **58 – 60**) into phosphonate-containing derivatives.

Scheme **58** depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester **58.1** is transformed, via a diazotization procedure as described above (Scheme **57**) into the corresponding phenol or thiol **58.2**. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate **58.3**, under the conditions of the Mitsonobu reaction, to afford the phosphonate ester **58.4**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **58.4**. Basic hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **58.5**. The product is then coupled with a suitably protected aminoacid derivative **58.6** to afford the amide **58.7**. The reaction is performed under similar conditions t those described above for the preparation of the amide **1.6** (Scheme **1**). The ester protecting group is the removed to yield the carboxylic acid **58.8**.

For example, methyl 6-amino-2-quinoline carboxylate **58.9**, prepared as described in J. Het. Chem., 1989, 26, 929, is converted, by means of the diazotization procedure described above, into methyl 6-mercaptoquinoline-2-carboxylate **58.10**. This material is reacted with a dialkyl hydroxymethylphosphonate **58.11** (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether **58.12**. Basic hydrolysis

then afford the carboxylic acid **58.13**. The latter compound is then converted, as described above, into the aminoacid derivative **58.16**.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline carboxylate **58.9**, different aminoquinoline carboxylic esters **58.1**, and/or different dialkyl hydroxymethylphosphonates **58.3** the corresponding phosphonate ester products **58.8** are obtained.

Scheme **59** illustrates the preparation of quinoline-2-carboxylic acids incorporating phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester **59.1** is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate **59.2**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Thus, Heck coupling of the bromo compound **59.1** and the olefin **59.2** affords the olefinic ester **59.3**. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid **59.4**. The latter compound is then transformed, as described above, into the homolog **59.5**. Optionally, the unsaturated carboxylic acid **59.4** can be reduced to afford the saturated analog **59.6**. The reduction reaction can be effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5, or catalytically. The product **59.6** is then converted, as described above (Scheme **58**) into the aminoacid derivative **59.7**.

For example, methyl 7-bromoquinoline-2-carboxylate, **59.8**, prepared as described in J. Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60° with a dialkyl vinylphosphonate **59.9** (Aldrich) in the presence of 2 mol% of tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product **59.10** The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid **59.11**. The latter compound is reacted with diimide, prepared by basic

hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product **59.12**. The latter compound is then converted, as described above, into the aminoacid derivative **59.13**. The unsaturated product **59.11** is similarly converted into the analog **59.14**.

Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate **59.8**, different bromoquinoline carboxylic esters **59.1**, and/or different dialkyl alkenylphosphonates **59.2**, the corresponding phosphonate ester products **59.5** and **59.7** are obtained.

Scheme **60** depicts the preparation of quinoline-2-carboxylic acid derivatives **60.5** in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate **60.1** is reacted with a phosphonate aldehyde **60.2** under reductive amination conditions, to afford the aminoalkyl product **60.3**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product **60.3** is then hydrolyzed to yield the free carboxylic acid **60.4**. The latter compound is then converted, as described above, into the aminoacid derivative **60.5**.

For example, methyl 7-aminoquinoline-2-carboxylate **60.6**, prepared as described in J. Am. Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **60.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **60.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **60.9**. The latter compound is then converted, as described above, into the aminoacid derivative **60.10**.

Using the above procedures, but employing, in place of the formylmethyl phosphonate **60.7**, different formylalkyl phosphonates **60.2**, and/or different aminoquinolines **60.1**, the corresponding products **60.5** are obtained.

Preparation of 5-hydroxyisoquinoline derivatives 13.1 incorporating phosphonate moieties.

Schemes **61** - **65** illustrate methods for the preparation of the 5-hydroxyisoquinoline derivatives **13.1** which are employed in the preparation of the intermediate phosphonate esters **4**.

A number of substituted 5-hydroxyisoquinolines are commercially available, or have syntheses described in the literature. The synthesis of substituted 5-hydroxyisoquinolines is described, for example, in Heterocyclic Compounds, Vol. 38, Part 3, E. M. Coppola, H. F. Schuster, eds., Wiley, 1995, p. 229ff, and in Heterocyclic Chemistry, by T. L. Gilchrist, Longman, 1992, p. 162ff.

Scheme **61** illustrates methods for the preparation of substituted 5-hydroxyisoquinolines. As shown in Method **1**, variously substituted 3-hydroxybenzaldehydes or 3-hydroxyphenyl ketones **61.1** are reacted with substituted or unsubstituted 2, 2-dialkoxyethylamines **61.2** in a procedure known as the Pomeranz-Fritsch reaction. The reactants are combined in a hydrocarbon solvent such as toluene at reflux temperature with azeotropic removal of water, to yield the imine product **61.3**. The latter compound is then subjected to acid-catalyzed cyclization, for example as described in Heterocyclic Chemistry, by T. L. Gilchrist, Longman, 1992, p. 164, to yield the substituted 5-hydroxyisoquinoline **61.4**.

Scheme **61**, Method **2** illustrates the preparation of variously substituted 5-hydroxyisoquinolines from the corresponding amino-substituted compounds. In this procedure, a suitably protected amino-substituted 5-hydroxyisoquinoline **61.5** is subjected to a diazotization reaction to afford the diazonium tetrafluoborate, using the conditions described above in Scheme **57**. The diazonium salt is then converted, as described above, into the corresponding hydroxy, mercapto or halo derivative **61.7**.

Scheme **62** illustrates the preparation of the isoquinolinyl-5-oxyacetic acids **62.2** and the conversion of these compounds into the corresponding aminoacid derivatives **13.1**. In this procedure, the 5-hydroxyisoquinoline substrate **62.1**, in which the substituent A is either the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH_2], Br, etc, as described herein, is converted into the corresponding aryloxyacetic acid **62.2**. The procedures

employed for this transformation are the same as those described above, (Scheme **50**) for the conversion of 2,6-dimethoxyphenol derivatives into the corresponding phenoxyacetic acids. The product **62.2** is then transformed, as described above, (Scheme **57**) into the aminoacid derivative **13.1**.

Schemes **63** - **65** illustrate the preparation of 5-hydroxyisoquinoline derivatives incorporating phosphonate substituents. The quinolinol products are then converted, as described above, into analogs of the aminoacid derivative **13.1**.

Scheme **63** illustrates the preparation of 5-hydroxyisoquinoline derivatives in which a phosphonate substituent is attached by means of an amide bond. In this procedure, an amino-substituted 5-hydroxyisoquinoline **63.1** is reacted with a dialkyl carboxyalkyl phosphonate **63.2** to afford the amide **63.3**. The reaction is effected as described above for the preparation of the amides **1.3** and **1.6**.

For example, 8-amino-5-hydroxyisoquinoline **63.4**, the preparation of which is described in Syn. Comm., 1986, 16, 1557, is reacted in tetrahydrofuran solution with one molar equivalent of a dialkyl 2-carboxyethyl phosphonate **63.5** (Epsilon) and dicyclohexyl carbodiimide, to produce the amide **63.6**.

Using the same procedures, but employing, in place of the 8-amino quinolinol **63.4**, different aminoquinolinols **63.1**, and/or different dialkyl carboxyalkyl phosphonates **63.2**, the corresponding products **63.3** are obtained.

Scheme **64** illustrates the preparation of 5-hydroxyisoquinoline derivatives in which a phosphonate substituent is attached by means of a carbon link or a carbon and a heteroatom link. In this procedure, a methyl-substituted 5-hydroxyisoquinoline **64.1** is protected, and the product **64.2** is reacted with a free radical brominating agent, for example N-bromosuccinimide, as described in Chem. Rev., 63, 21, 1963, to afford the bromomethyl derivative **64.3**. The latter compound is reacted with a trialkyl phosphite $(R^1O)_3P$ under the conditions of the Arbuzov reaction, as described in Scheme **55**, to yield the phosphonate **64.4**; deprotection then affords the phenol **64.5**.

Alternatively, the protected bromomethyl derivative **64.3** is reacted with a dialkyl hydroxy, mercapto or amino-substituted alkyl phosphonate **64.6**, to afford the alkylation product **64.7**. The displacement reaction is conducted in a polar organic solvent such as dimethyl formamide,

acetonitrile and the like, in the presence of a base such as sodium hydride or lithium hexamethyldisilazide, for substrates in which X is O, or potassium carbonate for substrates in which X is S or N. The protecting group is then removed from the product **64.7** to yield the phenolic product **64.8**.

For example, 5-hydroxy-1-methylisoquinoline **64.9**, prepared as described in J. Med. Chem., 1968, 11, 700, is reacted with acetic anhydride in pyridine to afford 5-acetoxy-1-methylisoquinoline **64.10**. The latter compound is reacted with N-bromosuccinimide in refluxing ethyl acetate to yield 5-acetoxy-1-bromomethylisoquinoline **64.11**. The product is then reacted with five molar equivalents of a trialkyl phosphite at 120° to give the phosphonate product **64.12**. The acetoxy group is hydrolyzed by reaction with sodium bicarbonate in aqueous methanol as described in J. Am. Chem. Soc., 93, 746, 1971, to produce the phenol **64.13**.

Using the above procedures, but employing, in place of 5-hydroxy-1-methylisoquinoline **64.9**, different hydroxymethylisoquinolines **64.1**, the corresponding products **64.5** are obtained.

As a further illustration of the method of Scheme **64**, as shown in Example **2**, 5-hydroxy-3-methylisoquinoline **64.14**, prepared as described in J. Med. Chem., 1998, 41, 4062, is reacted with one molar equivalent of tert. butyl chlorodimethylsilane and imidazole in dichloromethane to yield the silyl ether **64.15**. The product is brominated, as described above, to afford 3-bromomethyl-5-tert. butyldimethylsilyloxyisoquinoline **64.16**. The bromomethyl compound is then reacted in dimethylformamide at 60° with one molar equivalent of a dialkyl mercaptoethyl phosphonate **64.17**, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, and potassium carbonate, to give the thioether product **64.18**; deprotection, for example by treatment with 1M tetrabutylammonium fluoride in tetrahydrofuran, then yields the phenol **64.19**.

Using the above procedures, but employing, in place of 5-hydroxy-3-methylisoquinoline **64.11**, different hydroxymethylisoquinolines **64.1**, and/or different hetero-substituted alkyl phosphonates **64.6**, the corresponding products **64.8** are obtained.

Scheme **65** illustrates the preparation of 5-hydroxyisoquinoline derivatives incorporating a phosphonate moiety attached by means of a heteroatom and an alkylene chain. In this procedure, the phenolic hydroxyl group of 5-hydroxyisoquinolin-1-one **65.1** (Acros) is protected. The protection of phenolic hydroxyl groups is described, for example, in Protective

Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 143ff. The product **65.2** is then converted into the bromo analog **65.3**, for example by reaction with phosphorus oxybromide, as described in Heterocyclic Compounds, Vol. 38, Part 2, E. M. Coppola, H. F. Schuster, eds., Wiley, 1995, p. 13ff. The bromo compound is then reacted with a dialkyl hydroxy, mercapto or amino-substituted alkyl phosphonate **65.4**, to afford the displacement product **65.5**. The displacement reaction of 2-haloisoquinolines with nucleophiles to produce ethers, thioethers and amines is described in Heterocyclic Chemistry, by T. L. Gilchrist, Longman, 1992, p. 165. The reaction is conducted in an organic solvent such as dimethylformamide, toluene and the like, in the presence of a base such as sodium hydride or potassium carbonate. The phenolic hydroxyl group is then deprotected to yield the phenol **65.6**.

For example, 5-hydroxyisoquinolin-1-one **65.1** is reacted with one molar equivalent of benzoyl chloride in pyridine to afford the ester **65.7**. The latter compound is treated with phosphorus oxybromide in refluxing toluene to produce the 5-benzoyloxy-1-bromoisoquinoline **65.8**. This material is reacted with a dialkyl 3-hydroxypropyl phosphonate **65.9**, prepared as described in Zh. Obschei. Khim., 1974, 44, 1834, and sodium hydride in tetrahydrofuran to prepare the ether product **65.10**. Deprotection, for example by reaction with aqueous alcoholic sodium bicarbonate, then yields the phenol **65.11**.

Using the above procedures, but employing, in place of a dialkyl 3-hydroxypropyl phosphonate **65.9**, different dialkyl hydroxy, mercapto or amino-substituted alkyl phosphonates **65.4**, the corresponding products **65.6** are obtained.

Scheme **66** described the preparation of 5-hydroxyisoquinolines in which a phosphonate substituent is attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted 5-hydroxyisoquinoline **66.1** is protected, as described above. The product **66.2** is coupled, in the presence of a palladium catalyst, with a dialkyl alkenyl phosphonate **66.3**. The coupling of aryl bromides and alkenes is described above (Scheme **52**). The product **66.4** is then deprotected to yield the phenol **66.5**. Optionally, the compound **66.5** is reduced, for example by treatment with diimide or diborane, to afford the saturated analog **66.6**.

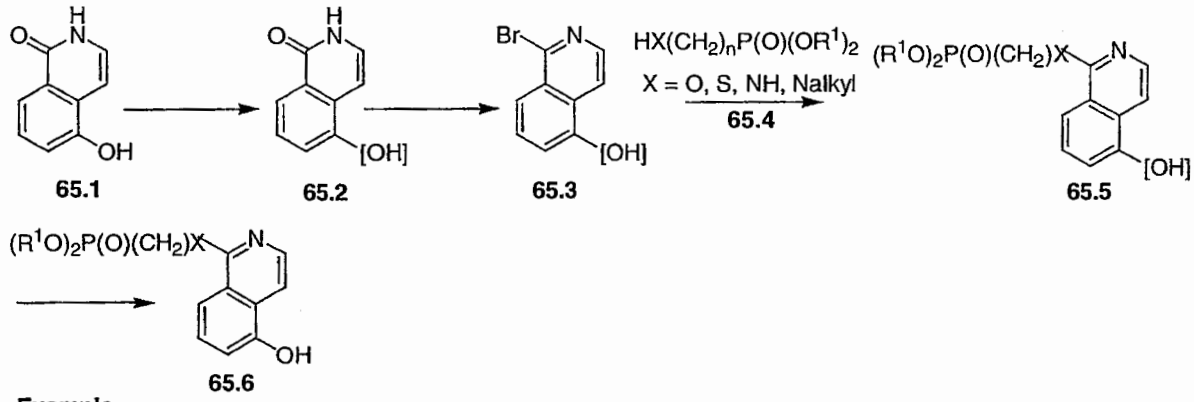
For example, 5-hydroxyisoquinoline **66.7** is reacted with bromine in carbon tetrachloride to afford 8-bromo-5-hydroxyisoquinoline **66.8**. The product is reacted with acetic anhydride in

pyridine to give 5-acetoxy-8-bromoisoquinoline **66.9**. The latter compound is coupled with a dialkyl propenyl phosphonate **66.10** (Aldrich) in the presence of ca. 3 mol % of bis(triphenylphosphine) palladium(II) chloride and triethylamine, in dimethylformamide at ca. 60°, to produce the coupled product **66.11**. The acetyl protecting group is then removed by reaction with dilute aqueous methanolic ammonia, as described in J. Chem. Soc., 2137, 1964, to afford the phenol **66.12**. The product is optionally reduced to yield the saturated analog **66.13**. The reduction reaction is effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5, or catalytically.

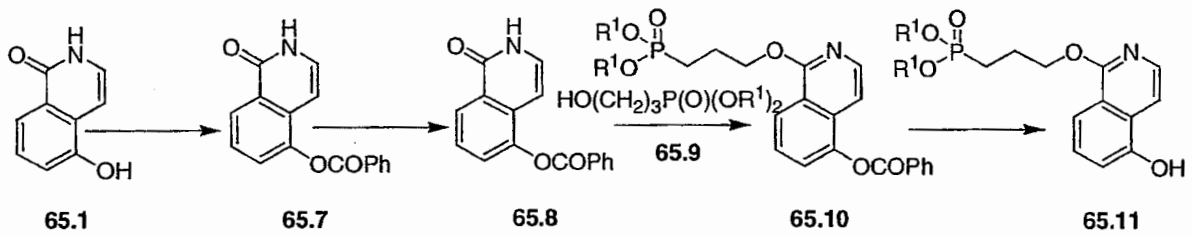
Using the above procedures, but employing, in place of 8-bromo-5-hydroxyisoquinoline **66.8**, different bromo-substituted 5-hydroxyisoquinolines **66.1**, and/or different dialkyl alkenyl phosphonates **66.3**, the corresponding products **66.5** and **66.6** are obtained.

Scheme 65

Method

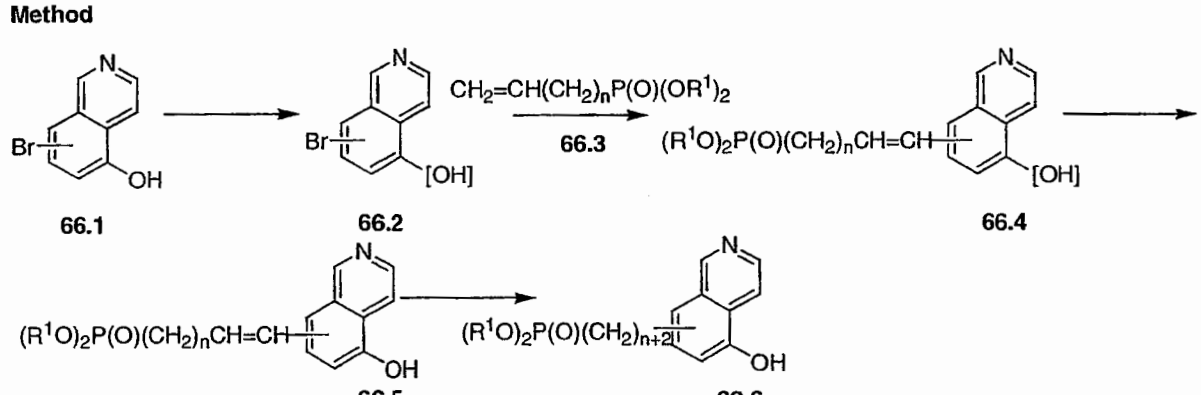


Example

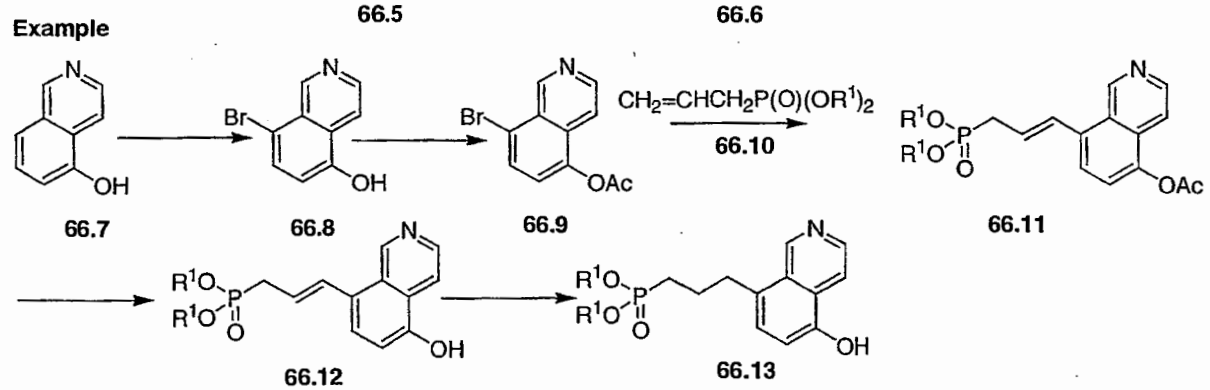


Scheme 66

Method



Example



Preparation of phenylalanine derivatives 17.1 incorporating phosphonate moieties.

Schemes **67** - **71** illustrate the preparation of phosphonate-containing phenylalanine derivatives **17.1** which are employed in the preparation of the intermediate phosphonate esters **5**.

Scheme **67** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives **67.1**.

In this procedure, a hydroxy or mercapto-substituted phenylalanine is converted into the benzyl ester **67.2**. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester **67.2** is then protected. Protection methods for phenols and thiols are described respectively, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 10, p 277. For example, suitable protecting groups for phenols and thiophenols include tert-butyldimethylsilyl or tert-butyldiphenylsilyl. Thiophenols may also be protected as S-adamantyl groups, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289 The protected hydroxy- or mercapto ester **67.3** is then converted into the BOC derivative **67.4**. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p10, p 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride and the like, in a solvent such as tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972. S-Adamantyl groups can be removed by treatment with mercuric trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.

The resultant phenol or thiophenol **67.5** is then reacted under various conditions to provide protected phenylalanine derivatives **67.9**, **67.10** or **67.11**, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

In this step, the phenol or thiophenol **67.5** is reacted with a dialkyl bromoalkyl phosphonate **67.6** to afford the ether or thioether product **67.9**. The alkylation reaction is effected in the

presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate, The reaction is performed at from ambient temperature to ca. 80°, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product **67.9**. Deprotection of the benzyl ester group, for example by means of catalytic hydrogenation over a palladium catalyst, then yields the carboxylic acid **67.12**. The benzyl esters **67.10** and **67.11**, the preparation of which is described above, are similarly deprotected to produce the corresponding carboxylic acids.

For example, as illustrated in Scheme **67**, Example **1**, a hydroxy-substituted phenylalanine derivative such as tyrosine, **67.13** is converted, as described above, into the benzyl ester **67.14**. The latter compound is then reacted with one molar equivalent of chloro tert-butyldimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether **67.15**. This compound is then converted, as described above, into the BOC derivative **67.16**. The silyl protecting group is removed by treatment of the silyl ether **67.16** with a tetrahydrofuran solution of tetrabutyl ammonium fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol **67.17**. The latter compound is then reacted in dimethylformamide at ca. 60°, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate **67.18** (Aldrich), in the presence of cesium carbonate, to afford the alkylated product **67.19**. Debenzylation then produces the carboxylic acid **67.20**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **67.13**, different hydroxy or thio-substituted phenylalanine derivatives **67.1**, and/or different bromoalkyl phosphonates **67.6**, the corresponding ether or thioether products **67.12** are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **67.5** is reacted with a dialkyl hydroxymethyl phosphonate **67.7** under the conditions of the Mitsonobu reaction, to afford the ether or thioether compounds **67.10**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **67.10**.

For example, as shown in Scheme **67**, Example **2**, 3-mercaptophenylalanine **67.21**, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester **67.22**. The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether **67.23**. This compound is then converted, as described above for the preparation of the compound **67.4**, into the BOC-protected derivative **67.24**. The 4-methoxybenzyl group is then removed by the reaction of the thioether **67.24** with mercuric trifluoroacetate and anisole in trifluoroacetic acid, as described in J.Org. Chem., 52, 4420, 1987, to afford the thiol **67.25**. The latter compound is reacted, under the conditions of the Mitsonobu reaction, with a dialkyl hydroxymethyl phosphonate **67.7**, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product **67.26**. The benzyl ester protecting group is then removed to afford the carboxylic acid **67.27**.

Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative **67.21**, different hydroxy or mercapto-substituted phenylalanines **67.1**, and/or different dialkyl hydroxymethyl phosphonates **67.7**, the corresponding products **67.10** are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative **67.5** is reacted with an activated derivative of a dialkyl hydroxymethylphosphonate **67.8** in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base such as triethylamine or cesium carbonate, to afford the ether or thioether products **67.11**.

For example, as illustrated in Scheme **67**, Example **3**, 3-hydroxyphenylalanine **67.28** (Fluka) is converted, using the procedures described above, into the protected compound **67.29**. The latter compound is reacted, in dimethylformamide at ca. 50°, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate **67.30**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product **67.31**. Debenzylation then produces the carboxylic acid **67.32**.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **67.28**, different hydroxy or mercapto-substituted phenylalanines **67.1**, and/or different dialkyl trifluoromethanesulfonyloxymethylphosphonates **67.8**, the corresponding products **67.11** are obtained.

Scheme **68** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a formyl-substituted tribenzylated phenylalanine derivative **68.3** and a dialkyl aminoalkylphosphonate **68.4**.

In this procedure, a hydroxymethyl-substituted phenylalanine **68.1** is converted, as described above, into the BOC protected benzyl ester **68.2**. The latter compound is then oxidized to afford the corresponding aldehyde **68.3**. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product **68.3**. For example, the carbinol **68.2** is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in J. Org. Chem., 43, 2480, 1978, to yield the aldehyde **68.3**. This compound is reacted with a dialkyl aminoalkylphosphonate **68.4** in the presence of a suitable reducing agent to afford the amine product **68.5**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The benzyl protecting group is then removed to prepare the carboxylic acid **68.6**.

For example, 3-(hydroxymethyl)-phenylalanine **68.7**, prepared as described in Acta Chem. Scand. Ser. B, 1977, B31, 109, is converted, as described above, into the formylated derivative **68.8**. This compound is then reacted with a dialkyl aminoethylphosphonate **68.9**, prepared as described in J. Org. Chem., 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated product **68.10**, which is then deprotected to give the carboxylic acid **68.11**.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine **68.7**, different hydroxymethyl phenylalanines **68.1**, and/or different aminoalkyl phosphonates **68.4**, the corresponding products **68.6** are obtained.

Scheme **69** depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine **69.1** is converted, as described above, (Scheme **68**) into the protected derivative **69.2**. The product is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite **69.3** to produce the phosphonate ester **69.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The product is then deprotected to afford the carboxylic acid **69.5**. For example, 3-bromophenylalanine **69.6**, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme **68**) into the protected compound **69.7**. This compound is then reacted, in toluene solution at reflux, with diethyl phosphite **69.8**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product **69.9**. Debenzylation then yields the carboxylic acid **69.10**.

Using the above procedures, but employing, in place of 3-bromophenylalanine **69.6**, different bromophenylalanines **69.1**, and/or different dialkylphosphites **69.3**, the corresponding products **69.5** are obtained.

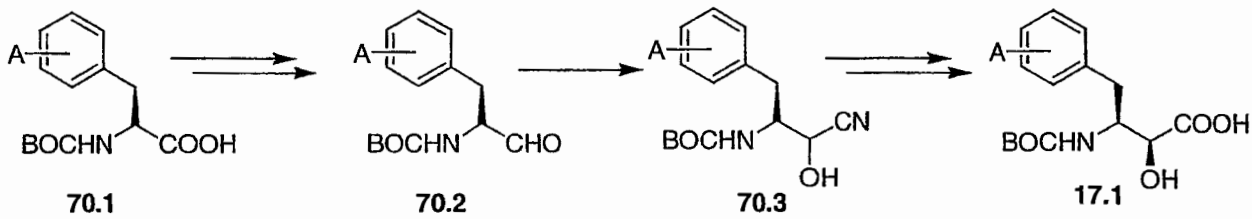
Schemes **70** and **71** illustrate two methods for the conversion of the compounds **70.1**, in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, into the homologated derivatives **17.1** which are employed in the preparation of the intermediate phosphonate esters **5**.

As shown in Scheme **70**, the BOC-protected phenylalanine derivative **70.1** is converted, using the procedures described above in Scheme **41**, into the aldehyde **70.2**. The aldehyde is then converted, via the cyanohydrin **70.3**, into the homologated derivative **17.1**. The reaction sequence and conditions employed are the same as shown in Scheme **41** for the conversion of the BOC-protected aminoacid **41.1** into the homologated derivative **1.5**.

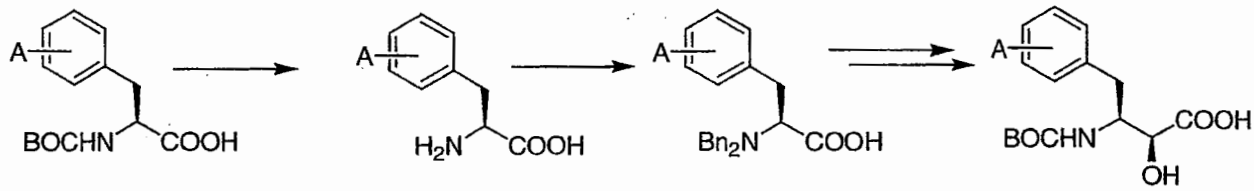
Alternatively, as illustrated in Scheme **71**, the BOC-protected aminoacid **70.1** is deprotected to afford the amine **71.1**. The product is then converted, as described in Scheme **42**, into the

dibenzylated product **71.2**. The latter compound is then transformed, using the sequence of reactions and conditions shown in Scheme **42** for the conversion of the dibenzylated aminoacid **42.1** into the hydroxyacid **1.5**, into the homologated derivative **17.1**.

Scheme 70



Scheme 71



Preparation of the phosphonate-containing thiophenol derivatives 19.1.

Schemes **72** - **83** describe the preparation of phosphonate-containing thiophenol derivatives **19.1** which are employed as described above (Schemes **19** and **20**) in the preparation of the phosphonate ester intermediates **5** in which X is sulfur. Schemes **72** - **81** described the syntheses of the thiophenol components; Schemes **82** and **83** described methods for the incorporation of the thiophenols into the reactants **19.1**.

Scheme **72** depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol **72.1** is protected, as described above (Scheme **67**) to afford the protected product **72.2**. The product is then coupled, in the presence of a palladium catalyst, with a dialkyl phosphite **72.3**, to afford the phosphonate ester **72.4**. The preparation of arylphosphonates by the coupling of aryl halides with dialkyl phosphites is described above, (Scheme **69**). The thiol protecting group is then removed, as described above, to afford the thiol **72.5**.

For example, 3-bromothiophenol **72.6** is converted into the 9-fluorenylmethyl (Fm) derivative **72.7** by reaction with 9-fluorenylmethyl chloride and diisopropylethylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite **72.3**, as described for the preparation of the phosphonate **69.4** (Scheme **69**), to afford the phosphonate ester **72.8**. The Fm protecting group is then removed by treatment of the product with piperidine in dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol **72.9**. Using the above procedures, but employing, in place of 3-bromothiophenol **72.6**, different thiophenols **72.1**, and/or different dialkyl phosphites **72.3**, the corresponding products **72.5** are obtained.

Scheme **73** illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol **73.2** is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative **73.3**. The latter compound is reacted with a halodialkyl phosphite **73.4** to afford the product **73.5;** deprotection then affords the thiophenol **73.6**

For example, 4-bromothiophenol **73.7** is converted into the S-triphenylmethyl (trityl) derivative **73.8**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **73.9** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorophosphite **73.10** to afford the phosphonate **73.11**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **73.12**.

Using the above procedures, but employing, in place of the bromo compound **73.7**, different halo compounds **73.1**, and/or different halo dialkyl phosphites **73.4**, there are obtained the corresponding thiols **73.6**.

Scheme **74** illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol **74.1** is subjected to free-radical bromination to afford a bromomethyl product **74.2**. This compound is reacted with a sodium dialkyl phosphite **74.3**

or a trialkyl phosphite, to give the displacement or rearrangement product **74.4**, which upon deprotection affords the thiophenol **74.5**.

For example, 2-methylthiophenol **74.6** is protected by conversion to the benzoyl derivative **74.7**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **74.8.** This material is reacted with a sodium dialkyl phosphite **74.3**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **74.9**. Alternatively, the bromomethyl compound **74.8** is converted into the phosphonate **74.9** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **74.8** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100^0 to produce the phosphonate **74.9**. Deprotection of the phosphonate **74.9**, for example by treatment with aqueous ammonia, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiol **74.10**.

Using the above procedures, but employing, in place of the bromomethyl compound **74.8**, different bromomethyl compounds **74.2**, there are obtained the corresponding thiols **74.5**.

Scheme **75** illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **75.1** is reacted with a dialkyl hydroxyalkylphosphonate **75.2** under the conditions of the Mitsonobu reaction, for example as described in Org. React., 1992, 42, 335, to afford the coupled product **75.3**. Deprotection then yields the O- or S-linked products **75.4**.

For example, the substrate 3-hydroxythiophenol, **75.5**, is converted into the monotrityl ether **75.6**, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **75.7** in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound **75.8**. Removal of the trityl protecting group, as described above, then affords the thiophenol **75.9**.

Using the above procedures, but employing, in place of the phenol **75.5**, different phenols or thiophenols **75.1**, there are obtained the corresponding thiols **75.4**.

Scheme **76** illustrates the preparation of thiophenols **76.4** bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **76.1** is reacted with an activated ester, for example the trifluoromethanesulfonate **76.2**, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product **76.3**. Deprotection then affords the thiol **76.4**.

For example, 4-methylaminothiophenol **76.5** is reacted in dichloromethane solution with one equivalent of acetyl chloride and a base such as pyridine, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the S-acetyl product **76.6**. This material is then reacted with a dialkyl trifluoromethanesulfonylmethyl phosphonate **76.7**, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product **76.8**. Preferably, equimolar amounts of the phosphonate **76.7** and the amine **76.6** are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product **76.8**. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiophenol **76.9**.

Using the above procedures, but employing, in place of the thioamine **76.5**, different phenols, thiophenols or amines **76.1**, and/or different phosphonates **76.2**, there are obtained the corresponding products **76.4**.

Scheme **77** illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate **77.2**. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol **77.1** is reacted with a dialkyl bromoalkyl phosphonate **77.2** to afford the product **77.3**. Deprotection then affords the free thiophenol **77.4.**

For example, 3-hydroxythiophenol **77.5** is converted into the S-trityl compound **77.6**, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate **77.7**, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of

potassium iodide, at about 50°, to yield the ether product **77.8**. Deprotection, as described above, then affords the thiol **77.9**.

Using the above procedures, but employing, in place of the phenol **77.5**, different phenols, thiophenols or amines **77.1**, and/or different phosphonates **77.2**, there are obtained the corresponding products **77.4**.

Scheme **78** depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate **78.2** is coupled with an aromatic bromo compound **78.1**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **78.3**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **78.4**, or the saturated analog **78.6**.

For example, 3-bromothiophenol is converted into the S-Fm derivative **78.7**, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate **78.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product **78.9**. Deprotection, as described above, then affords the thiol **78.10**. Optionally, the initially formed unsaturated phosphonate **78.9** is subjected to reduction, for example using diimide, as described above, to yield the saturated product **78.11**, which upon deprotection affords the thiol **78.12**.

Using the above procedures, but employing, in place of the bromo compound **78.7**, different bromo compounds **78.1**, and/or different phosphonates **78.2**, there are obtained the corresponding products **78.4** and **78.6**

Scheme **79** illustrates the preparation of an aryl-linked phosphonate ester **79.4** by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **79.1** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product **79.3** which is deprotected to yield the thiol **79.4**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **79.5**. This material is reacted with a dialkyl 4-bromophenylphosphonate **79.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **79.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **79.8**.

Using the above procedures, but employing, in place of the boronate **79.5**, different boronates **79.1**, and/or different phosphonates **79.2**, there are obtained the corresponding products **79.4**.

Scheme **80** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **80.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **80.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **80.3** is then deprotected to afford the thiol **80.4**. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **80.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **80.5** is then reacted with a dialkyl 4-(bromomethyl)phenylphosphonate, **80.6**, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The

thioether product **80.7** thus obtained is deprotected, as described above, to afford the thiol **80.8**.

Using the above procedures, but employing, in place of the thiophenol **80.5**, different phenols, thiophenols or amines **80.1**, and/or different phosphonates **80.2**, there are obtained the corresponding products **80.4**.

Scheme **81** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

In this procedure, a suitably protected thiophenol **81.1**, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **81.2**, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **81.3**. Deprotection, as described above, then affords the thiol **81.4**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p 707.

For example, 2,3-dihydro-1H-indole-5-thiol, **81.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **81.6**, as described above, and the ester is then reacted with the trifluoromethanesulfonate **81.7**, using the conditions described above for the preparation of the phosphonate **76.8**, (Scheme **76**), to yield the phosphonate **81.8**. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **81.9**.

Using the above procedures, but employing, in place of the thiol **81.5**, different thiols **81.1**, and/or different triflates **81.2**, there are obtained the corresponding products **81.4**.

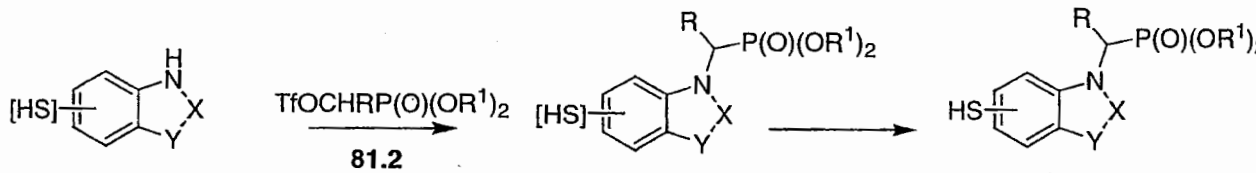
Schemes **82** and **83** illustrate alternative methods for the conversion of the thiophenols **82.1**, in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, prepared as described above, (Schemes **72** – **81**) in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, into the homologated derivatives **19.1** which are employed in the preparation of the intermediate phosphonate esters **5** in which X is sulfur.

As shown in Scheme **82**, the thiophenol **82.1** is reacted with the mesylate ester **43.2**, using the conditions described above for the preparation of the thioether **43.4**, to afford the corresponding thioether **82.2**. The latter compound is then transformed, using the same sequence of reactions and reaction conditions described above (Scheme **43**) for the conversion of the thioether **43.4** into the hydroxyacid **3.1**, into the hydroxyacid **19.1**.

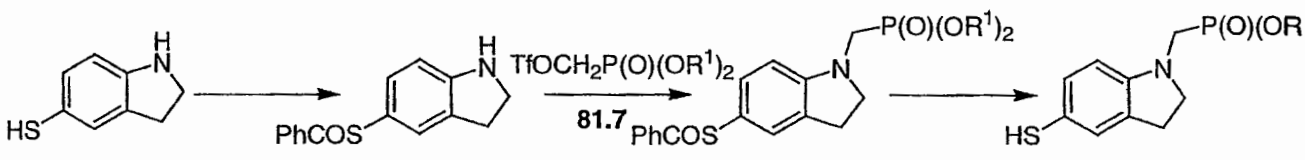
Alternatively, as shown in Scheme **83**, the aldehyde **82.3** is converted, as shown in Scheme **44**, into the diol **83.1**. The latter compound is then converted, as shown in Scheme **44** into the hydroxyacid **19.1**.

Scheme 81

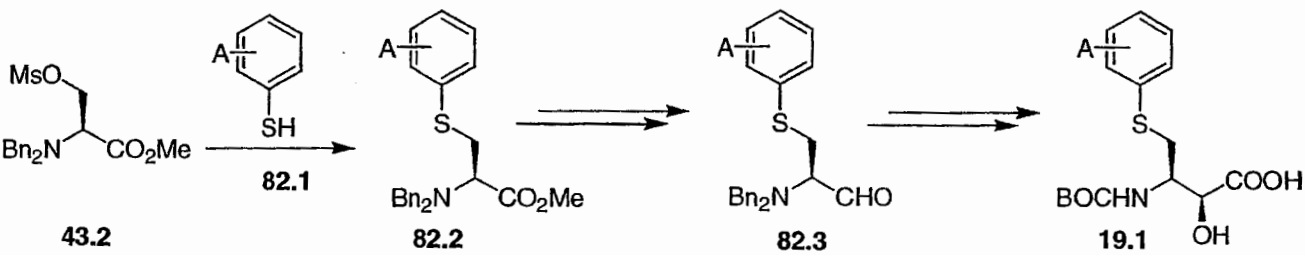
Method



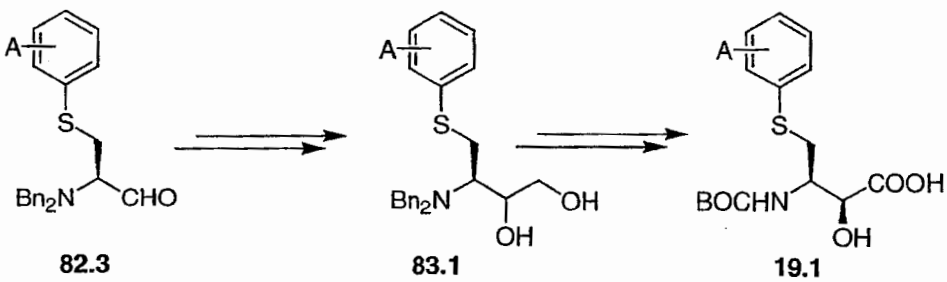
Example



Scheme 82



Scheme 83



Preparation of tert-butylamine derivatives 25.1 incorporating phosphonate groups.

Schemes **84** – **87** illustrate the preparation of the tert. butylamine derivatives **25.1** in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, which are employed in the preparation of the intermediate phosphonate esters **7**.

Scheme **84** describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2.2-dimethyl-2-aminoethyl

bromide **84.1** is reacted with a trialkyl phosphite **84.2**, under the conditions of the Arbuzov reaction, as described above, to afford the phosphonate **84.3**, which is then deprotected as described previously to give **84.4**

For example, the cbz derivative of 2,2-dimethyl-2-aminoethyl bromide **84.6**, is heated with a trialkyl phosphite at ca 150° to afford the product **84.7**. Deprotection, as previously described, then affords the free amine **84.8**.

Using the above procedures, but employing different trisubstituted phosphites, there are obtained the corresponding amines **84.4**.

Scheme **85** illustrates the preparation of phosphonate esters attached to the tert butylamine by means of a heteroatom and a carbon chain. An optionally protected alcohol or thiol **85.1** is reacted with a bromoalkylphosphonate **85.2,** to afford the displacement product **85.3**. Deprotection, if needed, then yields the amine **85.4**.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol **85.5** is reacted with a dialkyl 4-bromobutyl phosphonate **85.6**, prepared as described in Synthesis, 1994, 9, 909, in dimethylformamide containing potassium carbonate and a catalytic amount of potassium iodide, at ca 60° to afford the phosphonate **85.7** Deprotection, by hydrogenation over a palladium catalyst, then affords the free amine **85.8**.

Using the above procedures, but employing different alcohols or thiols **85.1**, and/or different bromoalkylphosphonates **85.2**, there are obtained the corresponding ether and thioether products **85.4**.

Scheme **86** describes the preparation of carbon-linked tert. butylamine phosphonate derivatives, in which the carbon chain can be unsaturated or saturated.

In the procedure, a terminal acetylenic derivative of tert-butylamine **86.1** is reacted, under basic conditions, with a dialkyl chlorophosphite **86.2**, to afford the acetylenic phosphonate **86.3**. The coupled product **86.3** is deprotected to afford the amine **86.4.** Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products **86.5** and **86.6** respectively.

For example, 2-amino-2-methylprop-1-yne **86.7**, the preparation of which is described in WO 9320804, is converted into the N-phthalimido derivative **86.8**, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and

P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide in tetrahydrofuran at -78°. The resultant anion is then reacted with a dialkyl chlorophosphite **86.2** to afford the phosphonate **86.9**. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine **86.10**. Partial catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p 566, produces the olefinic phosphonate **86.11**, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p. 3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate **86.12**. Using the above procedures, but employing different acetylenic amines **86.1**, and/or different dialkyl halophosphites, there are obtained the corresponding products **86.4**, **86.5** and **86.6**.

Scheme **87** illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.

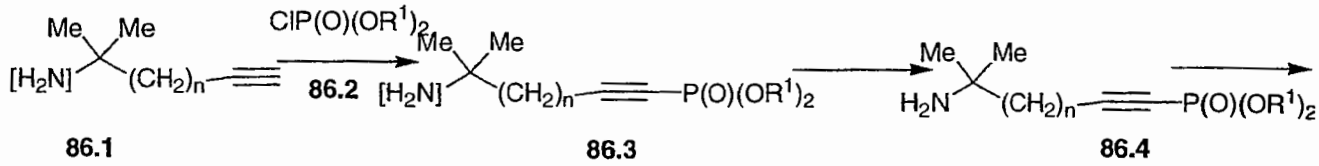
In this method, an aminoethyl-substituted cyclic amine **87.1** is reacted with a limited amount of a bromoalkyl phosphonate **87.2**, using, for example, the conditions described above (Scheme **78**) to afford the displacement product **87.3**.

For example, 3-(1-amino-1-methyl)ethylpyrrolidine **87.4**, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with one molar equivalent of a dialkyl 4-bromobutyl phosphonate **87.5**, prepared as described in Synthesis, 1994, 9, 909, to afford the displacement product **87.6**.

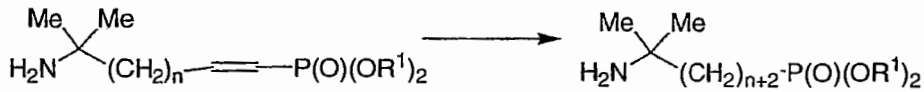
Using the above procedures, but employing, in place of 3-(1-amino-1-methyl)ethylpyrrolidine **87.4**, different cyclic amines **87.1**, and/or different bromoalkylphosphonates **87.2**, there are obtained the corresponding products **87.3**.

Scheme 86

Method

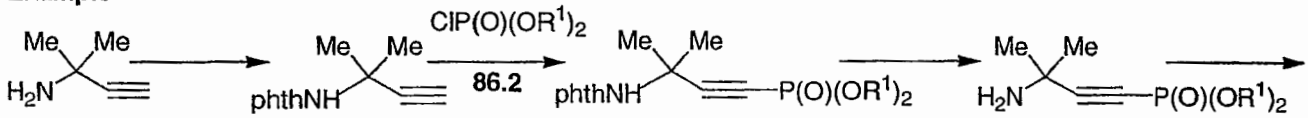


86.1 86.3 86.4



86.5 86.6

Example



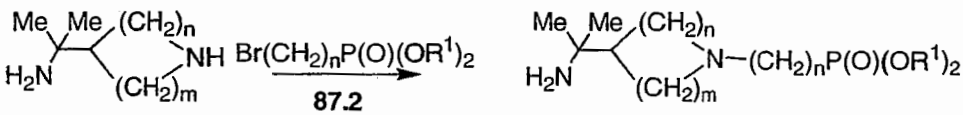
86.7 86.8 phth = phthalimido 86.9 86.10



86.11 86.12

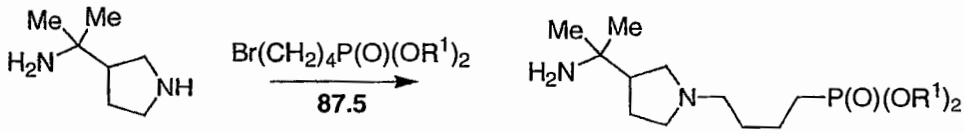
Scheme 87

Method



87.1 87.3

Example



87.4 87.6

Preparation of phosphonate-containing methyl-substituted benzylamines 29.1.

Schemes **88 – 90** illustrate the preparation of phosphonate-containing 2-methyl and 2,6-dimethylbenzylamines **29.1** in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, which are employed in the preparation of the phosphonate ester intermediates **8**, as described in Schemes **29 – 32**. A number of variously substituted 2-methyl and 2,6-dimethylbenzylamies are commercially available or have published syntheses. In addition, substituted benzylamines are prepared by various methods

known to those skilled in the art. For example, substituted benzylamines are obtained by reduction of the correspondingly substituted benzamides, for example by the use of diborane or lithium aluminum hydride, as described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 432ff.

Scheme **88** depicts the preparation of 2-methyl or 2,6-dimethylbenzyamines incorporating a phosphonate moiety directly attached to the benzene ring, or attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted 2-methyl or 2,6-dimethylbenzylamine **88.1** is protected to produce the analog **88.2**. The protection of amines is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 309ff. For example, the amine **88.1** is protected as an amide or carbamate derivative. The protected amine is then reacted with a dialkyl phosphite **88.3**, in the presence of a palladium catalyst, as described above (Scheme **69**) to afford the phosphonate product **88.4**. Deprotection then affords the free amine **88.5**. Alternatively, the protected bromo-substituted benzylamine **88.2** is coupled with a dialkyl alkenyl phosphonate **88.6**, using the conditions of the Heck reaction, as described above, (Scheme **59**) to afford the alkenyl product **88.7**. The amino protecting group is then removed to yield the free amine **88.8**. Optionally, the olefinic double bond is reduced, for example by the use of diborane or diimide, or by means of catalytic hydrogenation, as described above (Scheme **59**) to produce the saturated analog **88.9**.

For example, 4-bromo-2,6-dimethylbenzylamine **88.10**, (Trans World Chemicals) is converted into the BOC derivative **88.11**, as described above, and the product is coupled with a dialkyl phosphite **88.3**, in the presence of triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to yield the phosphonate ester **88.12**. Deprotection, for example by treatment with trifluoroacetic acid, then produces the free amine **88.13**.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylbenzylamine **88.10**, different bromobenzylamines **88.1**, the corresponding products **88.5** are obtained.

As an additional example of the methods of Scheme **88**, 4-bromo-2-methylbenzylamine **88.14** (Trans World Chemicals) is converted into the BOC derivative **88.15**. The latter compound is then reacted with a dialkyl vinylphosphonate **88.16**, (Aldrich) in the presence of 2 mol % of tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product **88.17**.

Deprotection then affords the amine **88.18**, and reduction of the latter compound with diimide gives the saturated analog **88.19**.

Using the above procedures, but employing, in place of 4-bromo-2-methylbenzylamine **88.14**, different bromobenzylamines **88.1**, and/or different alkenyl phosphonates **88.6**, the corresponding products **88.8** and **88.9** are obtained.

Scheme **89** depicts the preparation of 2-methyl or 2,6-dimethylbenzyamines incorporating a phosphonate moiety attached to the benzene ring by means of an amide linkage. In this procedure, the amino group of a carboxy-substituted 2-methyl or 2,6-dimethylbenzylamine **89.1** is protected to yield the product **89.2**. The latter compound is then reacted with a dialkyl aminoalkyl phosphonate **89.3** to afford the amide **89.4**. The reaction is performed as described above for the preparation of the amides **1.3** and **1.6**. The amine protecting group is then removed to give the free amine **89.5**.

For example, 4-carboxy-2-methylbenzylamine **89.6**, prepared as described in Chem. Pharm. Bull., 1979, 21, 3039, is converted into the BOC derivative **89.7**. This material is then reacted in tetrahydrofuran solution with one molar equivalent of a dialkyl aminoethyl phosphonate **89.8**, in the presence of dicyclohexylcarbodiimide and hydroxybenztriazole, to produce the amide **89.9**. Deprotection, for example by reaction with methanesulfonic acid in acetonitrile, then yields the amine **89.10**.

Using the above procedures, but employing, in place of 4-carboxy-2-methylbenzylamine **89.6**, different carboxy-substituted benzylamines **89.1**, and/or different aminoalkyl phosphonates **89.3**, the corresponding products **89.5** are obtained.

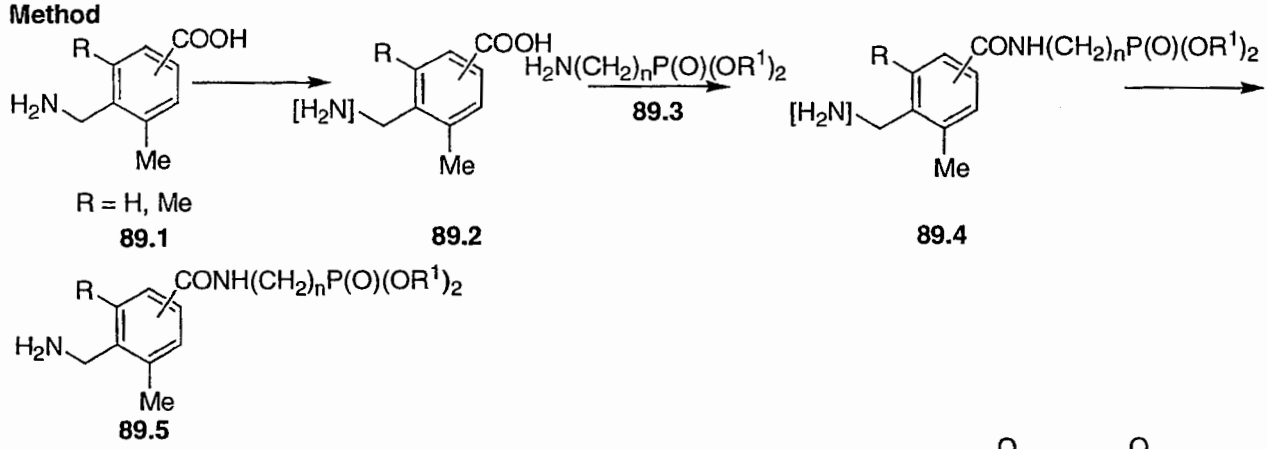
Scheme **90** depicts the preparation of 2-methyl or 2,6-dimethylbenzyamines incorporating a phosphonate moiety attached to the benzene ring by means of a heteroatom and an alkylene chain. In this procedure, the amino group of a hydroxy or mercapto-substituted methylbenzylamine **90.1** is protected to afford the derivative **90.2**. This material is then reacted with a dialkyl bromoalkyl phosphonate **90.3** to yield the ether or thioether product **90.4**. The reaction is conducted in a polar organic solvent such as dimethylformamide or N-methylpyrrolidinone, in the presence of a base such as diazabicyclononene or cesium carbonate. The amino protecting group is then removed to afford the product **90.5**.

For example, 2,6-dimethyl-4-hydroxybenzylamine **90.6**, prepared, as described above, from 2,6-dimethyl-4-hydroxybenzoic acid, the preparation of which is described in J. Org. Chem., 1985, 50, 2867, is protected to afford the BOC derivative **90.7**. The latter compound is then reacted with one molar equivalent of a dialkyl bromoethyl phosphonate **90.8**, (Aldrich) and cesium carbonate in dimethylformamide solution at 80° to give the ether **90.9**. Deprotection then afford the amine **90.10**.

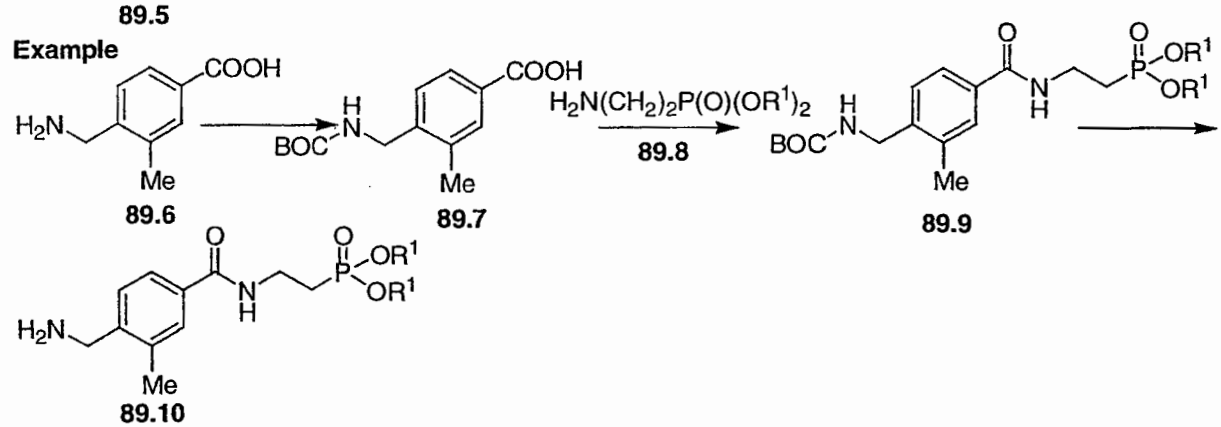
Using the above procedures, but employing, in place of 4-hydroxy-2,6-dimethylbenzylamine **90.6**, different hydroxy or mercapto-substituted benzylamines **90.1**, and/or different bromoalkyl phosphonates **90.3**, the corresponding products **90.5** are obtained.

Scheme 89

Method

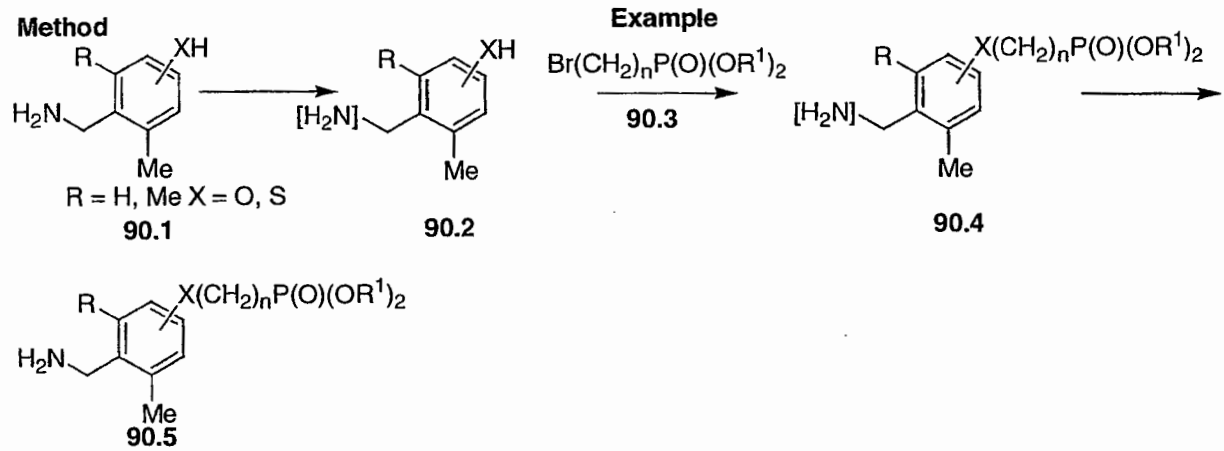


Example

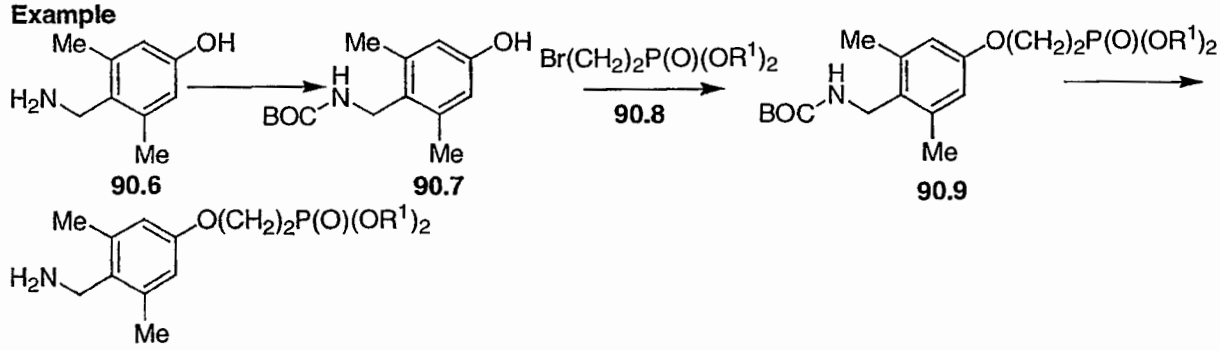


Scheme 90

Method



Example



Preparation of phosphonate-substituted decahydroquinolines 33.1.

Schemes **91 – 97** illustrate the preparation of decahydroisoquinoline derivatives **33.1** in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc. The compounds are employed in the preparation of the intermediate phosphonate esters **9**, (Schemes **33 – 36**)

Scheme **91** illustrates methods for the synthesis of intermediates for the preparation of decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the benzenoid intermediate **91.4** are shown.

In the first route, 2-hydroxy-6-methylphenylalanine **91.1**, the preparation of which is described in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative **91.2**. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product **91.2**, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product **91.3**. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound **91.3** is then treated with acid, for example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline **91.4**, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline **91.4** can be obtained from 2-hydroxyphenylalanine **91.5**, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem. Rev., 1995, 95, 1797.

Typically, the substrate **91.5** is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product **91.4**, in which R is H. Catalytic hydrogenation of the latter compound, using, for example, a platinum catalyst, as described in J. Am. Chem. Soc., 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-

substituted decahydroisoquinoline **91.6**. The reduction can also be performed electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline **91.4** is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at ca 50°, to afford the decahydroisoquinoline **91.6**.

Protection of the carboxyl and NH groups present in **91.6** for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH into the N-cbz group, as described above, followed by oxidation, using, for example, pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone **91.9**, in which R is trichloroethyl and R_1 is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in J. Am. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butyl aluminum hydride, as described in J. Am. Chem. Soc., 80, 5372, 1958, then affords the alcohol **91.10**.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as isopropanol, at ambient temperature, to afford the alcohol **91.10**.

The alcohol **91.6** can be converted into the thiol **91.13** and the amine **91.14**, by means of displacement reactions with suitable nucleophiles, with inversion of stereochemistry. For example, the alcohol **91.6** can be converted into an activated ester such as the trifluoromethanesulfonyl ester or the methanesulfonate ester **91.7**, by treatment with methanesulfonyl chloride and a base. The mesylate **91.7** is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol **91.13**.

For example, the mesylate **91.7** is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **91.12**, in which R is $COCH_3$. The product then treated with, a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol **91.13**.

The mesylate **91.7** can be treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p399, followed by deprotection as described previously, to afford the amine **91.14**.

For example, the mesylate **91.7** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such as, for example, dimethylformamide, at ambient temperature, to afford the displacement product **91.8**, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the amine **91.14**.

The application of the procedures described above for the conversion of the β-carbinol **91.6** to the α-thiol **91.13** and the α-amine **91.14** can also be applied to the α-carbinol **91.10**, so as to afford the β-thiol and β-amine, **91.11**.

Scheme **92** illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain.

In this procedure, an alcohol, thiol or amine **92.1** is reacted with a bromoalkyl phosphonate **92.2**, under the conditions described above for the preparation of the phosphonate **90.4** (Scheme **90**), to afford the displacement product **92.3**. Removal of the ester group, followed by conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme **96**) then yields the amine **92.8**.

For example, the compound **92.5**, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, **92.6**, the preparation of which is described in J. Am. Chem. Soc., 2000, 122, 1554 to afford the displacement product **92.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme **96**) then yields the amine **92.8**.

Using the above procedures, but employing, in place of the α-thiol **92.5**, the alcohols, thiols or amines **91.6, 91.10, 91.11, 91.13, 91.14**, of either α- or β-orientation, there are obtained the corresponding products **92.4**, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme **93** illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive Organic Transformations, by R. C. Larock, p421.

In this procedure, the amines **91.14** or **91.11** are reacted with a phosphonate aldehyde **93.1**, in the presence of a reducing agent, to afford the alkylated amine **93.2**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described herein, (Scheme **96**) then yields the amine **93.3**.

For example, the protected amino compound **91.14** is reacted with a dialkyl formylphosphonate **93.4**, the preparation of which is described in US Patent 3784590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate **93.5**. Deprotection of the ester group, followed by conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme **96**) then yields the amine **93.6**.

Using the above procedures, but employing, instead of the α-amine **91.14**, the β isomer, **91.11** and/or different aldehydes **93.1**, there are obtained the corresponding products **93.3**, in which the orientation of the side chain is the same as that of the amine precursor.

Scheme **94** depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain.

In this procedure, a thiol phosphonate **94.2** is reacted with a mesylate **94.1**, to effect displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product **94.3**. Deprotection of the ester group, followed by conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme **96**) then yields the amine **94.4**.

For example, the protected mesylate **94.5** is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate **94.6**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thio ether phosphonate **94.7**. Deprotection of the ester group, followed by

conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme **96**) then yields the amine **94.8**

Using the above procedures, but employing, instead of the phosphonate **94.6**, different phosphonates **94.2**, there are obtained the corresponding products **94.4**.

Scheme **95** illustrates the preparation of decahydroisoquinoline phosphonates **95.4** in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The compounds are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates **95.1** and a bromomethyl substituted phosphonate **95.2**. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant **95.1**. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate can be employed. If X is O, a strong base such as sodium hydride or lithium hexamethyldisilylazide is required. The displacement reaction affords the ether, thioether or amine compounds **95.3**. Deprotection of the ester group, followed by conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme **96**) then yields the amine **95.4**.

For example, the protected alcohol **95.5** is reacted at ambient temperature with a dialkyl 3-bromomethyl phenylmethylphosphonate **95.6**, the preparation of which is described above, (Scheme **80**). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a strong base, such as, for example, lithium hexamethyldisilylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate **95.6**, to afford the product **95.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme **96**) then yields the amine **95.8**.

Using the above procedures, but employing, instead of the β-carbinol **95.5**, different carbinols, thiols or amines **95.1**, of either α- or β-orientation, and/or different phosphonates **95.2**, in place of the phosphonate **95.6**, there are obtained the corresponding products **95.4** in which the orientation of the side-chain is the same as that of the starting material **95.1**.

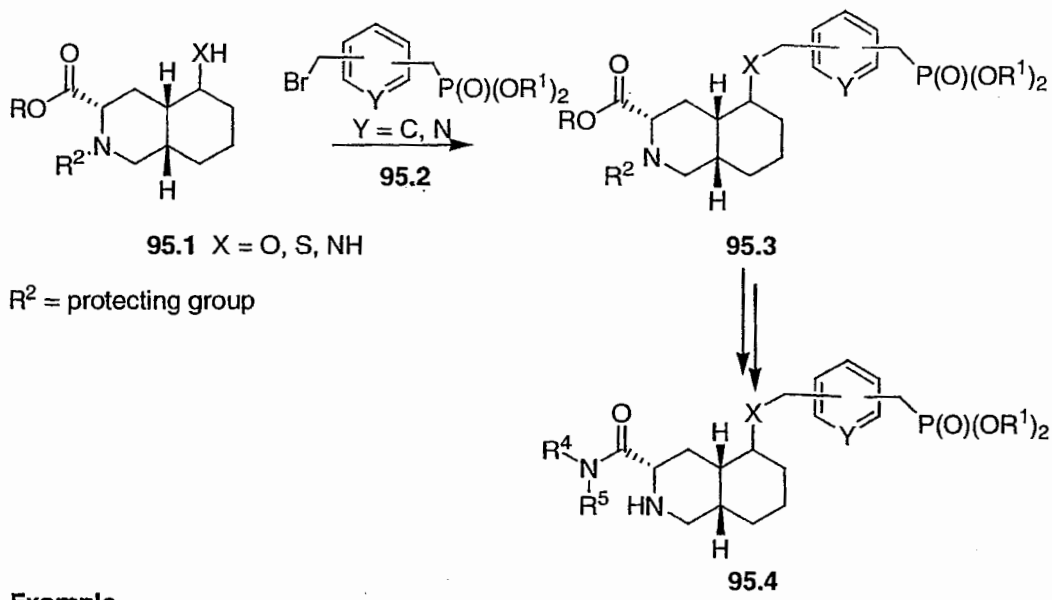
Schemes **92-95** illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

Scheme **96** illustrates the conversion of the latter group of compounds **96.1** (in which the group B is link-$P(O)(OR^1)_2$ or optionally protected precursor substituents thereto, such as, for example, OH, SH, NH_2) to the corresponding R^4R^5N amides **96.5**.

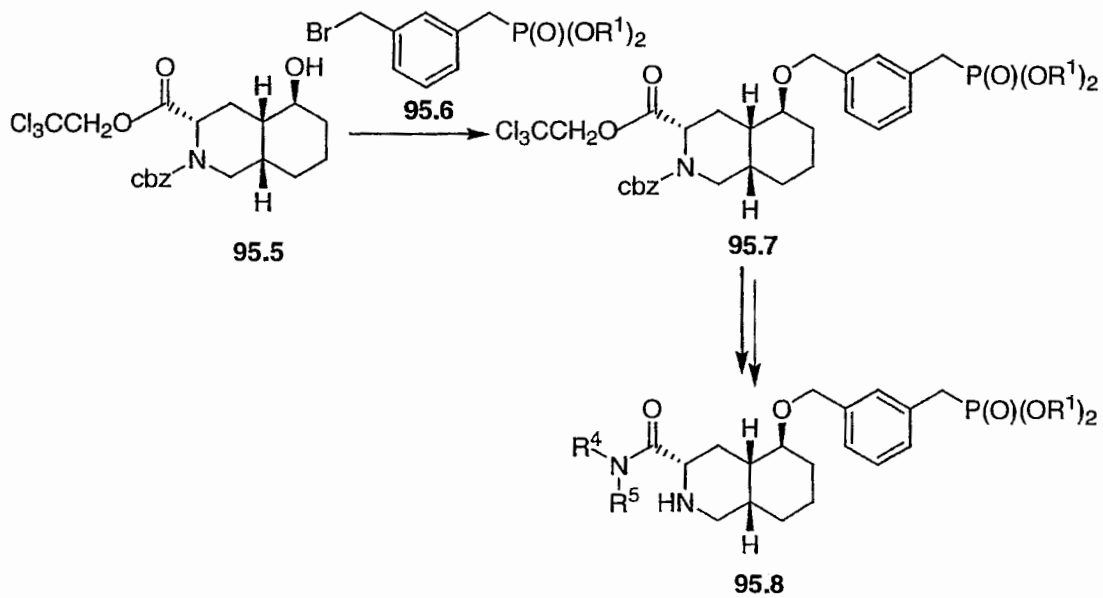
As shown in Scheme **96**, the ester compounds **96.1** are deprotected to form the corresponding carboxylic acids **96.2**. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R^2, and the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is removed by treatment with zinc in acetic acid, as described in J. Am. Chem. Soc., 88, 852, 1966.

Conversion of the carboxylic acid **96.2** to the R^4R^5N amide **96.4** is then accomplished by reaction of the carboxylic acid, or an activated derivative thereof, with the amine R^4R^5NH **96.3** to afford the amide **96.4**, using the conditions described above for the preparation of the amide **1.6**. Deprotection of the NR^2 group, as described above, then affords the free amine **96.5**.

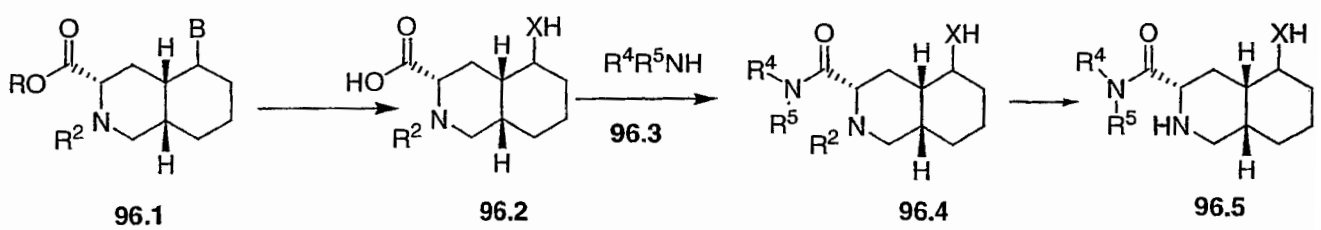
Scheme 95
Method



Example



Scheme 96
Method



Preparation of the phosphonate-containing tert. butylamides 37.1.

Scheme **97** illustrates the preparation of the amides **37.1** in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, which are employed in the preparation of the intermediate phosphonate esters **10** (Schemes **37 – 40**). In this procedure, the BOC-protected decahydroisoquinoline carboxylic acid **97.1** is reacted with the tert. butylamine derivative **25.1**, in which the substituent A is the group link-$P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], Br, etc, to afford the amide **97.2**. The reaction is conducted as described above for the preparation of the amides **1.3** and **1.6**. The BOC protecting group is then removed to yield the amine **37.1**.

Preparation of the phosphonate-containing thiazolidines 21.1.

Schemes **98** - **101** illustrate the preparation of the thiazolidine derivatives **37.1**, in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, which are employed in the preparation of the intermediate phosphonate esters **6**. The preparation of the penicillamine analogs **98.5** in which R is alkyl is described in J. Org. Chem., 1986, 51, 5153 and in J. Labelled. Comp. Radiochem., 1987, 24, 1265. The conversion of the penicillamine analogs **98.5** into the corresponding thiazolidines **98.7** is described in J. Med. Chem., 1999, 42, 1789 and in J. Med. Chem., 1989, 32, 466. The above-cited procedures, and their use to afford analogs of the thiazolidines **98.7** are shown in Scheme **98**.
In this procedure, a methyl ketone **98.2** is reacted with methyl isocyanoacetate **98.1** to afford the aminoacrylate product **98.3**. The condensation reaction is conducted in the presence of a base such as butyllithium or sodium hydride, in a solvent such as tetrahydrofuran at from -80° to 0°, to afford after treatment with aqueous ammonium chloride the N-formyl acrylate ester **98.3**. The latter compound is then reacted with phosphorus pentasulfide or Lawessons reagent and the like to yield the thiazoline derivative **98.4**. The reaction is performed in an aprotic solvent such as benzene, for example as described in J. Org. Chem., 1986, 51, 5153. The thiazoline product **98.4** is then treated with dilute acid, for example dilute hydrochloric acid, to produce the aminothiol **98.5**. This compound is reacted with aqueous formaldehyde at pH 5, for example as described in J. Med. Chem., 1999, 42, 1789, to prepare the thiazolidine **98.6**. The product is then converted, as described previously, into the BOC-protected analog **98.7**.

Some examples of the use of the reactions of Scheme **98** for the preparation of functionally substituted thiazolidines **98.7** are shown below.

Scheme **98**, Example **1** illustrates the preparation of the BOC-protected hydroxymethyl thiazolidine **98.11**. In this procedure, methyl isocyanoacetate **98.1** is reacted with hydroxyacetone **98.8** in the presence of a base such as sodium hydride, to yield the aminoacrylate derivative **98.9**. The product is then reacted with phosphorus pentasulfide, as described above, to prepare the thiazoline **98.10**. The latter compound is then converted, as described above, into the thiazolidine derivative **98.11**.

Scheme **98**, Example **2**, depicts the preparation of bromophenyl-substituted thiazolidines **98.14**. In this reaction sequence, methyl isocyanoacetate **98.1** is condensed, as described above, with a bromoacetophenone **98.12** to give the aminocinnamate derivative **98.13**. The latter compound is then transformed, as described above, into the thiazolidine derivative **98.14**.

Scheme **98**, Example **3** depicts the preparation of the BOC-protected thiazolidine-5-carboxylic acid **98.18**. In this procedure, methyl isocyanoacetate **98.1** is reacted, as described above, with trichloroethyl pyruvate **98.15** to afford the aminoacrylate derivative **98.16**. This compound is then transformed, as described above, into the thiazolidine diester **98.17**. The trichloroethyl ester is then cleaved, for example by treatment with zinc in aqueous tetrahydrofuran at pH 4.2, as described in J. Am. Chem. Soc., 88, 852, 1966, to afford the 5-carboxylic acid **98.18**.

Scheme **98**, Example **4**, depicts the preparation of the BOC-protected thiazolidine-4-carboxylic acid incorporating a phosphonate moiety. In this procedure, methyl isocyanoacetate **98.1** is condensed, as described above, with a dialkyl 2-oxopropyl phosphonate **98.19**, (Aldrich); the product **98.20** is then transformed, as described above, into the corresponding 4-carbomethoxythiazolidine. Hydrolysis of the methyl ester, for example by the use of one equivalent of lithium hydroxide in aqueous tetrahydrofuran, then yields the carboxylic acid **98.21**.

Scheme **99** illustrates the preparation of BOC-protected thiazolidine-4-carboxylic acids incorporating a phosphonate group attached by means of an oxygen atom and an alkylene chain. In this procedure, the hydroxymethyl thiazolidine **98.11** is reacted with a dialkyl bromoalkyl phosphonate **99.1** to afford the ether product **99.2**. The hydroxymethyl substrate

98.11 is treated in dimethylformamide solution with a strong base such as sodium hydride or lithium hexamethyldisilylazide, and an equimolar amount of the bromo compound **99.1** is added. The product **99.2** is then treated with aqueous base, as described above, to effect hydrolysis of the methyl ester to yield the carboxylic acid **99.3**.

For example, the hydroxymethyl thiazolidine **98.11** is reacted with sodium hydride and a dialkyl bromoethyl phosphonate **99.4** (Aldrich) in dimethylformamide at 70°, to produce the phosphonate product **99.5**. Hydrolysis of the methyl ester then affords the carboxylic acid **99.6**.

Using the above procedures, but employing, in place of the dialkyl bromoethyl phosphonate **99.4**, different bromoalkyl phosphonates **99.1**, the corresponding products **99.3** are obtained.

Scheme **100** illustrates the preparation of BOC-protected thiazolidine-4-carboxylic acids incorporating a phosphonate group attached by means of a phenyl group. In this procedure, a bromophenyl-substituted thiazolidine **98.14** is coupled, as described above (Scheme **46**) in the presence of a palladium catalyst, with a dialkyl phosphite **100.1**, to produce the phenylphosphonate derivative **100.2**. The methyl ester is then hydrolyzed to afford the carboxylic acid **100.3**.

For example, the BOC-protected 5-(4-bromophenyl)thiazolidine **100.4** is coupled with a dialkyl phosphite **100.1** to yield the product **100.5**, which upon hydrolysis affords the carboxylic acid **100.6**.

Using the above procedures, but employing, in place of the 4-bromophenyl thiazolidine **100.4**, different bromophenyl thiazolidines **98.14**, the corresponding products **100.3** are obtained.

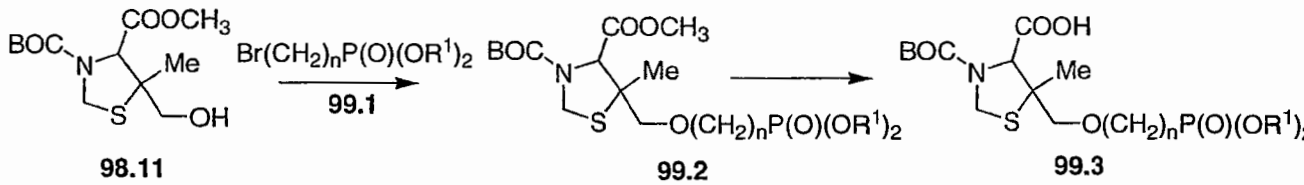
Scheme **101** illustrates the preparation of BOC-protected thiazolidine-4-carboxylic acids incorporating a phosphonate group attached by means of an amide linkage. In this procedure, a thiazolidine-5-carboxylic acid **98.18** is reacted with a dialkyl aminoalkyl phosphonate **101.1** to produce the amide **101.2**. The reaction is conducted as described above for the preparation of the amides **1.3** and **1.6**. The methyl ester is then hydrolyzed to afford the carboxylic acid **101.3**.

For example, the carboxylic acid **98.18** is reacted in tetrahydrofuran solution with an equimolar amount of a dialkyl aminopropyl phosphonate **101.4** (Acros) and dicyclohexylcarbodiimide, to afford the amide **101.5.** The methyl ester is then hydrolyzed to afford the carboxylic acid **101.6.**

Using the above procedures, but employing, in place of the dialkyl aminopropyl phosphonate **101.4**, different aminoalkyl phosphonates **101.1**, the corresponding products **101.3** are obtained.

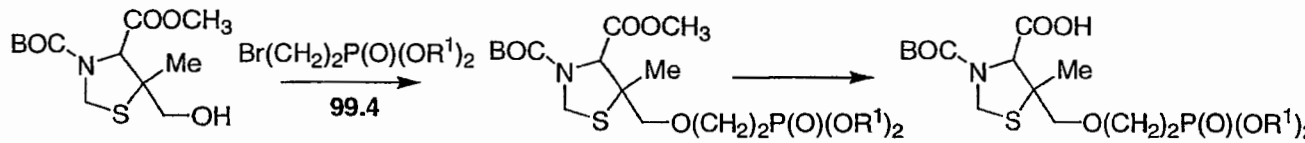
Scheme 99

Method



98.11 99.2 99.3

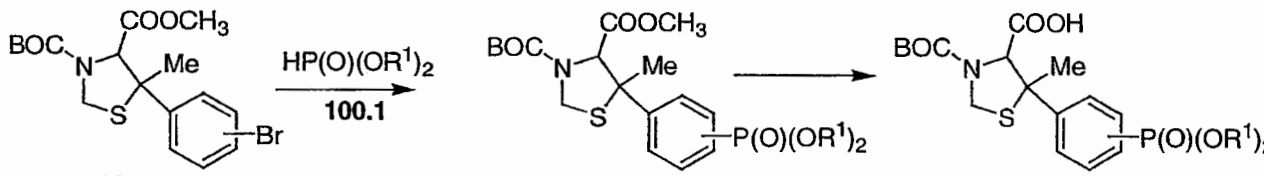
Example



98.11 99.5 99.6

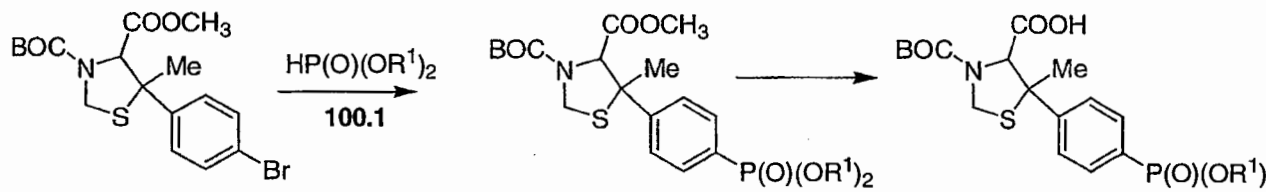
Scheme 100

Method



98.14 100.2 100.3

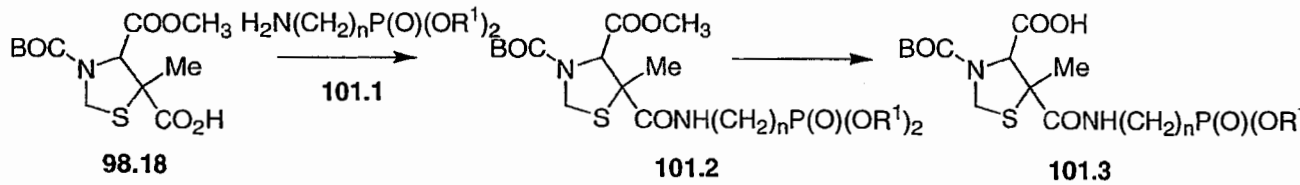
Example



100.4 100.5 100.6

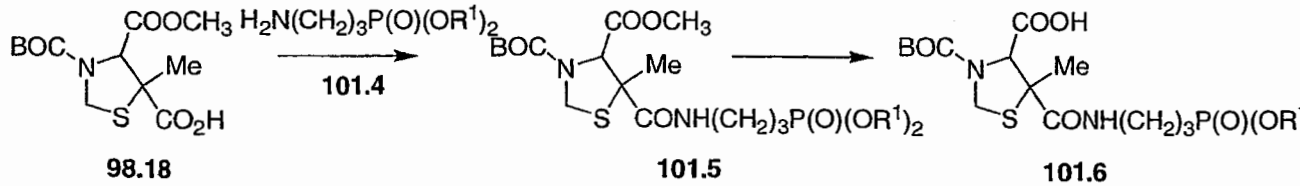
Scheme 101

Method



98.18 101.2 101.3

Example



98.18 101.5 101.6

Preparation of carbamates.

The phosphonate esters **5** - **12** in which the R^8CO groups are formally derived from the carboxylic acids **C38** - **C49** (Chart **2c**) contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme **102** illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme **102**, in the general reaction generating carbamates, a carbinol **102.1**, is converted into the activated derivative **102.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described herein. The activated derivative **102.2** is then reacted with an amine **102.3**, to afford the carbamate product **102.4**. Examples **1** – **7** in Scheme **102** depict methods by which the general reaction can be effected. Examples **8** - **10** illustrate alternative methods for the preparation of carbamates.

Scheme **102**, Example **1** illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **102.5**. In this procedure, the carbinol **102.5** is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **102.6**. The latter compound is then reacted with the amine component **102.3**, in the presence of an organic or inorganic base, to afford the carbamate **102.7**. For example, the chloroformyl compound **102.6** is reacted with the amine **102.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **102.7**. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme **102**, Example **2** depicts the reaction of the chloroformate compound **102.6** with imidazole to produce the imidazolide **102.8**. The imidazolide product is then reacted with the amine **102.3** to yield the carbamate **102.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme **102** Example **3**, depicts the reaction of the chloroformate **102.6** with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester **102.10**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **102.19** - **102.24** shown in Scheme **102**, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **102.19**, N-hydroxysuccinimide **102.20**, or pentachlorophenol, **102.21**, the mixed carbonate **102.10** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **102.22** or 2-hydroxypyridine **102.23** can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme **102** Example **4** illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **102.8** is employed. In this procedure, a carbinol **102.5** is reacted with an equimolar amount of carbonyl diimidazole **102.11** to prepare the intermediate **102.8.** The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **102.8** is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **102.7**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate **102.7**.

Scheme **102**, Example **5** illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **102.13**. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **102.12**, to afford the alkoxycarbonyl product **102.13**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. The product is then reacted with the amine $R'NH_2$ to afford the carbamate **102.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80° as described in Syn., 1977, 704.

Scheme **102**, Example **6** illustrates the preparation of carbamates in which a carbonate $(R"O)_2CO$, **102.14**, is reacted with a carbinol **102.5** to afford the intermediate alkyloxycarbonyl intermediate **102.15**. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate **102.7**. The procedure in which the reagent **102.15** is derived from

hydroxybenztriazole **102.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **102.15** is derived from N-hydroxysuccinimide **102.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **102.15** is derived from 2-hydroxypyridine **102.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **102.15** is derived from 4-nitrophenol **102.24** is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate **102.14** is conducted in an inert organic solvent at ambient temperature.

Scheme **102**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides **102.16**. In this procedure, an alkyl chloroformate **102.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **102.16**. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **102.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme **102**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine **102.17**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **102.7**.

Scheme **102**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **102.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **102.7**.

Scheme **102**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **102.7**.

Interconversions of the phosphonates R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH) and R-link-P(O)(OH)$_2$.

Schemes **1** - **102** described the preparations of phosphonate esters of the general structure R-link-P(O)(OR^1)$_2$, in which the groups R^1, the structures of which are defined in Chart **1**, may be the same or different. The R^1 groups attached to a phosphonate esters **1** - **12**, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme **103**. The group R in Scheme **103** represents the substructure to which the substituent link-P(O)(OR^1)$_2$ is attached, either in the compounds **1** - **12** or in precursors thereto. The R^1 group may be changed, using the procedures described below, either in the precursor compounds, or in the esters **1** - **12**. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **103.1** into the corresponding phosphonate monoester **103.2** (Scheme **103**, Reaction **1**) can be accomplished by a number of methods. For example, the ester **103.1** in which R^1 is an aralkyl group such as benzyl, can be converted into the monoester compound **103.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester **103.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **103.2** can be effected by treatment of the ester **103.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **103.1** in which one of the groups R^1 is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **103.2** in which R^1 is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, can be converted into the monoester **103.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **103.1** or a phosphonate monoester **103.2** into the corresponding phosphonic acid **103.3** (Scheme **103**, Reactions **2** and **3**) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **103.2** in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **103.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **103.2** in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **103.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **103.1** in which R^1 is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **103.1** in which R^1 is phenyl is described in J. Am. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester **103.2** into a phosphonate diester **103.1** (Scheme **103**, Reaction **4**) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **103.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **103.2** to the diester **103.1** can be effected by the use of the Mitsonobu reaction, as described above (Scheme **47**). The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **103.2** can be transformed into the phosphonate diester **103.1**, in

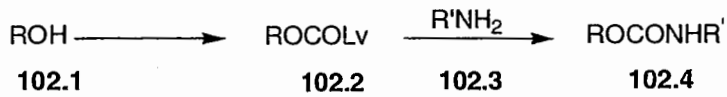
which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **103.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **103.1**.

A phosphonic acid R-link-$P(O)(OH)_2$ can be transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **103**, Reaction **5**) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ **103.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

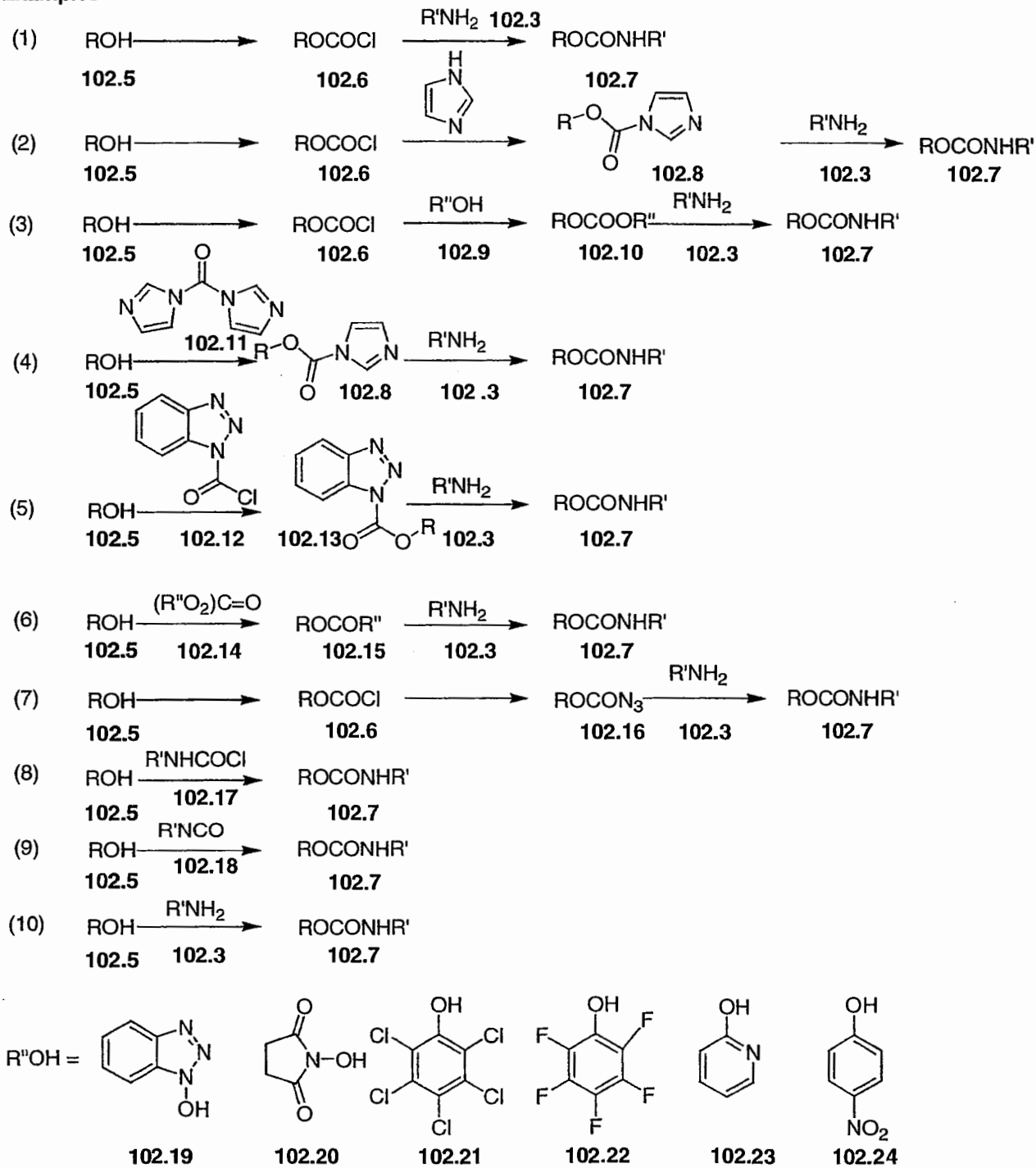
A phosphonic acid R-link-$P(O)(OH)_2$ **103.3** can be transformed into a phosphonate diester R-link-$P(O)(OR^1)_2$ **103.1** (Scheme **103**, Reaction **6**) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **103.3** can be transformed into phosphonic esters **103.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°. Alternatively, phosphonic acids **103.3** can be transformed into phosphonic esters **103.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **103.1**.

Scheme 102

General reaction

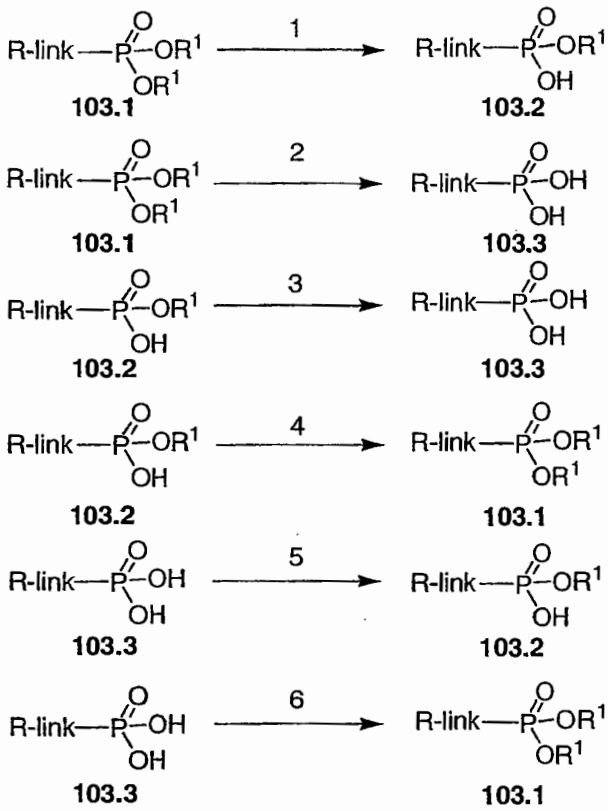


Examples



R"OH =

Scheme 103



General applicability of methods for introduction of phosphonate substituents.

The procedures described herein for the introduction of phosphonate moieties (Schemes **45 - 101**) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into hydroxymethyl benzoic acids (Schemes **45 - 52**) are applicable to the introduction of phosphonate moieties into the dimethoxyphenol, quinoline, phenylalanine, thiophenol, tert. butylamine, benzylamine, decahydroisoquinoline or thiazolidine substrates, and the methods described herein for the introduction of phosphonate moieties into the dimethoxyphenol, quinoline, phenylalanine, thiophenol, tert. butylamine, benzylamine, decahydroisoquinoline or thiazolidine substrates, (Schemes **53 - 101**) are applicable to the introduction of phosphonate moieties into carbinol substrates.

Preparation of phosphonate intermediates 11 and 12 with phosphonate moieties incorporated into the groups R^8CO and $R^{10}R^{11}N$.

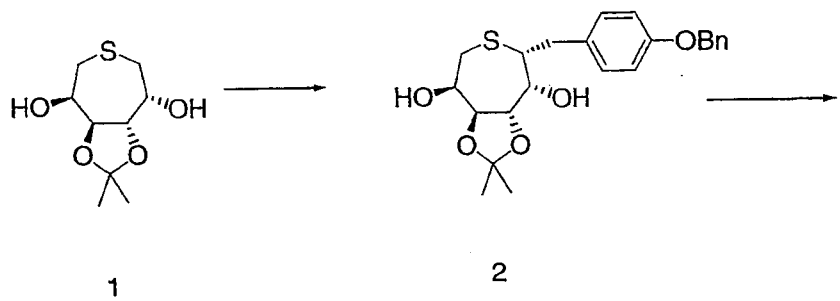
The chemical transformations described in Schemes **1 - 103** illustrate the preparation of compounds **1 -10** in which the phosphonate ester moiety is attached to the benzoic acid moiety, (Schemes **46** - **52**), the dimethylphenol moiety (Schemes **53 - 56**), the quinoline carboxamide moiety (Schemes **57 - 61**), the 5-hydroxyisoquinoline moiety (Schemes **62 - 66**), the phenylalanine moiety (Schemes **67 - 71**), the thiophenol moiety, (Schemes **72** - **83**), the tert. butylamine moiety, (Schemes **84** - **87**), the benzylamine moiety, (Schemes **88** - **90**), the decahydroisoquinoline moiety, (Schemes **91** - **97**) or the thiazolidine moiety, (Schemes **98** - **101**). The various chemical methods employed for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of a phosphonate ester group into the compounds R^8COOH and $R^{10}R^{11}NH$, as defined in Charts **3a**, **3b**, **3c** and **4**. The resultant phosphonate-containing analogs, designated as $R^{8a}COOH$ and $R^{10a}R^{11a}NH$ can then, using the procedures described above, be employed in the preparation of the compounds **11** and **12**. The procedures required for the utilization of the phosphonate-containing analogs $R^{8a}COOH$ and $R^{10a}R^{11a}NH$ are the same as those described above for the utilization of the R^8COOH and $R^{10}R^{11}NH$ reactants.

Cyclic carbonyl phosphonate protease inhibitors (CCPPI)

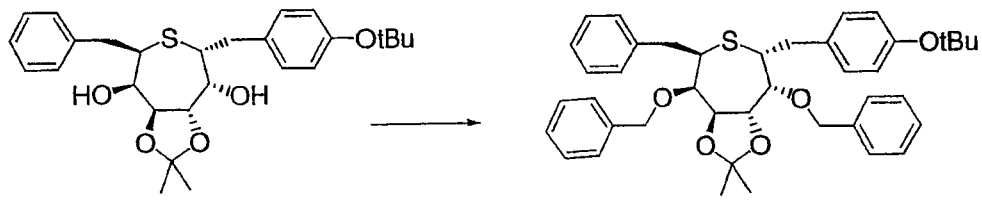
Scheme Section B

Schemes 1 and 2 are described below in the Examples.

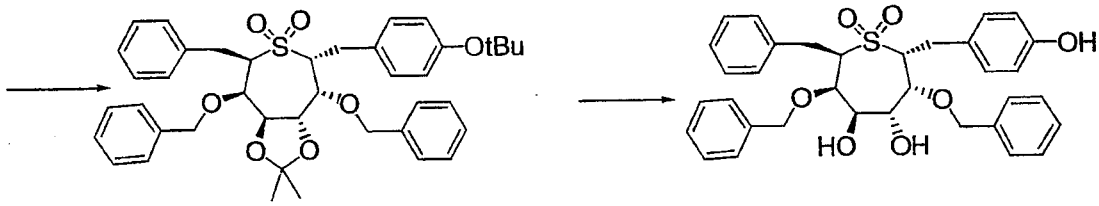
Scheme 1



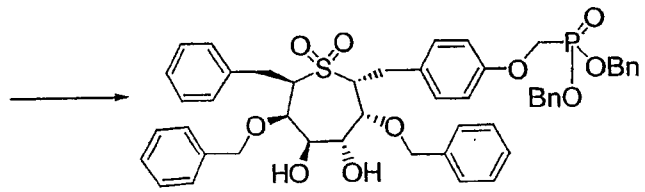
1 2



3 4

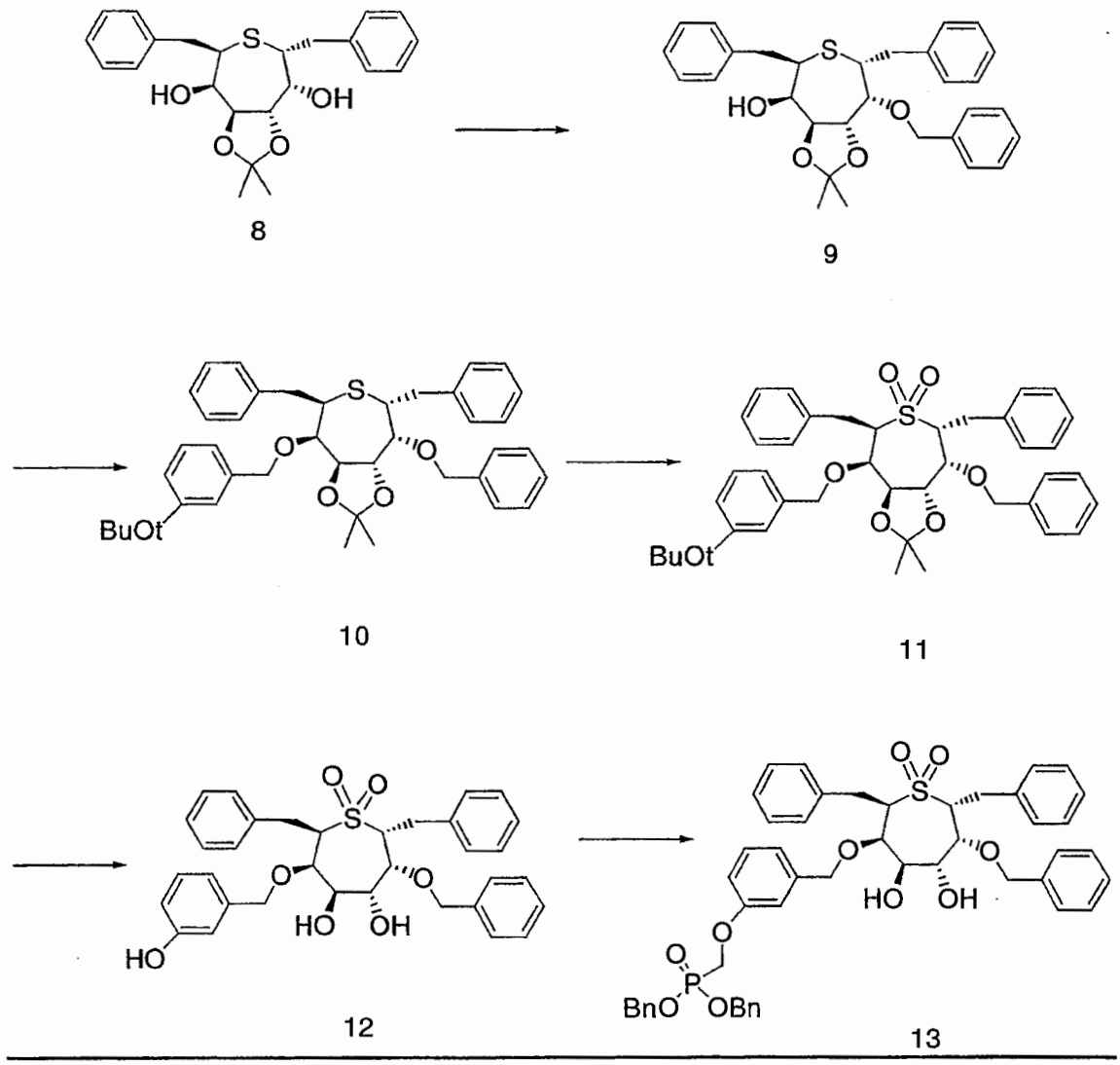


5 6



7

Scheme 2



Example Section B

Example 1

Scheme 1 : Example, [4-(7-Benzyl-3,6-bis-benzyloxy-4,5-dihydroxy-1,1-dioxo-1l6-thiepan-2-ylmethyl)-phenoxymethyl]-phosphonic acid dibenzyl ester (7)

The cyclic sulfide **1** is prepared according to the procedures reported by Kim et al. (J. Med. Chem. 1996, 39, 3431-3434) and Bischofberger (WO96/14314, Gilead Sciences). Treatment of the sulfide **1** with 4-benzyloxybenzaldehyde affords the benzyl ether **2** (J. Med. Chem. 1996, 39, 3431-3434). A second alkylation with benzaldehyde gives **3** which is subsequently treated with excess benzylbromide to afford the full substituted product **4**. Ozone is used to covert the sulfide to the sulfone **5** (J. Med. Chem. 1996, 39, 3431-3434). Sulfone **5** is treated with TFA to give the phenol **6** which upon alkyaltion with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) gives the dibenzyl phosphonate **7**.

The meta analog, [3-(7-Benzyl-3,6-bis-benzyloxy-4,5-dihydroxy-1,1-dioxo-1l6-thiepan-2-ylmethyl)-phenoxymethyl]-phosphonic acid dibenzyl ester and ortho analog, [2-(7-Benzyl-3,6-bis-benzyloxy-4,5-dihydroxy-1,1-dioxo-1l6-thiepan-2-ylmethyl)-phenoxymethyl]-phosphonic acid dibenzyl ester are prepared using Scheme 1 except 4-benzyloxybenzaldehyde is replaced with 3-benzyloxybenzaldehyde and 2-benzyloxybenzaldehyde respectively.

Example 2

Scheme 2 : Example, [3-(2,7-Dibenzyl-6-benzyloxy-4,5-dihydroxy-1,1-dioxo-1l6-thiepan-3-yloxymethyl)-phenoxymethyl]-phosphonic acid dibenzyl ester (13).

The sulfide **8** is prepared according to the procedure of Kim et al. (J. Med. Chem. 1996, 39, 3431-3434) and is then treated with benzyl bromide in the presence of sodium hydride to give the benzyl ether **9**. A second treatment with 3-t-butyloxybenzylchloride in the presence of sodium hydride affords the benzyl ether **10**. Ozone treatment of the benzyl ether **10** gives the sulfone **11**.(J. Med. Chem. 1996, 39, 3431-3434) which is then treated with TFA to give the phenol **12** (Green). Phenol **12** is treated with trifluoro-methanesulfonic acid bis-

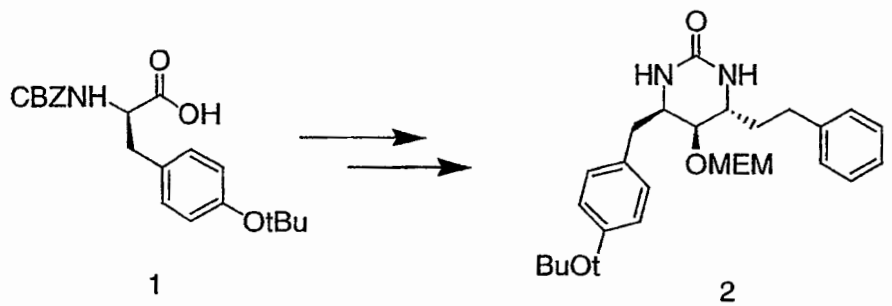
benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) to give the dibenzyl phosphonate **13**.

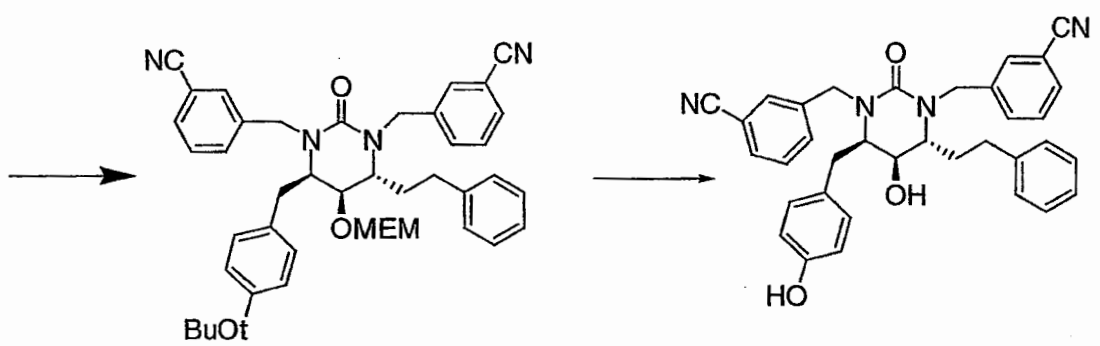
The para analog, [3-(2,7-Dibenzyl-6-benzyloxy-4,5-dihydroxy-1,1-dioxo-1l6-thiepan-3-yloxymethyl)-phenoxymethyl]-phosphonic acid dibenzyl ester, and ortho analog, [3-(2,7-Dibenzyl-6-benzyloxy-4,5-dihydroxy-1,1-dioxo-1l6-thiepan-3-yloxymethyl)-phenoxymethyl]-phosphonic acid dibenzyl ester, are prepared using the same procedures found in Scheme 2 except utilizing the 4-t-butyloxybenzylchloride and 2-t-butyloxybenzylchloride instead of 3-t-butyloxybenzylchloride. The benzylchlorides are prepared from the corresponding commercially available benzylalcohols by treatment with thionyl chloride (*Jour. Chem. Soc.* (1956), 2455-2461).

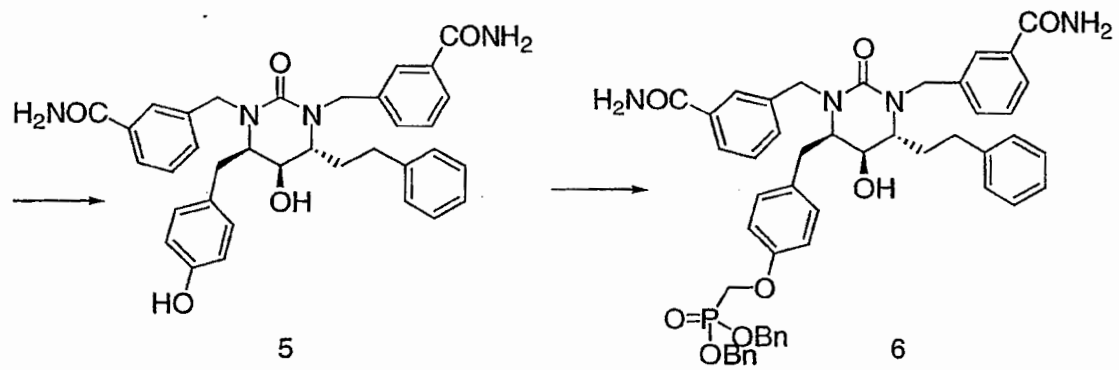
Scheme Section C

Schemes 1-4 are described in the Examples.

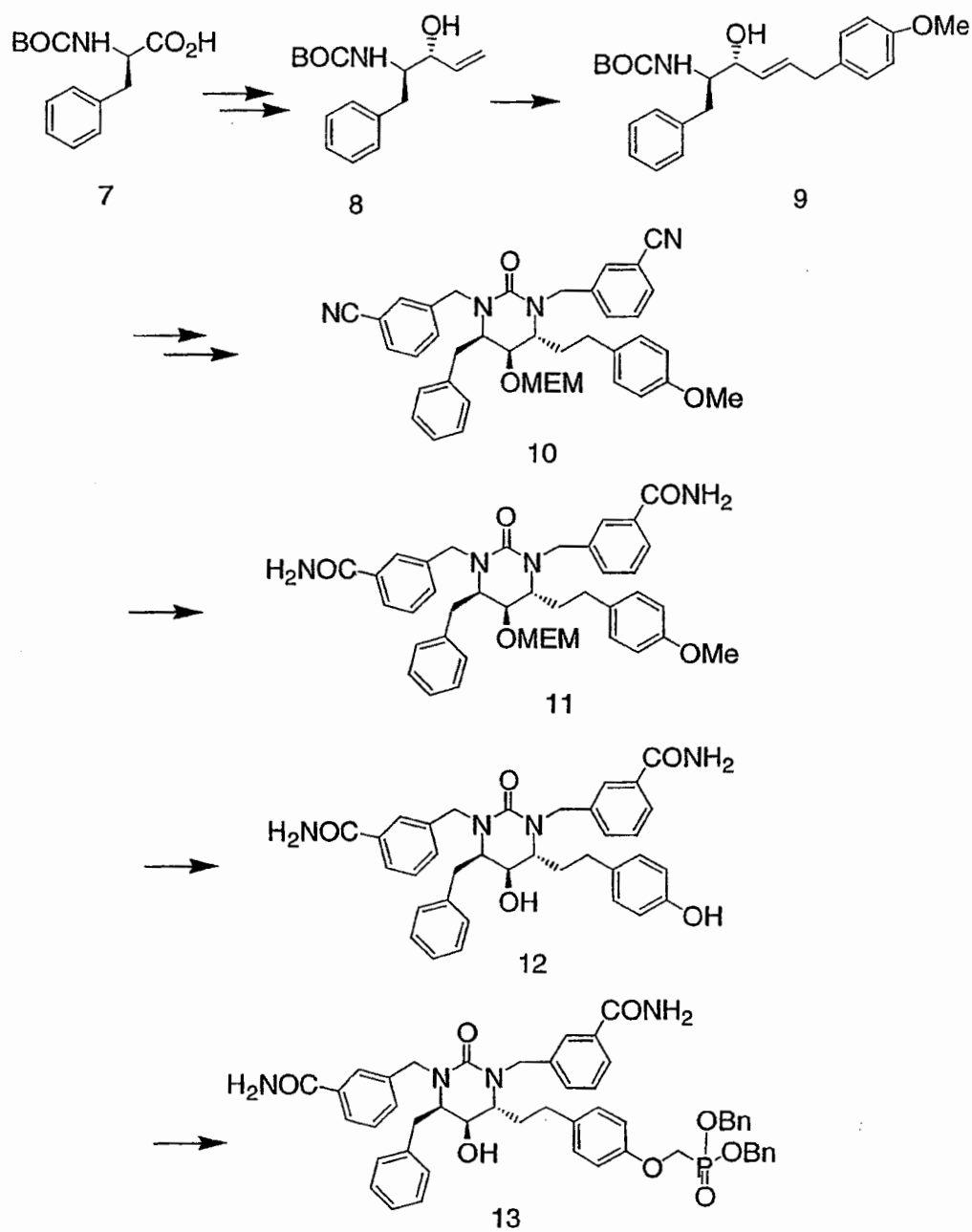
Scheme 1



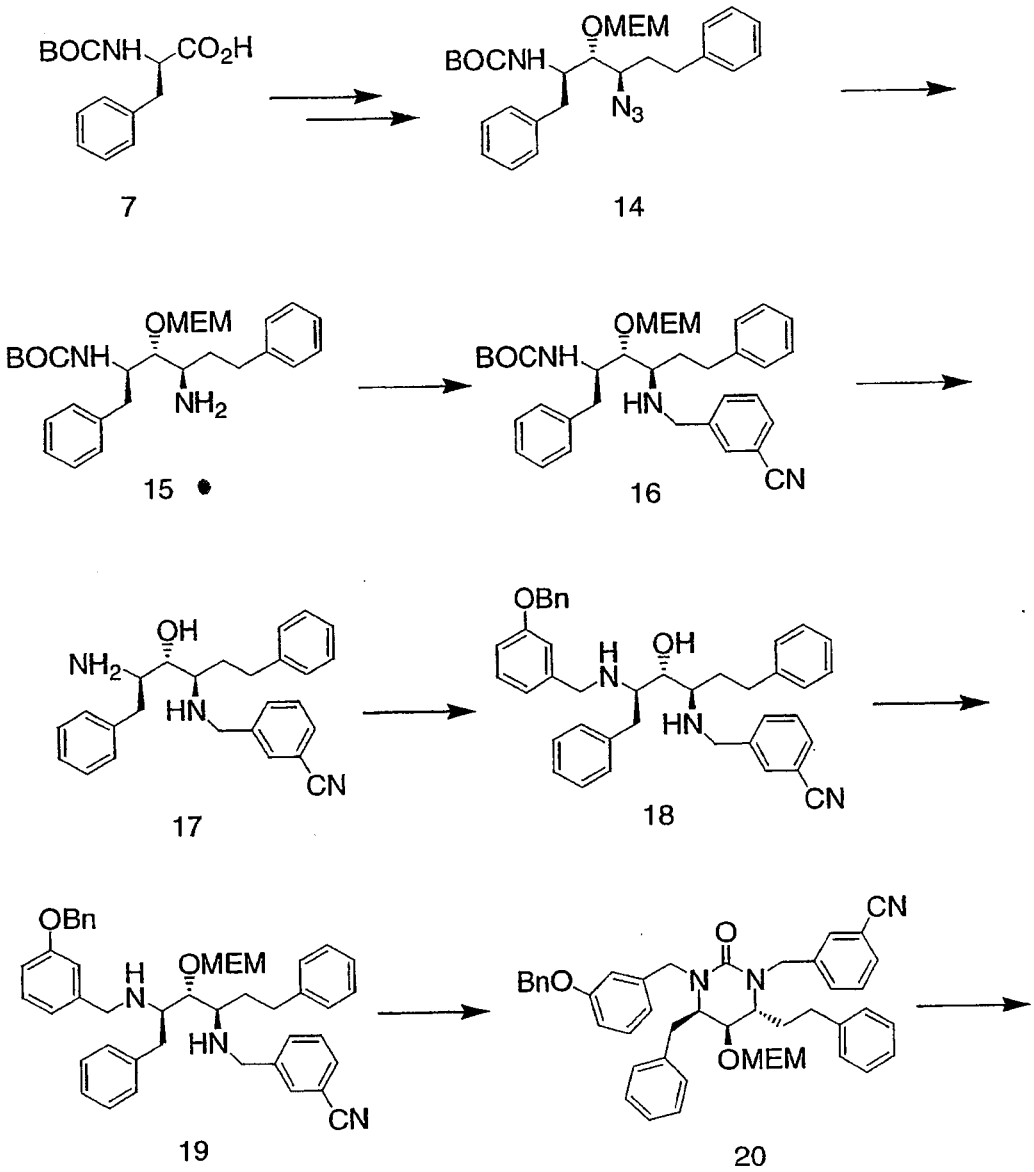




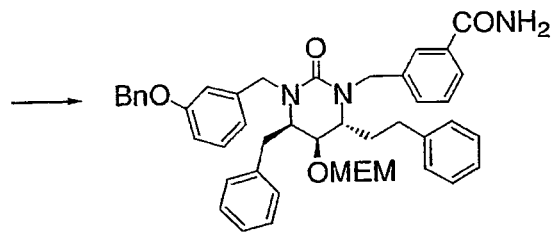
Scheme 2



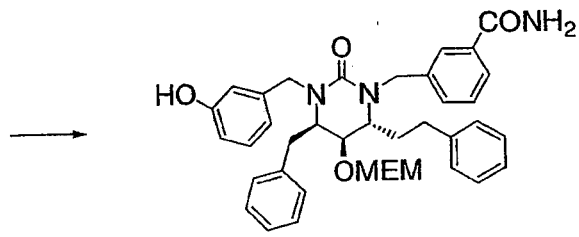
Scheme 3


BOCNH
CO2H
7
OMEM
BOCNH
N3
14
OMEM
BOCNH
NH2
15
OMEM
BOCNH
HN
CN
16
NH2
OH
HN
CN
17
OBn
H
N
OH
HN
CN
18
OBn
H
N
OMEM
HN
CN
19
CN
O
BnO
N
N
OMEM
20

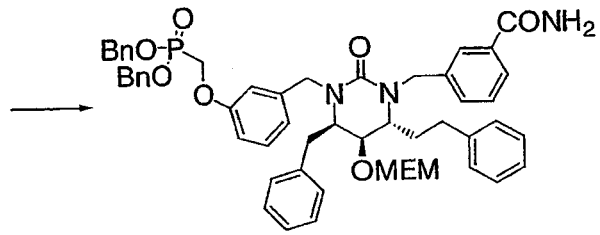
Scheme 3



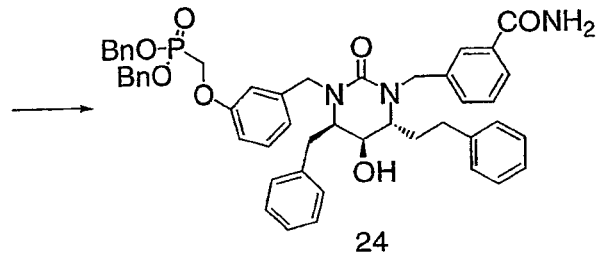
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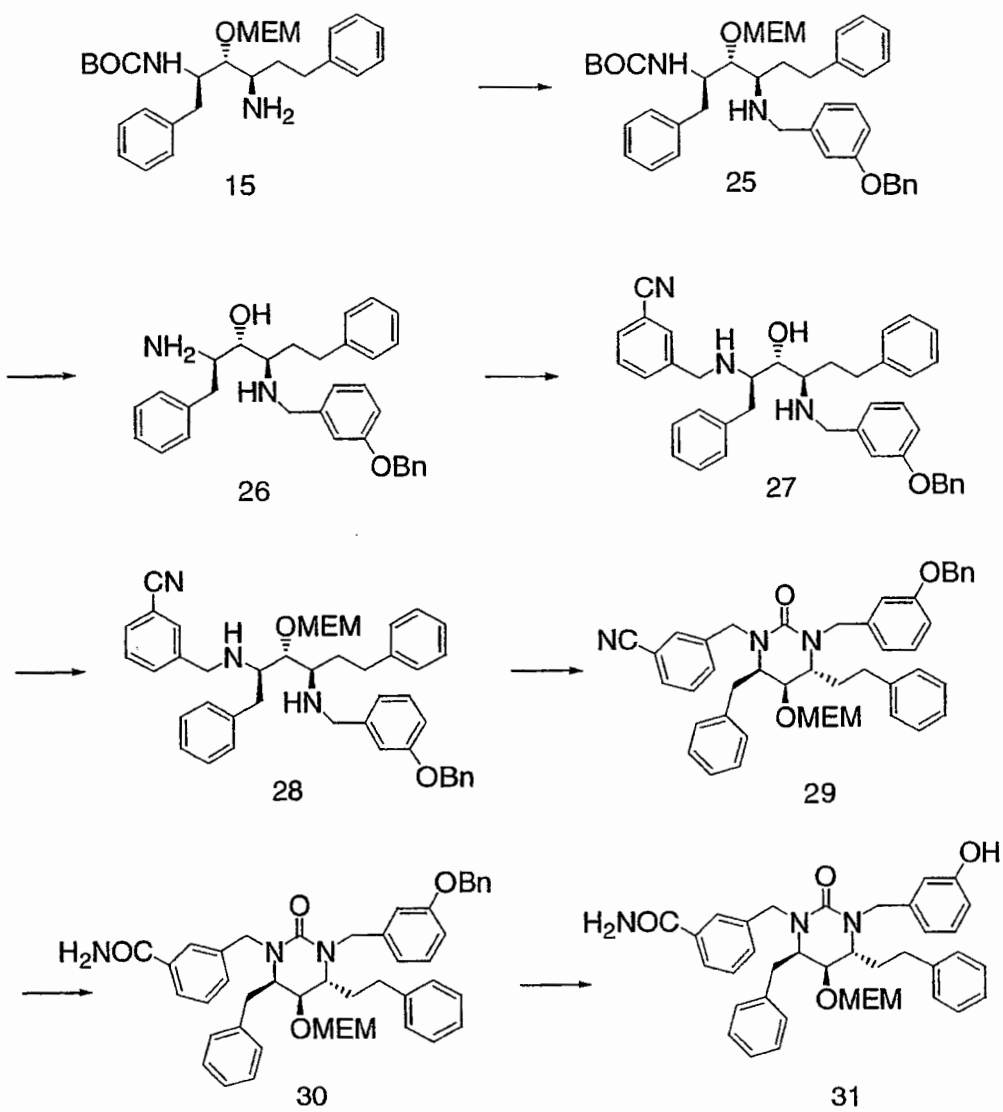


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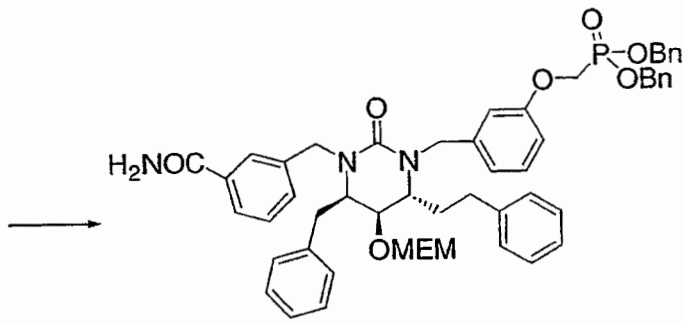


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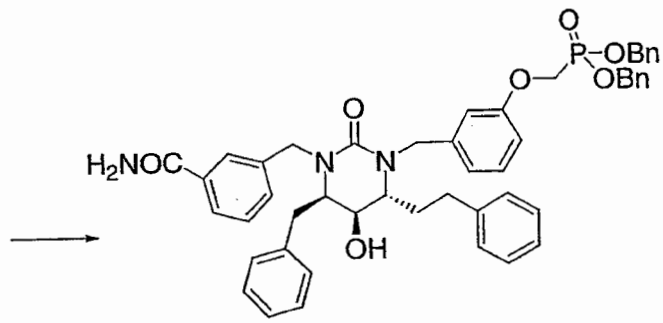
Scheme 4


OMEM
BOCNH
NH2
15
OMEM
BOCNH
HN
OBn
25
OH
NH2
HN
OBn
26
CN
H
N
OH
HN
OBn
27
CN
H
N
OMEM
HN
OBn
28
OBn
O
NC
N
N
OMEM
29
OBn
O
H2NOC
N
N
OMEM
30
OH
O
H2NOC
N
N
OMEM
31

Scheme 4 (continued)



32



33

Example Section C

Example 1

Scheme 1 : Example, {4-[1,3-Bis-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-hexahydro-pyrimidin-4-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester (6)

Commercially available Z-D-Tyr(TBU)-OH 1 is converted to the tetrahydropyrimidine 2 using the same procedures reported by De Lucca for conversion of Z-Phe into the analogous tetrahydropyrimidinone (J. Med. Chem. 1997, 40, 1707-1719). Bis-alkylation by treatment with excess m-cyanobenzylbromide affords the disubstituted urea 3 (J. Med. Chem. 1997, 40, 1707-1719). Removal of the MEM group and the t-butyl ether using standard conditions e.g. TFA (Green) affords the diol 4. Treatment of the diol 4 with hydrogen peroxide in DMSO affords the carboxamide 5. Alkyation of 5 with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) affords the dibenzyl phosphonate 6.

The meta analog, {3-[1,3-Bis-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-hexahydro-pyrimidin-4-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester and para analog, {2-[1,3-Bis-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-hexahydro-pyrimidin-4-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester are prepared using Scheme 1 except substituting Z-D-m-Tyr(TBU)-OH and Z-D-o-Tyr(TBU)-OH for Z-D-Tyr(TBU)-OH respectively. The Z-D-m-Tyr(TBU)-OH and Z-D-o-Tyr(TBU)-OH amino acids are prepared from the unprotecetd amino acids. Thus, D-m-Tyr-OH and D-o-Tyr-OH (see Abbott scheme 1) are treated with dibenzyl dicarbonate in the presence of base e.g. triethylamine to afford the Z-D-m-Tyr-OH and Z-D-o-Tyr-OH protected amino acids respectively. Further treatment of Z-D-m-Tyr-OH and Z-D-o-Tyr-OH with t-butyl chloride in the presence of base e.g. pyridine affords the Z-D-m-Tyr(TBU)-OH and Z-D-o-Tyr(TBU)-OH amino acids respectively (Green).

Example 2

Scheme 2 : Example, (4-{2-[6-Benzyl-1,3-bis-(3-carbamoyl-benzyl)-5-(2-methoxy-ethoxymethoxy)-2-oxo-hexahydro-pyrimidin-4-yl]-ethyl}-phenoxymethyl)-phosphonic acid dibenzyl ester (13)

Boc-Phe 7 is converted to the allylic alcohol 8 using the same procedures reported by De Lucca et al. for the conversion of Z-Phe to the corresponding Z- allylic alcohol (J. Med. Chem. 1997, 40, 1707-1719). The allylic alcohol 8 is reacted with 4-methoxybenzylmagnesium chloride to afford the alkene 9 (J. Med. Chem. 1997, 40, 1707-1719). The 4-methoxybenzylmagnesium chloride is prepared from 4-methoxybenzylchloride according to the procedure of Van Campen et al. (J. Amer. Chem. Soc. 1948, 70 p2296). The alkene 9 is converted to the tetrahydropyrimidinone 10 using the same series of procedures reported by De Lucca et al. (J. Med. Chem. 1997, 40, 1707-1719). Treatment of the nitrile 10 with hydrogen peroxide in DMSO affords the carboxamide 11 (Synthesis, 1989, 949-950). The carboxamide 11 is treated with trimethylsilylbromide to form the phenol 12 (Green) which is then alkylated with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) to yield the dibenzyl phosphonate 13.

The ortho, (2-{2-[6-Benzyl-1,3-bis-(3-carbamoyl-benzyl)-5-(2-methoxy-ethoxymethoxy)-2-oxo-hexahydro-pyrimidin-4-yl]-ethyl}-phenoxymethyl)-phosphonic acid dibenzyl ester and meta, (3-{2-[6-Benzyl-1,3-bis-(3-carbamoyl-benzyl)-5-(2-methoxy-ethoxymethoxy)-2-oxo-hexahydro-pyrimidin-4-yl]-ethyl}-phenoxymethyl)-phosphonic acid dibenzyl ester analogs, are prepared using the same procedures reported in Scheme 2 except 4-methoxybenzylmagnesium chloride is replaced with 2-methoxybenzylmagnesium chloride and 3-methoxybenzylmagnesium chloride respectively. The grignard reagents are prepared from commercially available benzyl chlorides using the procedure of Van Campen et al. (J. Amer. Chem. Soc. 1948, 70 p2296).

Example 3

Scheme 3 : Example, {3-[6-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-4-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester (24).

Boc-Phe 7 is converted into the azide 14 using the same procedures reported by De Lucca et al. for the conversion of CBZ-Phe into the analogous CBZ azide (J. Med. Chem. 1997, 40, 1707-1719). Catalytic hydrogenolysis of the azide affords the amine 15 (J. Med. Chem. 1997, 40, 1707-1719). Reductive amination of the amine with 3-cyanobenzaldehyde (US 6313110)

affords the secondary amine 16. Treatment with 4N HCl affords the primary amine 17 (Green). Reductive amination with 3-benzyloxybenzadehyde affords the benzyl ether 18 (US 6313110). Treatment of the benzyl ether 18 with MEM-chloride in the presence of base (e.g. DIEA) forms the MEM protected product 19 (J. Med. Chem. 1997, 40, 1707-1719). Treatment of diamine 19 with CDI affords the tetrahydropyrimidinone 20. Treatment of the nitrile 20 with DMSO and hydrogen peroxide (Synthesis 1989, 949-950) affords the carboxamide 21. Catalytic hydrogenolysis affords the phenol 22 (Green) which is then alkylated with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) to yield the dibenzyl phosphonate 23. Removal of the MEM group using trifluoroacetic acid affords the product 24 (Green).

The ortho {2-[6-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-4-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester. and para, {4-[6-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-4-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester are prepared using the same procedures reported in Scheme 3 except substituting 3-benzyloxybenzaldehyde with 2-benzyloxybenzaldehyde and 4-benzyloxybenzaldehyde respectively.

Example 4

Scheme 4 : Example, {3-[4-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester (33)

The amine 15 (Scheme 3) is transformed to the secondary amine 25 through reductive amination with 3-benzyloxybenzadehyde (US 6313110). Treatment of BOC-amine 25 with trifluoroacetic acid releases the primary amine 26 (Green) which is then subjected to a second reductive amination with 3-cyanobenzaldehyde to afford the bis-substituted amine 27 (US 6313110). Treatment of the benzyl ether 27 with MEM-chloride in the presence of base (e.g. DIEA) forms the MEM protected product 28 (J. Med. Chem. 1997, 40, 1707-1719). Treatment of diamine 28 with CDI affords the tetrahydropyrimidinone 29. Treatment of the nitrile 29 with DMSO and hydrogen peroxide (Synthesis 1989, 949-950) affords the carboxamide 30. Catalytic hydrogenolysis affords the phenol 31 (Green) which is then alkylated with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the

presence of base (e.g. cesium carbonate) to yield the dibenzyl phosphonate 32. Removal of the MEM group using trifluoroacetic acid affords the product 33 (Green).

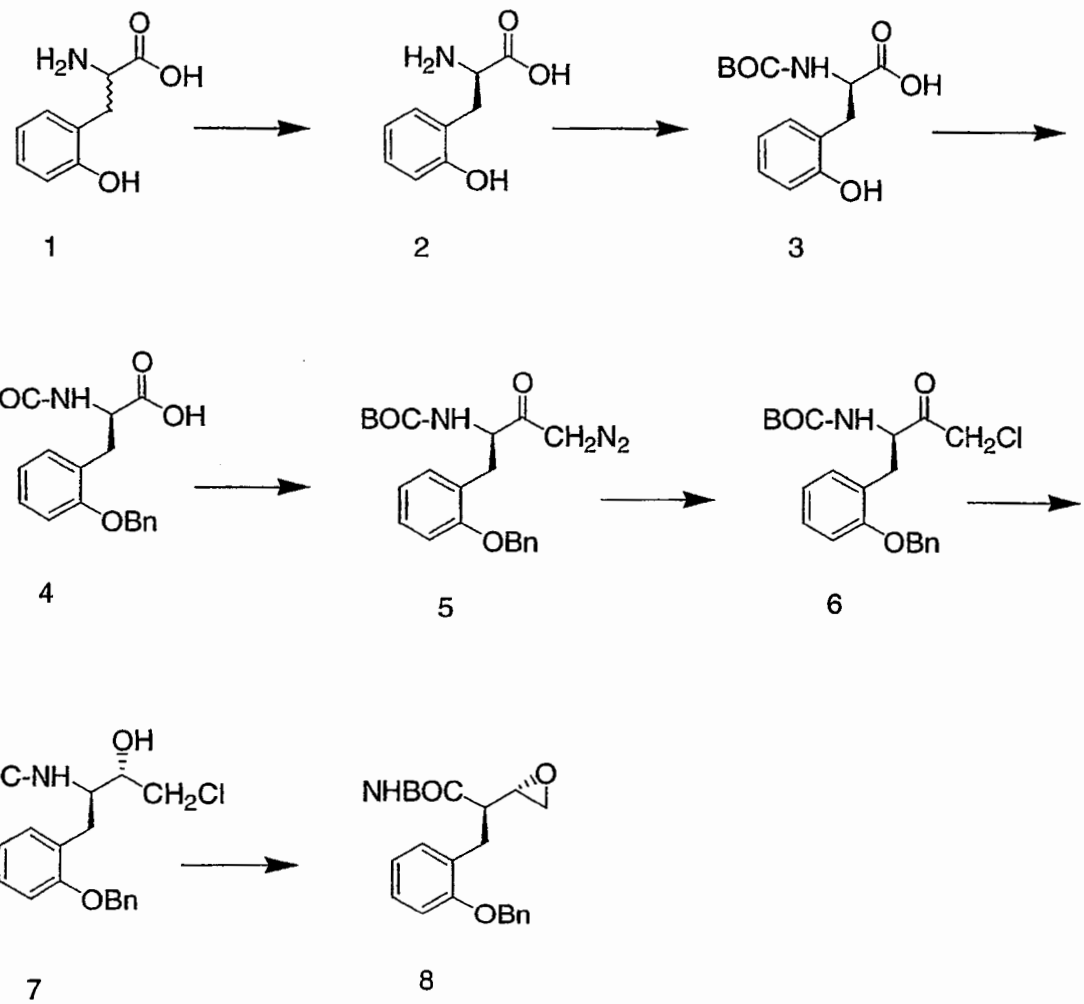
Example 5

Ortho analog, {2-[4-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester and para analog, {4-[4-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester are prepared using Scheme 4 except replacing 3-benzyloxybenzadehyde with 2- benzyloxybenzadehyde and 4-benzyloxybenzadehydes respectively.

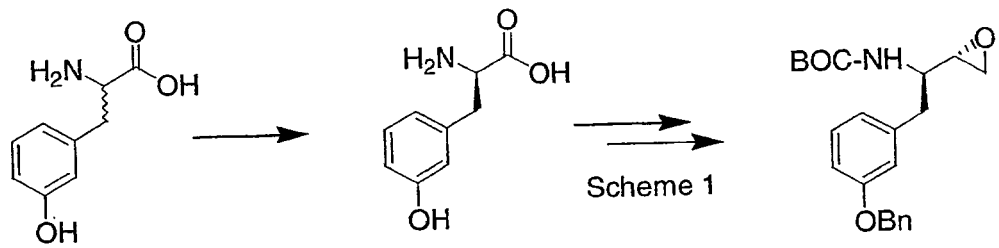
Scheme Section D

Schemes 1-6 are described in the examples.

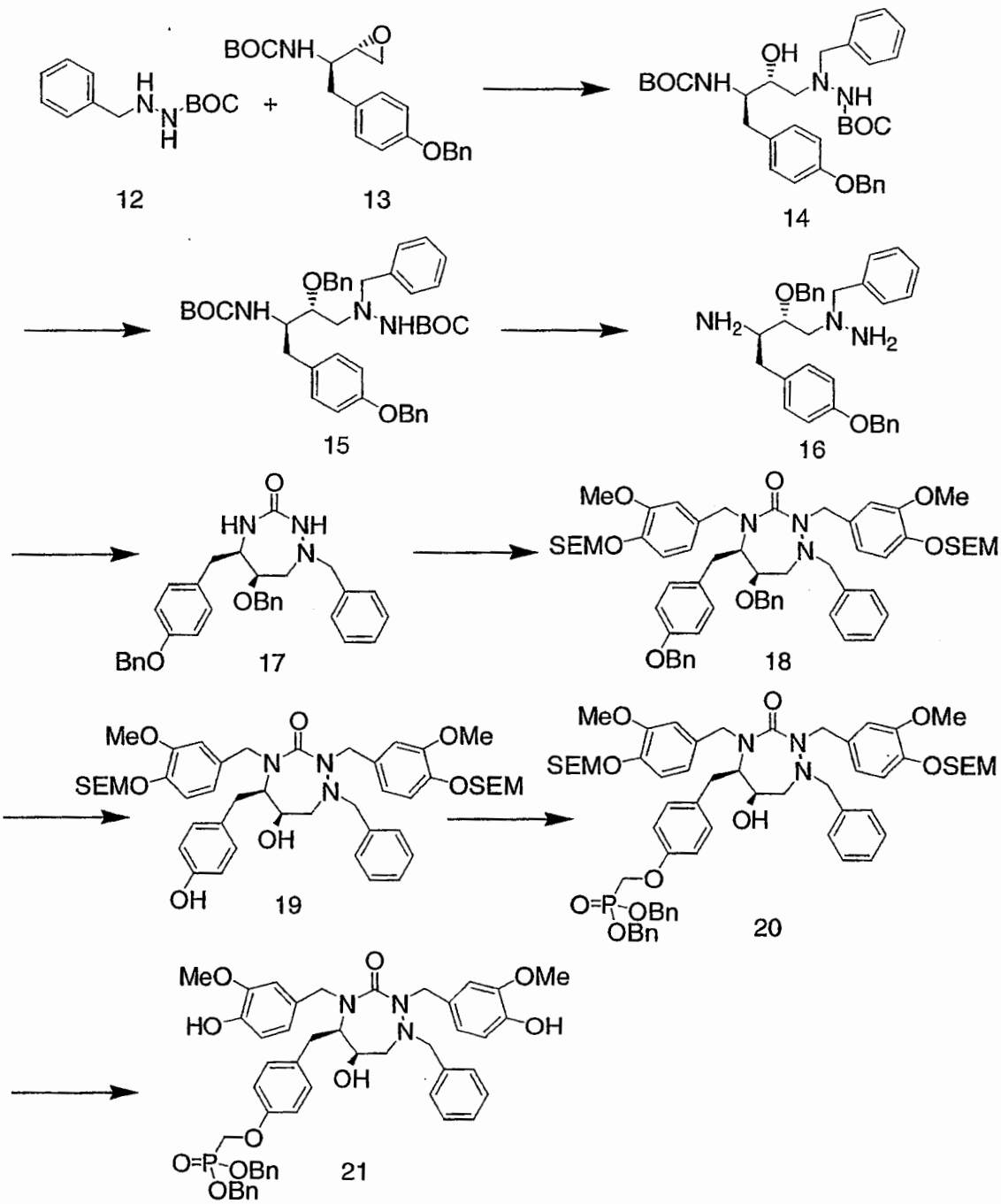
Scheme 1



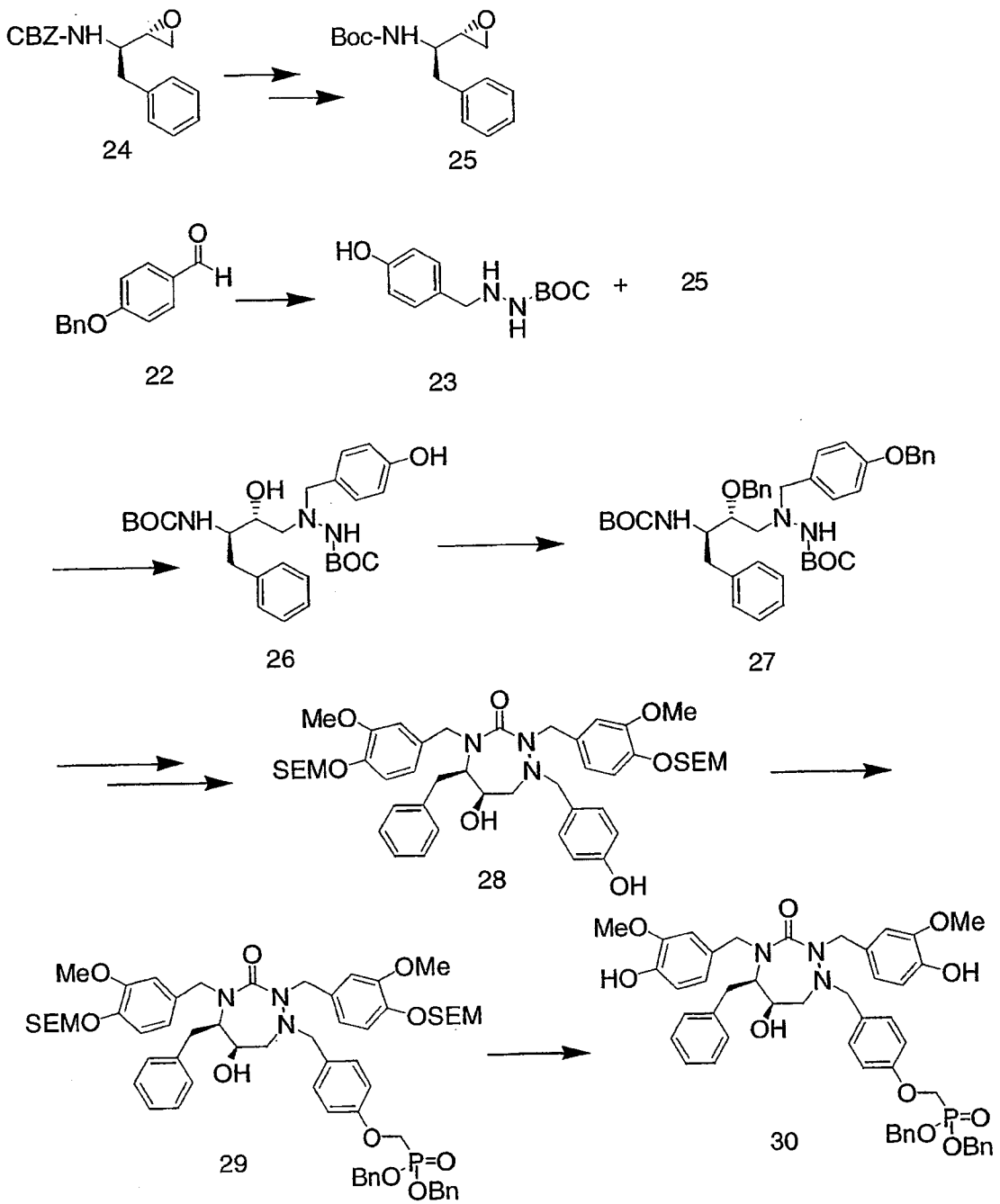
Scheme 2



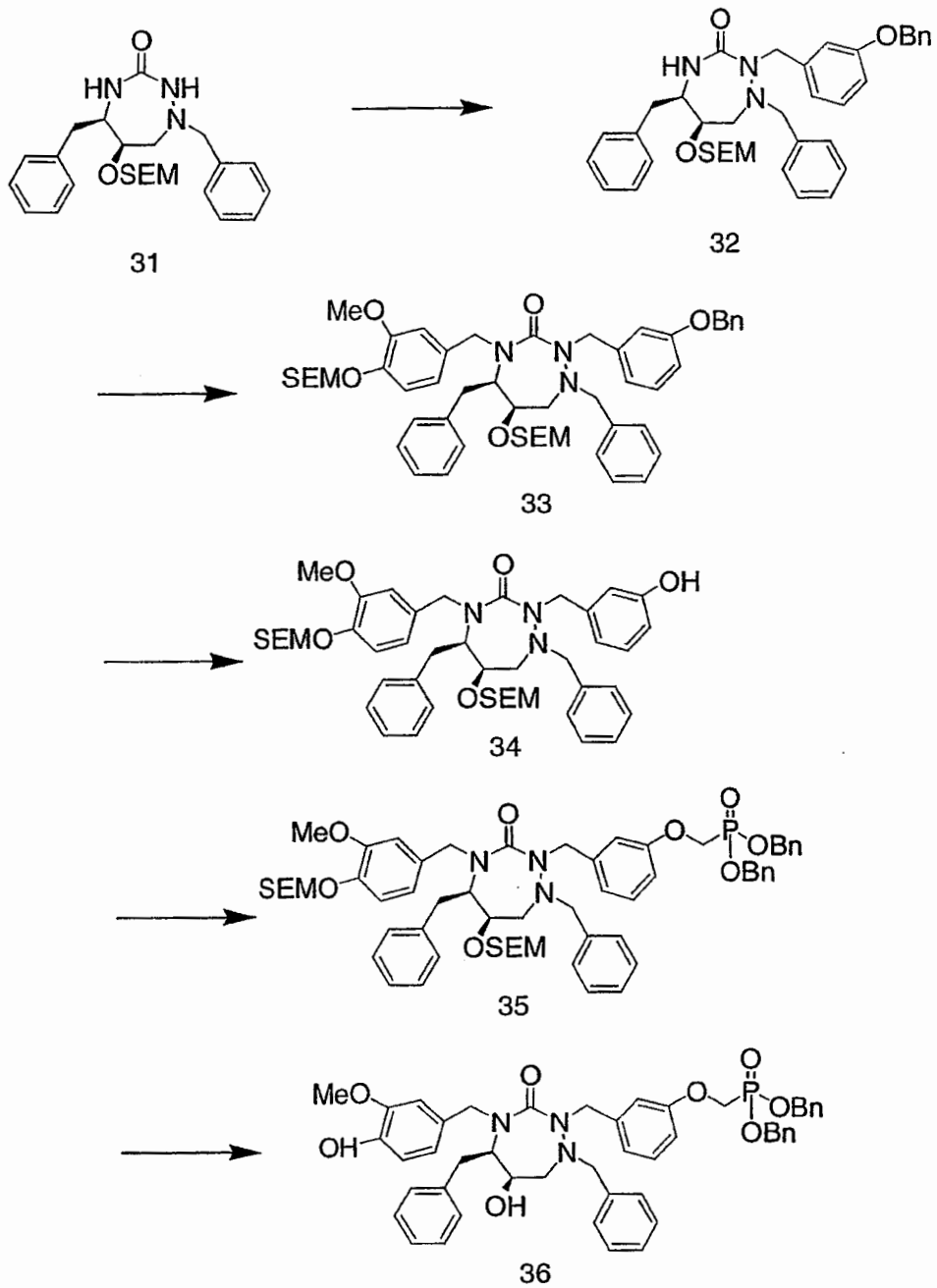
Scheme 3


BOCNH
OBn
12
13
14
15
16
17
18
19
20
21
MeO
SEMO
OMe
OSEM
HO
OH
BnO
O=P
OBn

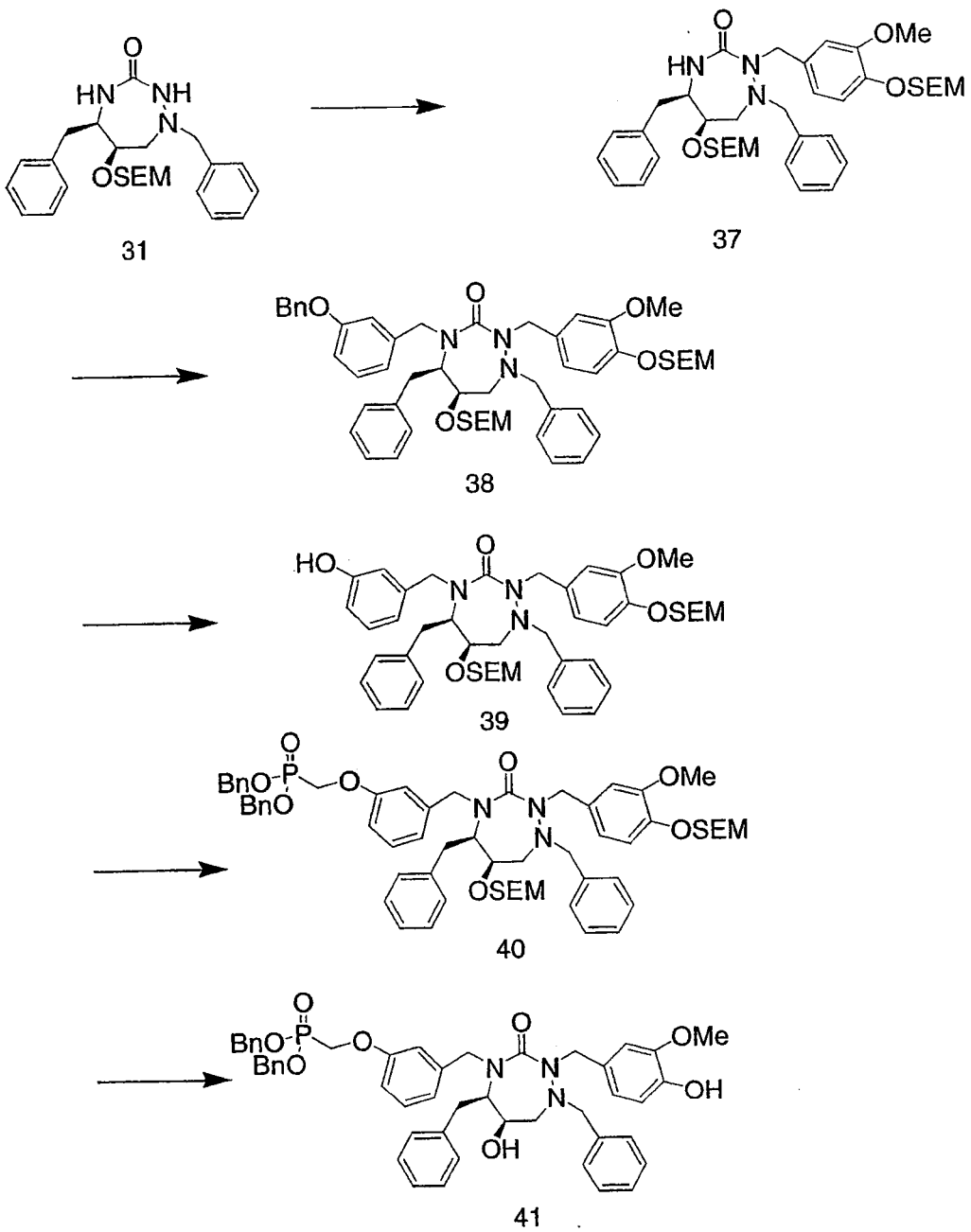
Scheme 4


CBZ-NH
Boc-NH
24
25
BnO
HO
BOC
+
25
22
23
BOCNH
OH
NH
BOC
OBn
26
27
MeO
SEMO
OMe
OSEM
28
29
30
BnO
OBn
P=O

Scheme 5



Scheme 6



Example Section D

Example 1

Scheme 1 : Example; [2-(2-Benzyloxy-phenyl)-1-oxiranyl-ethyl]-carbamic acid tert-butyl ester (8)

Commercially available DL-o-tyrosine **1** (Fluka) is treated with L-aminoacid oxidase and oxygen according to the procedure of Sun et al. (J. Med. Chem. 1998, 41, 1034-1041) to afford the D-o-tyrosine **2**. Reaction with di-t-butyl-dicarbonate in the presence of base affords the boc protected amino acid **3** (J. Med. Chem. 1998, 41, 1034-1041). The boc protected acid **3** is then treated with benzyl bromide in the presence of potassium carbonate to afford the benzyl ether **4** (J. Med. Chem. 1998, 41, 1034-1041). The four step sequence reported for the preparation of the corresponding epoxide of phenylalanine (see J. Med. Chem. 1994, 37, 1758-1768) is used to prepare the desired epoxides. Thus, the acid **4** is treated with isobutylchloroformate in the presence of N-methylmorpholine to afford the mixed anhydride which is then treated with diazomethane to afford the α-diazoketone **5** (see scheme 1). The ketone **5** is treated with HCl to form the α-chloroketone **6** which is then reduced with sodium borohydride to form the chloro alcohol **7**. The 2S, 3R diastereoisomer is separated by chromatography and treated with base (e.g. potassium hydroxide) to afford the epoxide **8**.

Commercially available DL-m-tyrosine **9** (Aldrich) is resolved by treatment with α-chymotrypsin to afford D-m-tyrosine **10** (Recl.: J. R. Neth. Chem. Soc. 1984, 103, 4, p110-111.) (Scheme 2). The tyrosine **10** is then treated in the same manner as the D-o-tyrosine (Scheme 1) to form the m-benzyloxy epoxide **11**.

The Boc-D-Tyr(Bzl)-OH acid is commerically available (Bachem) and is treated according to the four step procedure in Scheme 1 to generate the p-benzyloxy epoxide **13** shown in Scheme 3.

Example 2

Scheme 3 : Example, {4-[1-Benzyl-6-hydroxy-2,4-bis-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-5-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester

The boc protected benzylhydrazine 12 is prepared by condensation of boc-carbazate with benzaldehyde followed by catalytic hydrogenolysis (J. Chem. Soc. Perkin Trans. I 1975, 1712-1720). Treatment of the epoxide 13 with the boc protected benzylhydrazine 12 affords the alcohol 14 (J. Med. Chem. 1996, 39, 392-397). Benzylation of the secondary alcohol with benzylchloride in the presence of base (Green) affords the benzylether 15. Deprotection of the BOC groups with trifluoroacetic acid yields the diamine 16 (Green). CDI mediated cyclization affords the cyclic triazacycloheptanone 17 (J. Med. Chem. 1996, 39, 392-397). Alkyation of the nitrogens with [2-(4-chloromethyl-2-methoxy-phenoxymethoxy)-ethyl]-trimethyl-silane (prepared according to the reference J. Med. Chem. 1996, 39, 392-397) affords the bis-substituted triazacycloheptanone 18 (J. Med. Chem. 1996, 39, 392-397). Catalytic hydrogenolysis affords the unprotected phenol 19 (Green) which upon alkylation with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) yields the dibenzyl phosphonate 20. Removal of the silyl protecting groups using trimethylsilyl chloride or anhydrous HCl in methanol affords the dibenzyl phosphonate ester product 21 (J. Med. Chem. 1996, 39, 392-397).

The meta substituted analog {3-[1-Benzyl-6-hydroxy-2,4-bis-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-5-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester or the ortho analog, {2-[1-Benzyl-6-hydroxy-2,4-bis-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-5-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester, are prepared using the same methods except replacing the p-benzyloxyepoxide 13 with the meta- and ortho-substituted benzyloxy epoxides, 11 and 8, respectively.

Example 3

Scheme 4 : Example, {4-[5-Benzyl-6-hydroxy-2,4-bis-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-1-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester (30)

p-Benzyloxybenzaldehyde 22 is treated with boc-carbazate and then reduced by catalytic hydrogenolysis to afford the hydrazine 23 (J. Chem. Soc. Perkin Trans. I 1975, 1712-1720). The Boc epoxide 25 is prepared from the corresponding CBZ epoxide 24 by catalytic hydrogenolysis followed by treatment with BOC anhydride (Green). The CBZ- epoxide 24 is prepared according to the procedure of Sham et al. (J. Med. Chem. 1996, 39, 392-397).

Treatment of the epoxide 25 with the hydrazine 23 affords the alcohol 26. The alcohol 26 is treated with benzyl bromide in the presence of base (e.g. cesium carbonate) to afford the dibenzyl compound 27 (Green). The Boc groups are then removed using trifluoroacetic acid to yield diamine 28 (Green). Subjecting the diamine 28 to the same procedures shown in Scheme 1 then affords the dibenzyl phosphonate ester 29. Removal of the silyl protecting groups using trimethylsilyl chloride or anhydrous HCl in methanol affords the dibenzyl phosphonate ester product 30 (*J. Med. Chem.* 1996, 39, 392-397).

The corresponding meta- and ortho- analogs are prepared using the same procedures as in Scheme 4 except substituting p-benzyloxybenzaldehyde with m- or o-benzyloxybenzaldehyde respectively.

Example 4

Scheme 5: {3-[1,5-Dibenzyl-4-(4-hydroxy-3-methoxy-benzyl)-3-oxo-6-(2-trimethylsilanyl-ethoxymethoxy)-[1,2,4]triazepan-2-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester (36)

The SEM protected triazacycloheptanone 31 is prepared according to the reported procedure of Sham et al. (J. Med. Chem. 1996, 39, 392-397). Regioselective alkylation by treatment of the triazacycloheptanone with m-benzyloxybenzylchloride and sodium hydride in DMF affords 32 which is then alkylated a second time under similar conditions to afford the bis-substituted compound 33 (J. Med. Chem. 1996, 39, 392-397). Catalytic hydrogenolysis affords the phenol 34 (Green). Alkylation with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester using the standard conditions affords the dibenzyl ester 35. Removal of the silyl protecting groups using trimethylsilyl chloride or anhydrous HCl in methanol affords the dibenzyl phosphonate ester product 36 (J. Med. Chem. 1996, 39, 392-397).

Ortho analog {2-[1,5-Dibenzyl-4-(4-hydroxy-3-methoxy-benzyl)-3-oxo-6-(2-trimethylsilanyl-ethoxymethoxy)-[1,2,4]triazepan-2-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester and para analog {4-[1,5-Dibenzyl-4-(4-hydroxy-3-methoxy-benzyl)-3-oxo-6-(2-trimethylsilanyl-ethoxymethoxy)-[1,2,4]triazepan-2-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester are prepared using the same procedures except substituting o-benzyloxybenzylchloride and p-benzyloxybenzylchloride respectively, for the m-benzyloxybenzylchloride. O-benzyloxybenzylchloride is prepared from o-

benzyloxybenzaldehyde by reduction with sodium borohydride and then treatment with methanesulfonylchloride (J. Med. Chem. 1996, 39, 392-397).

Example 5

Scheme 6: {3-[1,5-Dibenzyl-6-hydroxy-2-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-4-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester (41)

The SEM protected triazacycloheptanone 31 is prepared according to the reported procedure of Sham et al. (J. Med. Chem. 1996, 39, 392-397). Regioselective alkylation by treatment of the triazacycloheptanone with SEM protected benzylchloride and sodium hydride in DMF affords 37 which is then alkylated with m-benzyloxybenzylchloride under similar conditions to afford the bis-substituted compound 38 (J. Med. Chem. 1996, 39, 392-397). Catalytic hydrogenolysis affords the phenol 39 (Green). Alkylation with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester using the standard conditions affords the dibenzyl ester 40. Removal of the silyl protecting groups using trimethylsilyl chloride or anhydrous HCl in methanol affords the dibenzyl phosphonate ester product 41 (J. Med. Chem. 1996, 39, 392-397).

Ortho analog, {2-[1,5-Dibenzyl-6-hydroxy-2-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-4-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester and para analog, {4-[1,5-Dibenzyl-6-hydroxy-2-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-4-ylmethyl]-phenoxymethyl}-phosphonic acid dibenzyl ester are prepared using the same procedures except substituting o-benzyloxybenzylchloride and p-benzyloxybenzylchloride respectively, for the m-benzyloxybenzylchloride.

Scheme General Section

General aspects of these exemplary methods are described below and in the Example. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

The terms "treated", "treating", "treatment", and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis is used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes above and in the examples (hereafter "exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example, size exclusion or ion exchange chromatography, high, medium, or low pressure liquid chromatography, small scale and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

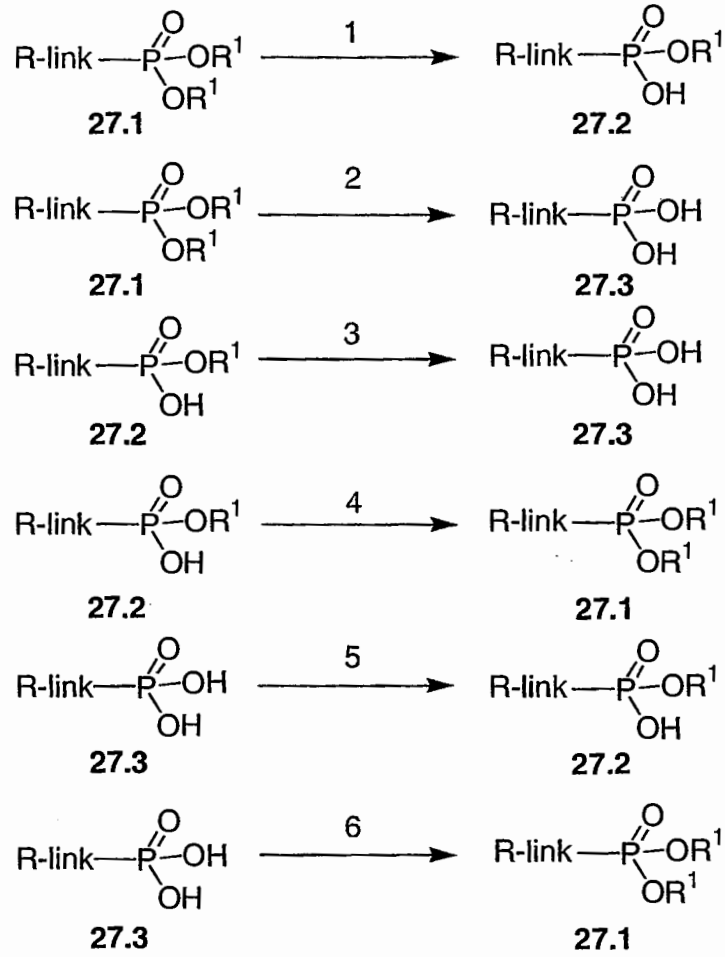
Another class of separation methods involves treatment of a mixture with a reagent

selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

All literature and patent citations above are hereby expressly incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following Embodiments. It is apparent that certain modifications of the methods and compositions of the following Embodiments can be made within the scope and spirit of the invention.

Scheme 1001



Scheme 1001 shows the interconversions of certain phosphonate compounds: acids - $P(O)(OH)_2$; mono-esters $-P(O)(OR_1)(OH)$; and diesters $-P(O)(OR_1)_2$ in which the R^1 groups are independently selected, and defined herein before, and the phosphorus is attached through a carbon moiety (link, i.e. linker), which is attached to the rest of the molecule, e.g. drug or drug intermediate (R). The R^1 groups attached to the phosphonate esters in Scheme 1001 may be changed using established chemical transformations. The interconversions may be carried out in the precursor compounds or the final products using the methods described below. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **27.1** into the corresponding phosphonate monoester **27.2** (Scheme 1001, Reaction 1) can be accomplished by a number of methods.

For example, the ester **27.1** in which R^1 is an arylalkyl group such as benzyl, can be converted into the monoester compound **27.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in *J. Org. Chem.*, 1995, 60:2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester **27.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **27.2** can be effected by treatment of the ester **27.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **27.2** in which one of the groups R^1 is arylalkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **27.2** in which R^1 is alkyl, by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, can be converted into the monoester **27.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in *J. Org. Chem.*, 38:3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **27.1** or a phosphonate monoester **27.2** into the corresponding phosphonic acid **27.3** (Scheme 1001, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in *J. Chem. Soc., Chem. Comm.*, 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **27.2** in which R^1 is arylalkyl such as benzyl, can be converted into the corresponding phosphonic acid **27.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxane. A phosphonate monoester **27.2** in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **27.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68:618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **27.1** in which R^1 is benzyl is described in *J. Org. Chem.*, 24:434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **27.1** in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, 78:2336, 1956.

The conversion of a phosphonate monoester **27.2** into a phosphonate diester **27.1** (Scheme 1001, Reaction 4) in which the newly introduced R^1 group is alkyl, arylalkyl, or

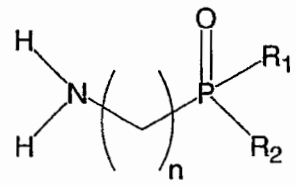
haloalkyl such as chloroethyl, can be effected by a number of reactions in which the substrate **27.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **27.1** to the diester **27.1** can be effected by the use of the Mitsunobu reaction. The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **27.2** can be transformed into the phosphonate diester **27.1**, in which the introduced R^1 group is alkenyl or arylalkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or arylalkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **27.2** is transformed into the chloro analog $-P(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $-P(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **27.1**.

A phosphonic acid $-P(O)(OH)_2$ can be transformed into a phosphonate monoester $-P(O)(OR^1)(OH)$ (Scheme 1001, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $-P(O)(OR^1)_2$ **27.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid $-P(O)(OH)_2$ **27.3** can be transformed into a phosphonate diester $-P(O)(OR^1)_2$ **27.1** (Scheme 1, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **27.3** can be transformed into phosphonic esters **27.1** in which

R^1 is aryl, such as phenyl, by means of a coupling reaction employing, for example, phenol and dicyclohexylcarbodiimide in pyridine at about 70°C. Alternatively, phosphonic acids **27.3** can be transformed into phosphonic esters **27.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, in the presence of a base such as cesium carbonate, to afford the phosphonic ester **27.1**.

Amino alkyl phosphonate compounds 809:



809

are a generic representative of compounds 811, 813, 814, 816 and 818. Some methods to prepare embodiments of 809 are shown in Scheme 1002. Commercial amino phosphonic acid 810 was protected as carbamate 811. The phosphonic acid 811 was converted to phosphonate 812 upon treatment with ROH in the presence of DCC or other conventional coupling reagents. Coupling of phosphonic acid 811 with esters of amino acid 820 provided bisamidate 817. Conversion of acid 811 to bisphenyl phosphonate followed by hydrolysis gave mono-phosphonic acid 814 (Cbz = $C_6H_5CH_2C(O)$–), which was then transformed to mono-phosphonic amidate 815. Carbamates 813, 816 and 818 were converted to their corresponding amines upon hydrogenation. Compounds 811, 813, 814, 816 and 818 are useful intermediates to form the phosphonate compounds of the invention.

Preparation of carboalkoxy-substituted phosphonate bisamidates, monoamidates, diesters and monoesters.

A number of methods are available for the conversion of phosphonic acids into amidates and esters. In one group of methods, the phosphonic acid is either converted into an isolated activated intermediate such as a phosphoryl chloride, or the phosphonic acid is activated in situ for reaction with an amine or a hydroxy compound.

The conversion of phosphonic acids into phosphoryl chlorides is accomplished by reaction with thionyl chloride, for example as described in J. Gen. Chem. USSR, 1983, 53, 480, Zh. Obschei Khim., 1958, 28, 1063, or J. Org. Chem., 1994, 59, 6144, or by reaction with oxalyl chloride, as described in J. Am. Chem. Soc., 1994, 116, 3251, or J. Org. Chem., 1994, 59, 6144, or by reaction with phosphorus pentachloride, as described in J. Org. Chem., 2001, 66, 329, or in J. Med. Chem., 1995, 38, 1372. The resultant phosphoryl chlorides are then reacted with amines or hydroxy compounds in the presence of a base to afford the amidate or ester products.

Phosphonic acids are converted into activated imidazolyl derivatives by reaction with carbonyl diimidazole, as described in J. Chem. Soc., Chem. Comm., 1991, 312, or Nucleosides Nucleotides 2000, 19, 1885. Activated sulfonyloxy derivatives are obtained by the reaction of phosphonic acids with trichloromethylsulfonyl chloride, as described in J. Med. Chem. 1995, 38, 4958, or with triisopropylbenzenesulfonyl chloride, as described in Tet. Lett., 1996, 7857, or Bioorg. Med. Chem. Lett., 1998, 8, 663. The activated sulfonyloxy derivatives are then reacted with amines or hydroxy compounds to afford amidates or esters. Alternatively, the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a diimide coupling agent. The preparation of phosphonic amidates and esters by means of coupling reactions in the presence of dicyclohexyl carbodiimide is described, for example, in J. Chem. Soc., Chem. Comm., 1991, 312, or J. Med. Chem., 1980, 23, 1299 or Coll. Czech. Chem. Comm., 1987, 52, 2792. The use of ethyl dimethylaminopropyl carbodiimide for activation and coupling of phosphonic acids is described in Tet. Lett., 2001, 42, 8841, or Nucleosides Nucleotides, 2000, 19, 1885.

A number of additional coupling reagents have been described for the preparation of amidates and esters from phosphonic acids. The agents include Aldrithiol-2, and PYBOP and BOP, as described in J. Org. Chem., 1995, 60, 5214, and J. Med. Chem., 1997, 40, 3842, mesitylene-2-sulfonyl-3-nitro-1,2,4-triazole (MSNT), as described in J. Med. Chem., 1996, 39, 4958, diphenylphosphoryl azide, as described in J. Org. Chem., 1984, 49, 1158, 1-(2,4,6-triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole (TPSNT) as described in Bioorg. Med. Chem. Lett., 1998, 8, 1013, bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP), as described in Tet. Lett., 1996, 37, 3997, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-

dioxaphosphinane, as described in Nucleosides Nucleotides 1995, 14, 871, and diphenyl chlorophosphate, as described in J. Med. Chem., 1988, 31, 1305.

Phosphonic acids are converted into amidates and esters by means of the Mitsonobu reaction, in which the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The procedure is described in Org. Lett., 2001, 3, 643, or J. Med. Chem., 1997, 40, 3842.

Phosphonic esters are also obtained by the reaction between phosphonic acids and halo compounds, in the presence of a suitable base. The method is described, for example, in Anal. Chem., 1987, 59, 1056, or J. Chem. Soc. Perkin Trans., I, 1993, 19, 2303, or J. Med. Chem., 1995, 38, 1372, or Tet. Lett., 2002, 43, 1161.

Schemes **1** - **4** illustrate the conversion of phosphonate esters and phosphonic acids into carboalkoxy-substituted phosphorobisamidates (Scheme **1**), phosphoroamidates (Scheme **2**), phosphonate monoesters (Scheme **3**) and phosphonate diesters, (Scheme **4**).

Scheme **1** illustrates various methods for the conversion of phosphonate diesters **1.1** into phosphorobisamidates **1.5**. The diester **1.1**, prepared as described previously, is hydrolyzed, either to the monoester **1.2** or to the phosphonic acid **1.6**. The methods employed for these transformations are described above. The monoester **1.2** is converted into the monoamidate **1.3** by reaction with an aminoester **1.9**, in which the group R^2 is H or alkyl, the group R^4 is an alkylene moiety such as, for example, $CHCH_3$, $CHPr^I$, $CH(CH_2Ph)$, $CH_2CH(CH_3)$ and the like, or a group present in natural or modified aminoacids, and the group R^5 is alkyl. The reactants are combined in the presence of a coupling agent such as a carbodiimide, for example dicyclohexyl carbodiimide, as described in J. Am. Chem. Soc., 1957, 79, 3575, optionally in the presence of an activating agent such as hydroxybenztriazole, to yield the amidate product **1.3**. The amidate-forming reaction is also effected in the presence of coupling agents such as BOP, as described in J. Org. Chem., 1995, 60, 5214, Aldrithiol, PYBOP and similar coupling agents used for the preparation of amides and esters. Alternatively, the reactants **1.2** and **1.9** are transformed into the monoamidate **1.3** by means of a Mitsonobu reaction. The preparation of amidates by means of the Mitsonobu reaction is described in J. Med. Chem., 1995, 38, 2742. Equimolar amounts of the reactants are

combined in an inert solvent such as tetrahydrofuran in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The thus-obtained monoamidate ester **1.3** is then transformed into amidate phosphonic acid **1.4**. The conditions used for the hydrolysis reaction depend on the nature of the R^1 group, as described previously. The phosphonic acid amidate **1.4** is then reacted with an aminoester **1.9**, as described above, to yield the bisamidate product **1.5**, in which the amino substituents are the same or different.

An example of this procedure is shown in Scheme **1**, Example **1**. In this procedure, a dibenzyl phosphonate **1.14** is reacted with diazabicyclooctane (DABCO) in toluene at reflux, as described in J. Org. Chem., 1995, 60, 2946, to afford the monobenzyl phosphonate **1.15**. The product is then reacted with equimolar amounts of ethyl alaninate **1.16** and dicyclohexyl carbodiimide in pyridine, to yield the amidate product **1.17**. The benzyl group is then removed, for example by hydrogenolysis over a palladium catalyst, to give the monoacid product **1.18**. This compound is then reacted in a Mitsonobu reaction with ethyl leucinate **1.19**, triphenyl phosphine and diethylazodicarboxylate, as described in J. Med. Chem., 1995, 38, 2742, to produce the bisamidate product **1.20**.

Using the above procedures, but employing, in place of ethyl leucinate **1.19** or ethyl alaninate **1.16**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

Alternatively, the phosphonic acid **1.6** is converted into the bisamidate **1.5** by use of the coupling reactions described above. The reaction is performed in one step, in which case the nitrogen-related substituents present in the product **1.5** are the same, or in two steps, in which case the nitrogen-related substituents can be different.

An example of the method is shown in Scheme **1**, Example **2**. In this procedure, a phosphonic acid **1.6** is reacted in pyridine solution with excess ethyl phenylalaninate **1.21** and dicyclohexylcarbodiimide, for example as described in J. Chem. Soc., Chem. Comm., 1991, 1063, to give the bisamidate product **1.22**.

Using the above procedures, but employing, in place of ethyl phenylalaninate, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

As a further alternative, the phosphonic acid **1.6** is converted into the mono or bis-activated derivative **1.7**, in which Lv is a leaving group such as chloro, imidazolyl, triisopropylbenzenesulfonyloxy etc. The conversion of phosphonic acids into chlorides **1.7** (Lv = Cl) is effected by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17. The conversion of phosphonic acids into monoimidazolides **1.7** (Lv = imidazolyl) is described in J. Med. Chem., 2002, 45, 1284 and in J. Chem. Soc. Chem. Comm., 1991, 312. Alternatively, the phosphonic acid is activated by reaction with triisopropylbenzenesulfonyl chloride, as described in Nucleosides and Nucleotides, 2000, 10, 1885. The activated product is then reacted with the aminoester **1.9**, in the presence of a base, to give the bisamidate **1.5**. The reaction is performed in one step, in which case the nitrogen substituents present in the product **1.5** are the same, or in two steps, via the intermediate **1.11**, in which case the nitrogen substituents can be different.

Examples of these methods are shown in Scheme **1**, Examples **3** and **5**. In the procedure illustrated in Scheme **1**, Example **3**, a phosphonic acid **1.6** is reacted with ten molar equivalents of thionyl chloride, as described in Zh. Obschei Khim., 1958, 28, 1063, to give the dichloro compound **1.23**. The product is then reacted at reflux temperature in a polar aprotic solvent such as acetonitrile, and in the presence of a base such as triethylamine, with butyl serinate **1.24** to afford the bisamidate product **1.25**.

Using the above procedures, but employing, in place of butyl serinate **1.24**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

In the procedure illustrated in Scheme **1**, Example **5**, the phosphonic acid **1.6** is reacted, as described in J. Chem. Soc. Chem. Comm., 1991, 312, with carbonyl diimidazole to give the imidazolide **1.32**. The product is then reacted in acetonitrile solution at ambient temperature, with one molar equivalent of ethyl alaninate **1.33** to yield the monodisplacement product **1.34**. The latter compound is then reacted with carbonyl diimidazole to produce the activated intermediate **1.35**, and the product is then reacted, under the same conditions, with ethyl N-methylalaninate **1.33a** to give the bisamidate product **1.36**.

Using the above procedures, but employing, in place of ethyl alaninate **1.33** or ethyl N-methylalaninate **1.33a**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

The intermediate monoamidate **1.3** is also prepared from the monoester **1.2** by first converting the monoester into the activated derivative **1.8** in which Lv is a leaving group such as halo, imidazolyl etc, using the procedures described above. The product **1.8** is then reacted with an aminoester **1.9** in the presence of a base such as pyridine, to give an intermediate monoamidate product **1.3**. The latter compound is then converted, by removal of the R^1 group and coupling of the product with the aminoester **1.9**, as described above, into the bisamidate **1.5**.

An example of this procedure, in which the phosphonic acid is activated by conversion to the chloro derivative **1.26**, is shown in Scheme **1**, Example **4**. In this procedure, the phosphonic monobenzyl ester **1.15** is reacted, in dichloromethane, with thionyl chloride, as described in Tet. Let., 1994, 35, 4097, to afford the phosphoryl chloride **1.26**. The product is then reacted in acetonitrile solution at ambient temperature with one molar equivalent of ethyl 3-amino-2-methylpropionate **1.27** to yield the monoamidate product **1.28**. The latter compound is hydrogenated in ethyl acetate over a 5% palladium on carbon catalyst to produce the monoacid product **1.29**. The product is subjected to a Mitsonobu coupling procedure, with equimolar amounts of butyl alaninate **1.30**, triphenyl phosphine, diethylazodicarboxylate and triethylamine in tetrahydrofuran, to give the bisamidate product **1.31**.

Using the above procedures, but employing, in place of ethyl 3-amino-2-methylpropionate **1.27** or butyl alaninate **1.30**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

The activated phosphonic acid derivative **1.7** is also converted into the bisamidate **1.5** via the diamino compound **1.10**. The conversion of activated phosphonic acid derivatives such as phosphoryl chlorides into the corresponding amino analogs **1.10**, by reaction with ammonia, is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976. The diamino compound **1.10** is then reacted at elevated temperature with a haloester

1.12, in a polar organic solvent such as dimethylformamide, in the presence of a base such as dimethylaminopyridine or potassium carbonate, to yield the bisamidate **1.5**.
An example of this procedure is shown in Scheme **1**, Example **6**. In this method, a dichlorophosphonate **1.23** is reacted with ammonia to afford the diamide **1.37**. The reaction is performed in aqueous, aqueous alcoholic or alcoholic solution, at reflux temperature. The resulting diamino compound is then reacted with two molar equivalents of ethyl 2-bromo-3-methylbutyrate **1.38**, in a polar organic solvent such as N-methylpyrrolidinone at ca. 150°C, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the bisamidate product **1.39**.

Using the above procedures, but employing, in place of ethyl 2-bromo-3-methylbutyrate **1.38**, different haloesters **1.12** the corresponding products **1.5** are obtained.

The procedures shown in Scheme **1** are also applicable to the preparation of bisamidates in which the aminoester moiety incorporates different functional groups. Scheme **1**, Example **7** illustrates the preparation of bisamidates derived from tyrosine. In this procedure, the monoimidazolide **1.32** is reacted with propyl tyrosinate **1.40**, as described in Example **5**, to yield the monoamidate **1.41**. The product is reacted with carbonyl diimidazole to give the imidazolide **1.42**, and this material is reacted with a further molar equivalent of propyl tyrosinate to produce the bisamidate product **1.43**.

Using the above procedures, but employing, in place of propyl tyrosinate **1.40**, different aminoesters **1.9**, the corresponding products **1.5** are obtained. The aminoesters employed in the two stages of the above procedure can be the same or different, so that bisamidates with the same or different amino substituents are prepared.

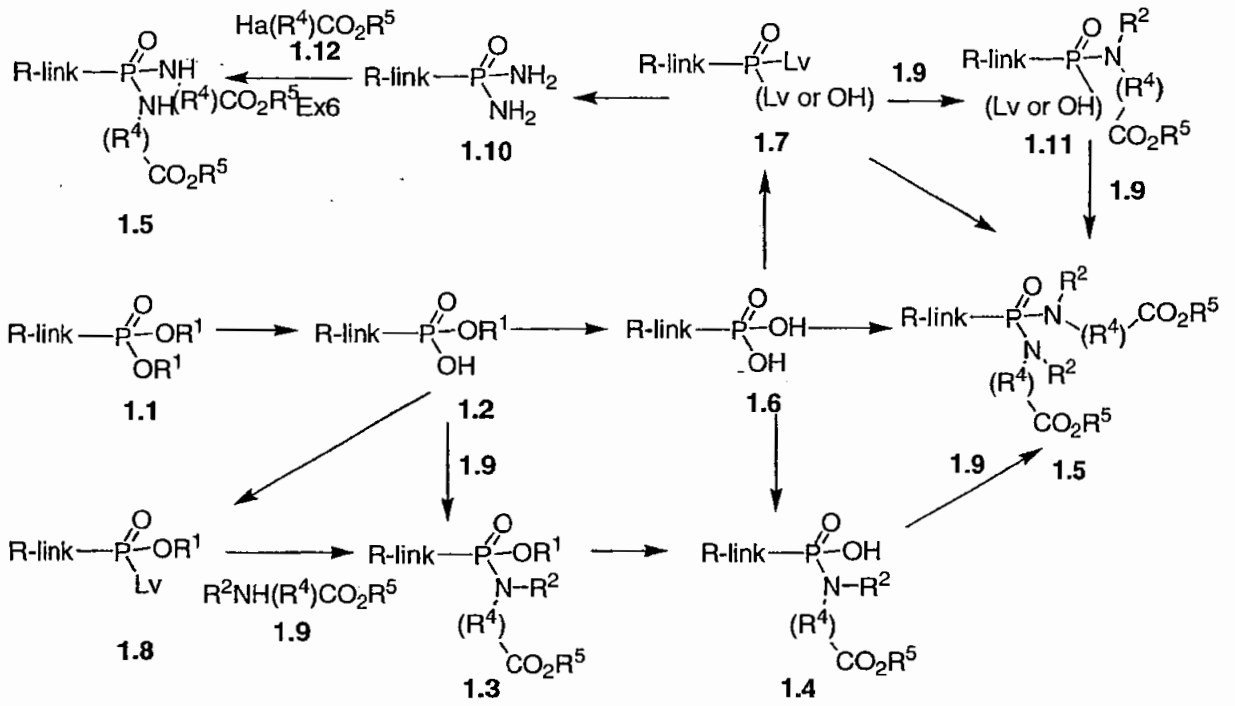
Scheme **2** illustrates methods for the preparation of phosphonate monoamidates.
In one procedure, a phosphonate monoester **1.1** is converted, as described in Scheme **1**, into the activated derivative **1.8**. This compound is then reacted, as described above, with an aminoester **1.9**, in the presence of a base, to afford the monoamidate product **2.1**.
The procedure is illustrated in Scheme **2**, Example **1**. In this method, a monophenyl phosphonate **2.7** is reacted with, for example, thionyl chloride, as described in J. Gen. Chem.

USSR., 1983, 32, 367, to give the chloro product **2.8**. The product is then reacted, as described in Scheme **1**, with ethyl alaninate **2.9**, to yield the amidate **2.10**.

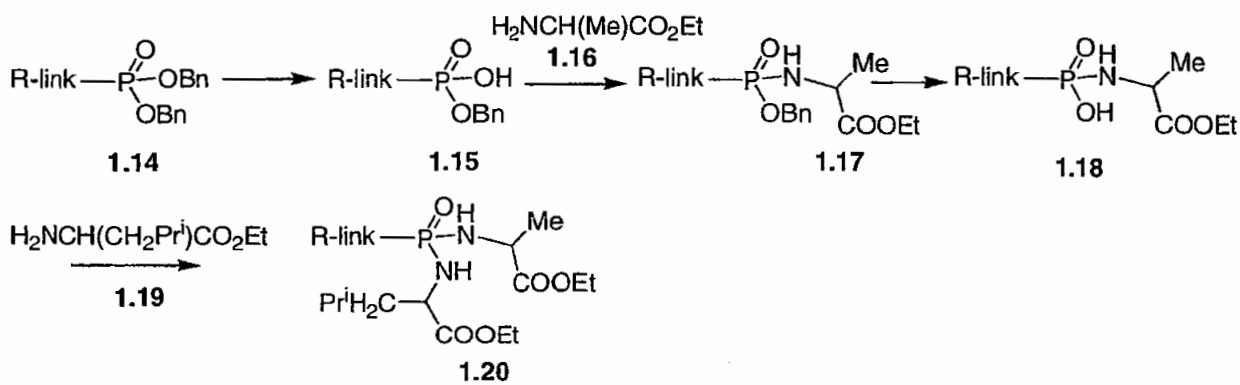
Using the above procedures, but employing, in place of ethyl alaninate **2.9**, different aminoesters **1.9**, the corresponding products **2.1** are obtained.

Alternatively, the phosphonate monoester **1.1** is coupled, as described in Scheme **1**, with an aminoester **1.9** to produce the amidate **2.1**. If necessary, the R^1 substituent is then altered, by initial cleavage to afford the phosphonic acid **2.2**. The procedures for this transformation depend on the nature of the R^1 group, and are described above. The phosphonic acid is then transformed into the ester amidate product **2.3**, by reaction with the hydroxy compound R^3OH, in which the group R^3 is aryl, heteroaryl, alkyl, cycloalkyl, haloalkyl etc, using the same coupling procedures (carbodiimide, Aldrithiol-2, PYBOP, Mitsonobu reaction etc) described in Scheme **1** for the coupling of amines and phosphonic acids.

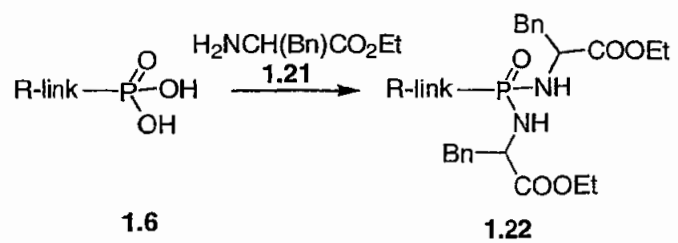
Scheme 1



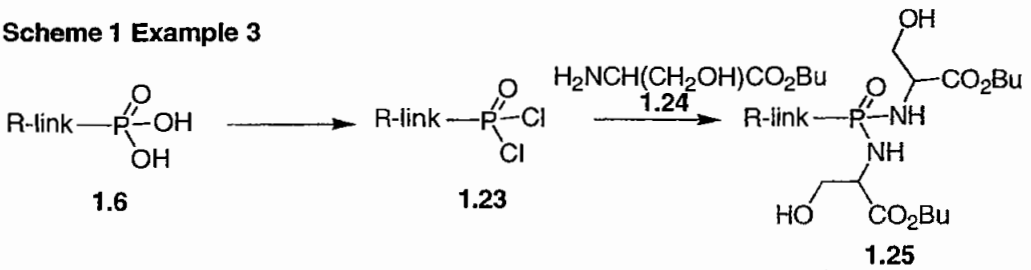
Scheme 1 Example 1



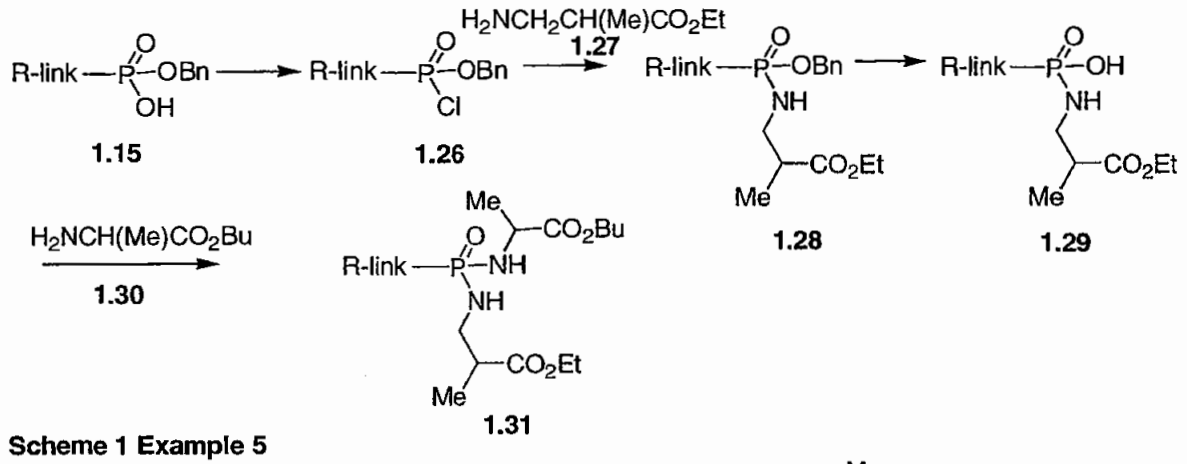
Scheme 1 Example 2



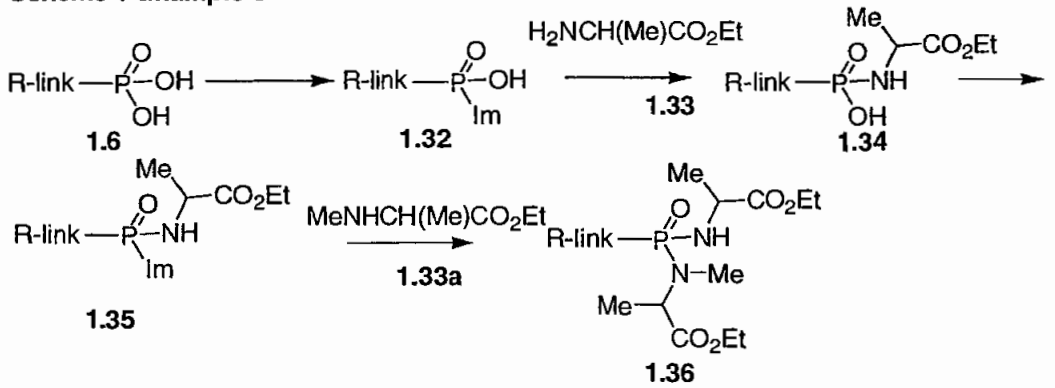
Scheme 1 Example 3



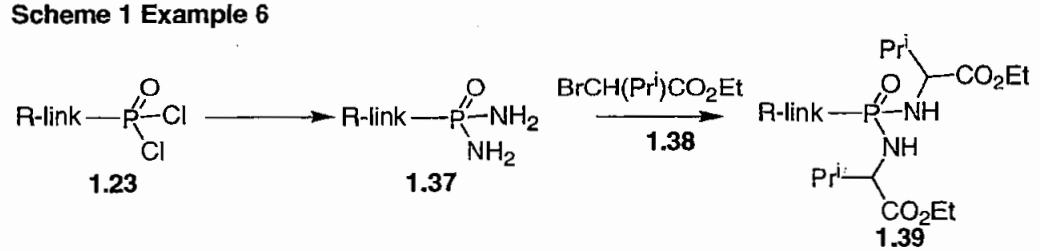
Scheme 1 Example 4



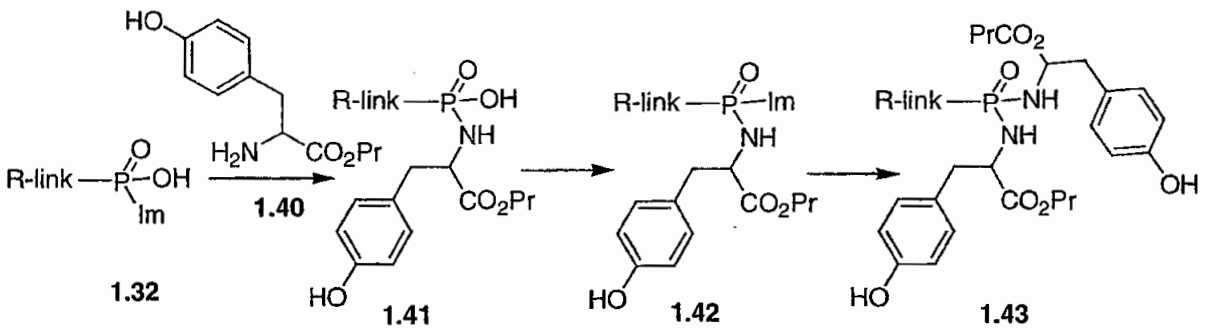
Scheme 1 Example 5



Scheme 1 Example 6



Scheme 1 Example 7



Examples of this method are shown in Scheme **2**, Examples and **2** and **3**. In the sequence shown in Example **2**, a monobenzyl phosphonate **2.11** is transformed by reaction with ethyl alaninate, using one of the methods described above, into the monoamidate **2.12**. The benzyl group is then removed by catalytic hydrogenation in ethyl acetate solution over a 5% palladium on carbon catalyst, to afford the phosphonic acid amidate **2.13**. The product is then reacted in dichloromethane solution at ambient temperature with equimolar amounts of 1-(dimethylaminopropyl)-3-ethylcarbodiimide and trifluoroethanol **2.14**, for example as described in Tet. Lett., 2001, 42, 8841, to yield the amidate ester **2.15**.

In the sequence shown in Scheme **2**, Example **3**, the monoamidate **2.13** is coupled, in tetrahydrofuran solution at ambient temperature, with equimolar amounts of dicyclohexyl carbodiimide and 4-hydroxy-N-methylpiperidine **2.16**, to produce the amidate ester product **2.17**.

Using the above procedures, but employing, in place of the ethyl alaninate product **2.12** different monoacids **2.2**, and in place of trifluoroethanol **2.14** or 4-hydroxy-N-methylpiperidine **2.16**, different hydroxy compounds R^3OH, the corresponding products **2.3** are obtained.

Alternatively, the activated phosphonate ester **1.8** is reacted with ammonia to yield the amidate **2.4**. The product is then reacted, as described in Scheme **1**, with a haloester **2.5**, in the presence of a base, to produce the amidate product **2.6**. If appropriate, the nature of the R^1 group is changed, using the procedures described above, to give the product **2.3**. The method is illustrated in Scheme **2**, Example **4**. In this sequence, the monophenyl phosphoryl

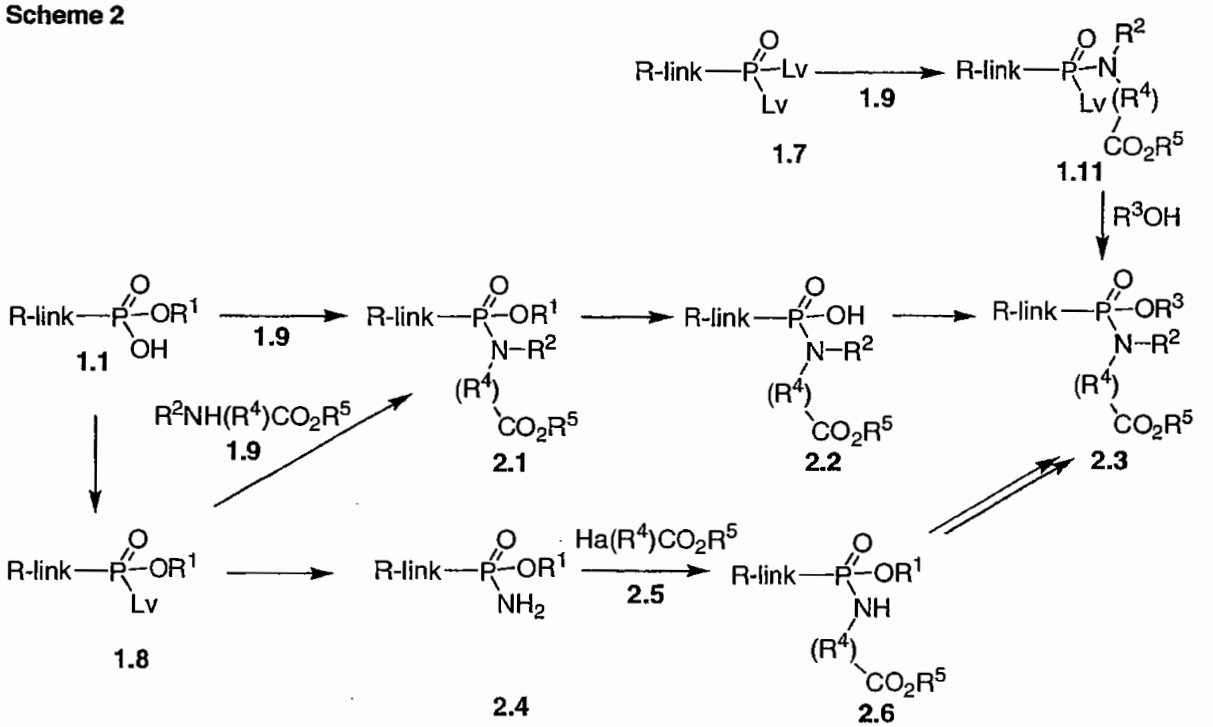
chloride **2.18** is reacted, as described in Scheme **1**, with ammonia, to yield the amino product **2.19**. This material is then reacted in N-methylpyrrolidinone solution at 170°C with butyl 2-bromo-3-phenylpropionate **2.20** and potassium carbonate, to afford the amidate product **2.21**. Using these procedures, but employing, in place of butyl 2-bromo-3-phenylpropionate **2.20**, different haloesters **2.5**, the corresponding products **2.6** are obtained.

The monoamidate products **2.3** are also prepared from the doubly activated phosphonate derivatives **1.7**. In this procedure, examples of which are described in Synlett., 1998, 1, 73, the intermediate **1.7** is reacted with a limited amount of the aminoester **1.9** to give the mono-displacement product **1.11**. The latter compound is then reacted with the hydroxy compound R^3OH in a polar organic solvent such as dimethylformamide, in the presence of a base such as diisopropylethylamine, to yield the monoamidate ester **2.3**.

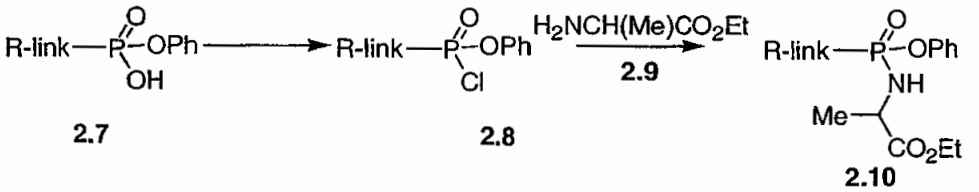
The method is illustrated in Scheme **2**, Example **5**. In this method, the phosphoryl dichloride **2.22** is reacted in dichloromethane solution with one molar equivalent of ethyl N-methyl tyrosinate **2.23** and dimethylaminopyridine, to generate the monoamidate **2.24**. The product is then reacted with phenol **2.25** in dimethylformamide containing potassium carbonate, to yield the ester amidate product **2.26**.

Using these procedures, but employing, in place of ethyl N-methyl tyrosinate **2.23** or phenol **2.25**, the aminoesters **1.9** and/or the hydroxy compounds R^3OH, the corresponding products **2.3** are obtained.

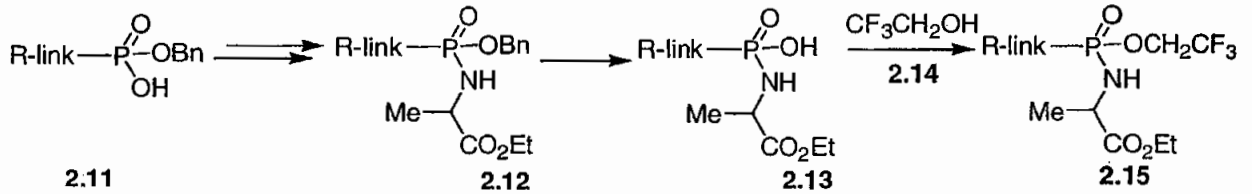
Scheme 2



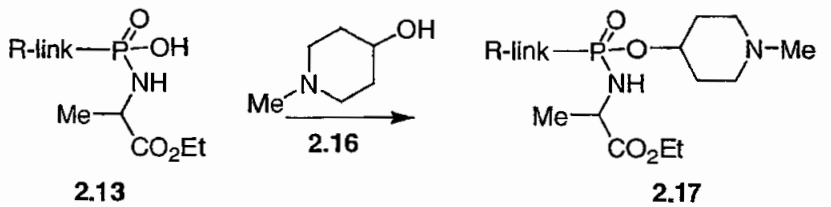
Scheme 2 Example 1



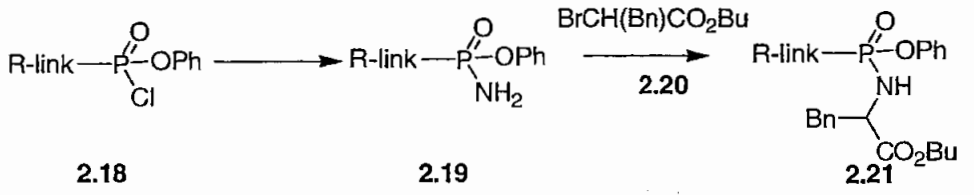
Scheme 2 Example 2



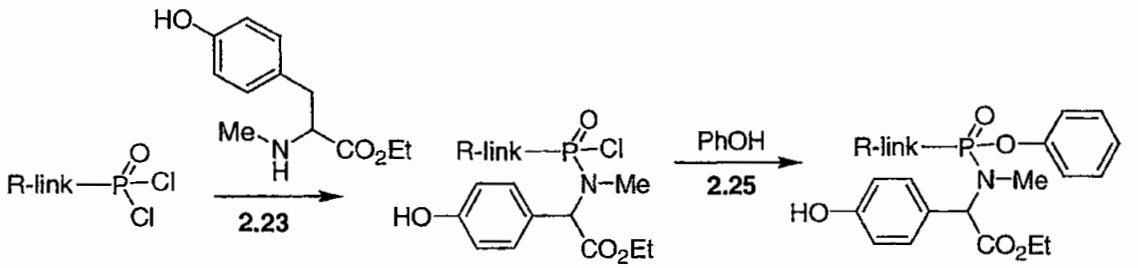
Scheme 2 Example 3



Scheme 2 Example 4



Scheme 2 Example 5



Scheme 3 illustrates methods for the preparation of carboalkoxy-substituted phosphonate diesters in which one of the ester groups incorporates a carboalkoxy substituent.

In one procedure, a phosphonate monoester **1.1**, prepared as described above, is coupled, using one of the methods described above, with a hydroxyester **3.1**, in which the groups R^4 and R^5 are as described in Scheme **1**. For example, equimolar amounts of the reactants are coupled in the presence of a carbodiimide such as dicyclohexyl carbodiimide, as described in Aust. J. Chem., 1963, 609, optionally in the presence of dimethylaminopyridine, as described in Tet., 1999, 55, 12997. The reaction is conducted in an inert solvent at ambient temperature.

The procedure is illustrated in Scheme **3**, Example **1**. In this method, a monophenyl phosphonate **3.9** is coupled, in dichloromethane solution in the presence of dicyclohexyl carbodiimide, with ethyl 3-hydroxy-2-methylpropionate **3.10** to yield the phosphonate mixed diester **3.11**.

Using this procedure, but employing, in place of ethyl 3-hydroxy-2-methylpropionate **3.10**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

The conversion of a phosphonate monoester **1.1** into a mixed diester **3.2** is also accomplished by means of a Mitsonobu coupling reaction with the hydroxyester **3.1**, as described in Org. Lett., 2001, 643. In this method, the reactants **1.1** and **3.1** are combined in a polar solvent such as tetrahydrofuran, in the presence of a triarylphosphine and a dialkyl azodicarboxylate, to give the mixed diester **3.2**. The R^1 substituent is varied by cleavage, using the methods described previously, to afford the monoacid product **3.3**. The product is then coupled, for example using methods described above, with the hydroxy compound R^3OH, to give the diester product **3.4**.

The procedure is illustrated in Scheme **3**, Example **2**. In this method, a monoallyl phosphonate **3.12** is coupled in tetrahydrofuran solution, in the presence of triphenylphosphine and diethylazodicarboxylate, with ethyl lactate **3.13** to give the mixed diester **3.14**. The product is reacted with tris(triphenylphosphine) rhodium chloride (Wilkinson catalyst) in acetonitrile, as described previously, to remove the allyl group and produce the monoacid product **3.15**. The latter compound is then coupled, in pyridine solution at ambient temperature, in the presence of dicyclohexyl carbodiimide, with one molar equivalent of 3-hydroxypyridine **3.16** to yield the mixed diester **3.17**.

Using the above procedures, but employing, in place of the ethyl lactate **3.13** or 3-hydroxypyridine, a different hydroxyester **3.1** and/or a different hydroxy compound R^3OH, the corresponding products **3.4** are obtained.

The mixed diesters **3.2** are also obtained from the monoesters **1.1** via the intermediacy of the activated monoesters **3.5**. In this procedure, the monoester **1.1** is converted into the activated compound **3.5** by reaction with, for example, phosphorus pentachloride, as described in J. Org. Chem., 2001, 66, 329, or with thionyl chloride or oxalyl chloride (Lv = Cl), or with triisopropylbenzenesulfonyl chloride in pyridine, as described in Nucleosides and Nucleotides, 2000, 19, 1885, or with carbonyl diimidazole, as described in J. Med. Chem., 2002, 45, 1284. The resultant activated monoester is then reacted with the hydroxyester **3.1**, as described above, to yield the mixed diester **3.2**.

The procedure is illustrated in Scheme **3**, Example **3**. In this sequence, a monophenyl phosphonate **3.9** is reacted, in acetonitrile solution at 70°C, with ten equivalents of thionyl

chloride, so as to produce the phosphoryl chloride **3.19**. The product is then reacted with ethyl 4-carbamoyl-2-hydroxybutyrate **3.20** in dichloromethane containing triethylamine, to give the mixed diester **3.21**.

Using the above procedures, but employing, in place of ethyl 4-carbamoyl-2-hydroxybutyrate **3.20**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

The mixed phosphonate diesters are also obtained by an alternative route for incorporation of the R^3O group into intermediates **3.3** in which the hydroxyester moiety is already incorporated. In this procedure, the monoacid intermediate **3.3** is converted into the activated derivative **3.6** in which Lv is a leaving group such as chloro, imidazole, and the like, as previously described. The activated intermediate is then reacted with the hydroxy compound R^3OH, in the presence of a base, to yield the mixed diester product **3.4**.

The method is illustrated in Scheme **3**, Example **4**. In this sequence, the phosphonate monoacid **3.22** is reacted with trichloromethanesulfonyl chloride in tetrahydrofuran containing collidine, as described in J. Med. Chem., 1995, 38, 4648, to produce the trichloromethanesulfonyloxy product **3.23**. This compound is reacted with 3-(morpholinomethyl)phenol **3.24** in dichloromethane containing triethylamine, to yield the mixed diester product **3.25**.

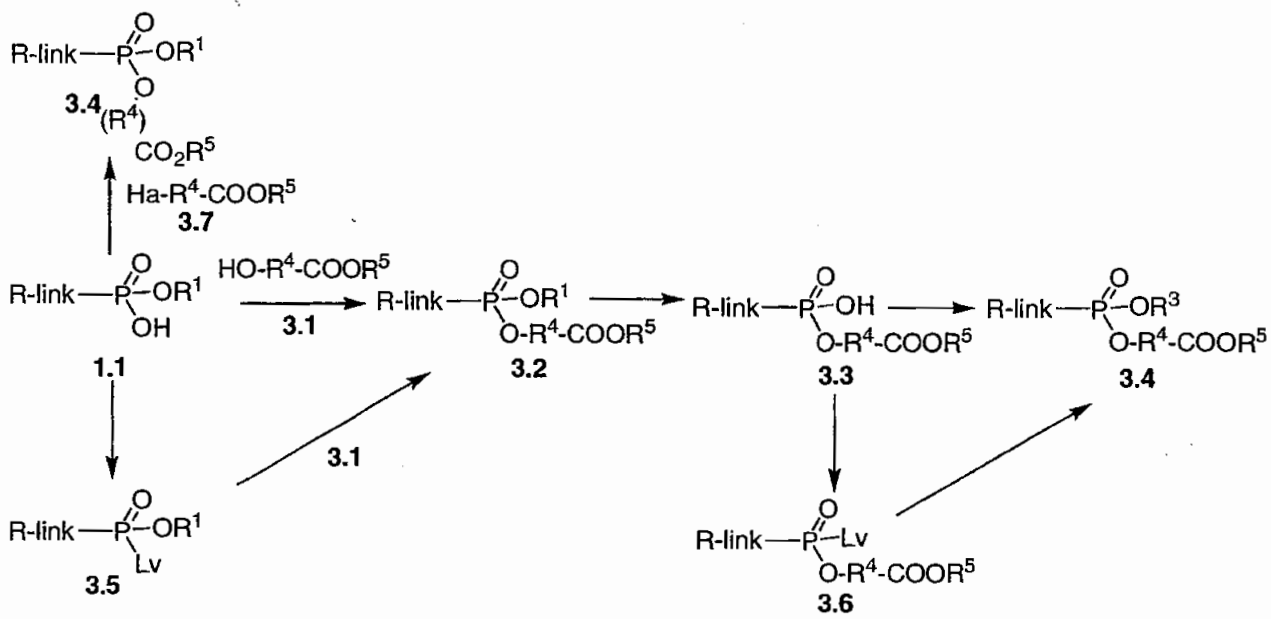
Using the above procedures, but employing, in place of with 3-(morpholinomethyl)phenol **3.24**, different carbinols R^3OH, the corresponding products **3.4** are obtained.

The phosphonate esters **3.4** are also obtained by means of alkylation reactions performed on the monoesters **1.1**. The reaction between the monoacid **1.1** and the haloester **3.7** is performed in a polar solvent in the presence of a base such as diisopropylethylamine, as described in Anal. Chem., 1987, 59, 1056, or triethylamine, as described in J. Med. Chem., 1995, 38, 1372, or in a non-polar solvent such as benzene, in the presence of 18-crown-6, as described in Syn. Comm., 1995, 25, 3565.

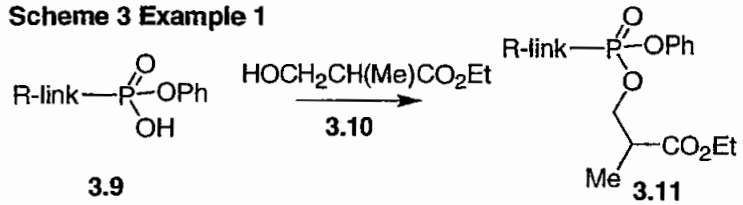
The method is illustrated in Scheme **3**, Example **5**. In this procedure, the monoacid **3.26** is reacted with ethyl 2-bromo-3-phenylpropionate **3.27** and diisopropylethylamine in dimethylformamide at 80°C to afford the mixed diester product **3.28**.

Using the above procedure, but employing, in place of ethyl 2-bromo-3-phenylpropionate **3.27**, different haloesters **3.7**, the corresponding products **3.4** are obtained.

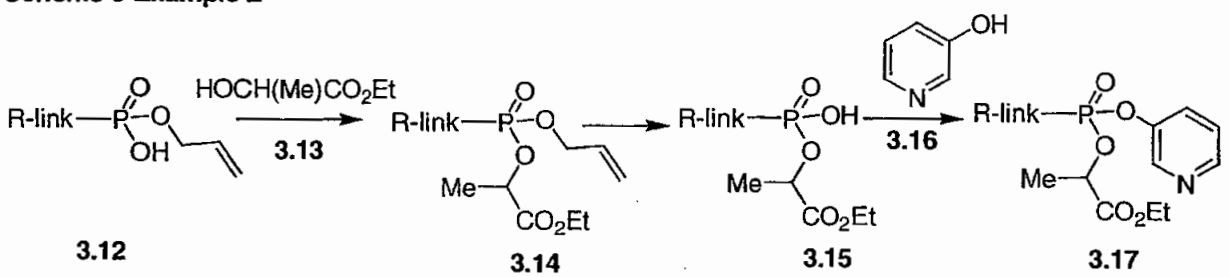
Scheme 3



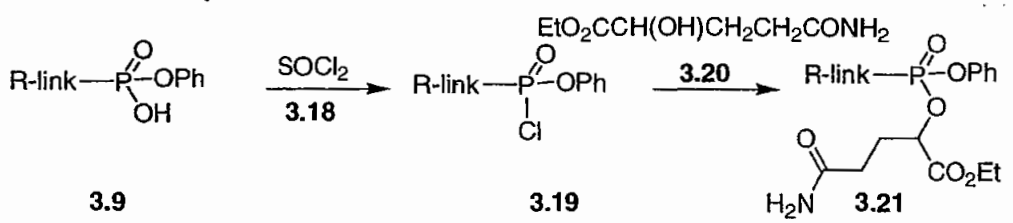
Scheme 3 Example 1



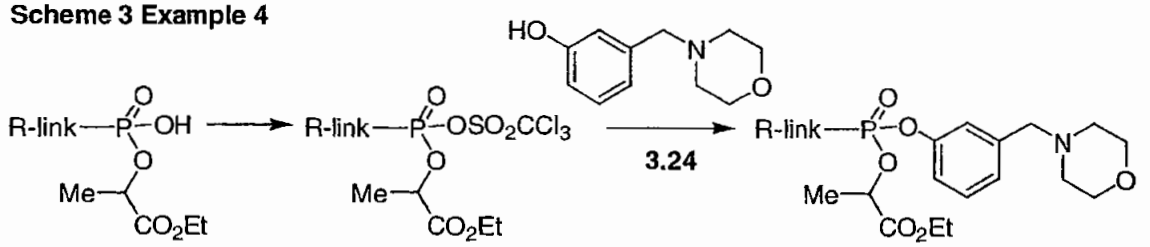
Scheme 3 Example 2



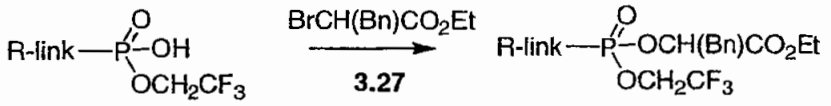
Scheme 3 Example 3



Scheme 3 Example 4



Scheme 3 Example 5



Scheme 4 illustrates methods for the preparation of phosphonate diesters in which both the ester substituents incorporate carboalkoxy groups.

The compounds are prepared directly or indirectly from the phosphonic acids **1.6**. In one alternative, the phosphonic acid is coupled with the hydroxyester **4.2**, using the conditions described previously in Schemes **1** - **3**, such as coupling reactions using dicyclohexyl carbodiimide or similar reagents, or under the conditions of the Mitsonobu reaction, to afford the diester product **4.3** in which the ester substituents are identical.

This method is illustrated in Scheme **4**, Example **1**. In this procedure, the phosphonic acid **1.6** is reacted with three molar equivalents of butyl lactate **4.5** in the presence of Aldrithiol-2 and triphenyl phosphine in pyridine at ca. 70°C, to afford the diester **4.6**.
Using the above procedure, but employing, in place of butyl lactate **4.5**, different hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

Alternatively, the diesters **4.3** are obtained by alkylation of the phosphonic acid **1.6** with a haloester **4.1**. The alkylation reaction is performed as described in Scheme **3** for the preparation of the esters **3.4**.

This method is illustrated in Scheme **4**, Example **2**. In this procedure, the phosphonic acid **1.6** is reacted with excess ethyl 3-bromo-2-methylpropionate **4.7** and diisopropylethylamine in dimethylformamide at ca. 80°C, as described in Anal. Chem., 1987, 59, 1056, to produce the diester **4.8**.

Using the above procedure, but employing, in place of ethyl 3-bromo-2-methylpropionate **4.7**, different haloesters **4.1**, the corresponding products **4.3** are obtained.

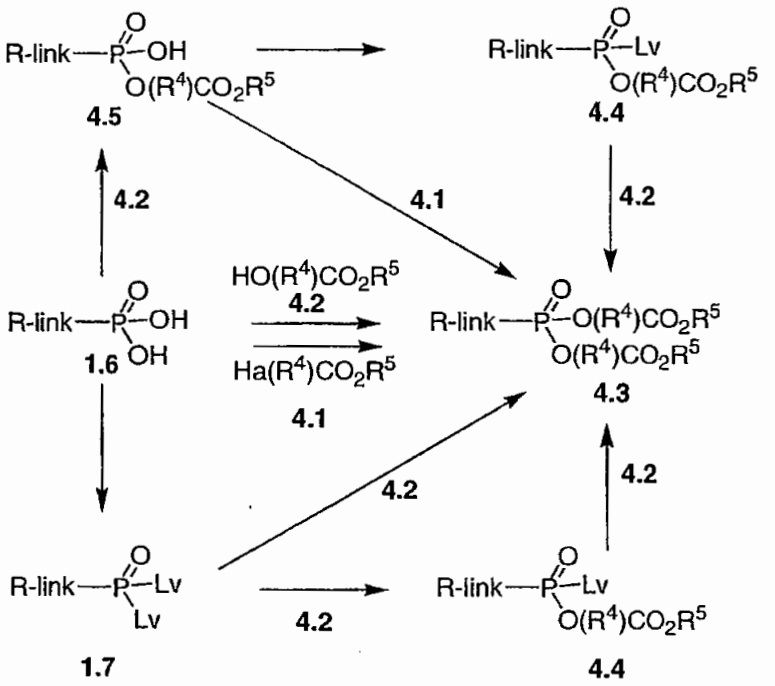
The diesters **4.3** are also obtained by displacement reactions of activated derivatives **1.7** of the phosphonic acid with the hydroxyesters **4.2**. The displacement reaction is performed in a polar solvent in the presence of a suitable base, as described in Scheme **3**. The displacement reaction is performed in the presence of an excess of the hydroxyester, to afford the diester product **4.3** in which the ester substituents are identical, or sequentially with limited amounts of different hydroxyesters, to prepare diesters **4.3** in which the ester substituents are different. The methods are illustrated in Scheme **4**, Examples **3** and **4**. As shown in Example **3**, the phosphoryl dichloride **2.22** is reacted with three molar equivalents of ethyl 3-hydroxy-2-(hydroxymethyl)propionate **4.9** in tetrahydrofuran containing potassium carbonate, to obtain the diester product **4.10**.

Using the above procedure, but employing, in place of ethyl 3-hydroxy-2-(hydroxymethyl)propionate **4.9**, different hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

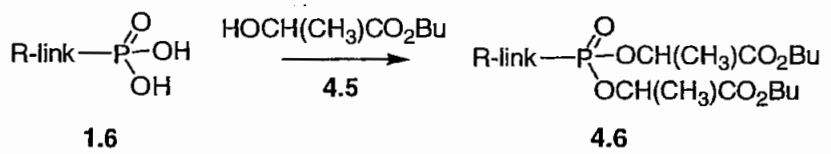
Scheme **4**, Example **4** depicts the displacement reaction between equimolar amounts of the phosphoryl dichloride **2.22** and ethyl 2-methyl-3-hydroxypropionate **4.11**, to yield the monoester product **4.12**. The reaction is conducted in acetonitrile at 70°C in the presence of diisopropylethylamine. The product **4.12** is then reacted, under the same conditions, with one molar equivalent of ethyl lactate **4.13**, to give the diester product **4.14**.

Using the above procedures, but employing, in place of ethyl 2-methyl-3-hydroxypropionate **4.11** and ethyl lactate **4.13**, sequential reactions with different hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

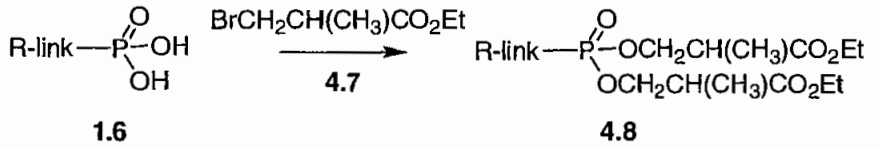
Scheme 4



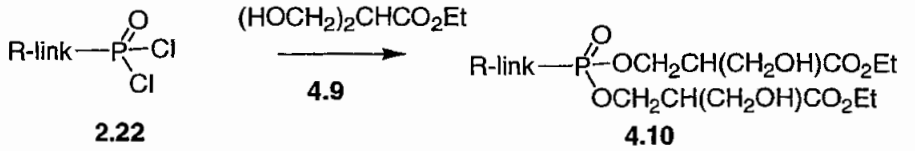
Scheme 4 Example 1



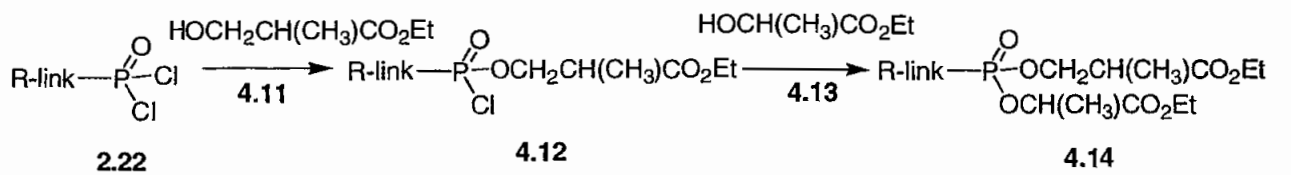
Scheme 4 Example 2



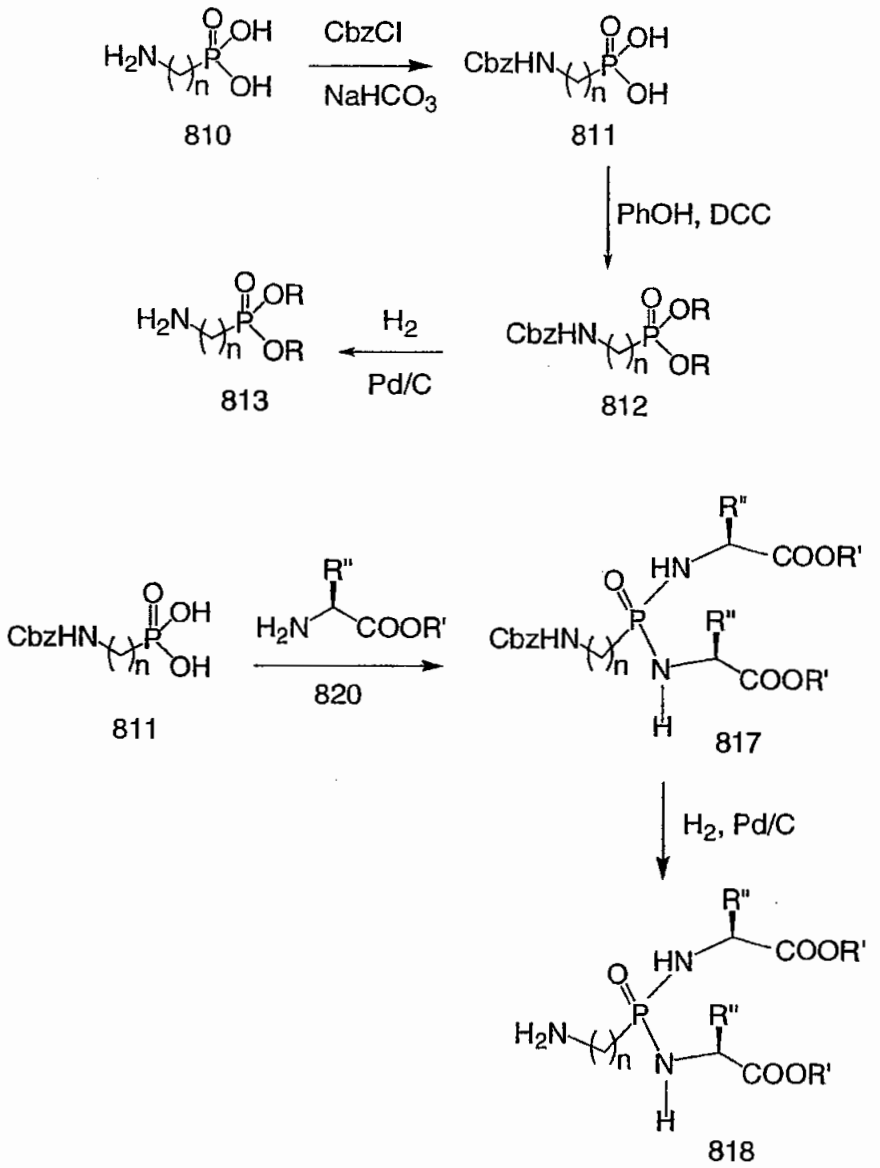
Scheme 4 Example 3

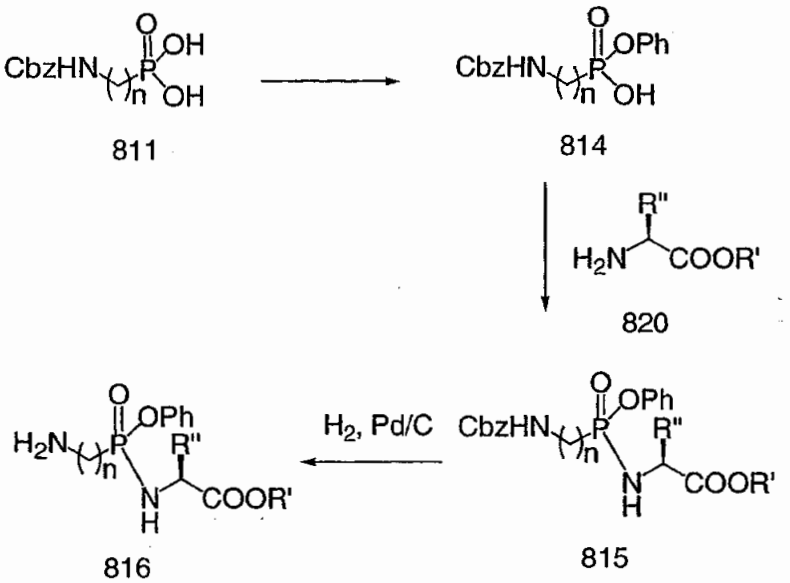


Scheme 4 Example 4



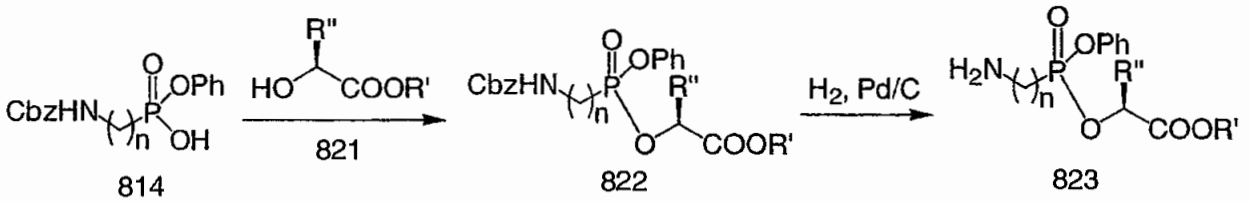
Scheme 1002



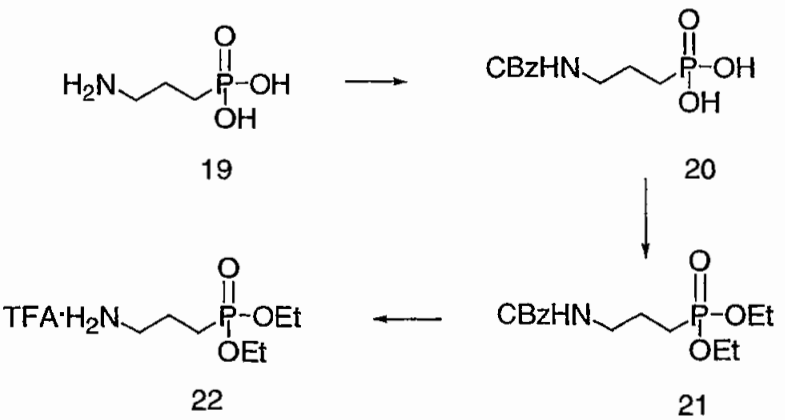


Following the similar procedures, replacement of amino acid esters 820 with lactates 821 (Scheme 1003) provides mono-phosphonic lactates 823. Lactates 823 are useful intermediates to form the phosphonate compounds of the invention.

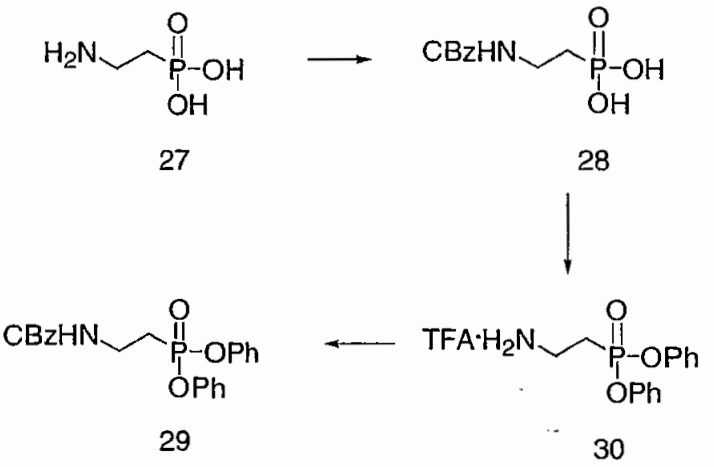
Scheme 1003



Scheme 1004



Scheme 1005



Example 1

To a solution of 2-aminoethylphosphonic acid (1.26 g, 10.1 mmol) in 2N NaOH (10.1 mL, 20.2 mmol) was added benzyl chloroformate (1.7 mL, 12.1 mmol). After the reaction mixture was stirred for 2 d at room temperature, the mixture was partitioned between Et_2O and water. The aqueous phase was acidified with 6N HCl until pH = 2. The resulting colorless solid was dissolved in MeOH (75 mL) and treated with Dowex 50WX8-200 (7 g). After the mixture was stirred for 30 minutes, it was filtered and evaporated under reduced pressure to give carbamate **28** (2.37 g, 91%) as a colorless solid (Scheme 1005).

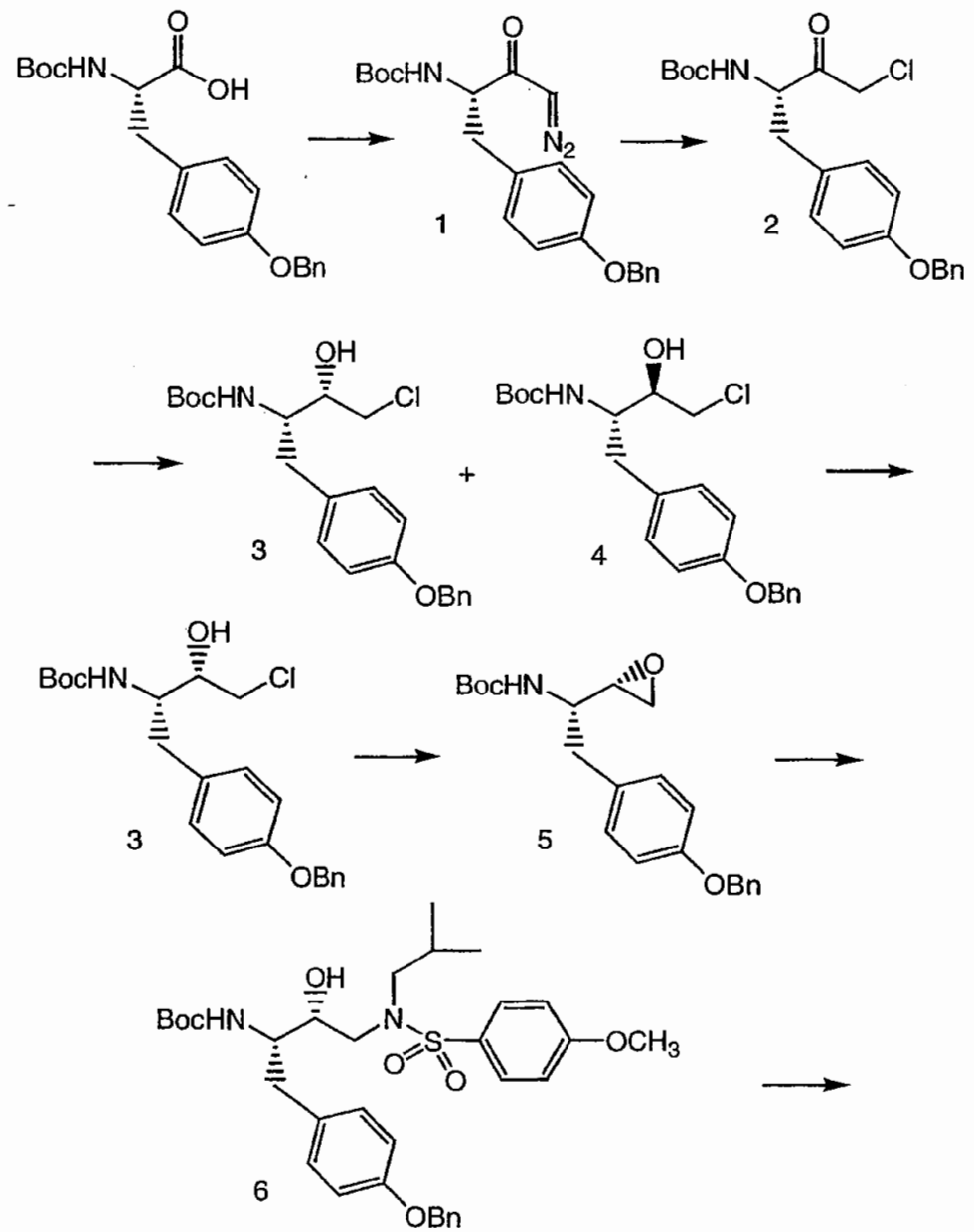
To a solution of carbamate **28** (2.35 g, 9.1 mmol) in pyridine (40 mL) was added phenol (8.53 g, 90.6 mmol) and 1,3-dicyclohexylcarbodiimide (7.47 g, 36.2 mmol). After the reaction mixture was warmed to 70°C and stirred for 5 h, the mixture was diluted with CH_3CN and filtered. The filtrate was concentrated under reduced pressure and diluted with EtOAc. The organic phase was washed with sat. NH_4Cl, sat. $NaHCO_3$, and brine, then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel twice (eluting 40-60% EtOAc/hexane) to give phosphonate **29** (2.13 g, 57%) as a colorless solid.

To a solution of phosphonate **29** (262 mg, 0.637 mmol) in iPrOH (5 mL) was added TFA (0.05 mL, 0.637 mmol) and 10% Pd/C (26 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 1 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give amine **30** (249 mg, 100%) as a colorless oil (Scheme 1005).

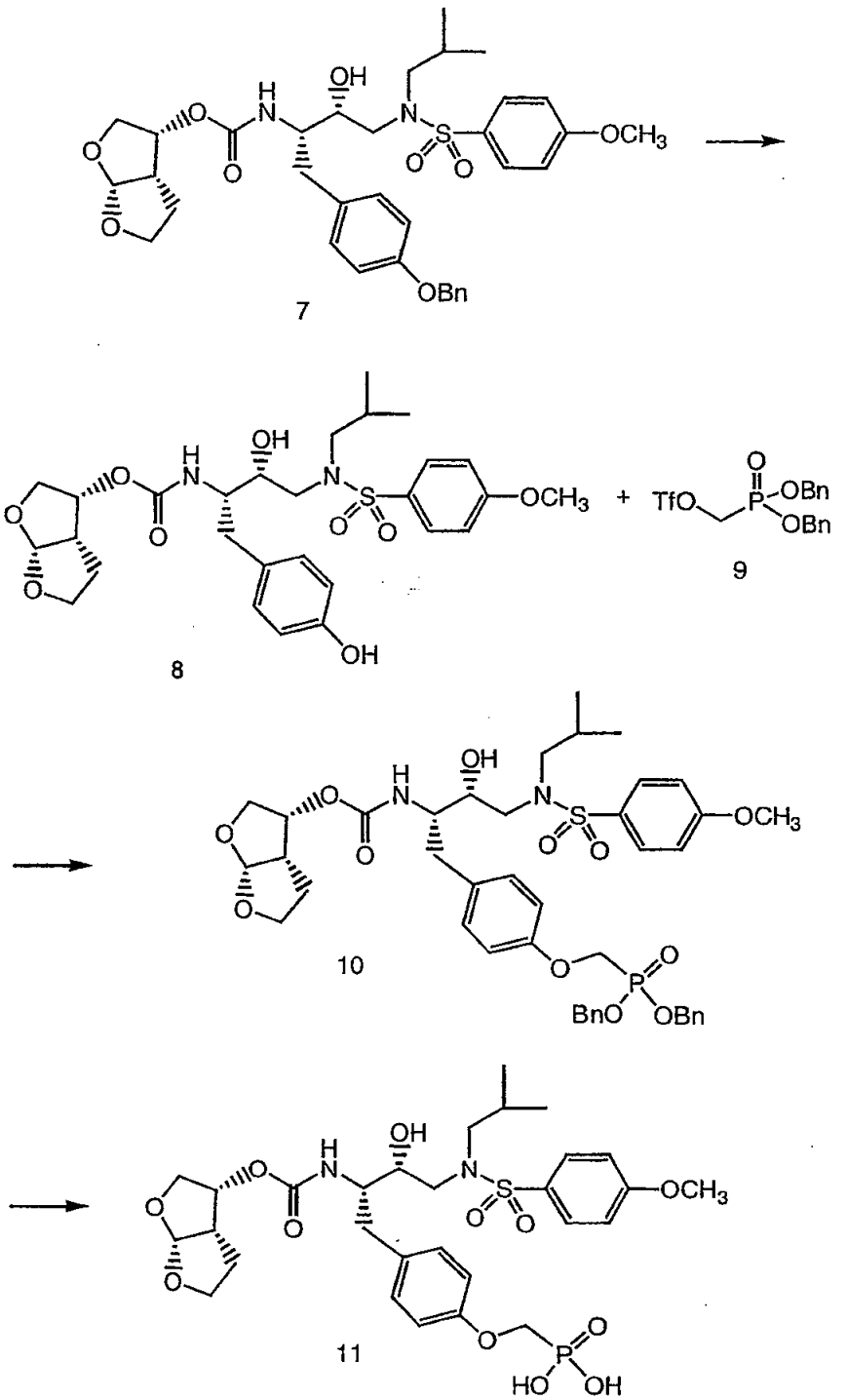
Scheme Section A

Exemplary methods of preparing the compounds of the invention are shown in **Schemes 1-7** below. A detailed description of the methods is found in the Experimental section below.

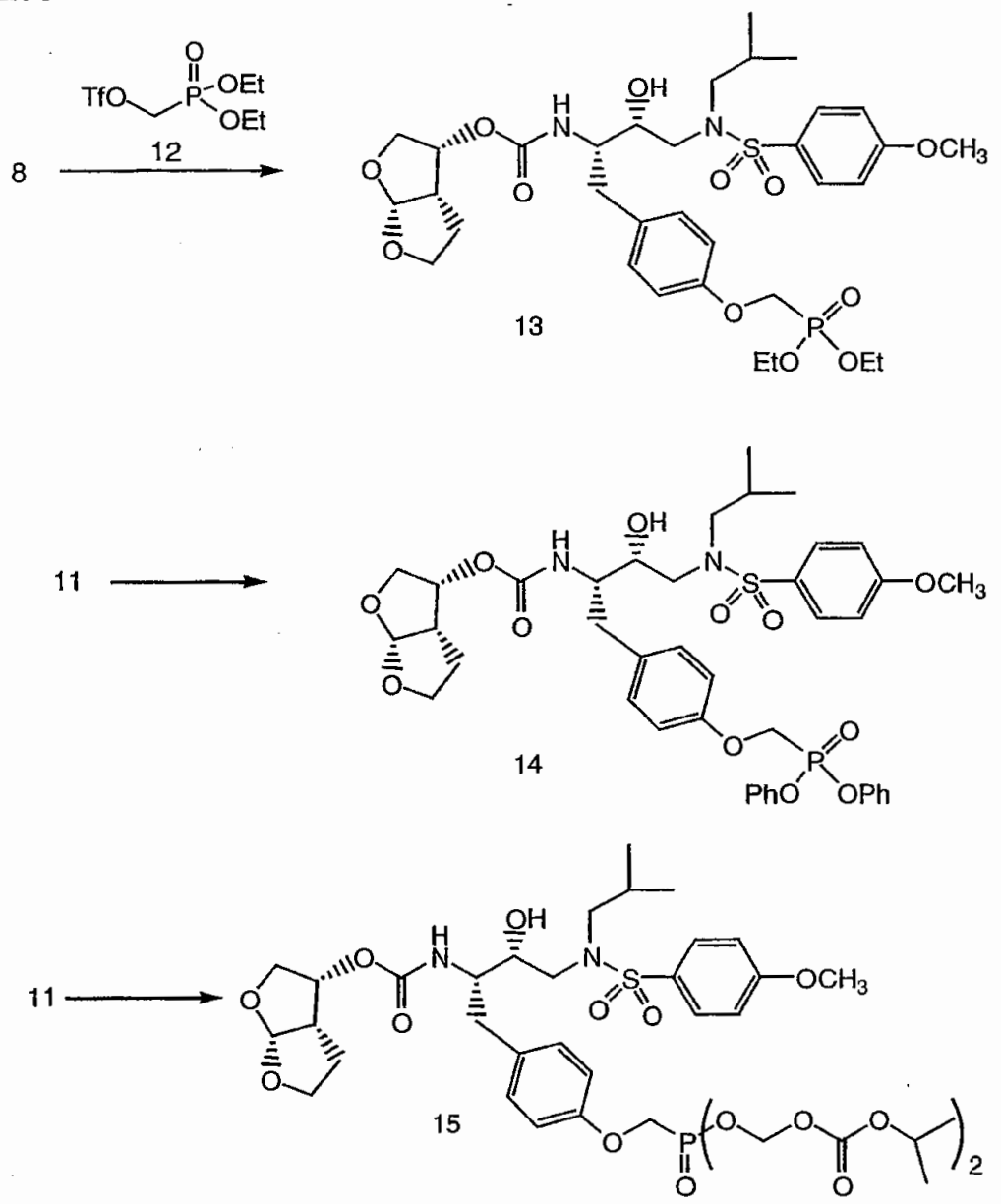
Scheme 1



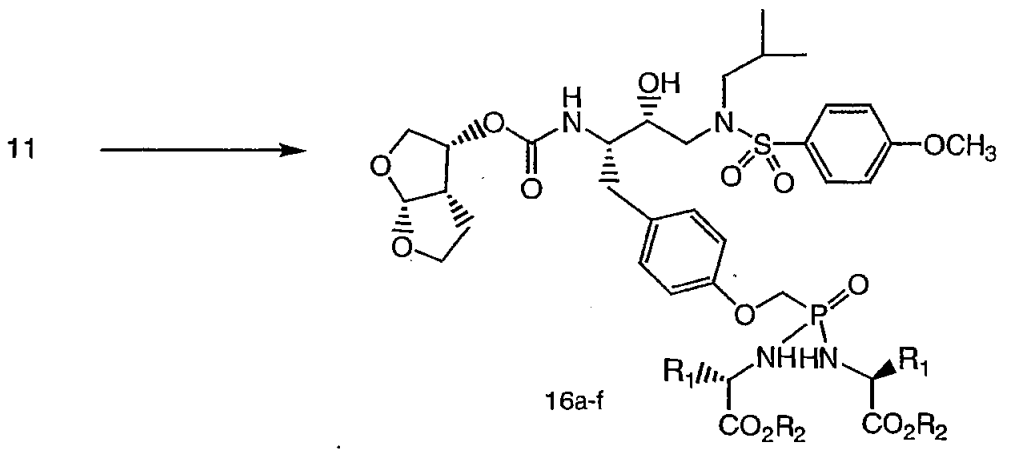
Scheme 2


OH
H
N
O
N
S
O
O
OCH3
OBn
7
OH
H
N
O
N
S
O
O
OCH3
OH
8
+
TfO
P
O
OBn
OBn
9
OH
H
N
O
N
S
O
O
OCH3
O
P
O
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OH
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OCH3
O
P
O
HO
OH
11

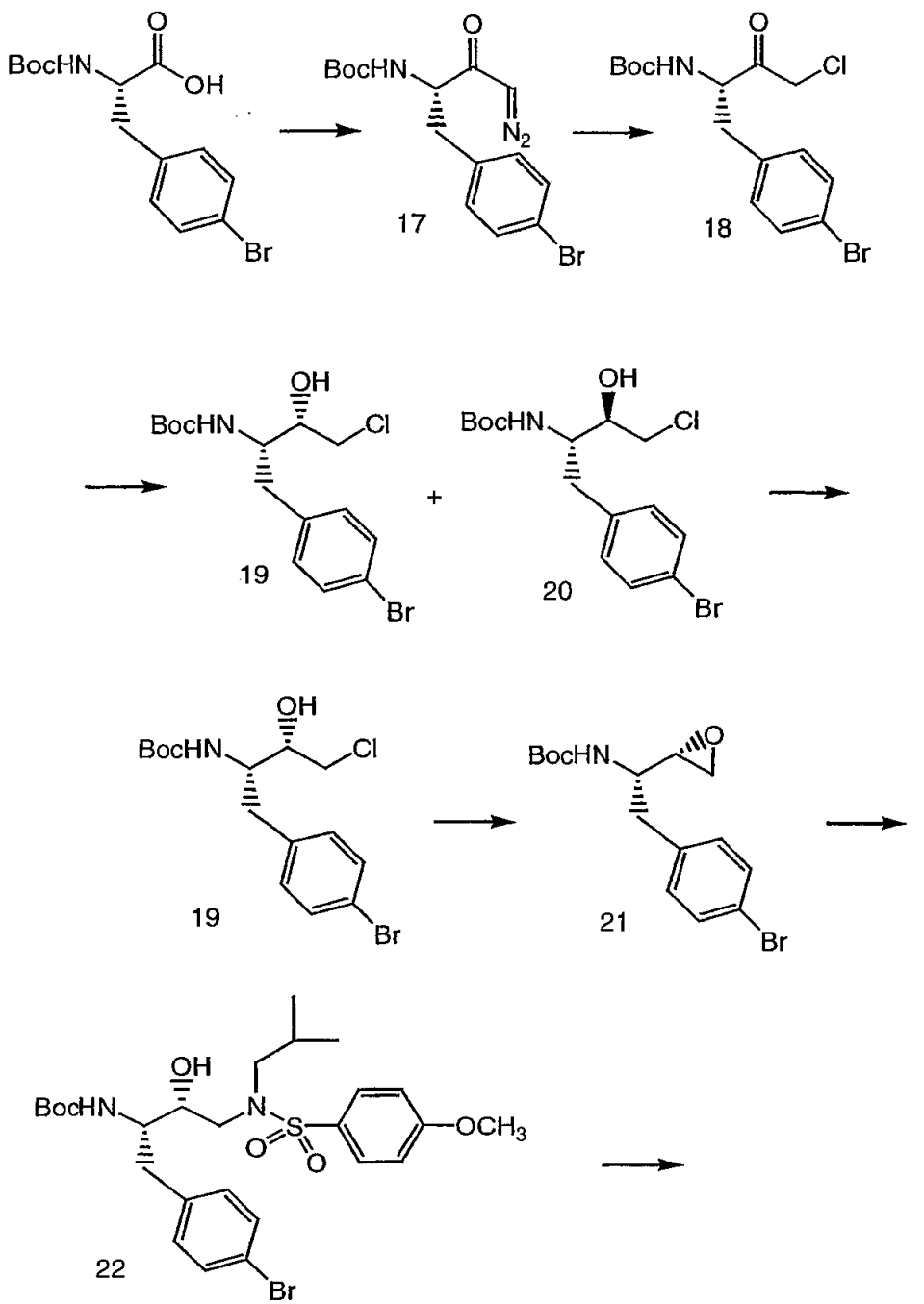
Scheme 3


TfO
P
OEt
OEt
O
12
8
OH
H
N
N
S
O
O
OCH3
O
O
O
O
O
P
O
EtO
OEt
13
11
14
PhO
OPh
15
2

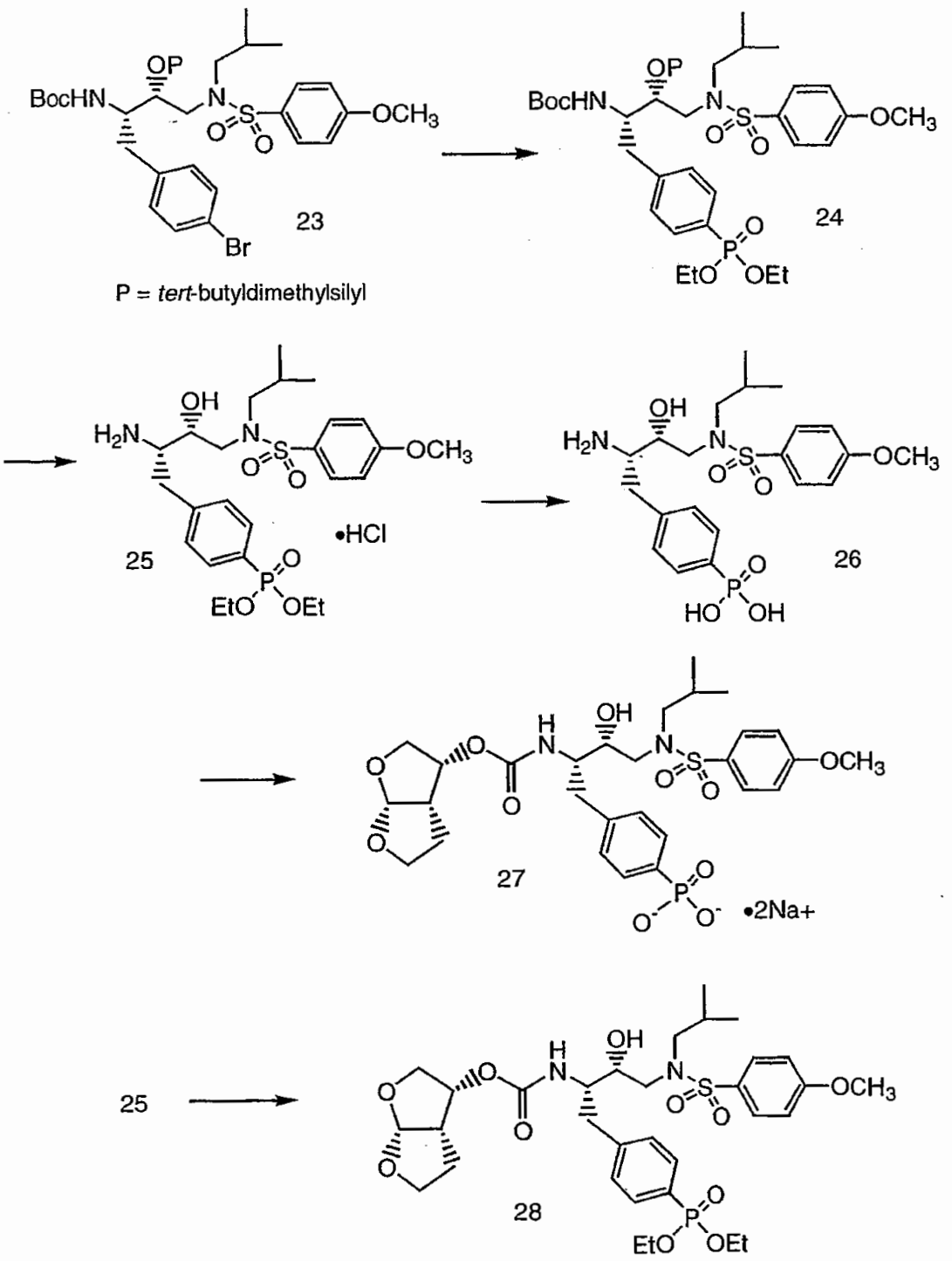
Scheme 4



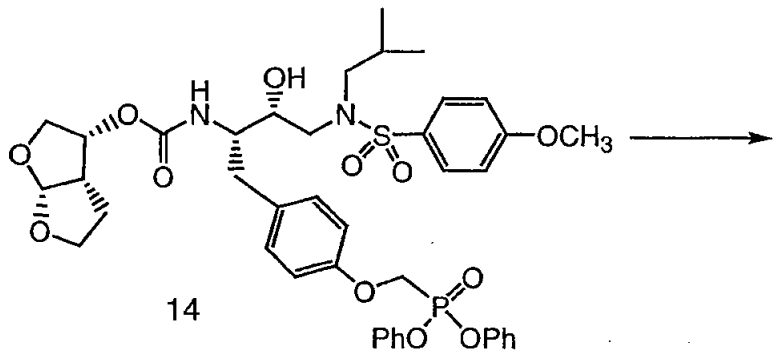
Scheme 5



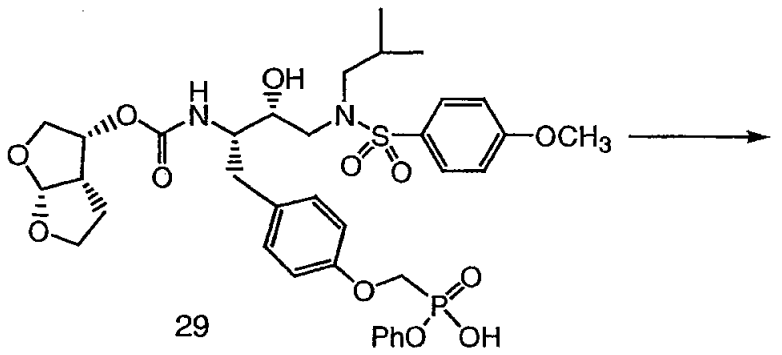
Scheme 6


BocHN
OP
N
S
O
O
OCH3
Br
23
P = tert-butyldimethylsilyl
24
EtO
OEt
H2N
OH
•HCl
25
26
HO
OH
27
•2Na+
28

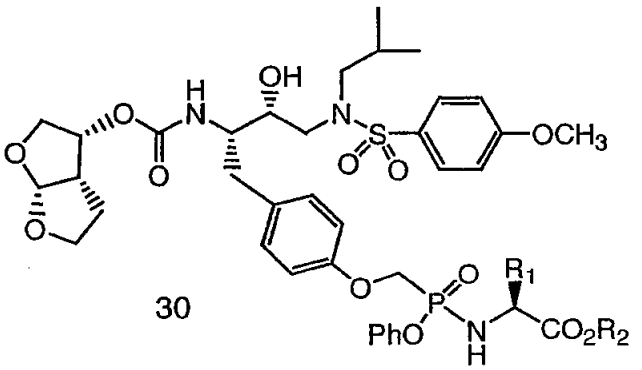
Scheme 7



14



29

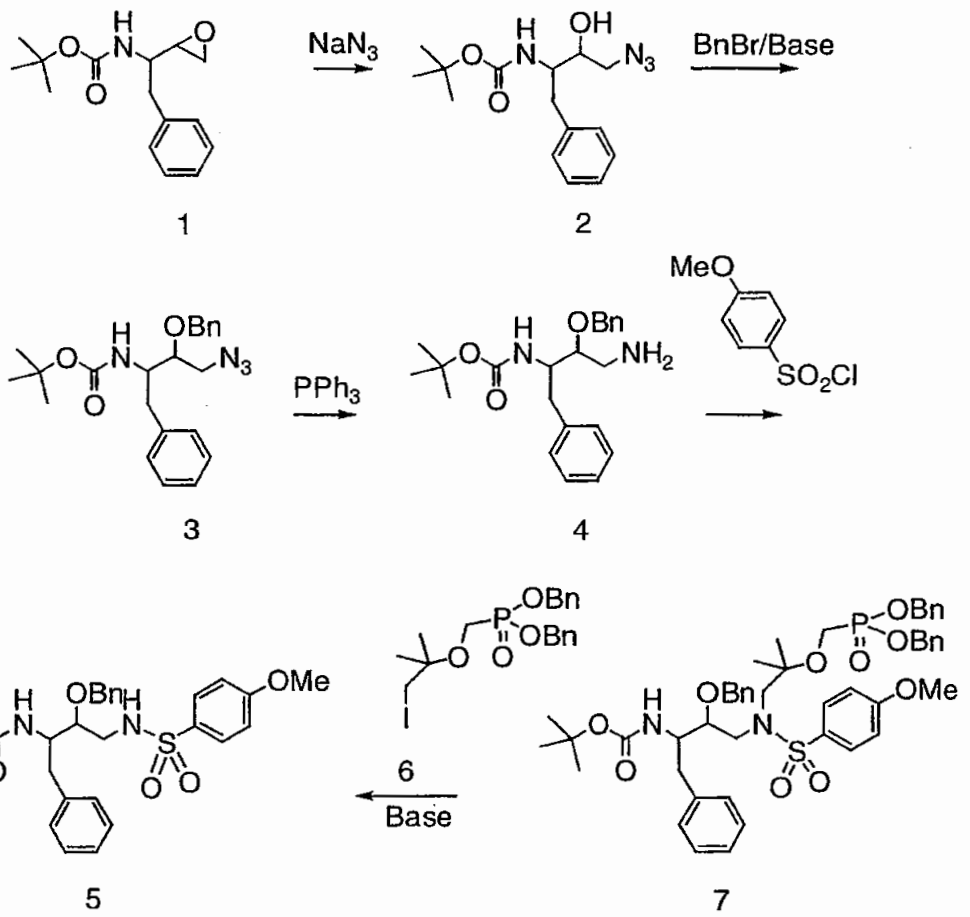


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Scheme Section B

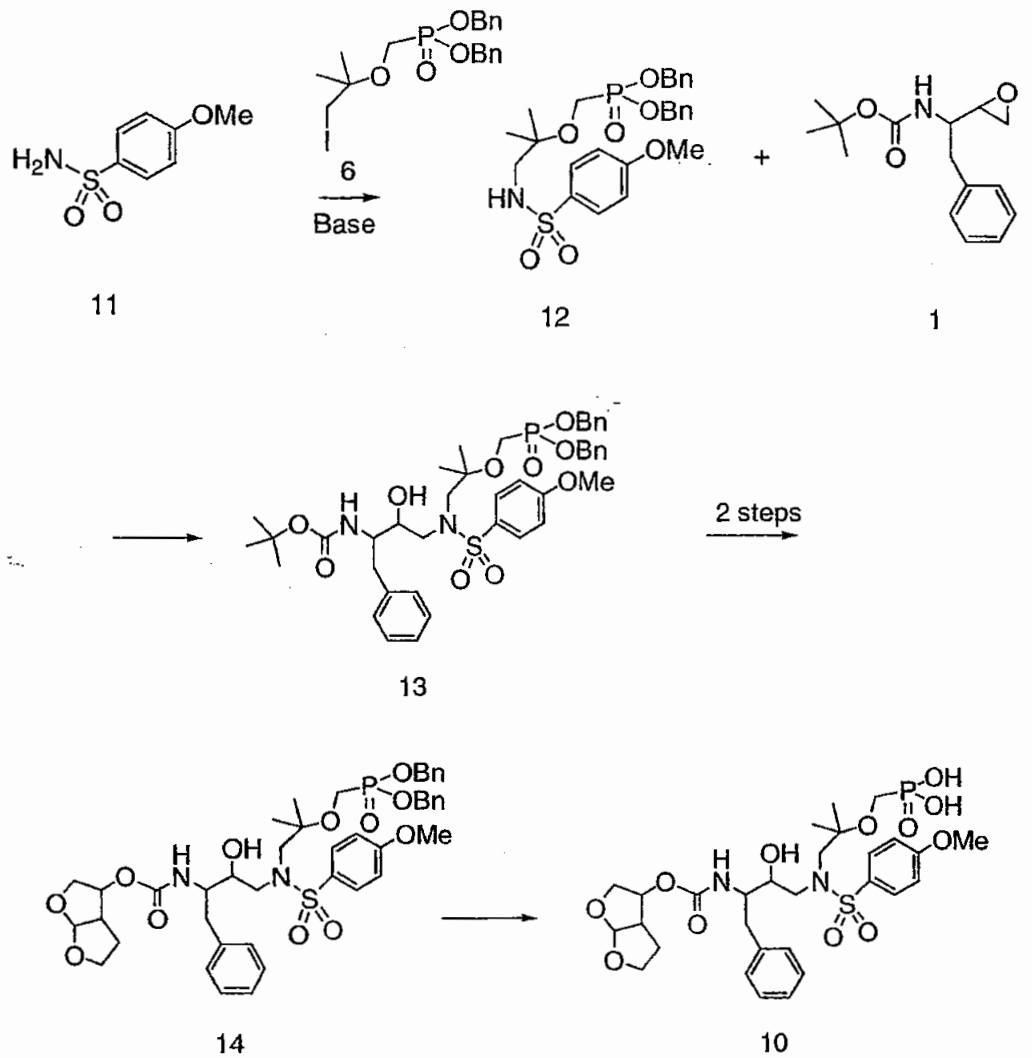
Alternative exemplary methods of preparing the compounds of the invention are shown in **Schemes 101-113** below.

Scheme 101



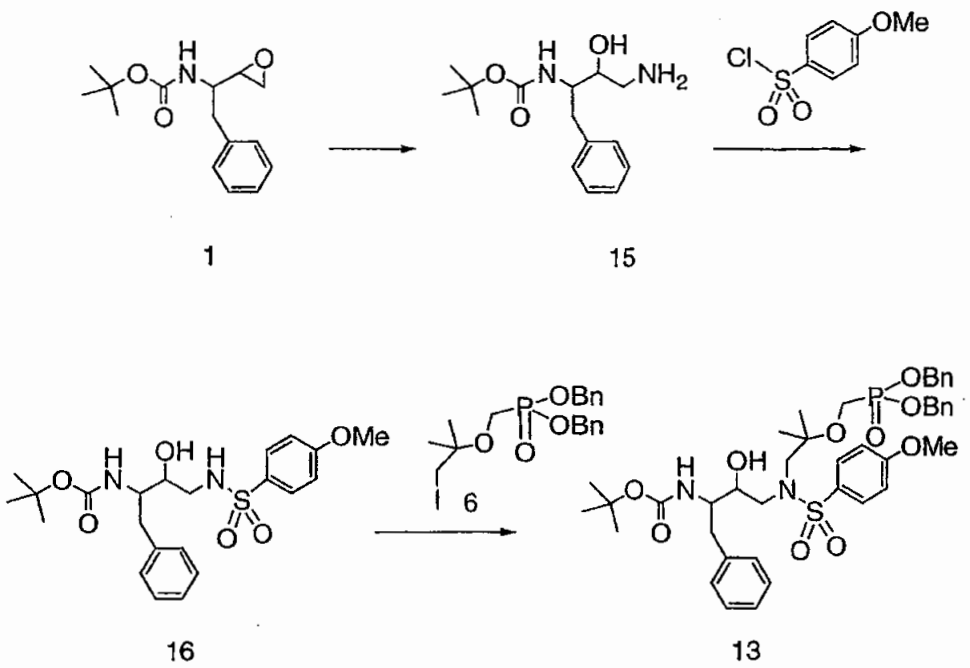
Treatment of commercially available epoxide 1 with sodum azide (Bioorg. & Med. Chem. Lett., 5, 459, 1995) furnishes the azide intermediate 2. The free hydroxyl is converted to benzyl ether 3 by treating it with benzyl bromide in the presence of base such as potassium carbonate. Compound 4 is achieved by the reduction of the azide group with triphenyl phosphine, as described in the publication Bioorg. & Med. Chem. Lett., 7, 1847, 1997. Conversion of the amino group to its sulfonamide derivative 5 is achieved by treating the amine with stoichiometric amounts of sulfonyl chloride. Regioselective alkylation is performed (as shown in the article J. Med. Chem., 40, 2525, 1997) on the sulfonamide nitrogen using the iodide 6 (J. Med. Chem., 35, 2958, 1992) to get the compound 7. Upon TFA catalyzed deprotection of BOC group followed by the reaction with bisfuranyl carbonate 8 (for a similar coupling see, J. Med. Chem., 39, 3278, 1996) furnishes the compound 9. Final deprotection of the protecting groups by catalytic hydrogenolysis result the compound 10.

Scheme 102



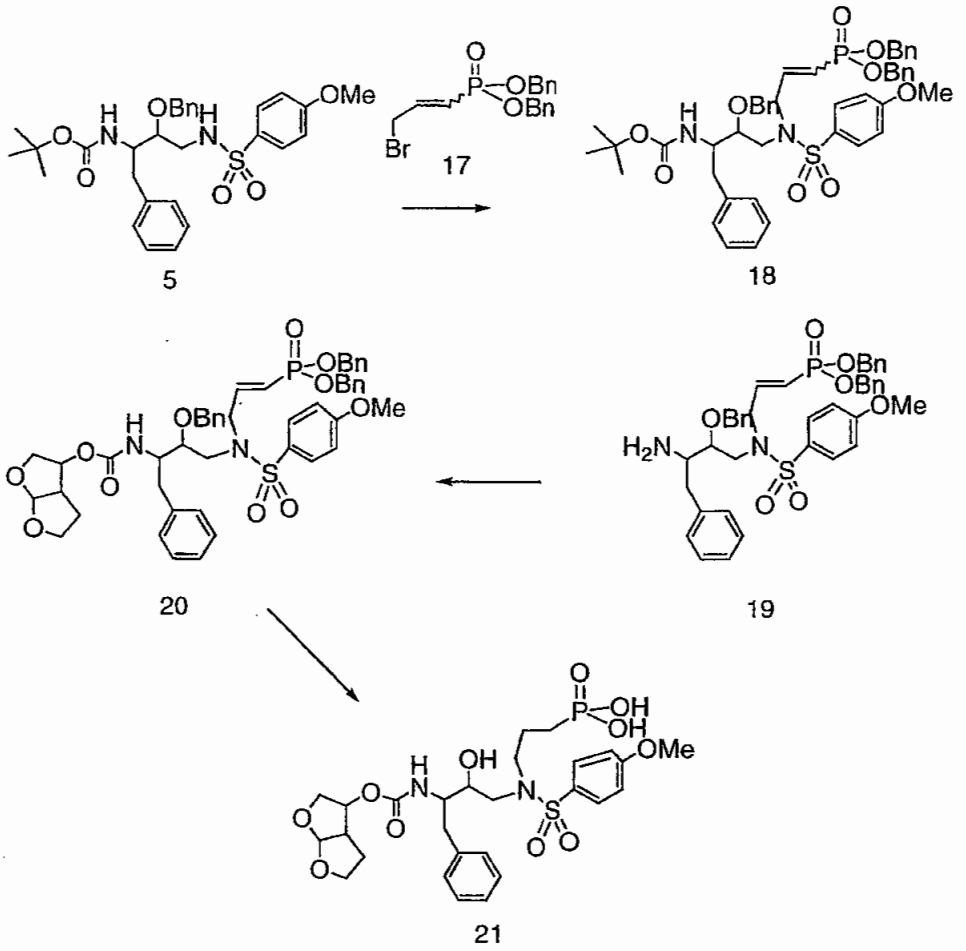
The sulfonamide 11 is readily alkylated with the iodide 6 (J. Med. Chem., 35, 2958, 1992) to get the intermediate 12. Regioselective epoxide opening (JP -9124630) of the epoxide 1 with 12 furnishes the intermediate 13. Deprotection of the BOC group followed by the treatment of bisfuranyl carbonate 8 yields the intermediate 14 which is subjected to hydrogenation to furnish the compound 10.

Scheme 103



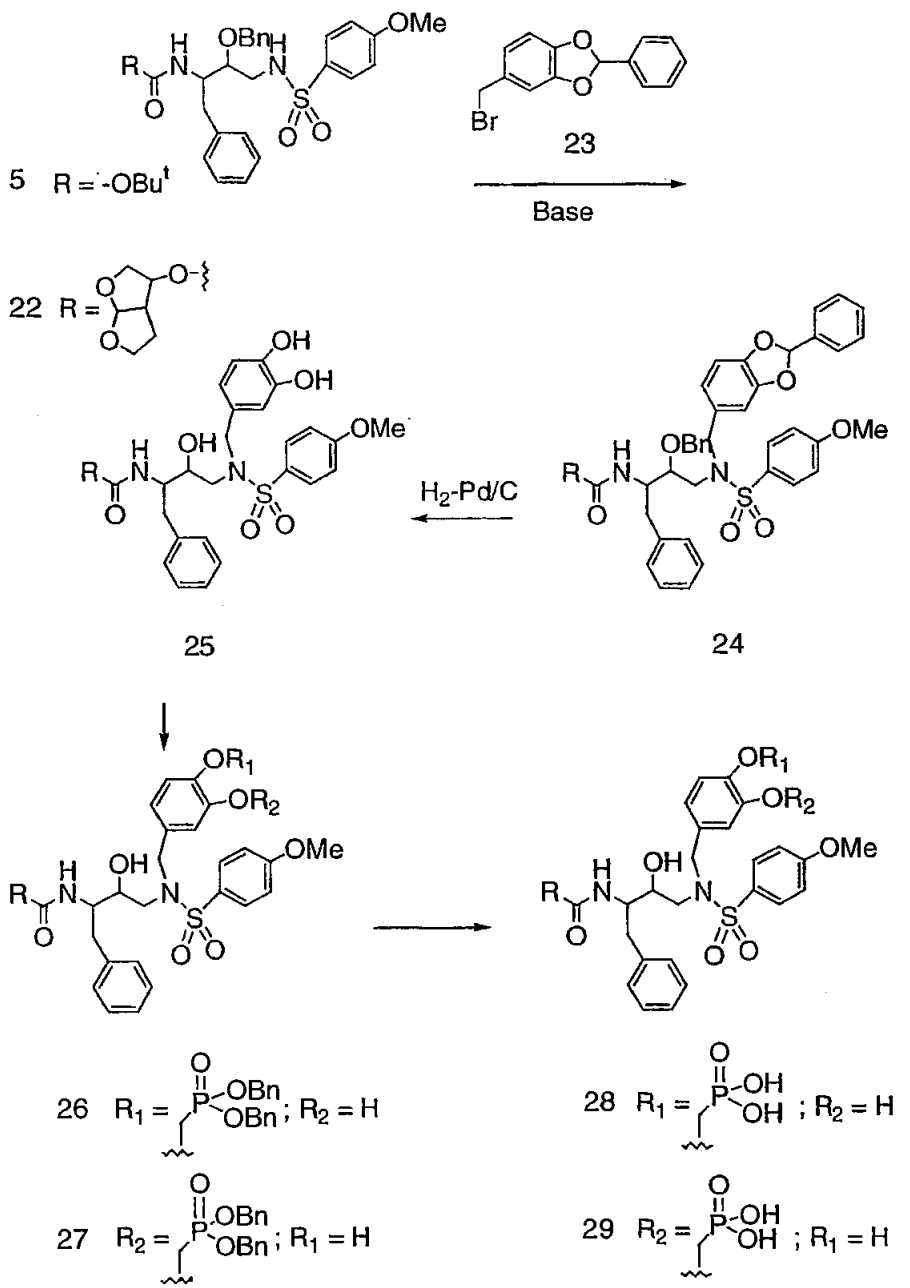
The epoxide 1 is converted to the aminohydroxyl derivative 15 using the known procedure (J. Med. Chem., 37, 1758, 1994). Sulfonylation of 15 using benzene sulfonylchloride affords the compound 16. Installation of the side chain to get the intermediate 13 is achieved by alkylation of sulfonamide nitrogen with iodide 6. The intermediate 13 is converted to the compound 10 using the same sequence as shown in scheme 102.

Scheme 104

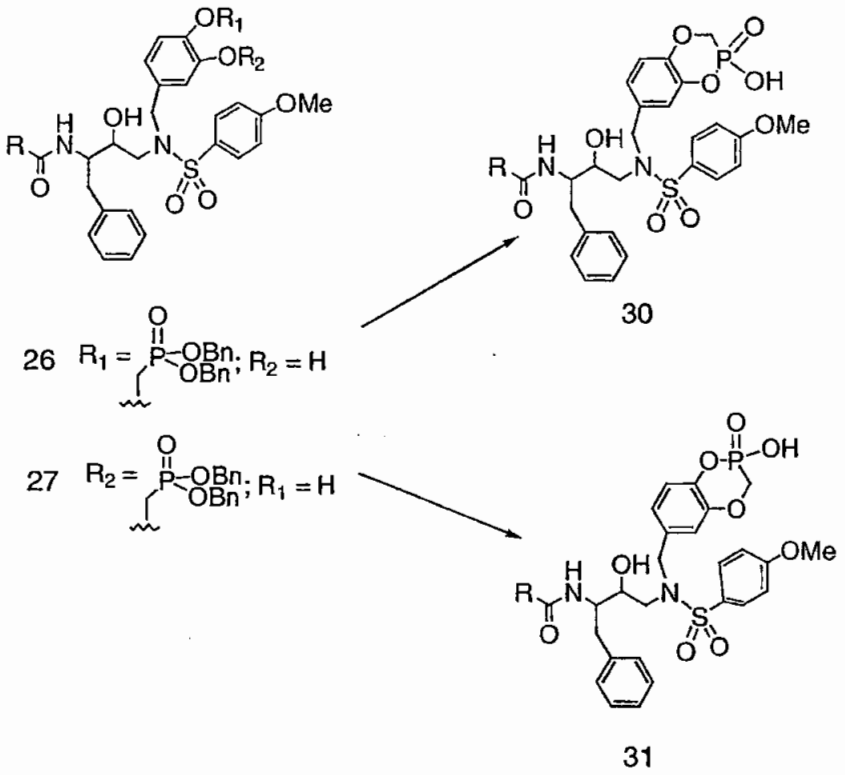


Sulfonamide 5 is alkylated under basic conditions using the allyl bromide 17 (Chem. Pharm. Bull., 30, 111, 1982) to get the intermediate 18. Similar transformation is reported in literature (J. Med. Chem., 40, 2525, 1997). Hydrolysis of BOC group with TFA and acylation of the resulting amine 19 with bisfuranyl carbonate 8 yields the compound 20. Hydrogenation using Pd/C catalysis under H_2 atmosphere affords the phosphonic acid 21.

Scheme 105


R = -OBu^t
23
Base
22
H2-Pd/C
25
24
26 R1 = OBn, OBn; R2 = H
27 R2 = OBn, OBn; R1 = H
28 R1 = OH, OH; R2 = H
29 R2 = OH, OH; R1 = H

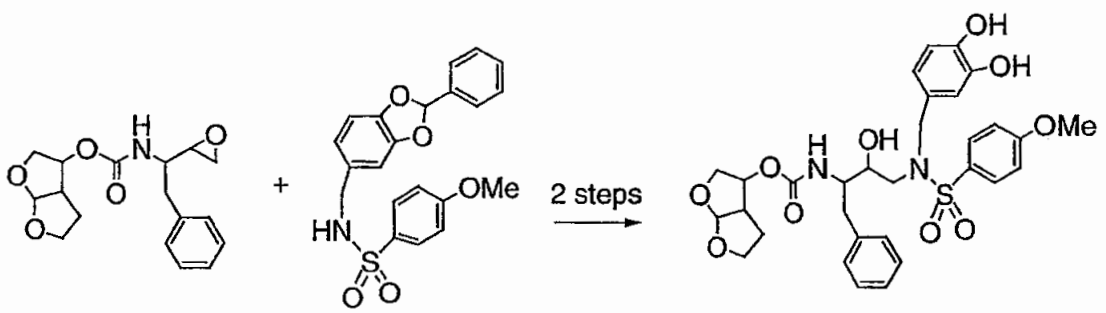
Scheme 105 (cont)



Sulfonamide 5 is converted to 22 via hydrolysis of BOC group with TFA and acylation with bisfuranyl carbonate 8. The sulfonamide 22 is alkylated with the bromide 23 (J. Med. Chem., 40, 2525, 1997) to get the compound 24, which upon hydrogenolysis gives the catechol 25. Alkylation of the phenolic groups using dibenzylhydroxymethyl phosphonate (J. Org. Chem., 53, 3457, 1988) affords regioisomeric compounds 26 and 27. These compounds 26 and 27 are hydrogenated to get the phophonic acids 28 and 29, respectively. Individual cyclic phosphonic acids 30 and 31 are obtained under basic (like NaH) conditions (US 5886179) followed by hydrogenolysis of the dibenzyl ester derivatives 26 and 27.

Scheme 106

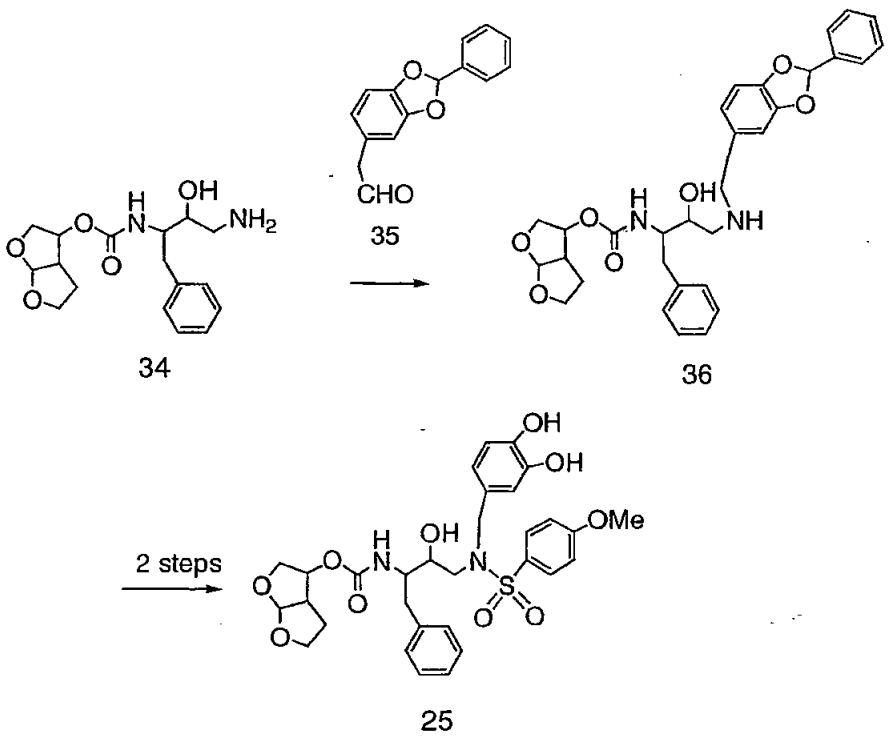
In this route, compound 25 is obtained by conducting a reaction between the epoxide 32 and the sulfonamide 33 using the conditions described in the Japanese Patent No. 9124630.



32 33 25

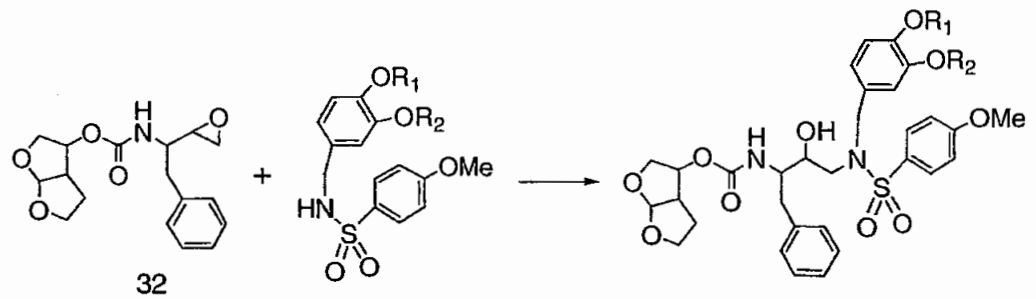
Epoxide 32 and sulfonamide 33 are synthesized utilizing similar methodology delineated in the same patent.

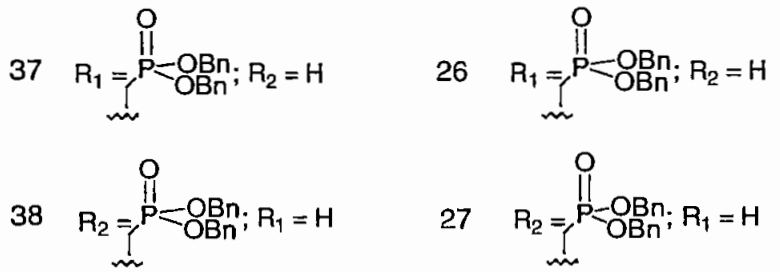
Scheme 107



Compound 34 is obtained from 32 using similar sequence depicted in J. Med. Chem., 37, 1758, 1994. Reductive amination (for similar transformation see WO 00/47551) of compound 34 with aldehyde 35 furnishes the intermediate 36 which is converted to the compound 25 by sulfonylation followed by hydrogenation.

Scheme 108

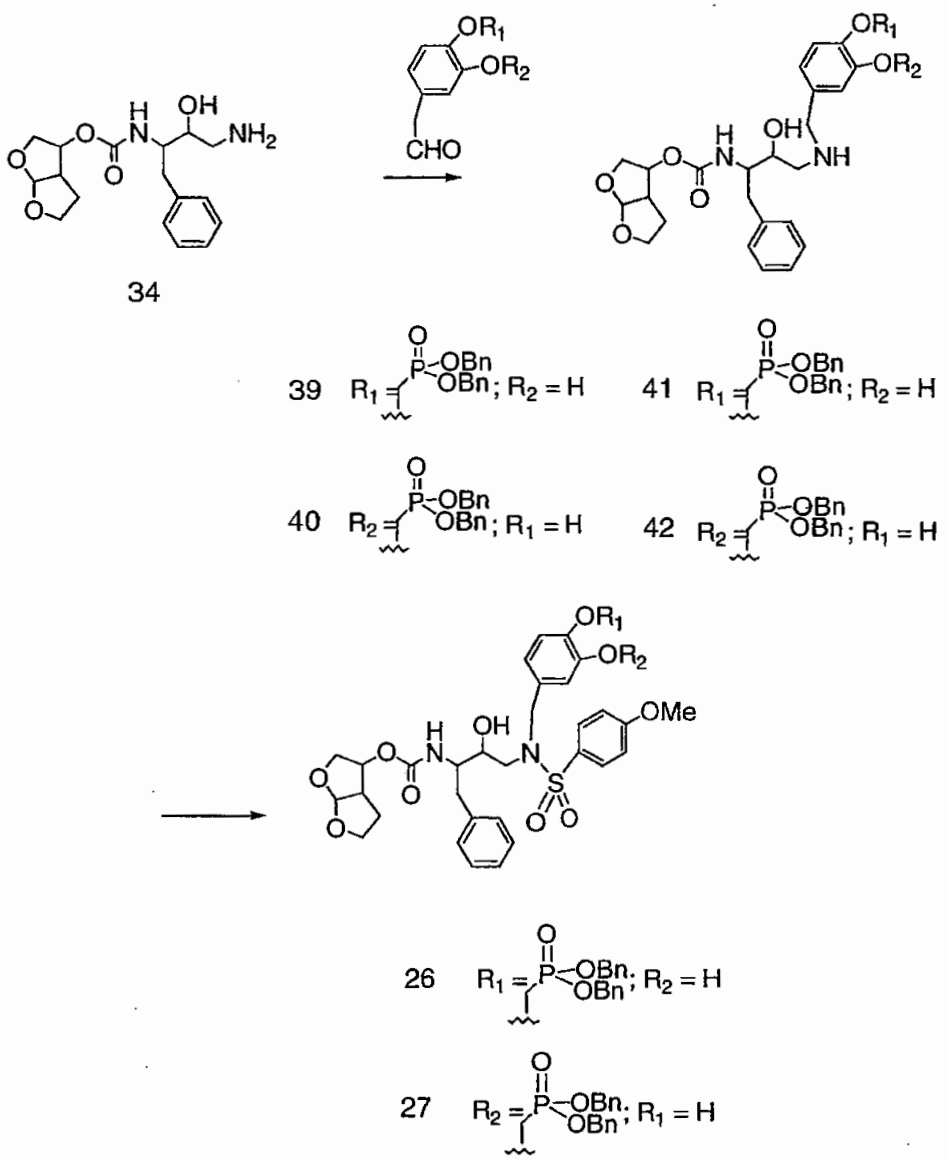




Treatment of epoxide 32 with sulfonamides 37 and/or 38 under conditions described in Japanese Patent No. 9124630 furnishes 26 and 27.

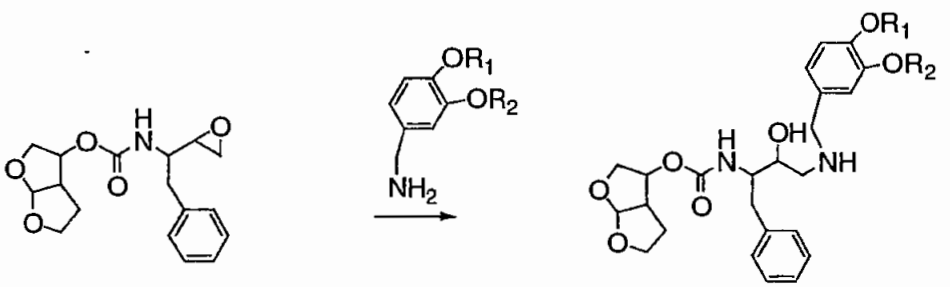
Scheme 109

Reductive amination of aminohydroxyl intermediate 34 with the aldehydes 39 and 40 as described in patent WO 00/47551, furnish 41 and 42 which undergoes smooth sulfonylation to give 26 and 27.

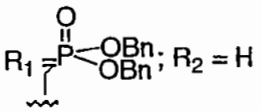
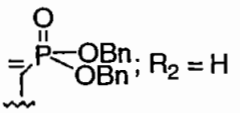


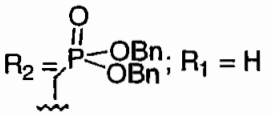
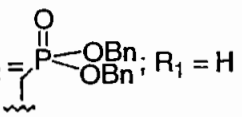
Scheme 110

In an alternate approach, where epoxide 32 is opened with benzyl amines 43 and 44 under conditions described above furnishes 41 and 42, respectively. Similar transformations were documented in the Japanese Patent No. 9124630.

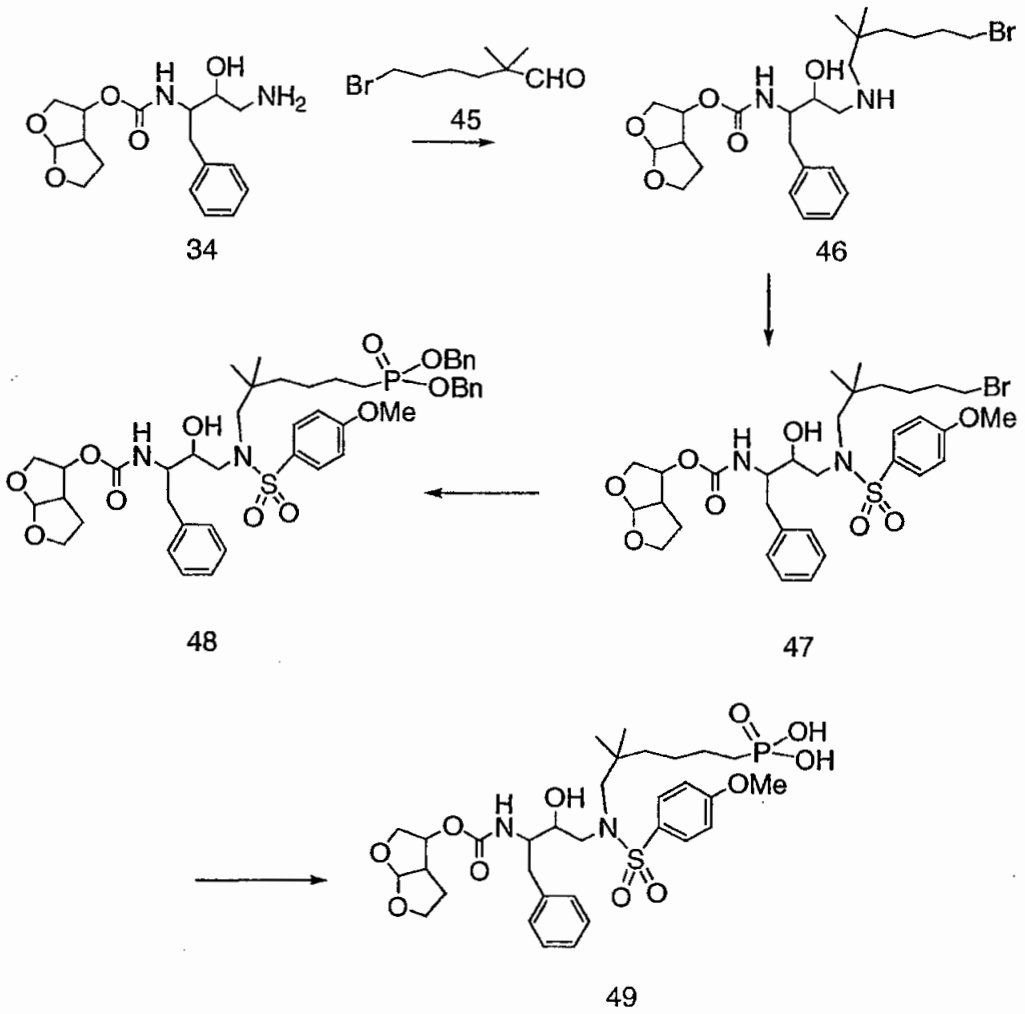


32

43  41 

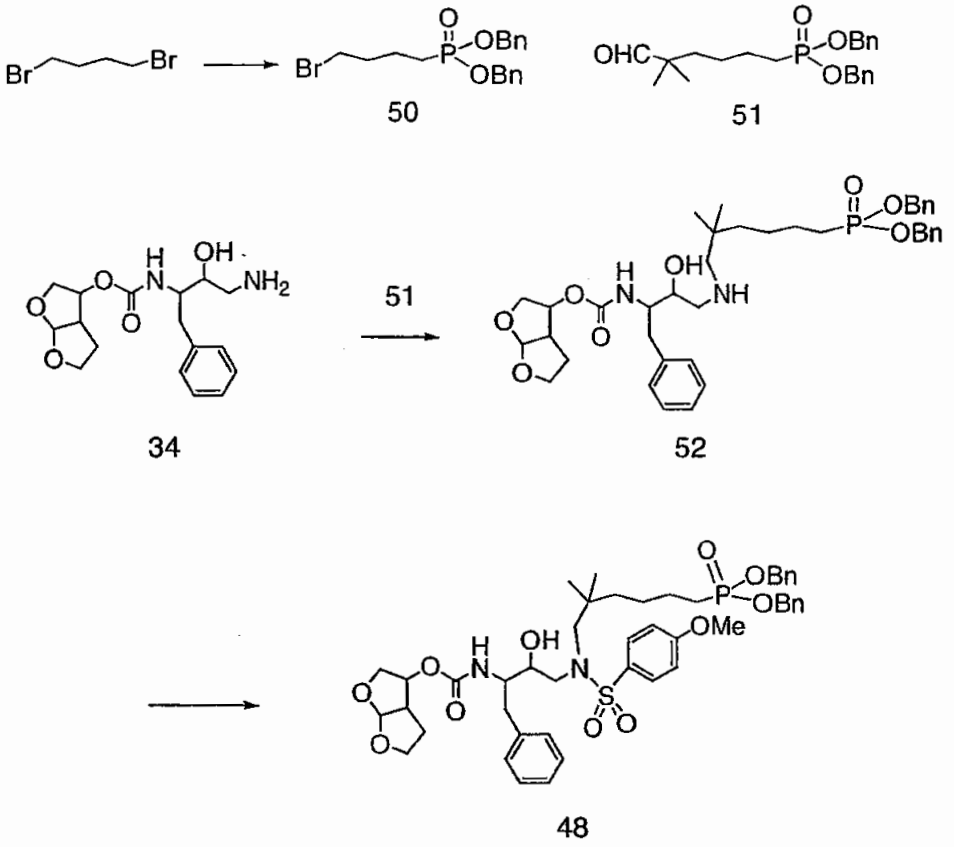
44  42 

Scheme 111



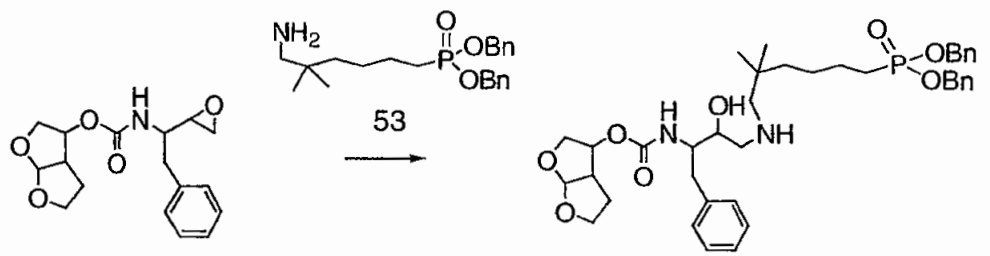
Reductive amination of the bromoaldehyde 45 (J. Organomet. Chem., FR; 122, 123, 1976) with the amine 34 gives 46 which then undergoes sulfonylation to furnish 47. The bromoderivative 47 is converted to the phosphonate 48 under Michaelis-Arbuzov reaction conditions (Bioorg. Med. Chem. Lett., 9, 3069, 1999). Final hydrogenation of 48 delivers the phosphonic acid 49.

Scheme 112



The intermediate 48 is also obtained as shown in scheme 112. Reductive amination of the aldehyde 52 with the amine 34 offers the phosphonate 52 and sulfonylation of this intermediate furnishes 48.

Scheme 113



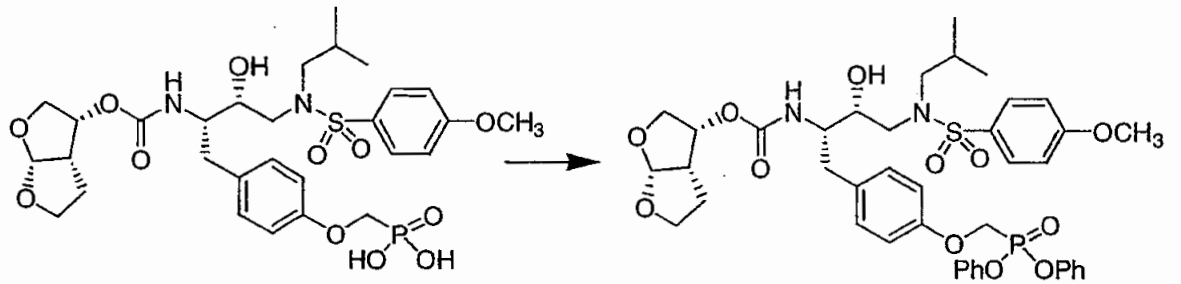
32 52

Alternatively, compound 52 is obtained from the epoxide 32 by a ring opening reaction with the aminophosphonate 53 (Scheme 113).

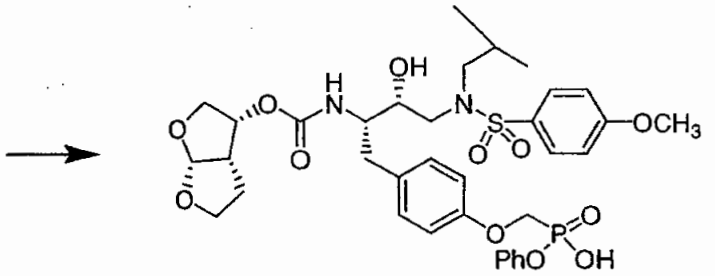
Scheme Section C

Scheme 9 is described in the Examples.

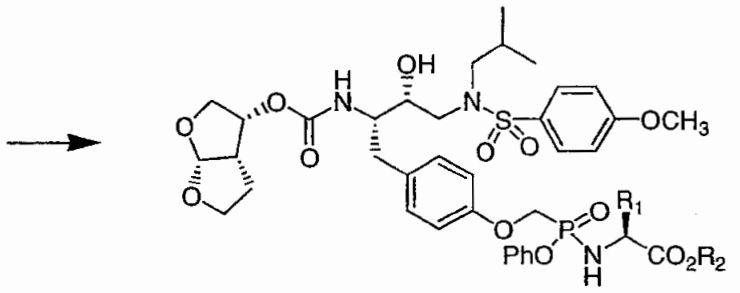
Scheme 9



30 31



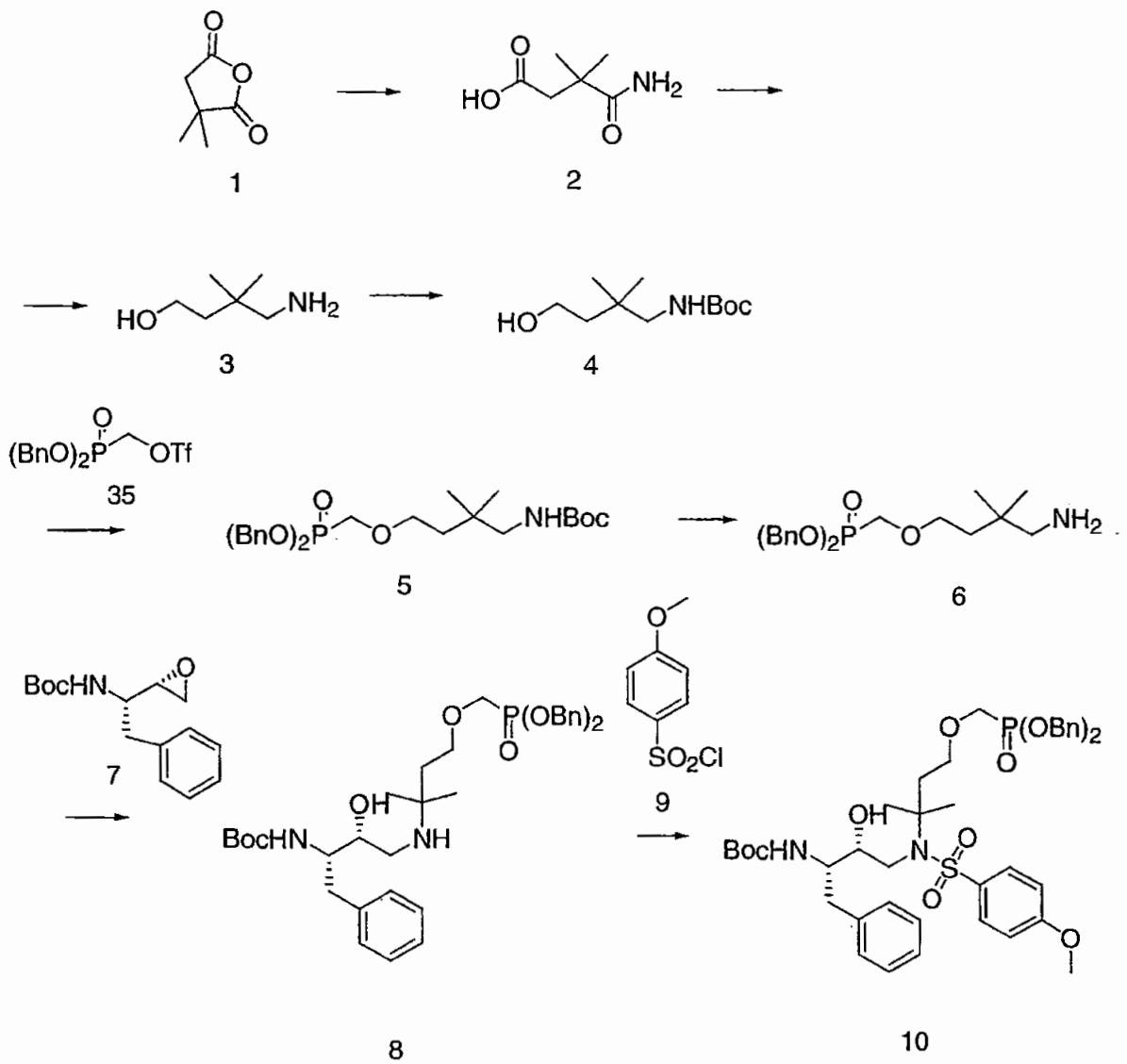
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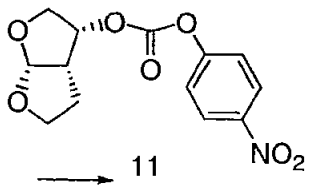


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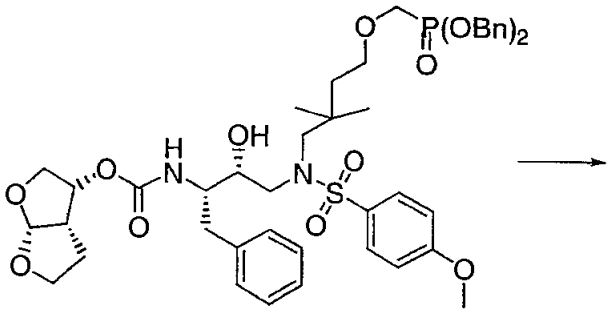
Scheme Section D

The following schemes are described in the Examples.

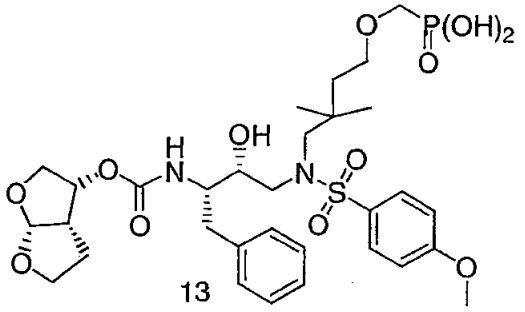




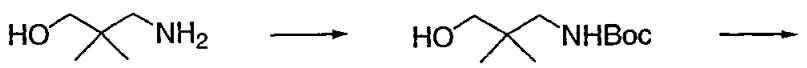
11



12



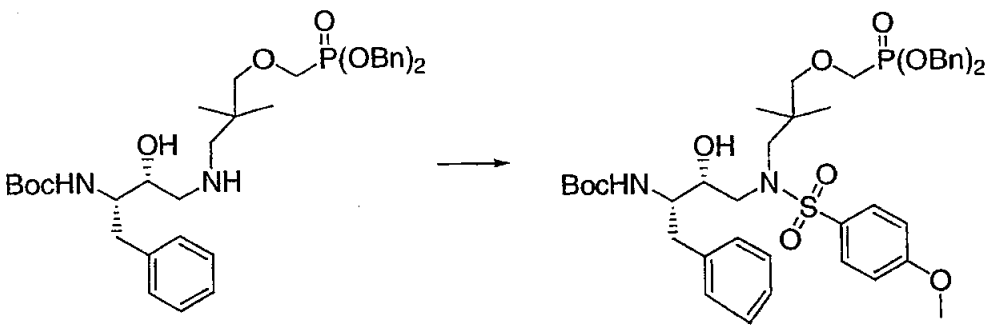
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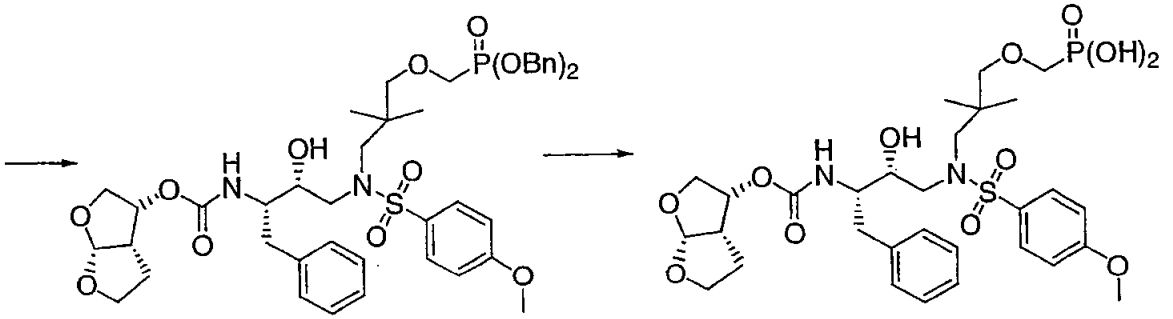
14 15



16 17



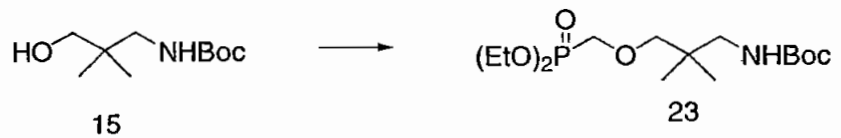
18 19



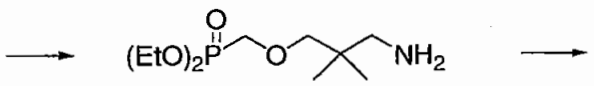
20 21



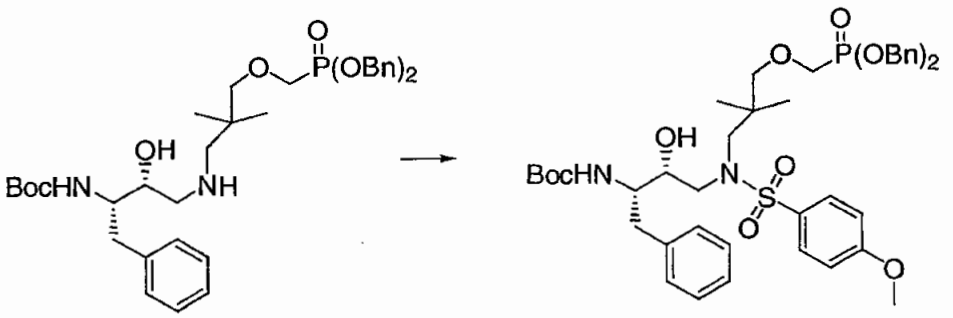
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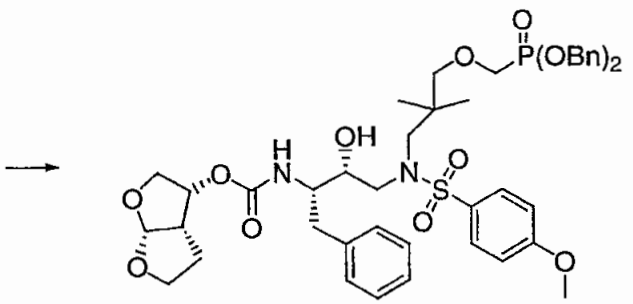
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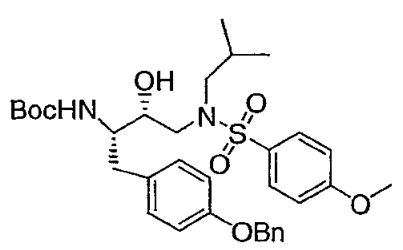
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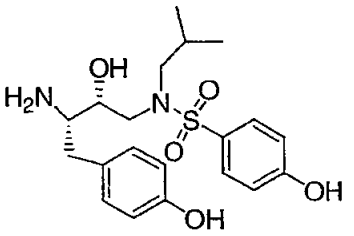
25 26



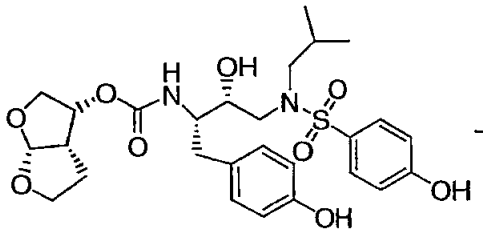
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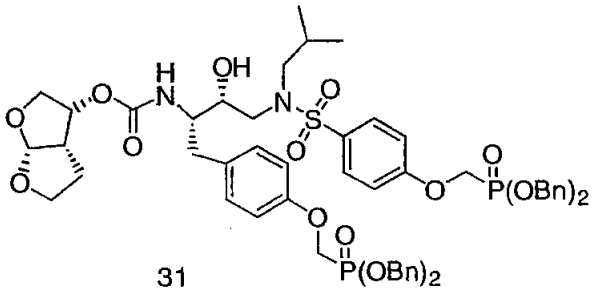
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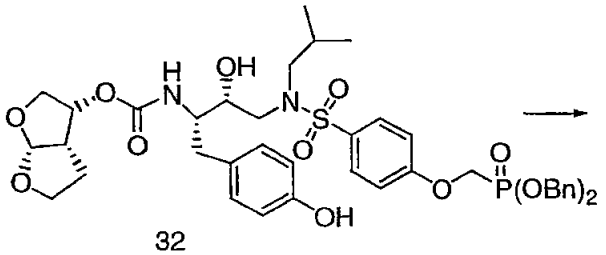
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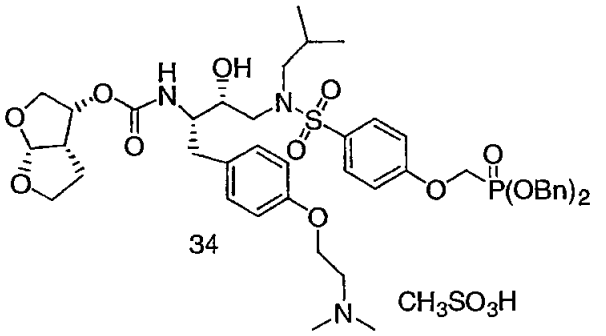
30



31



32

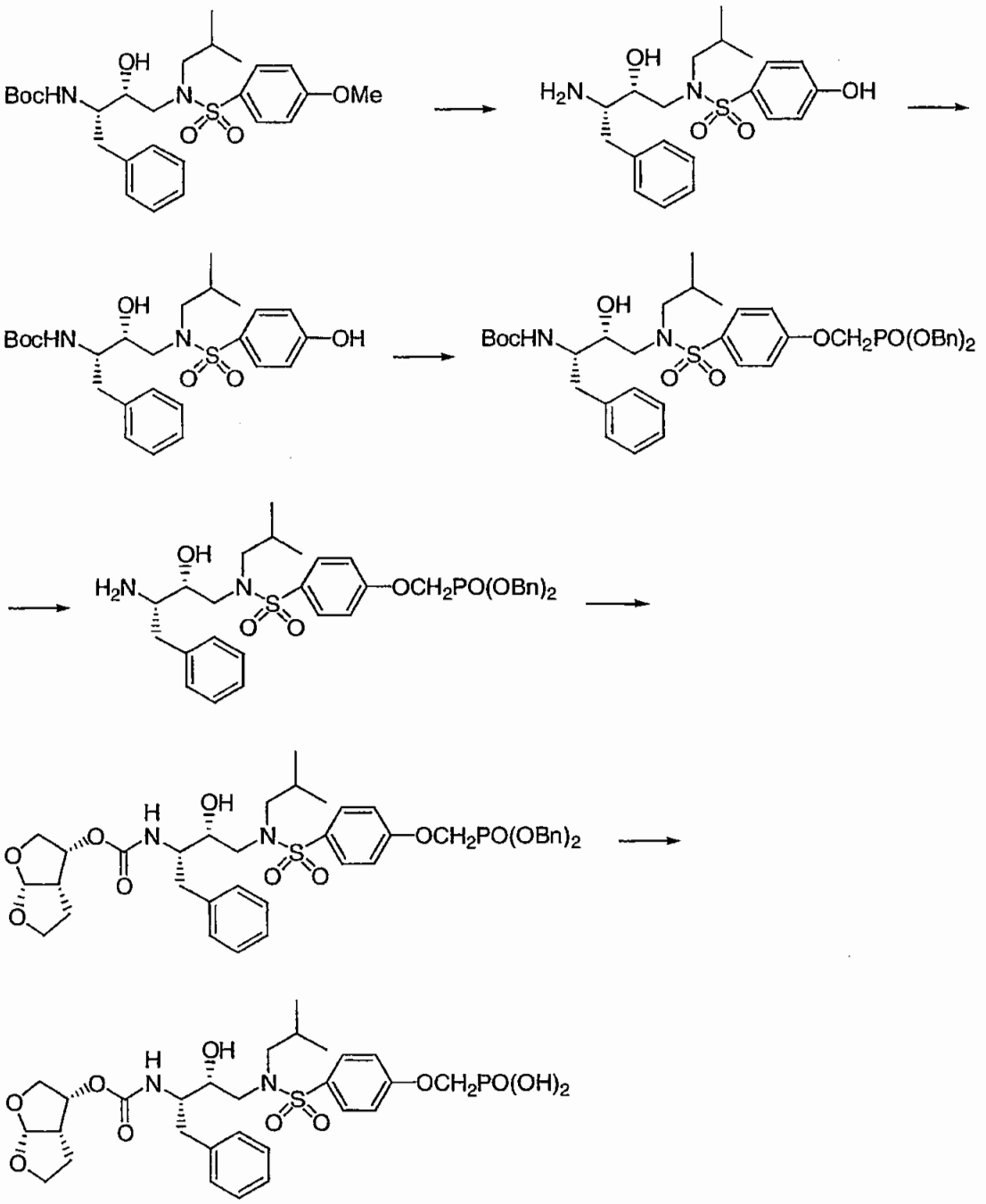


34

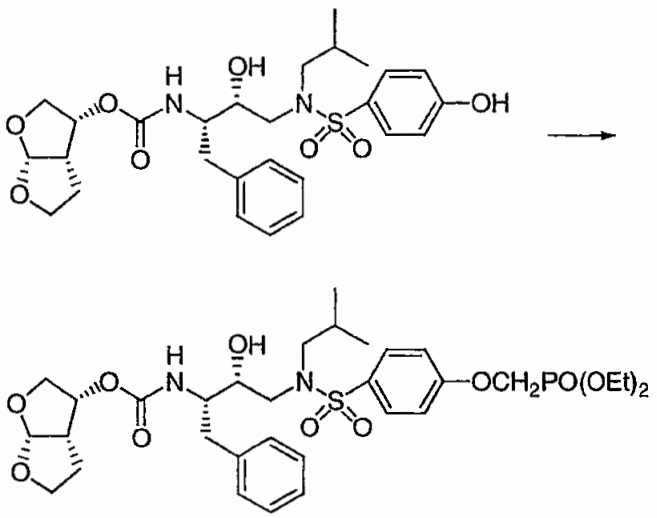
Scheme Section E

Schemes 1-3 are described in the examples.

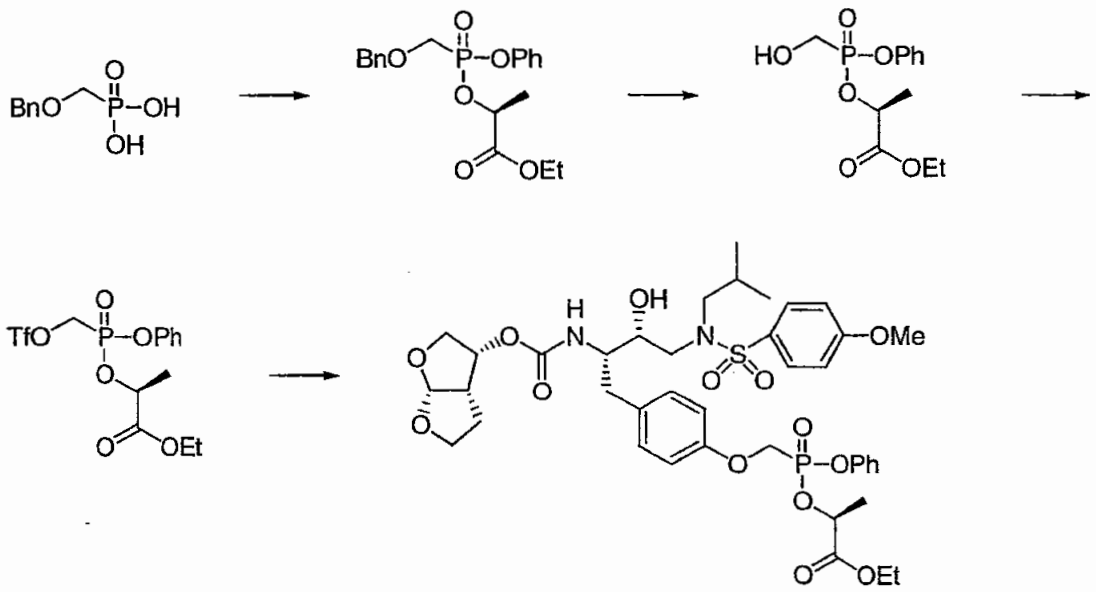
Scheme 1



Scheme 2



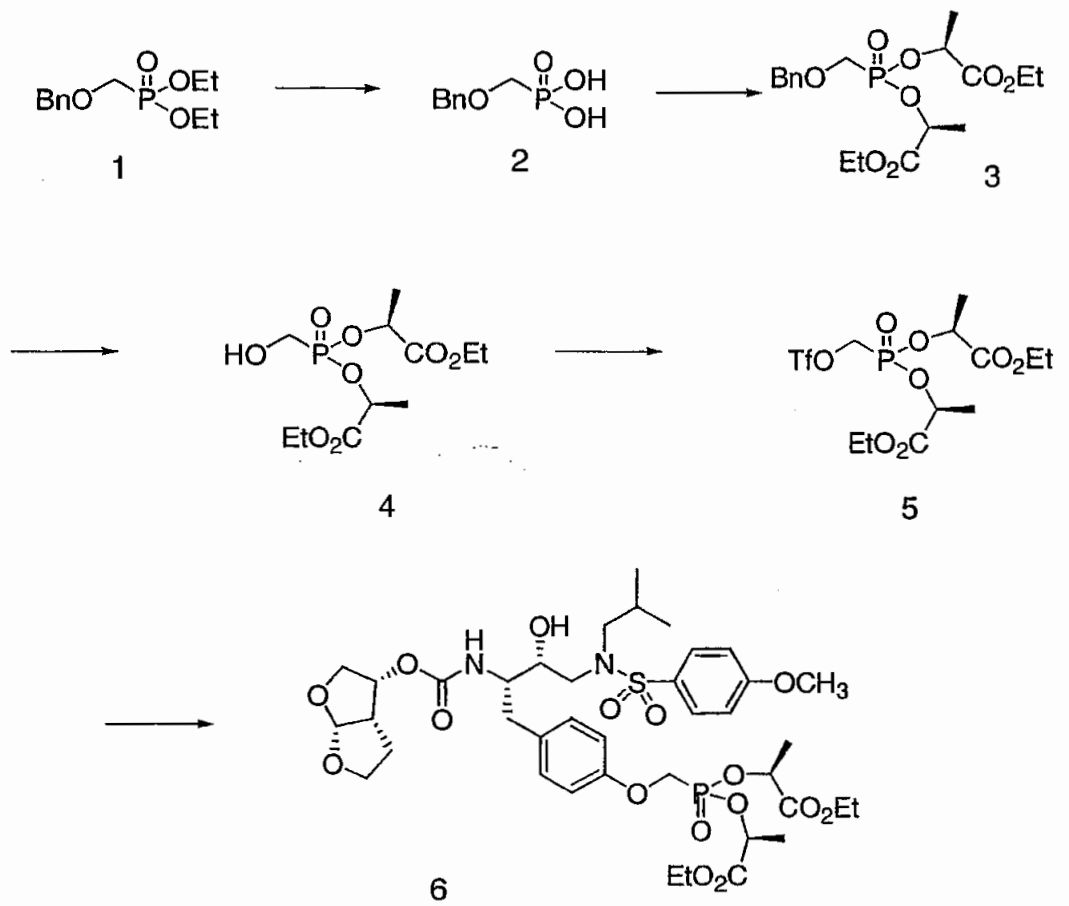
Scheme 3



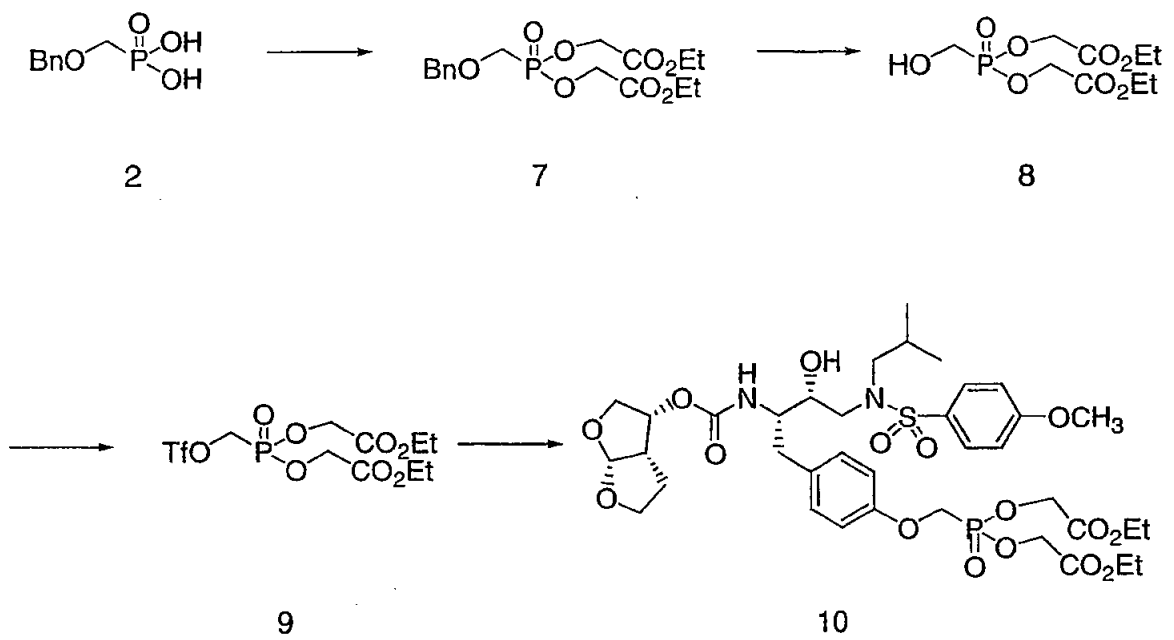
Scheme Section F

Schemes 1-5 are described in the examples.

Scheme 1



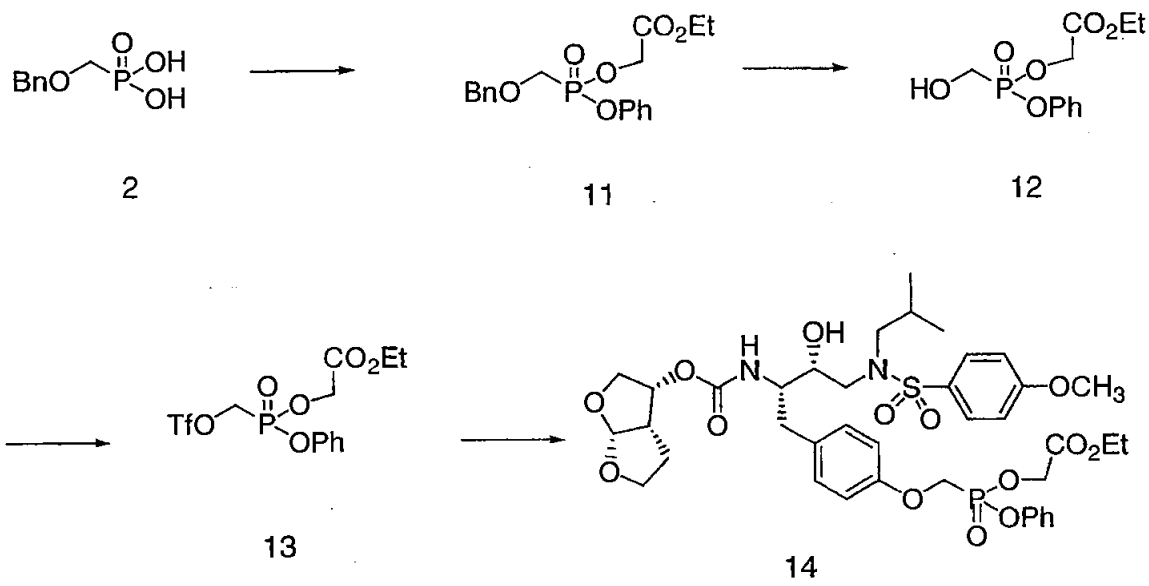
Scheme 2



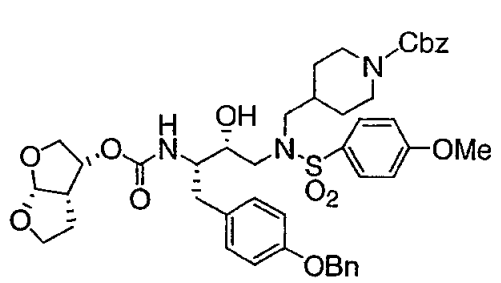
2 7 8

9 10

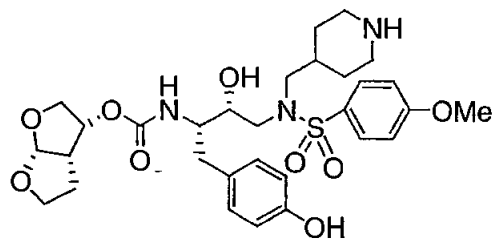
Scheme 3


BnO
OH
OH
2
CO2Et
BnO
OPh
11
CO2Et
HO
OPh
12
CO2Et
TfO
OPh
13
H
N
OH
N
S
OCH3
CO2Et
OPh
14

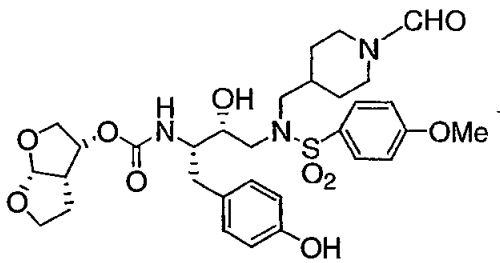
Scheme 4



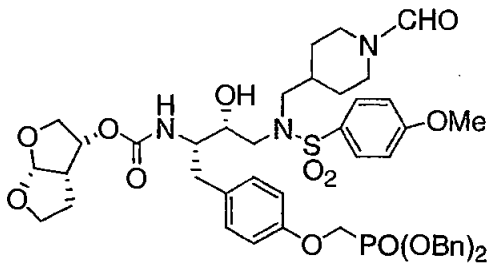
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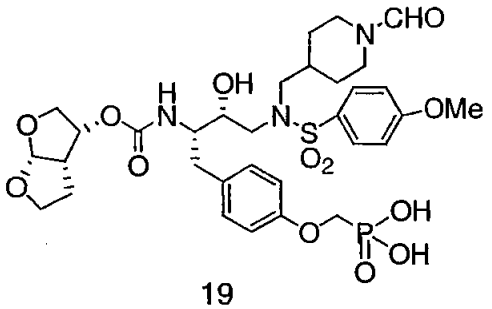
16



17



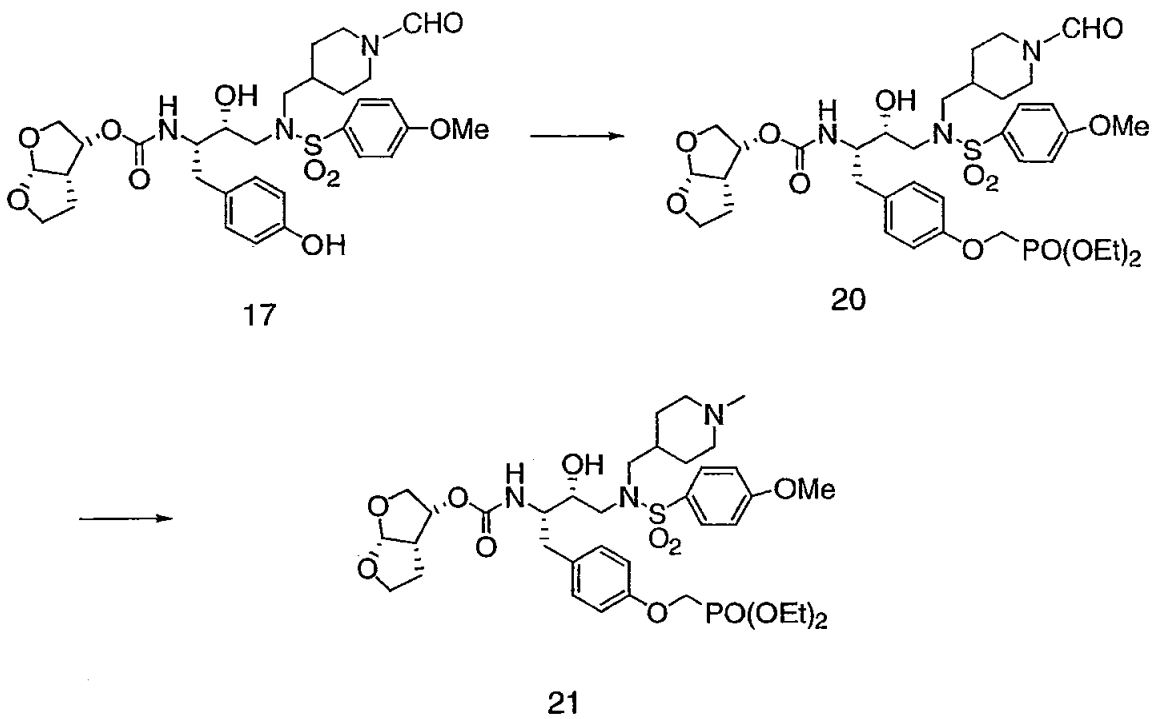
18



19

5

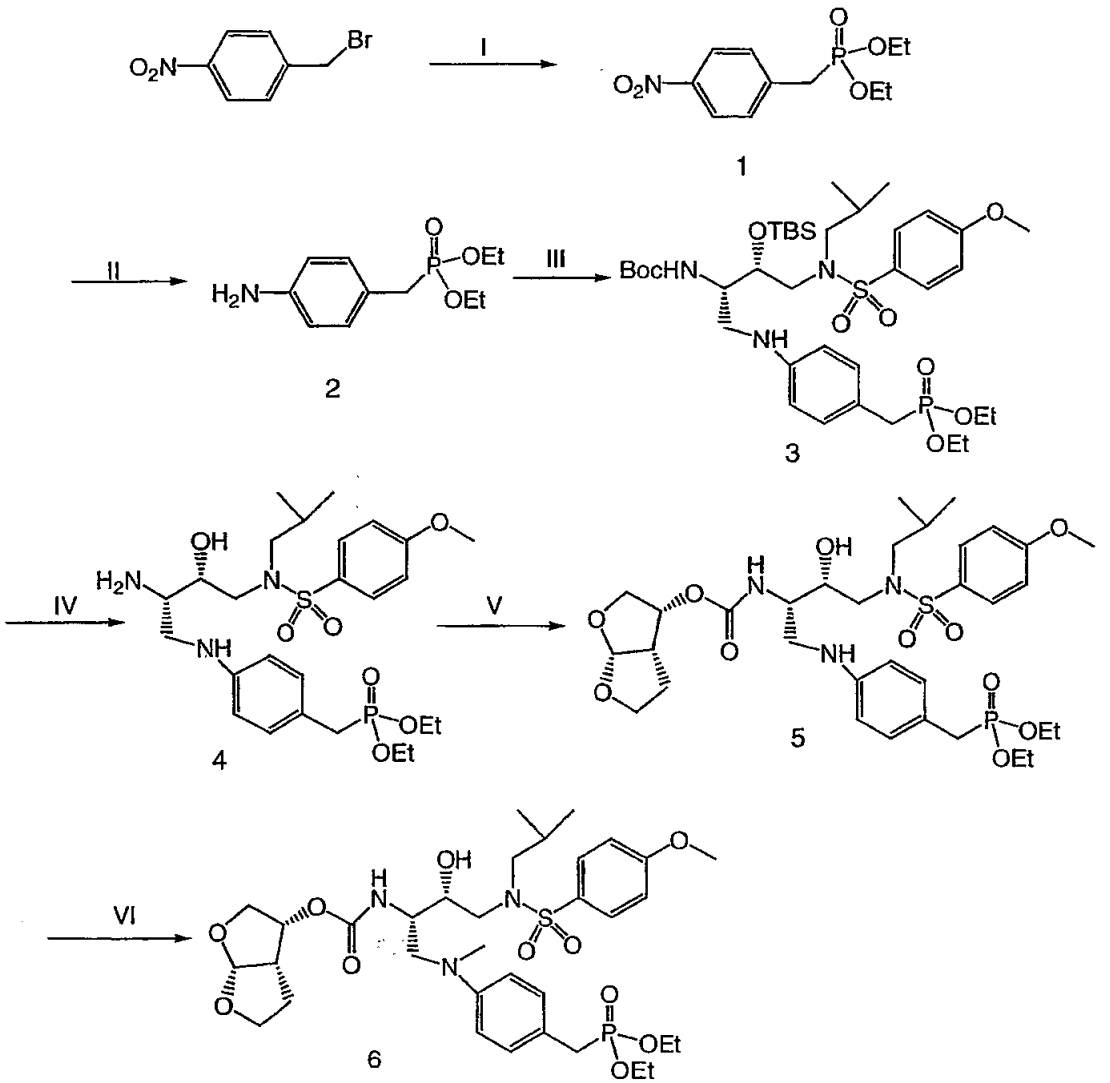
Scheme 5



Scheme Section G

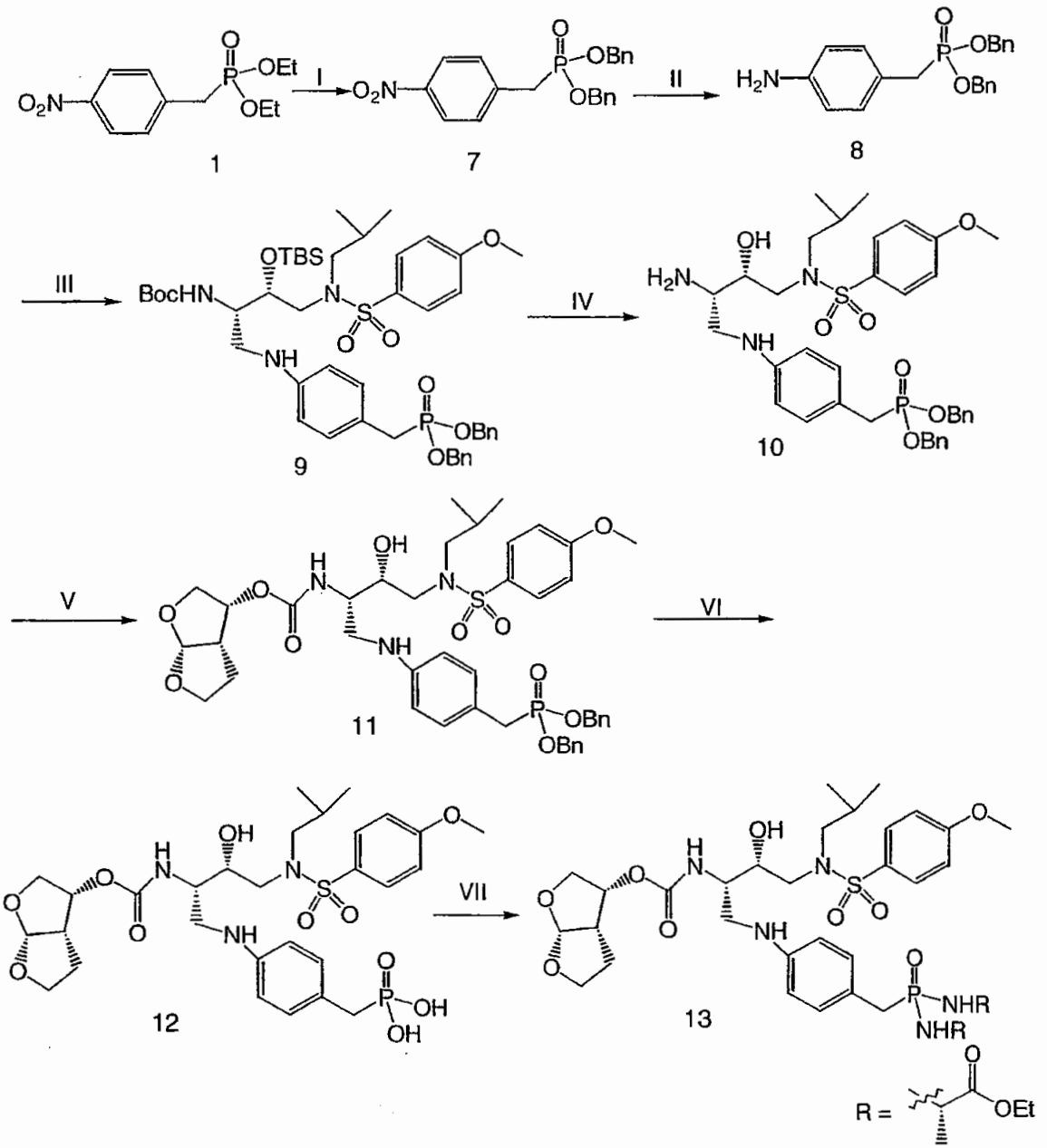
Schemes 1 to 9 are described in the examples.

Scheme 1



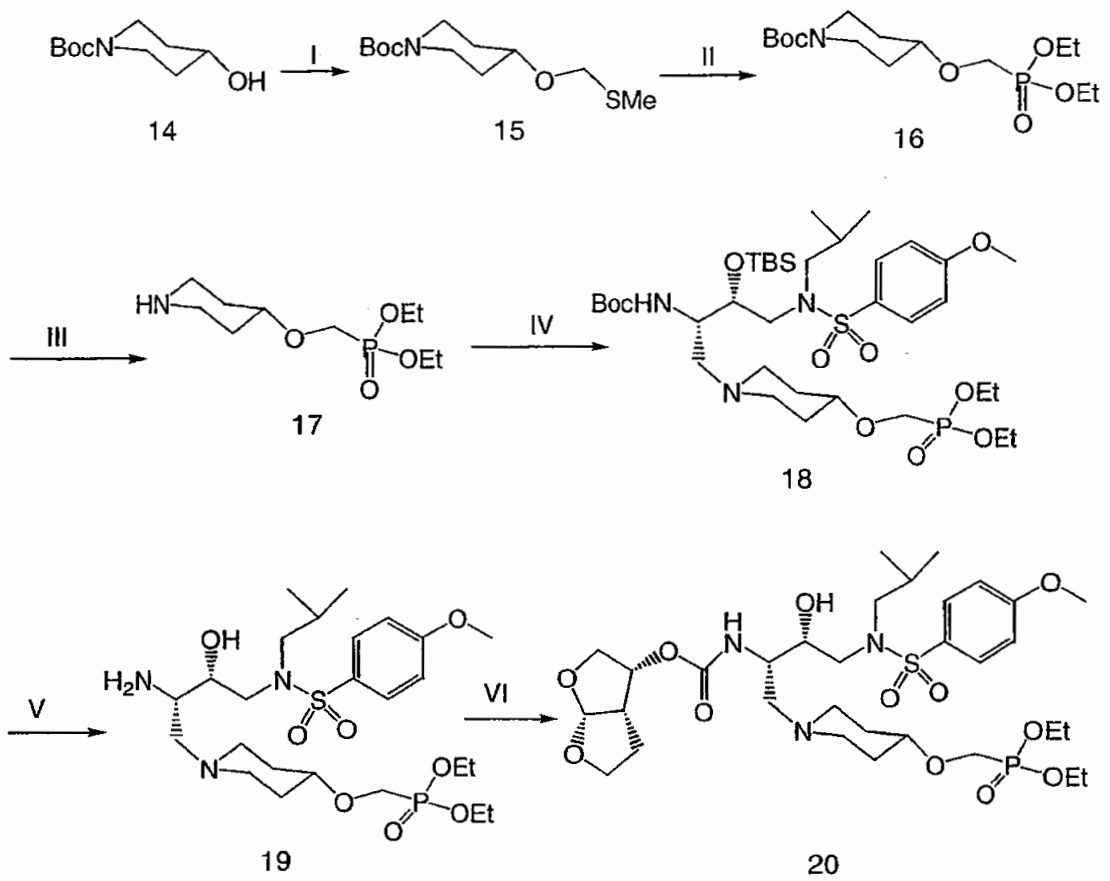
I. $P(OEt)_3$/120 C; II. H_2/10%Pd-C; III. See Scheme Section H, Scheme 13, Compound 48 /$NaBH_3CN$/HOAc/MeOH; IV. a. TFA; b. n-Bu_4NF; V. bisfurancarbonate/DMAP; VI. HCHO/$NaBH_3CN$/HOAc/MeOH

Scheme 2



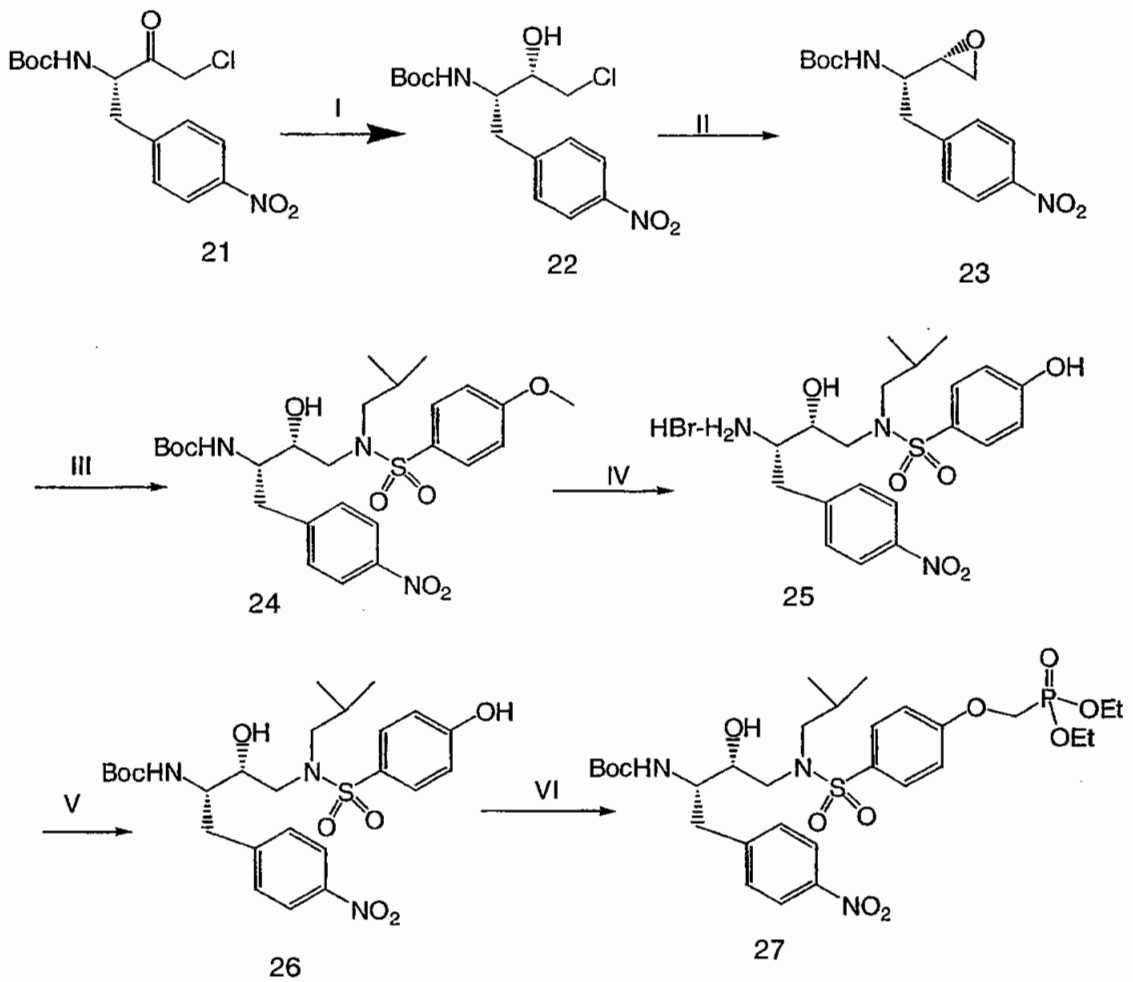
I. a.TMSBr; b. $SOCl_2$/60 C; c. $BnOH/Et_3N$; II. Zn/HOAc; III. See Scheme Section H, Scheme 13, Compound 48 /$NaBH_3CN$/HOAc/MeOH; IV. a. TFA; b. n-Bu_4NF; V. bisfurancarbonate/DMAP; VI. H_2/10%Pd-C; VIII.RNH_2/PPh_3/aldrithiol

Scheme 3



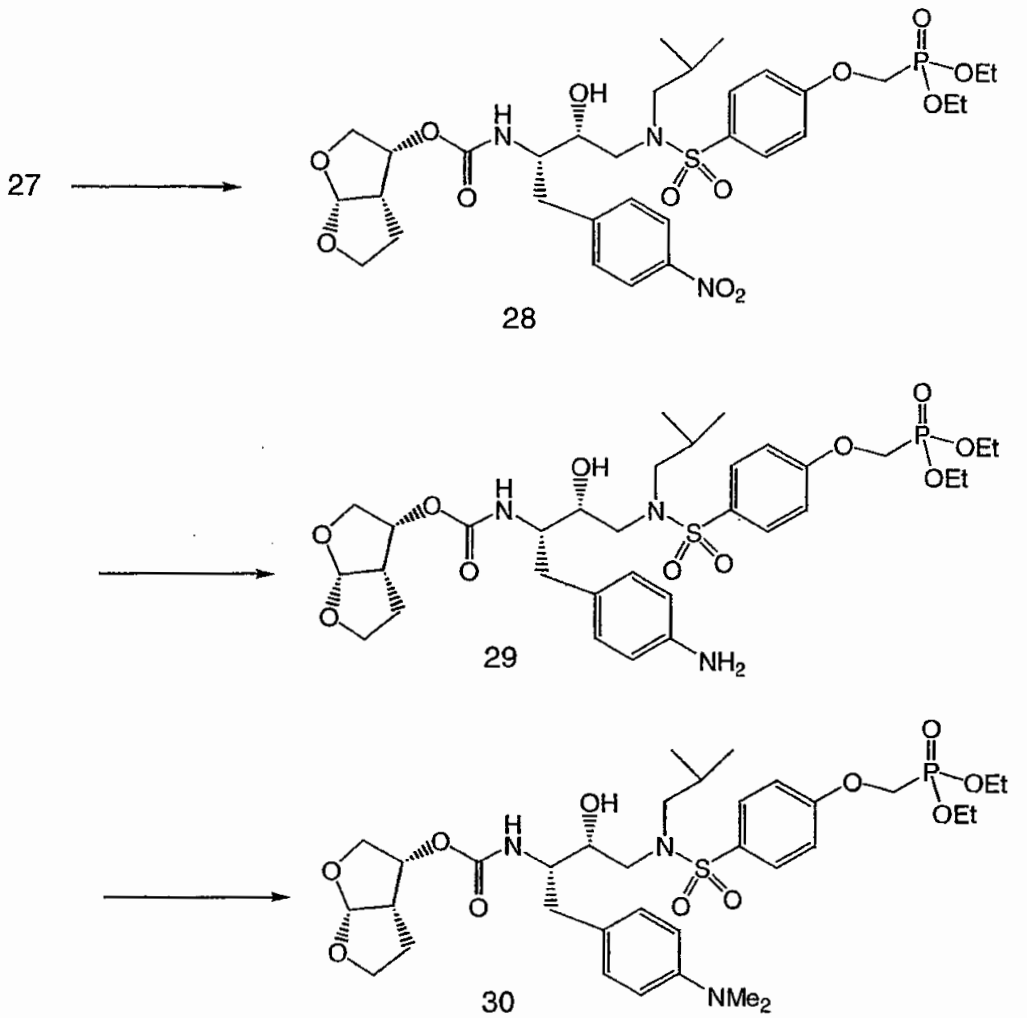
I. a. NaH; b. MTMCl; II. a. $SOCl_2$; b. $P(OEt)_3$/120 C; III. TFA; IV. See Scheme Section H, Scheme 13, Compound 48 /$NaBH_3CN$/HOAc/MeOH; V. a. TFA; b. n-Bu_4NF; VI. bisfurancarbonate/DMAP

Scheme 4



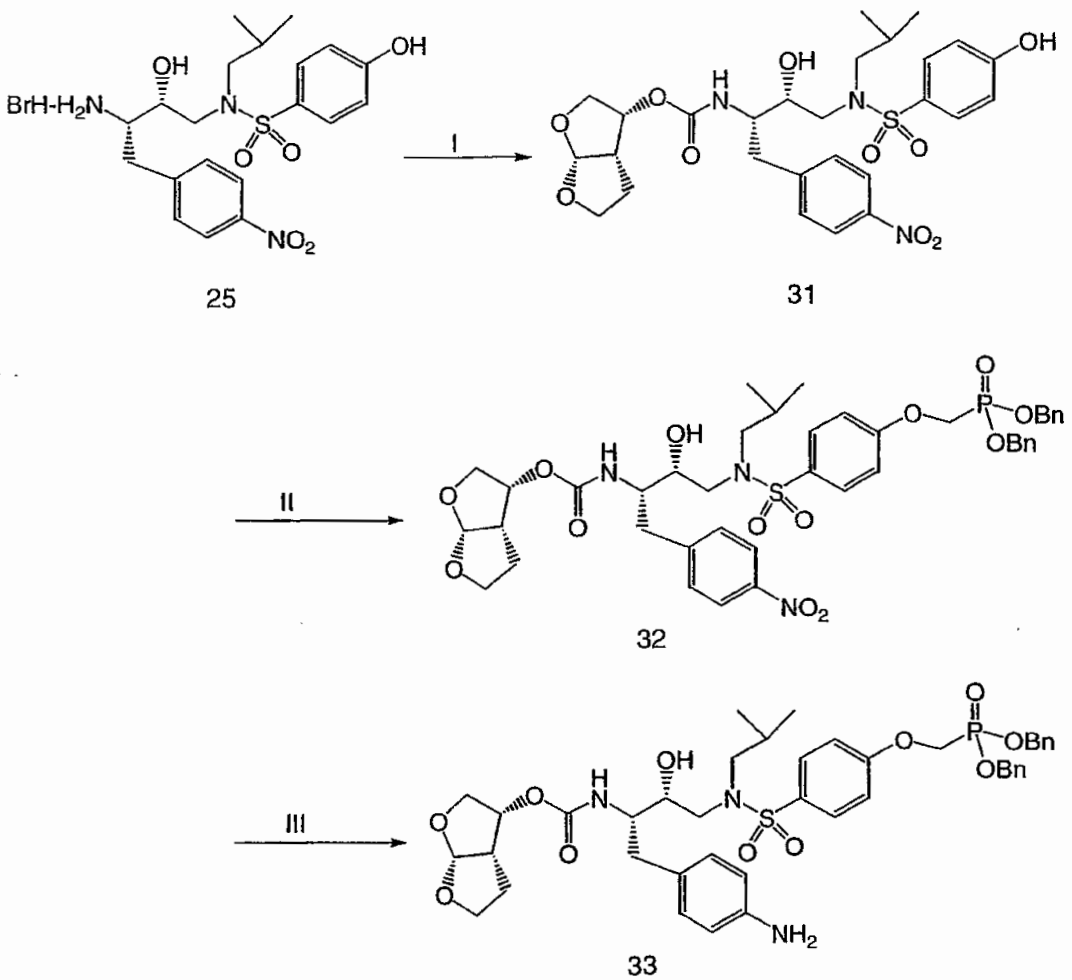
I. $NaBH_4/THF/H_2O$; II. KOH/EtOH; III. a. isobutylamine/iropropanol/80 C; b. 4-methoxybenzenesulfonyl chloride/Et_3N; IV.BBr_3/CH_2Cl_2; V. $Boc_2O/NaHCO_3$; VI. $TfOCH_2PO(OEt)_2/Cs_2CO_3$

Scheme 5



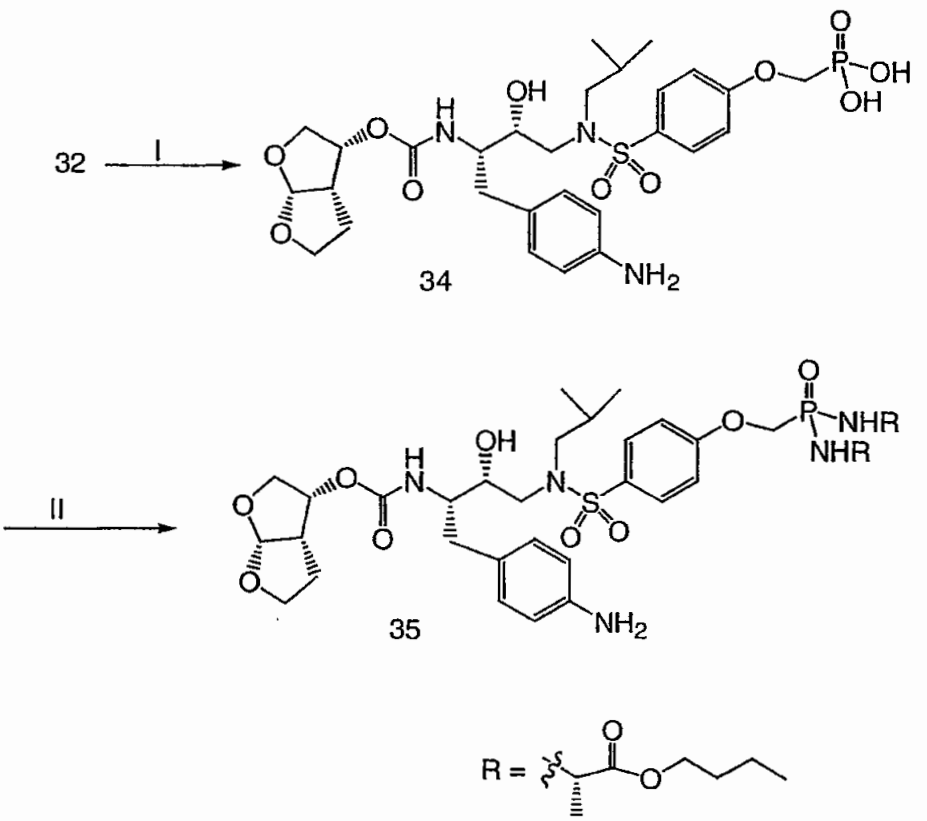
I. TFA/CH_2Cl_2; b. bisfurancarbonate/DMAP ; II. H_2/10% Pd-C/EtOH;
III. HCHO/$NaBH_3CN$/HOAc/MeOH

Scheme 6



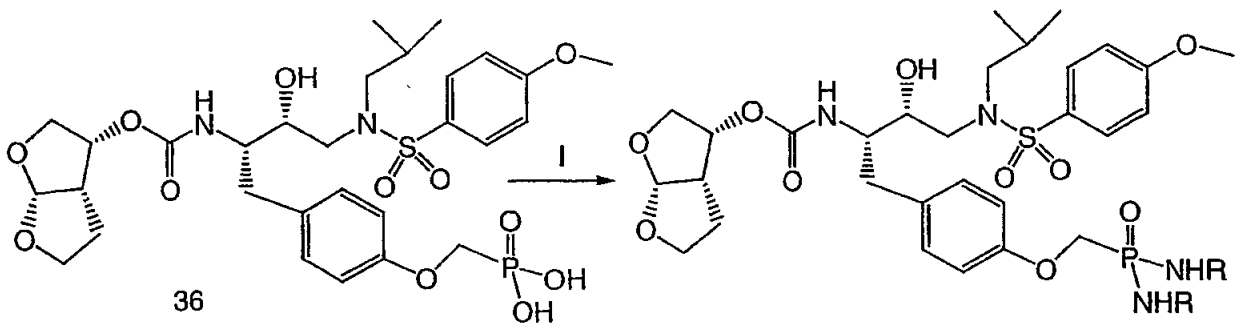
I.a. $TMSCl/Et_3N$; b. bisfurancarbonate/DMAP; c. $n\text{-}Bu_4NF/HOAc$; II. $TfOCH_2PO(OBn)_2/Cs_2CO_3$; III. Zn/HOAc

Scheme 7

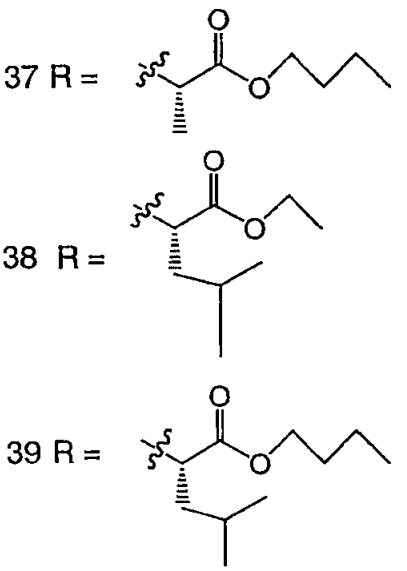


I. H_2/10% Pd-C; II. RNH_2/PPh_3/Aldrithiol/diisopropylethylamine/pyridine

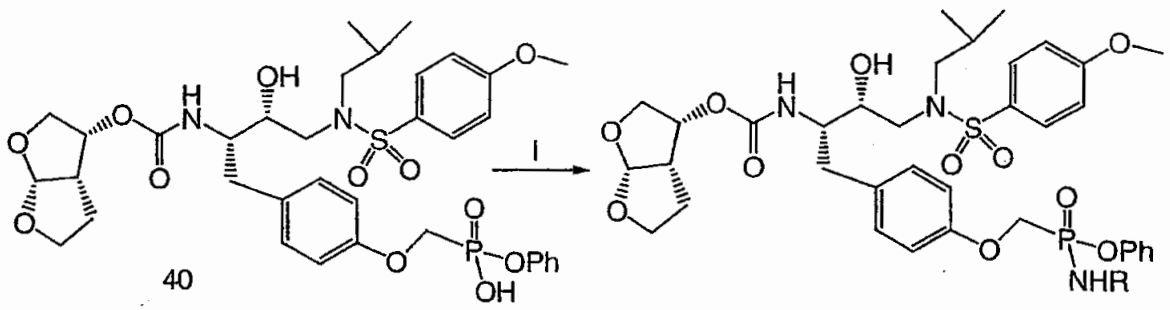
Scheme 8



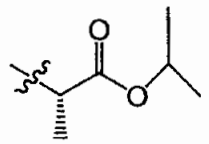
I. RNH_2/PPh_3/Aldrithiol/diisopropylethylamine/pyridine

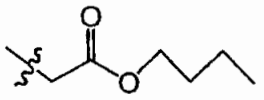


Scheme 9



I. RNH_2/PPh_3/Aldrithiol/diisopropylethylamine/ pyridine

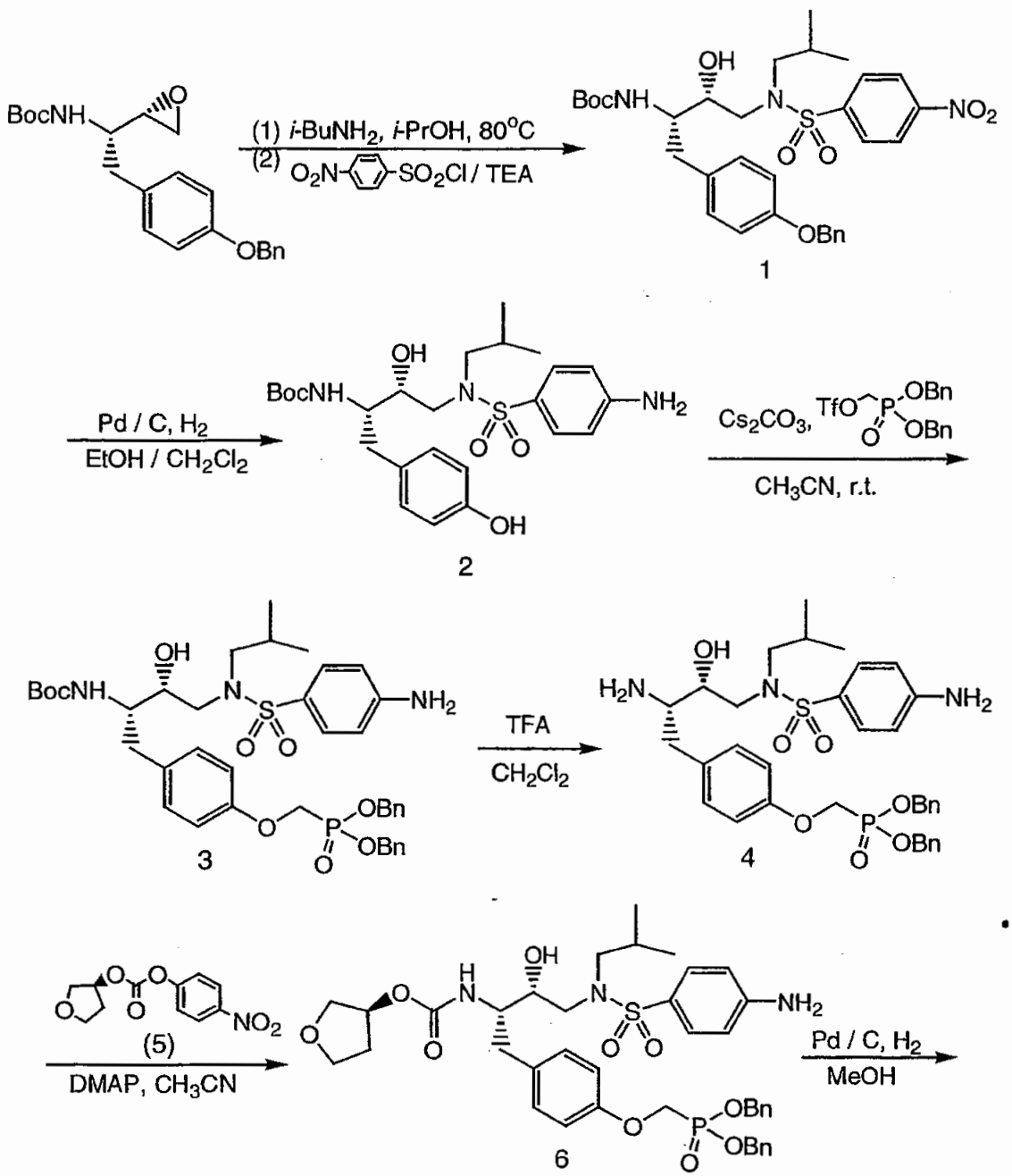
41 R = 

42 R = 

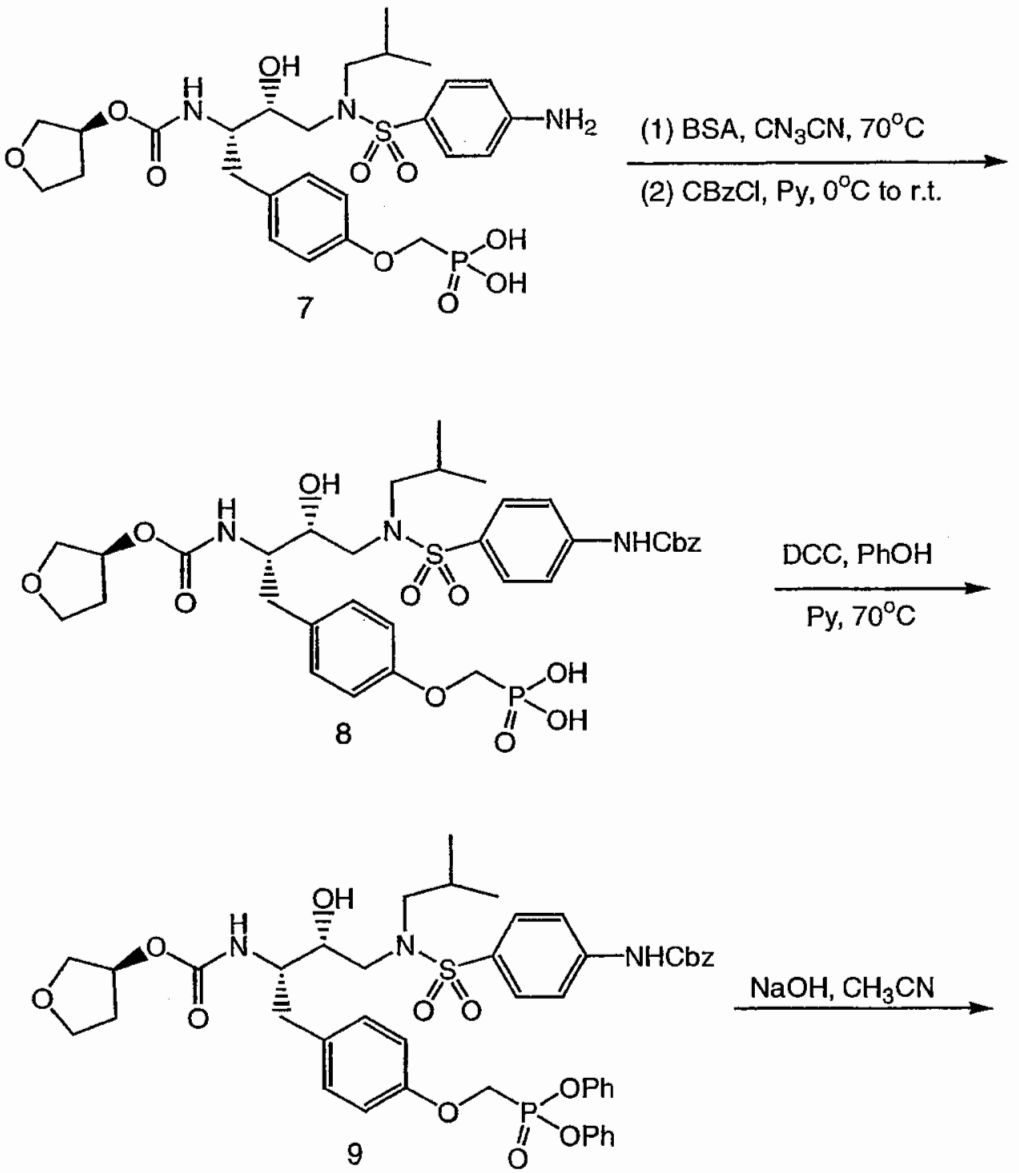
Scheme Section H

Schemes 1-14 are described in the examples.

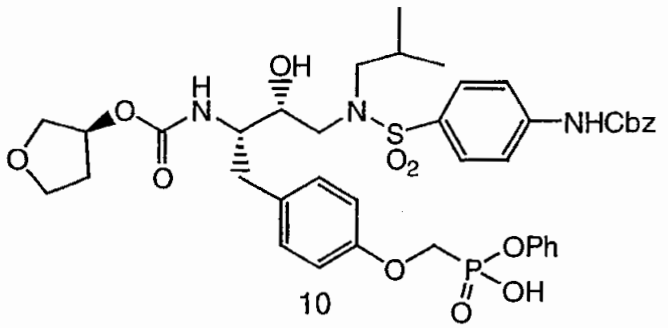
Scheme 1



Scheme 2


(1) BSA, CN_3CN, 70°C
(2) CBzCl, Py, 0°C to r.t.
DCC, PhOH
Py, 70°C
NaOH, CH_3CN
7
8
9

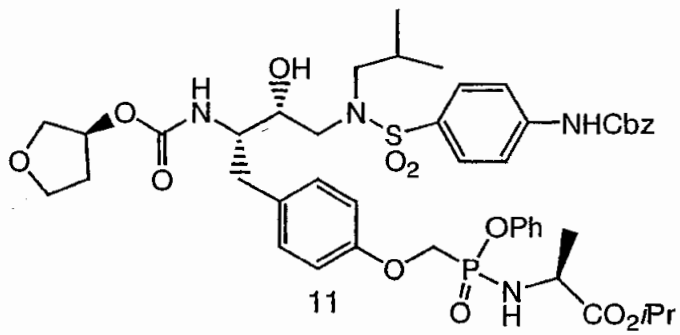
Scheme 3



10

$HCl.H_2N$ CO_2iPr

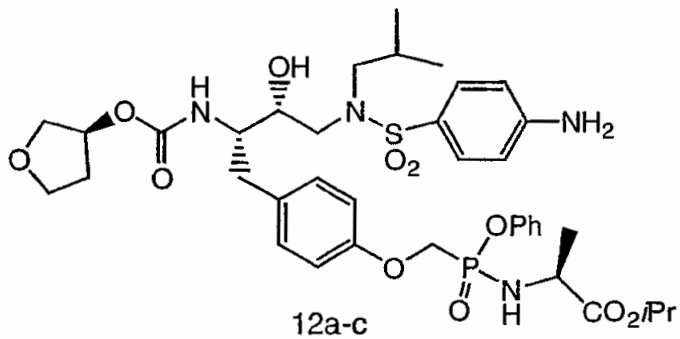
DCC, Py, 70°C



11

Pd / C, H_2

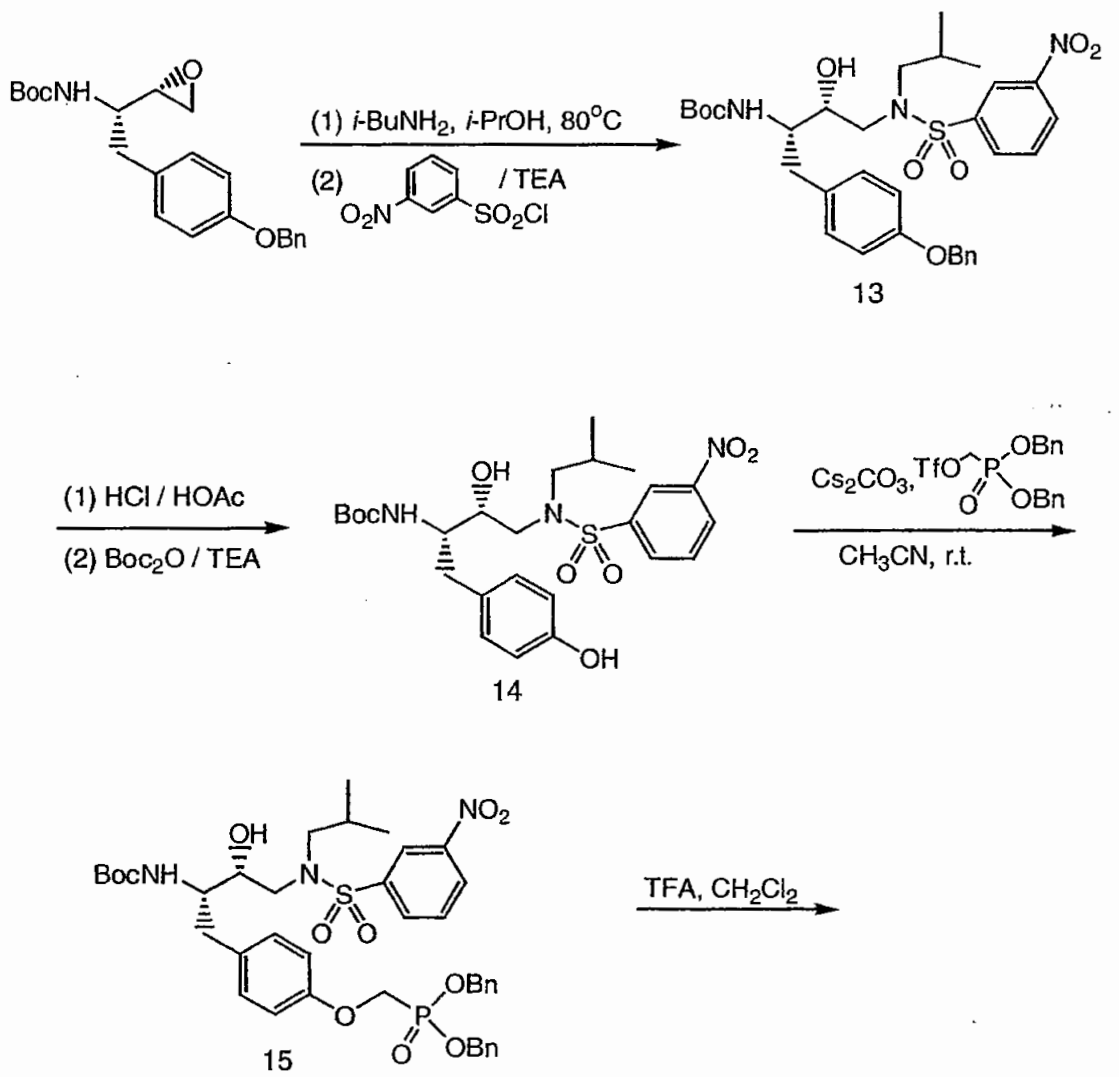
EtOAc



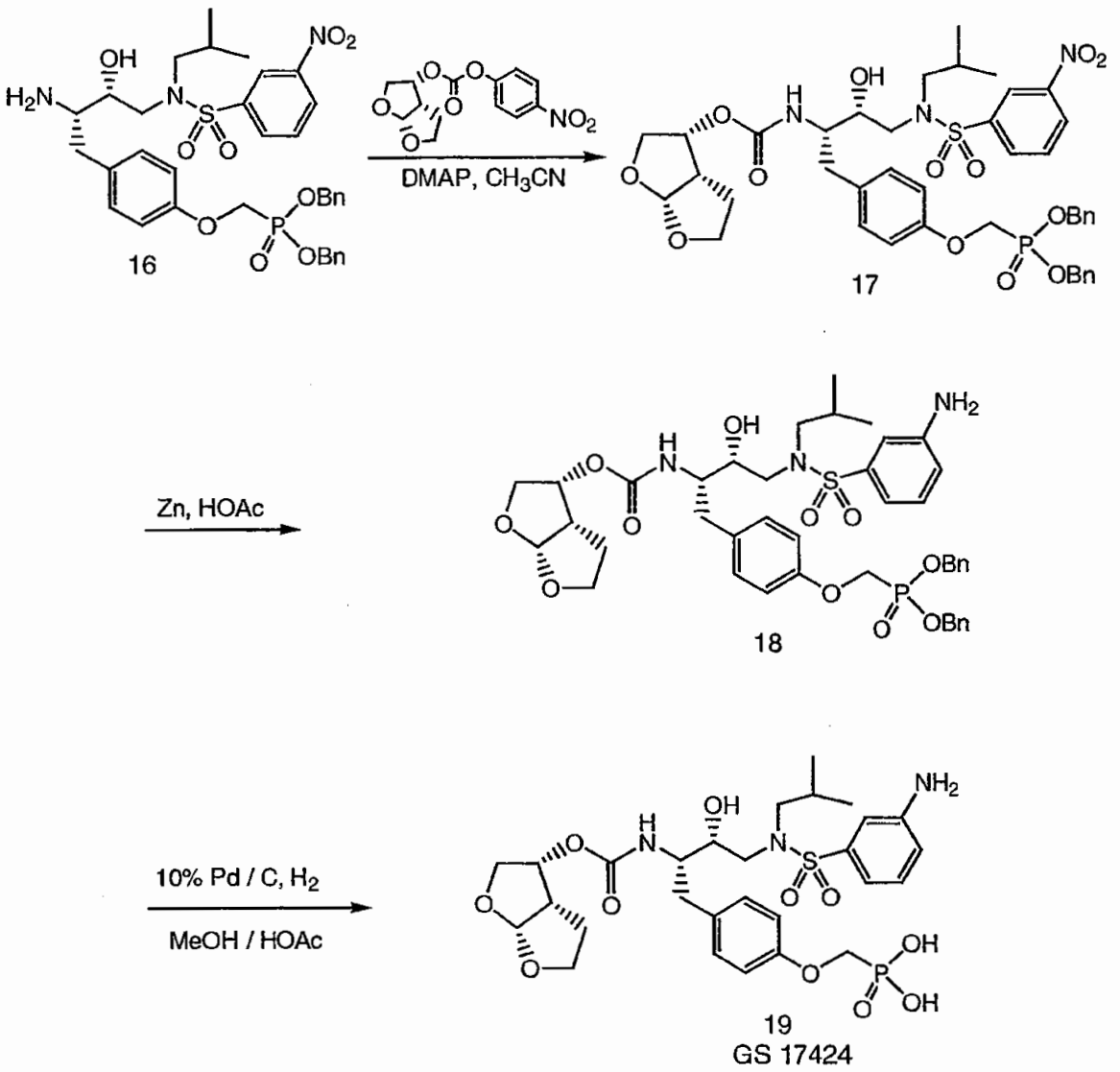
12a-c

12a, GS 108577 (isomer A / B = 1 : 1)
12b, GS 108578 (isomer A)
12c, GS 108579 (isomer B)

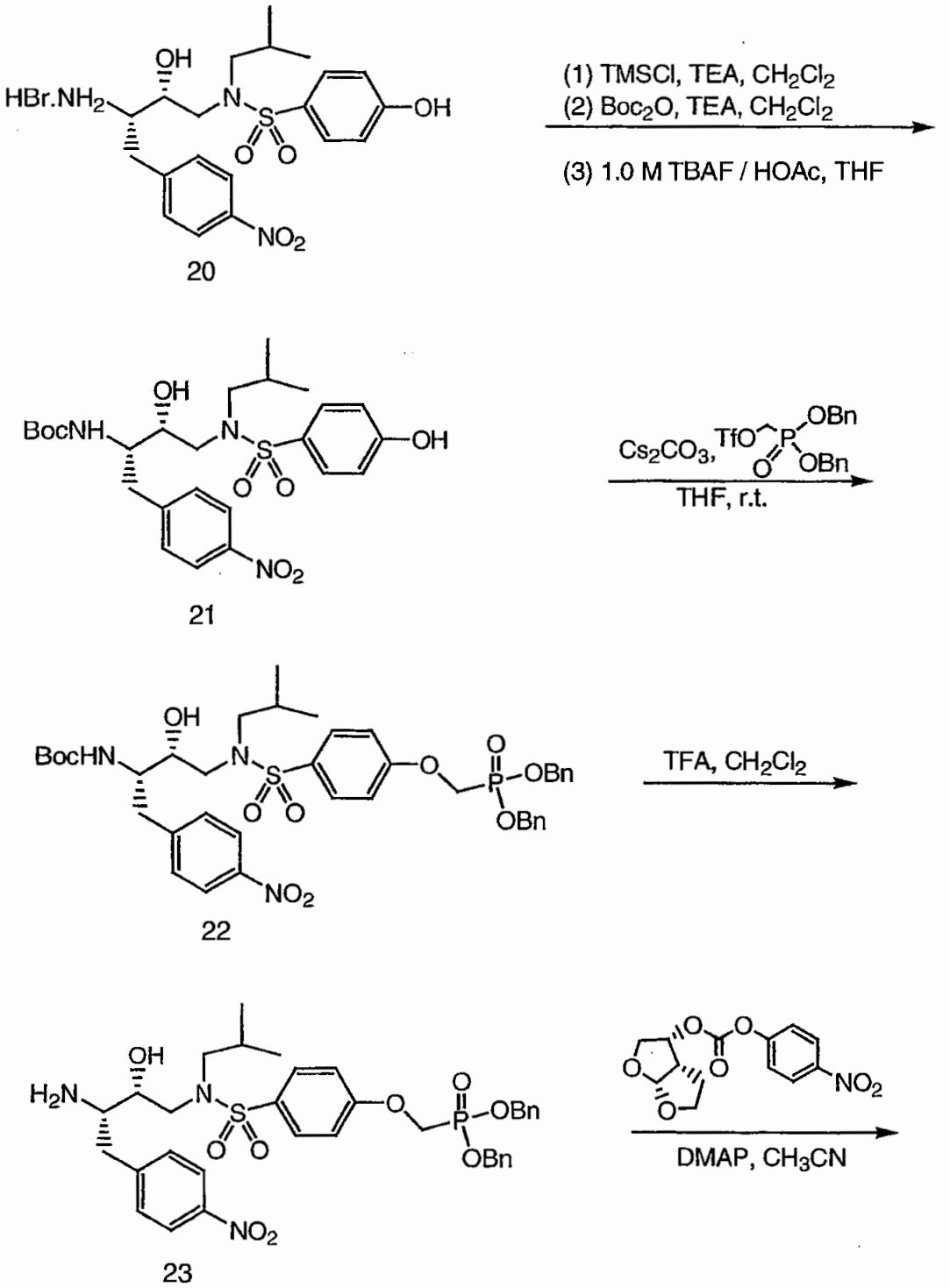
Scheme 4


BocNH
OBn
(1) i-BuNH2, i-PrOH, 80°C
(2)
/ TEA
O2N
SO2Cl
OH
NO2
N
S
O
13
(1) HCl / HOAc
(2) Boc2O / TEA
14
Cs2CO3, TfO
P
OBn
CH3CN, r.t.
15
TFA, CH2Cl2

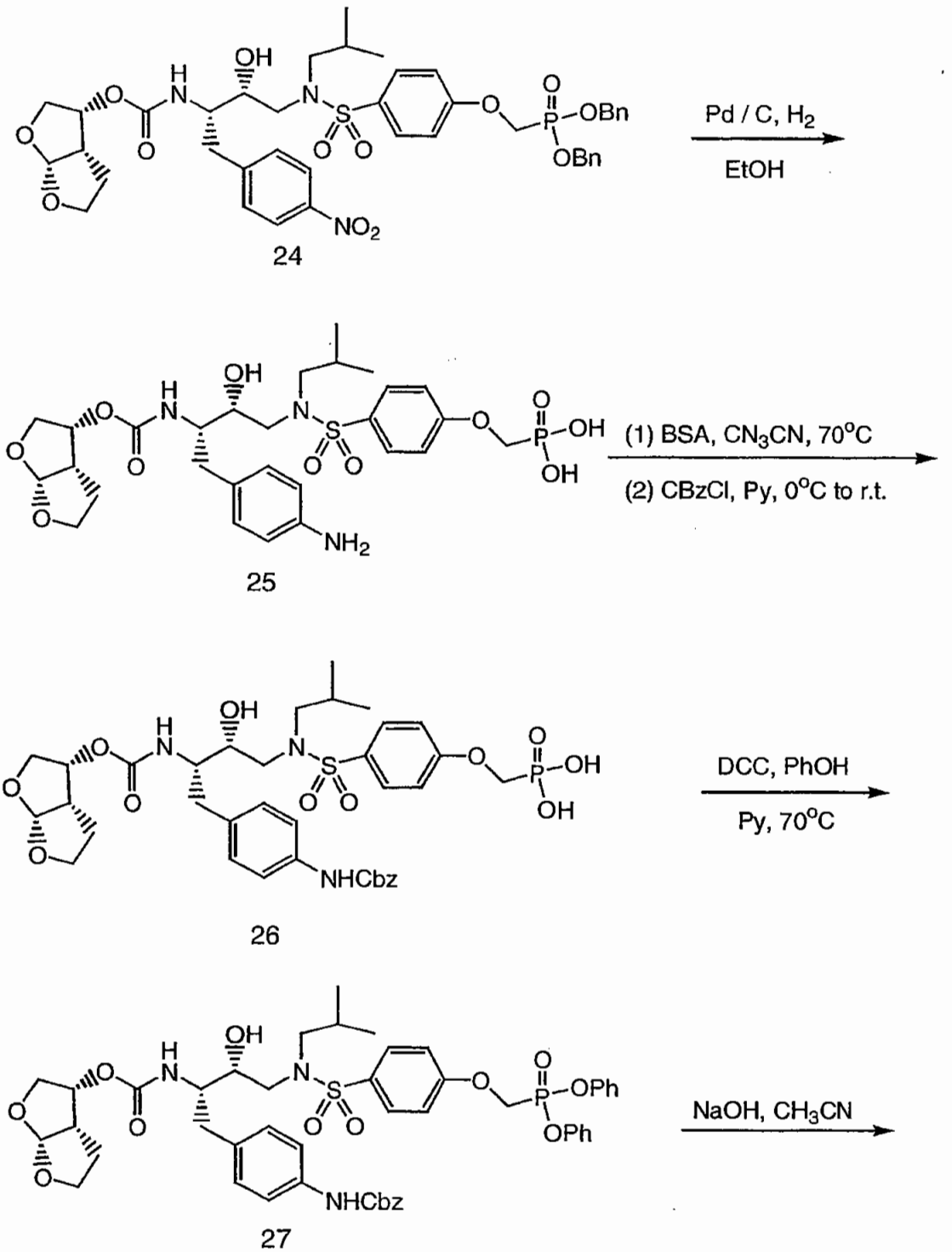
Scheme 5


NO2
OH
H2N
N
S
O
OBn
OBn
16
DMAP, CH3CN
NO2
17
Zn, HOAc
NH2
18
10% Pd / C, H2
MeOH / HOAc
OH
19
GS 17424

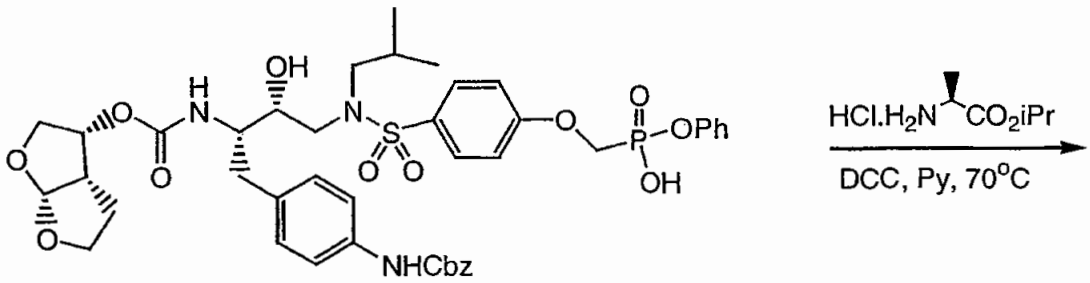
Scheme 6


HBr.NH2
OH
N
S
O
O
OH
NO2
20
(1) TMSCl, TEA, CH2Cl2
(2) Boc2O, TEA, CH2Cl2
(3) 1.0 M TBAF / HOAc, THF
BocNH
21
Cs2CO3, TfO
OBn
OBn
THF, r.t.
BocHN
22
TFA, CH2Cl2
H2N
23
DMAP, CH3CN

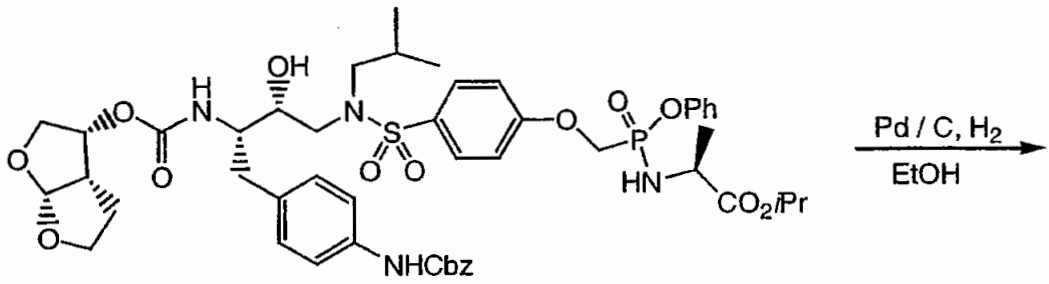
Scheme 7


OH
H
N
O
O
N
S
O
O
O
P
OBn
OBn
NO2
Pd / C, H2
EtOH
24
OH
H
N
O
O
N
S
O
O
O
P
OH
OH
NH2
(1) BSA, CN3CN, 70°C
(2) CBzCl, Py, 0°C to r.t.
25
OH
H
N
O
O
N
S
O
O
O
P
OH
OH
NHCbz
DCC, PhOH
Py, 70°C
26
OH
H
N
O
O
N
S
O
O
O
P
OPh
OPh
NHCbz
NaOH, CH3CN
27

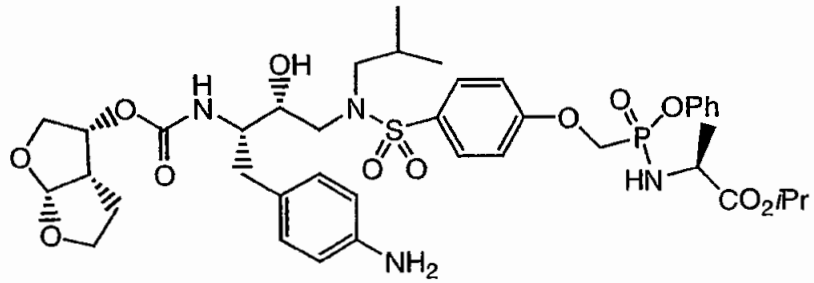
Scheme 8



28



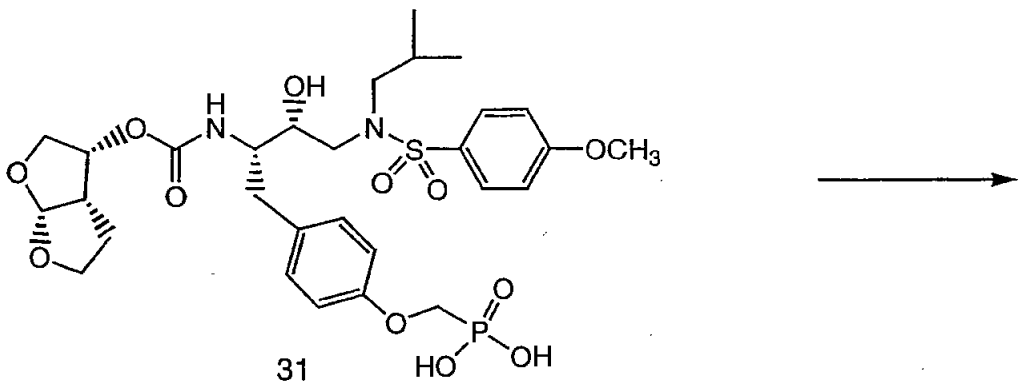
29



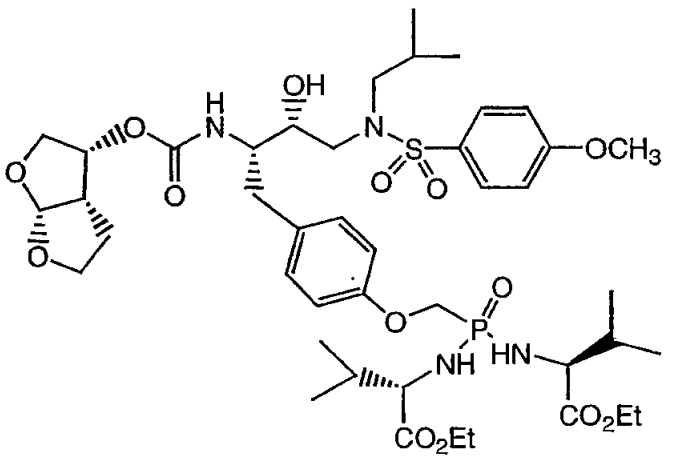
30 a-b

30a R = H, GS 77369
30b R = Et, GS 77425

Scheme 9



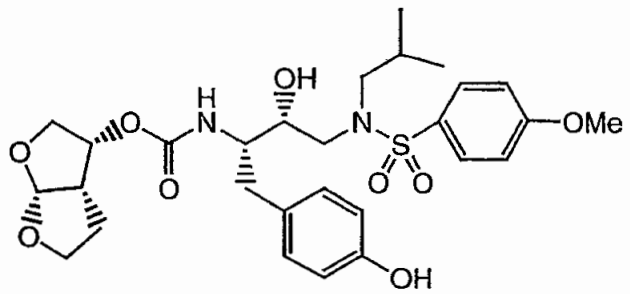
31



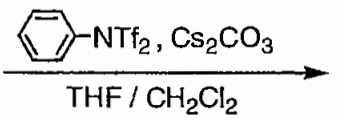
32

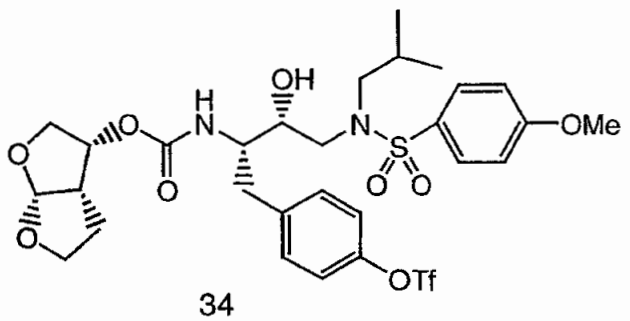
GS 17389

Scheme 10

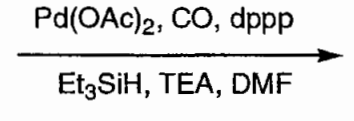


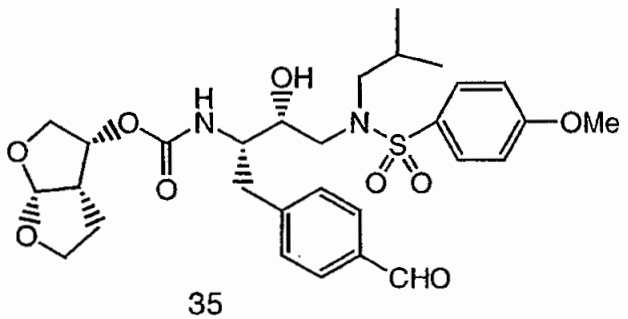
33



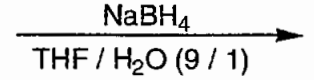


34

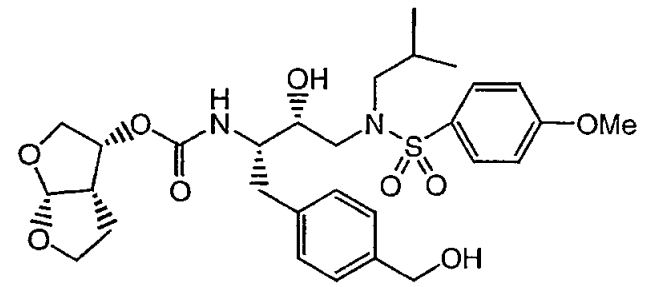




35



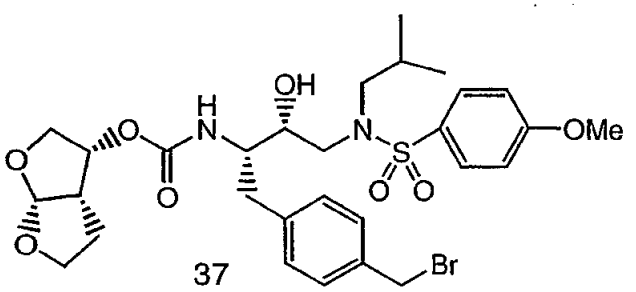
Scheme 11



36

(1) MsCl, TEA
THF / CH_2Cl_2

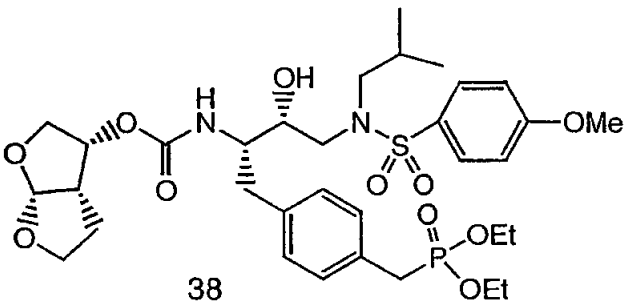
(2) LiBr, 45 min



37

$P(OEt)_3$, toluene

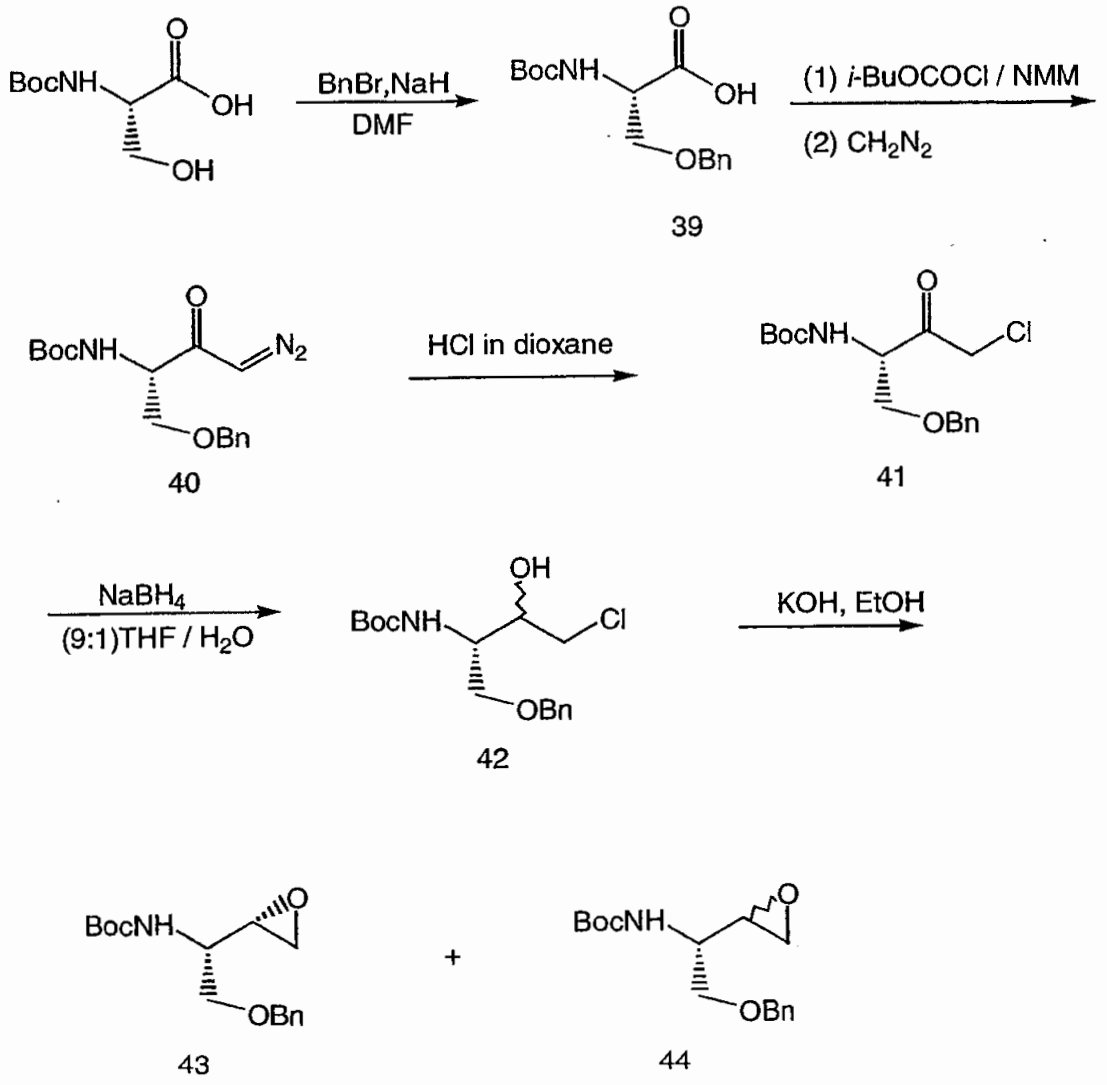
120°C, overnight



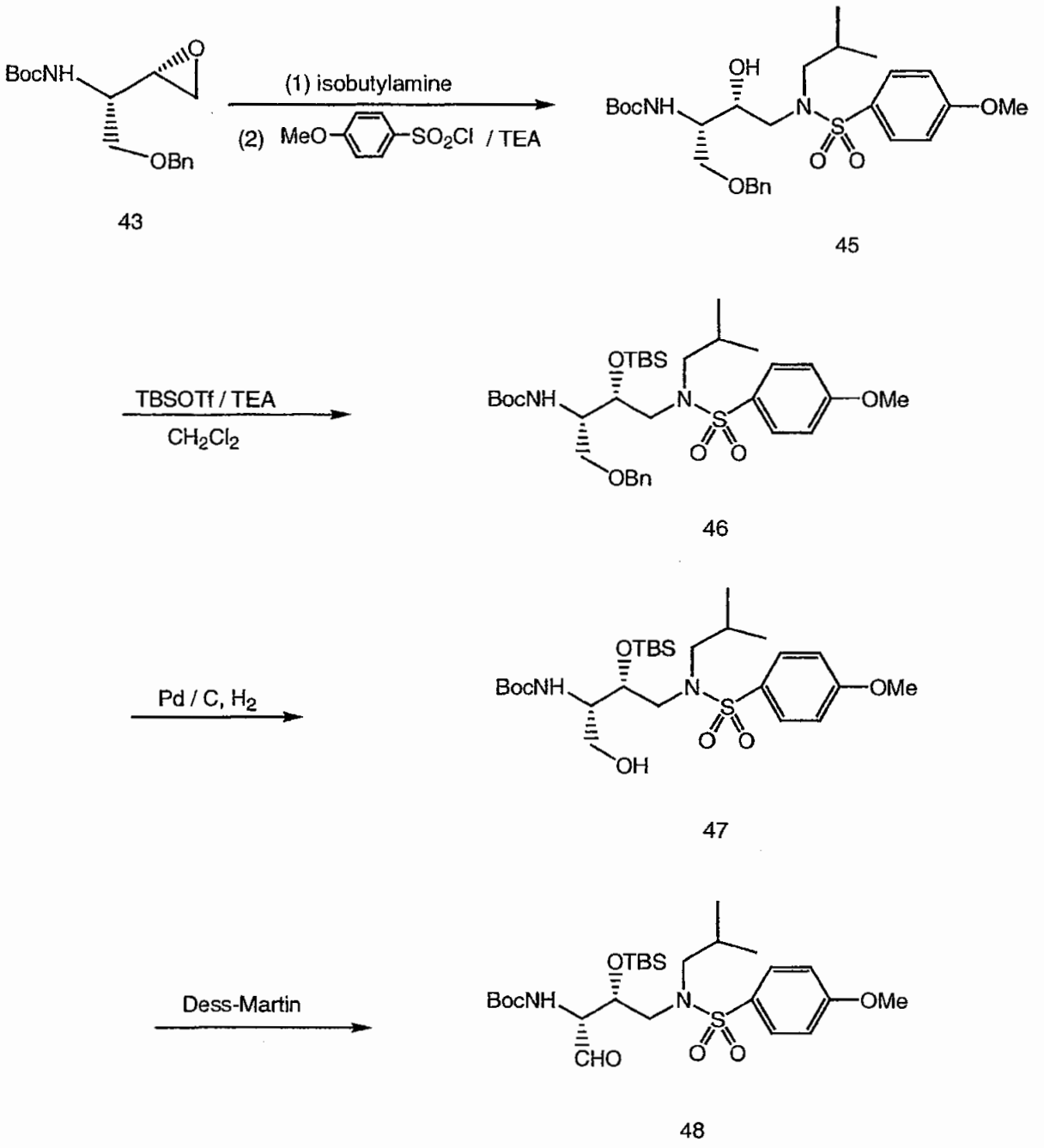
38

GS 191338

Scheme 12

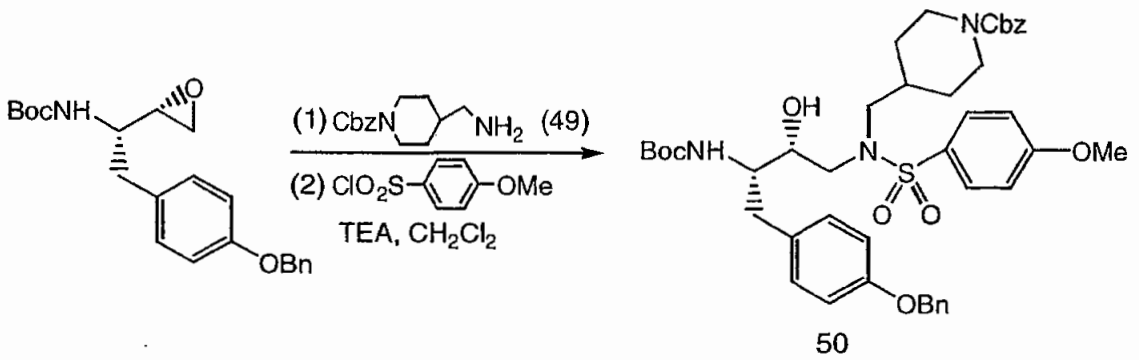

BocNH
OH
OH
O
BnBr,NaH
DMF
BocNH
OH
OBn
O
(1) i-BuOCOCl / NMM
(2) CH2N2
39
BocNH
N2
OBn
O
40
HCl in dioxane
BocNH
Cl
OBn
O
41
NaBH4
(9:1)THF / H2O
OH
BocNH
Cl
OBn
42
KOH, EtOH
BocNH
O
OBn
43
+
BocNH
O
OBn
44

Scheme 13

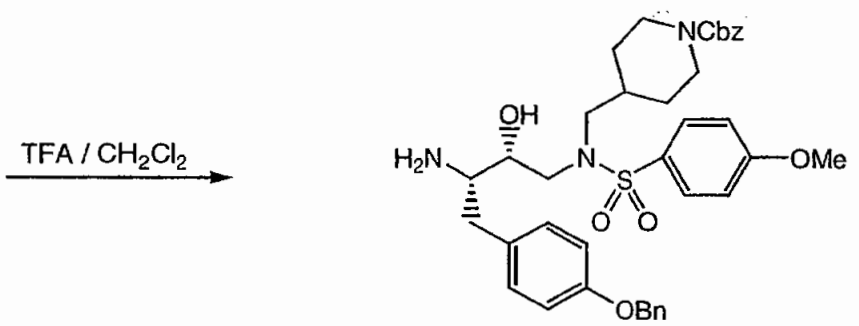


43 45 46 47 48

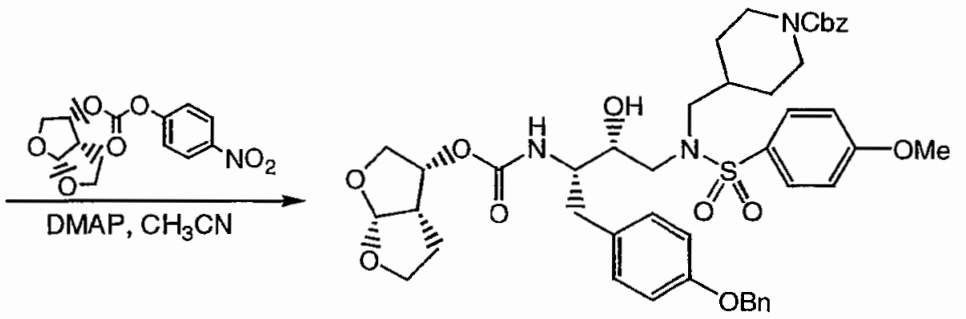
Scheme 14



50



51

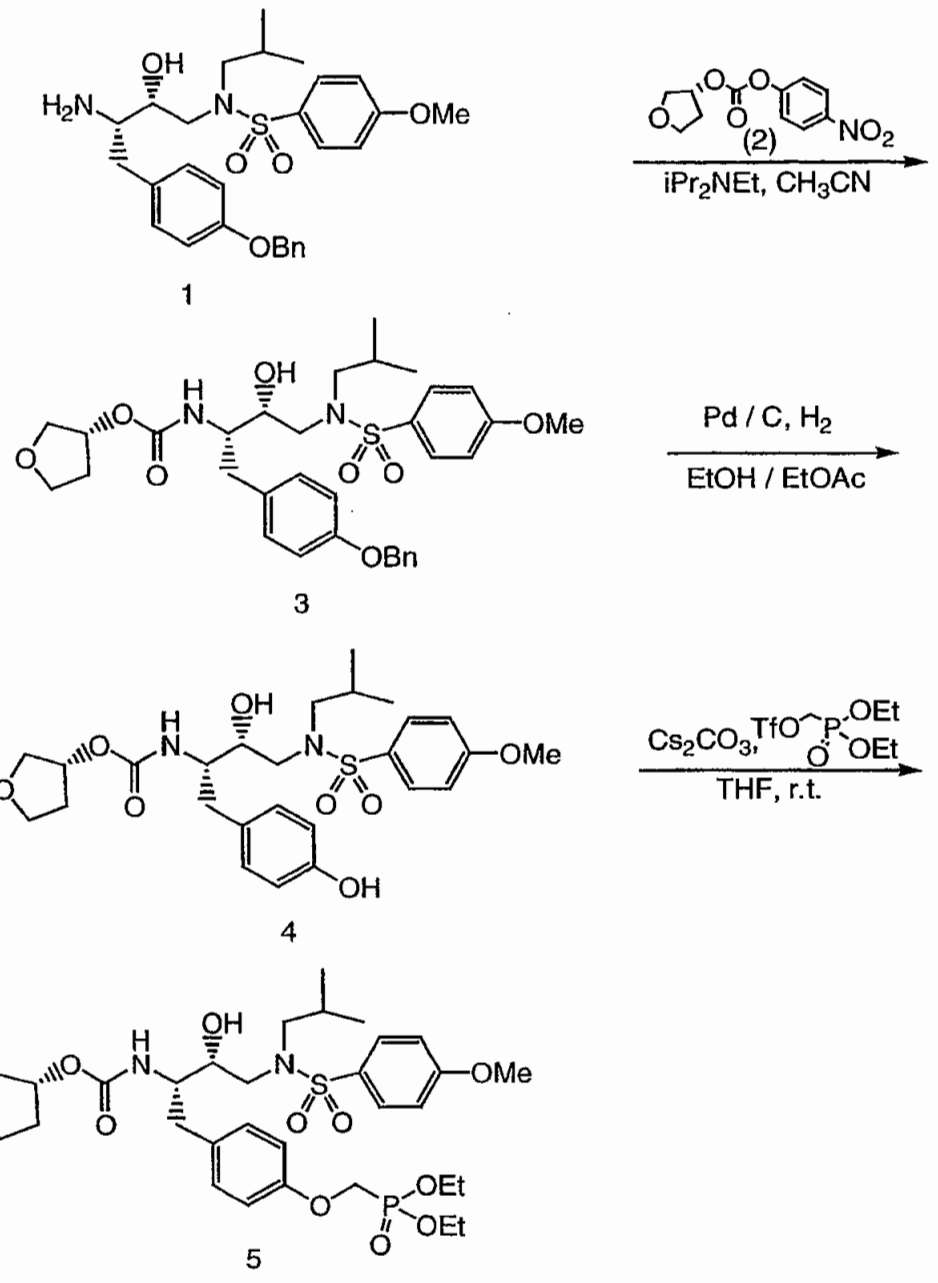


52

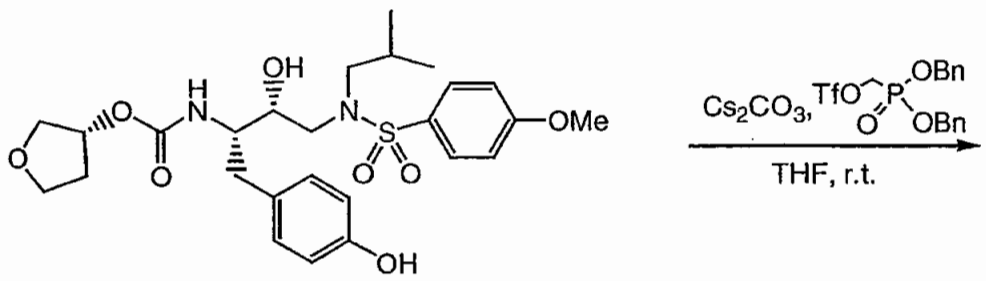
Scheme Section I

Schemes 1 to 3 are described in the examples.

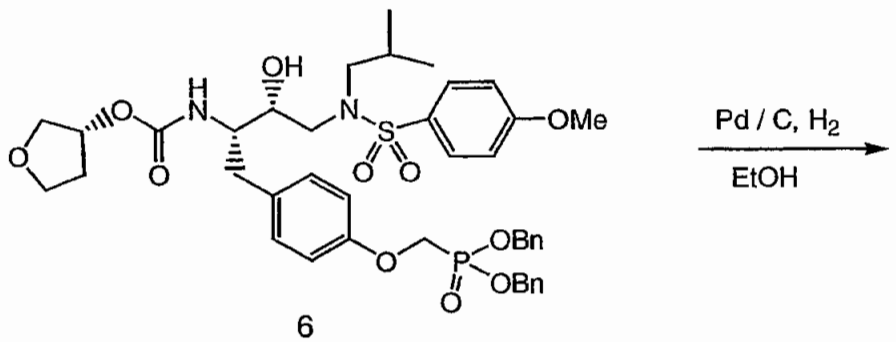
Scheme 1



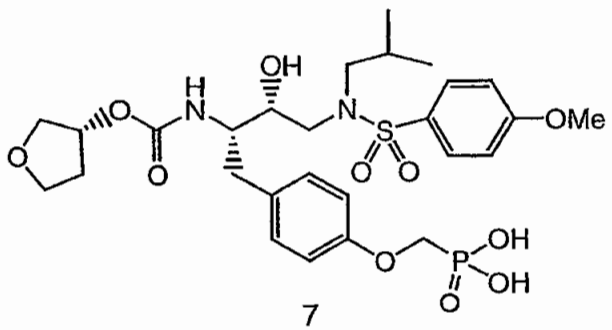
Scheme 2



4

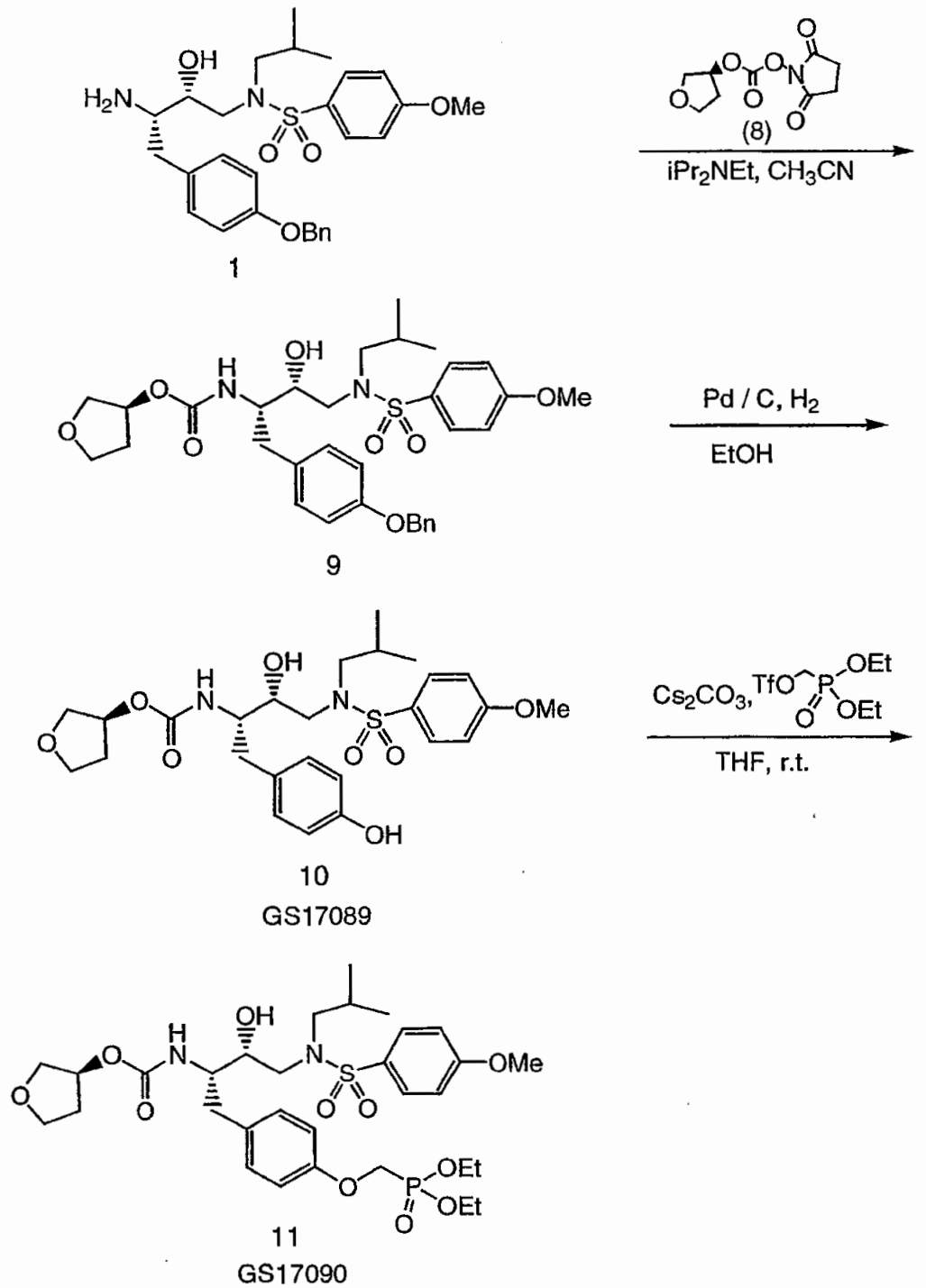


6
GS16574



7
GS16575

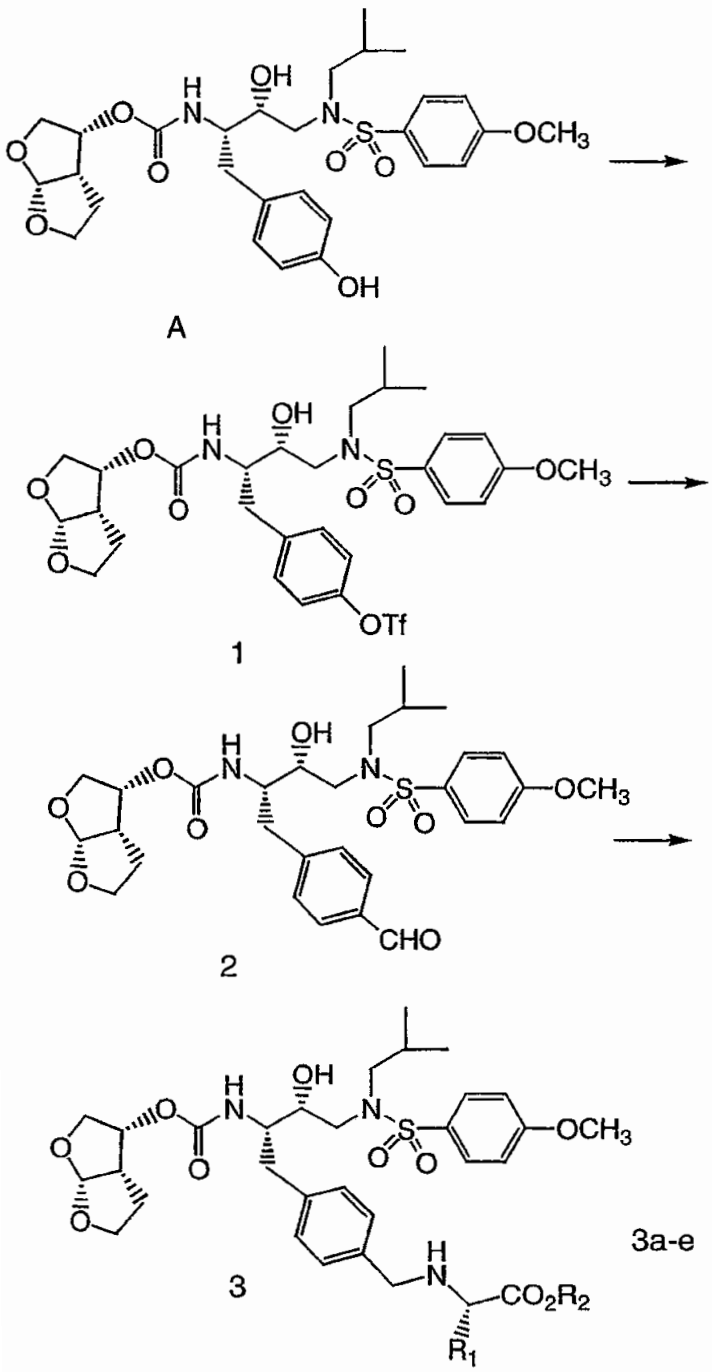
Scheme 3


OH
H2N
N
S
O
O
OMe
OBn
1
(8)
iPr2NEt, CH3CN
H
N
Pd / C, H2
EtOH
9
Cs2CO3, TfO
P
OEt
OEt
THF, r.t.
10
GS17089
11
GS17090

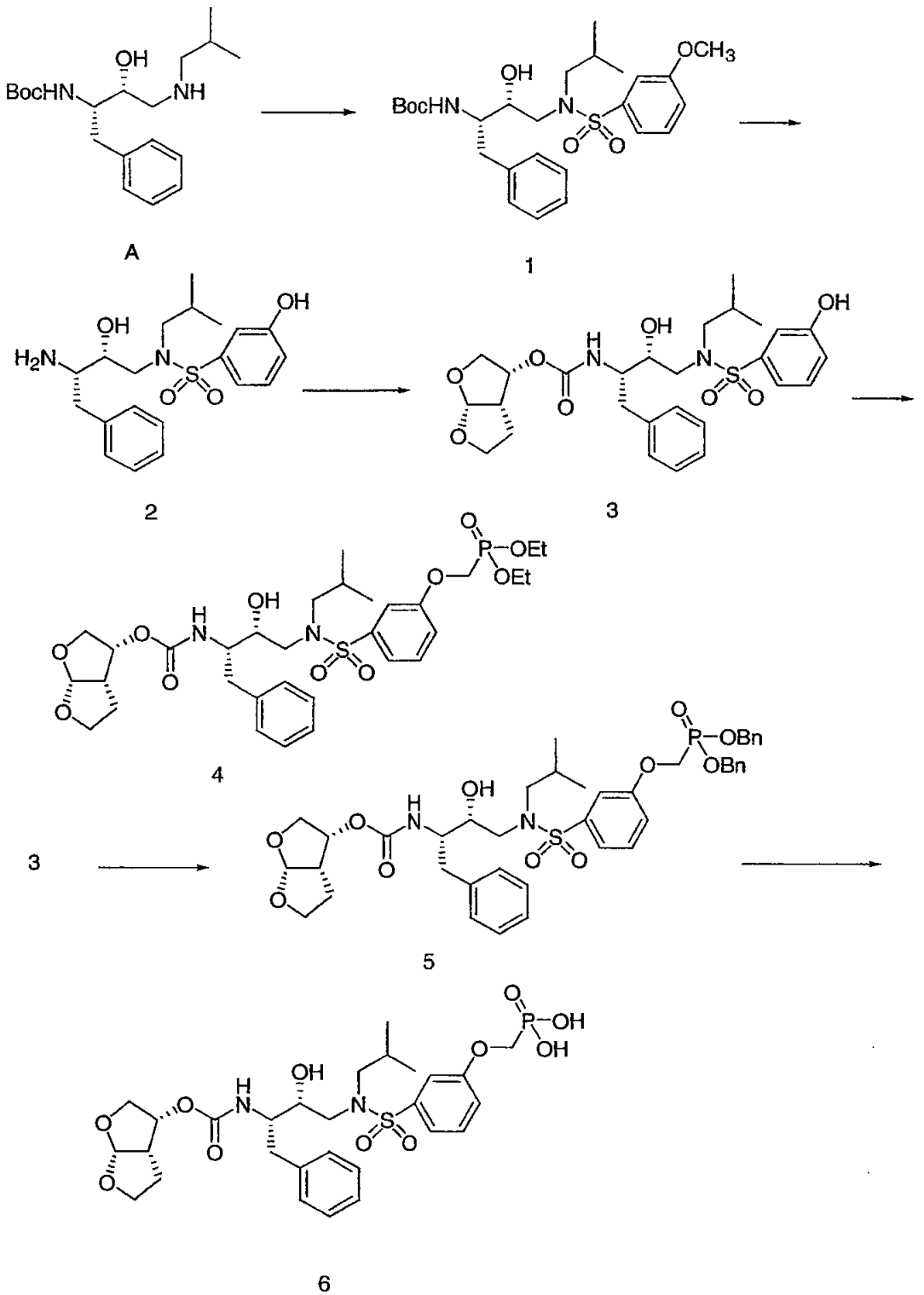
Scheme Section J

Schemes 1-4 are described in the examples.

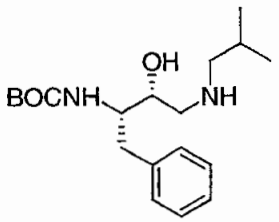
Scheme 1



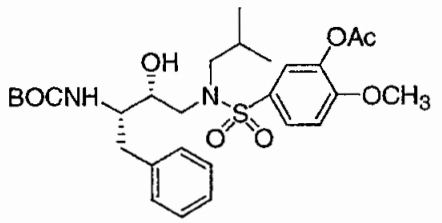
Scheme 2



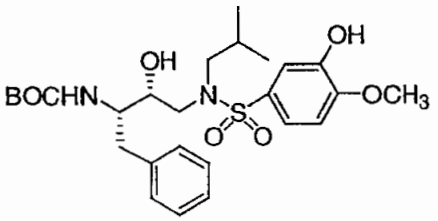
Scheme 3



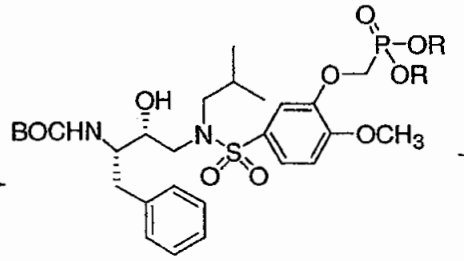
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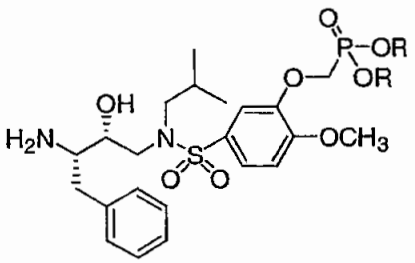
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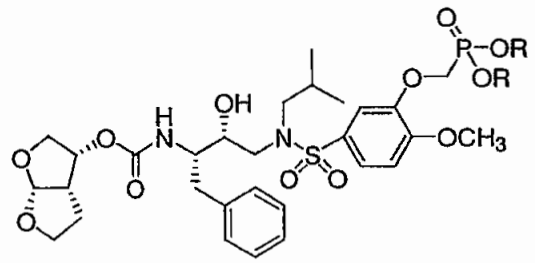
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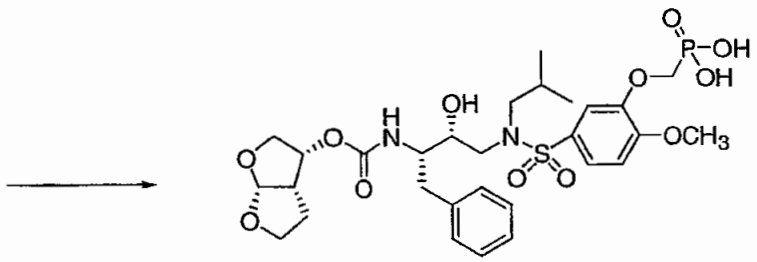
3a : R = -Bn
3b : R = -Et



4a : R = -Bn
4b : R = -Et

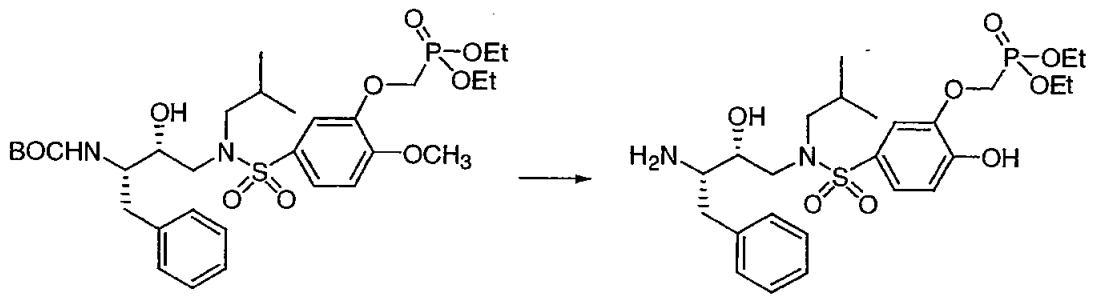


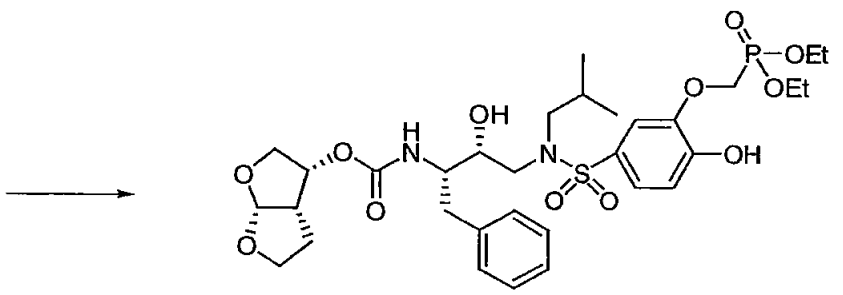
5a : R = -Bn
5b : R = -Et



6

Scheme 4

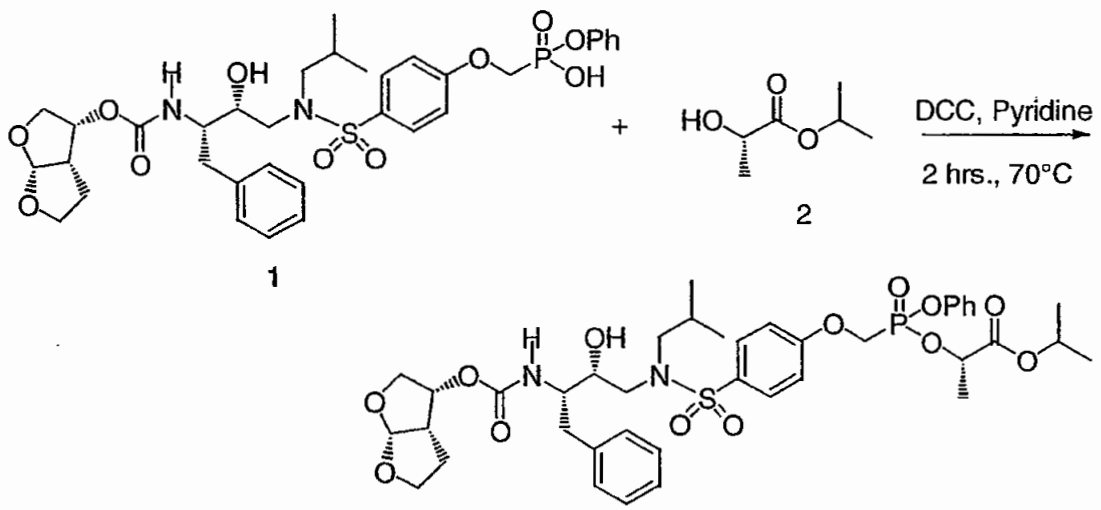

BOCHN
OH
N
S
O
O
O
P
OEt
OEt
OCH3
3b
H2N
OH
OH
7


O
O
O
O
H
N
O
OH
N
S
O
O
P
OEt
OEt
OH
8

Scheme Section K

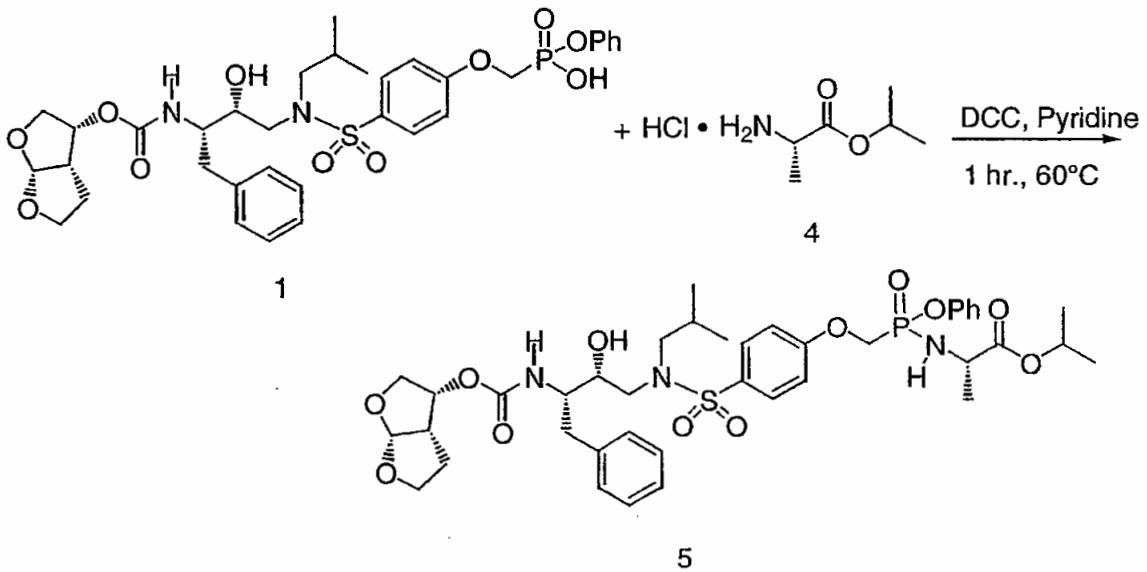
Schemes 1-9 are described in the examples.

Scheme 1



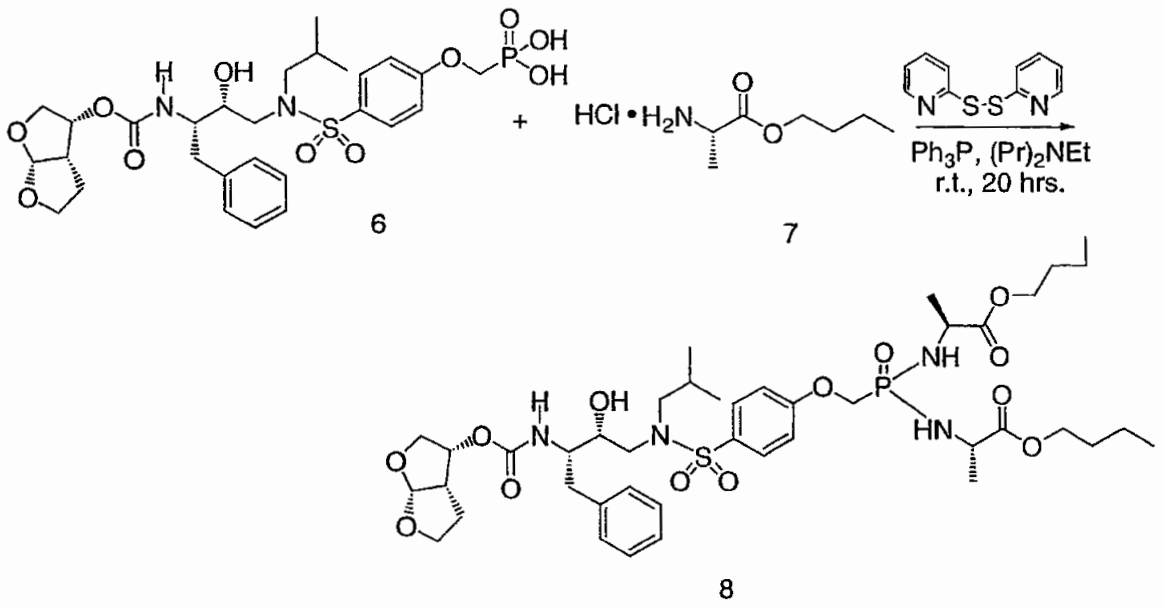
1 2 3

Scheme 2



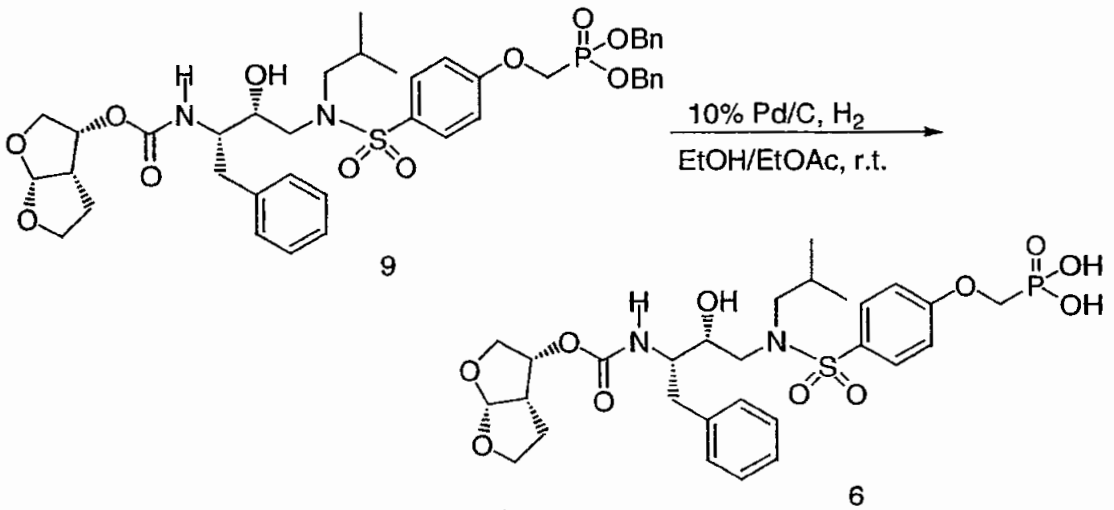
1 4 5

Scheme 3



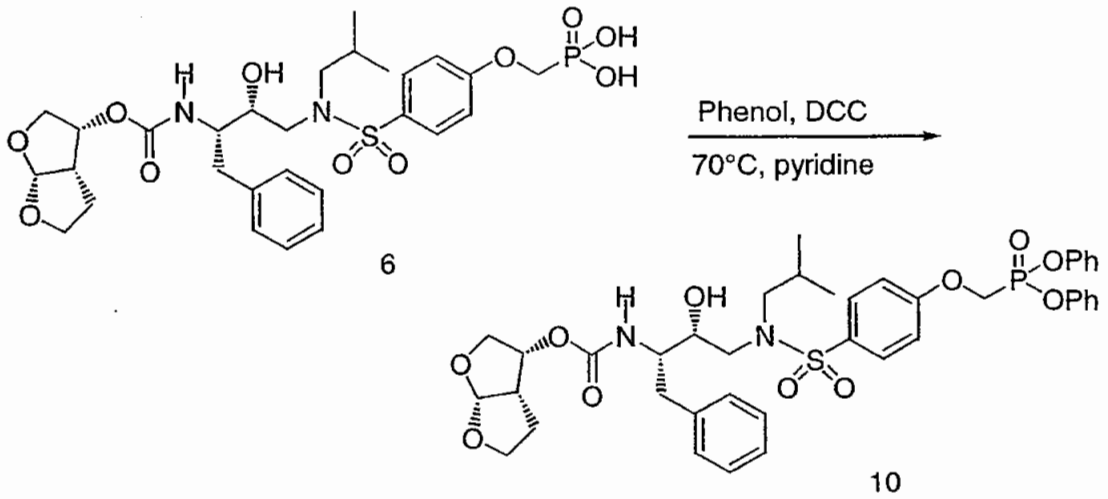
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Scheme 4

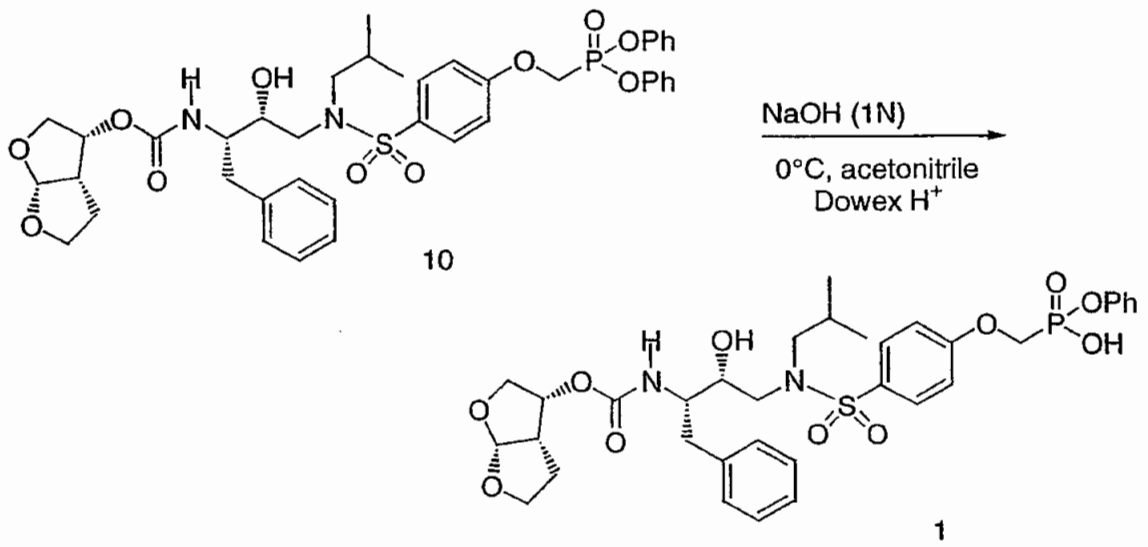


9 6

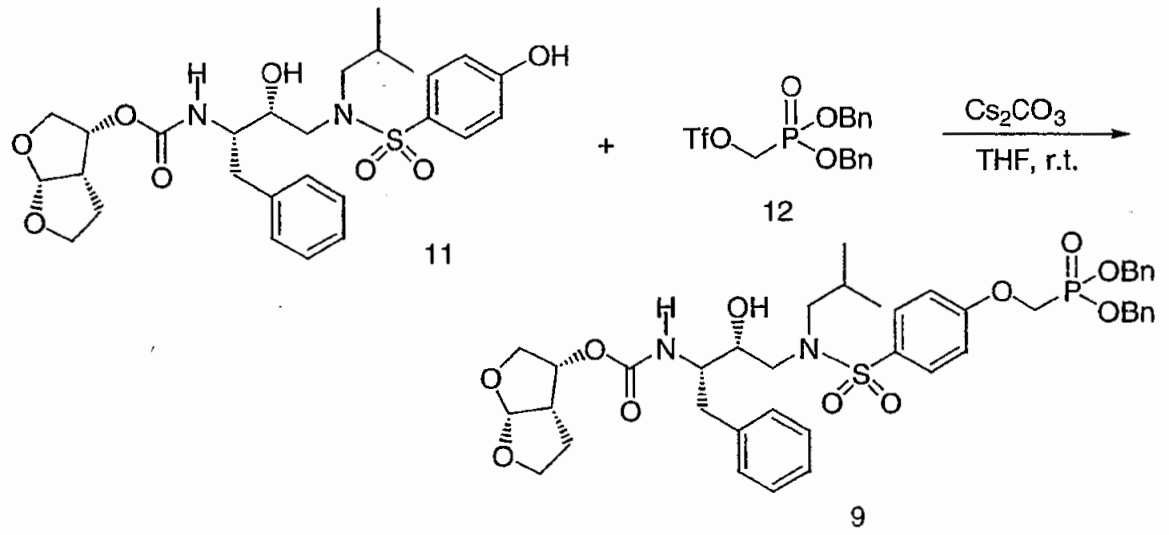
Scheme 5



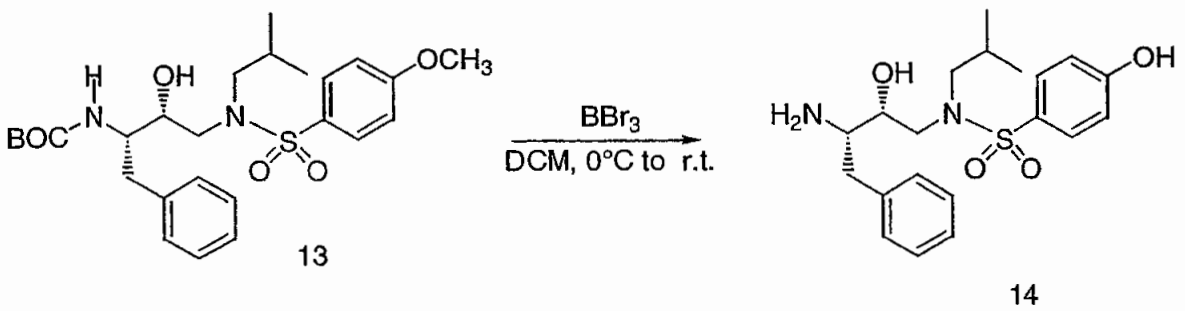
Scheme 6



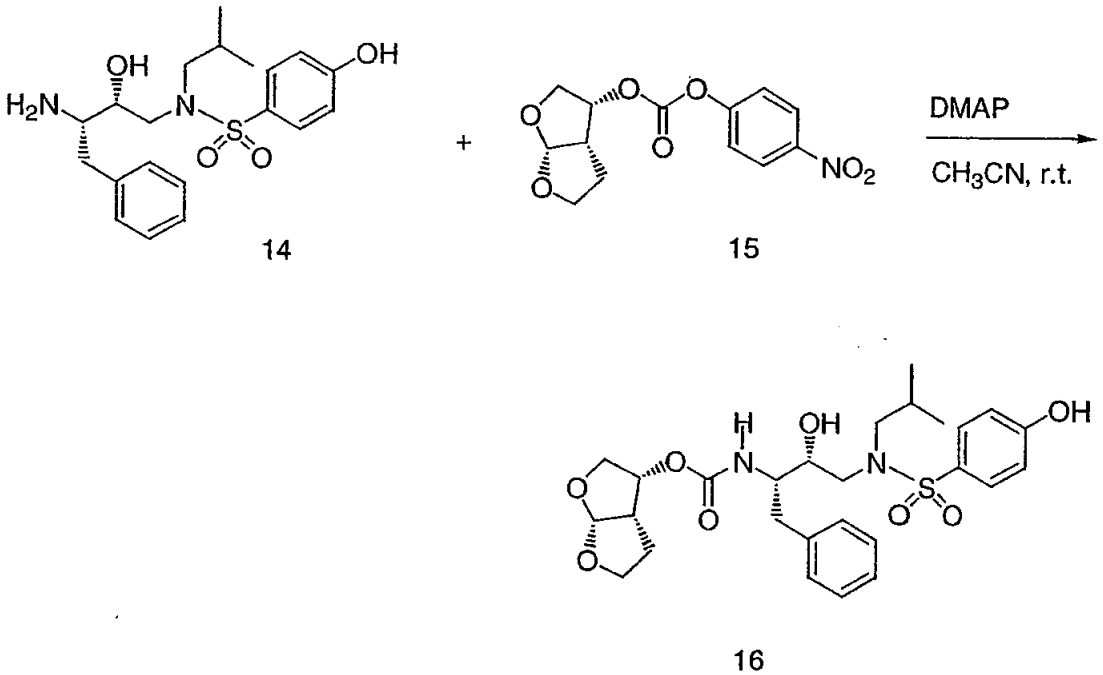
Scheme 7



Scheme 8



Scheme 9



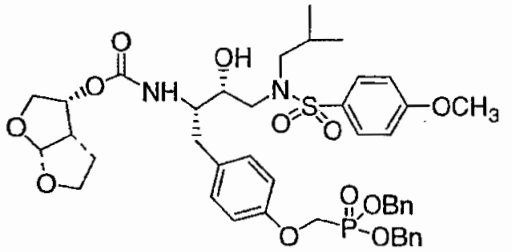
5

Scheme Section L

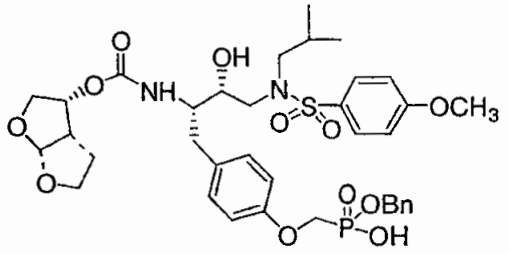
Schemes 1-9 are described in the examples.

Scheme 1

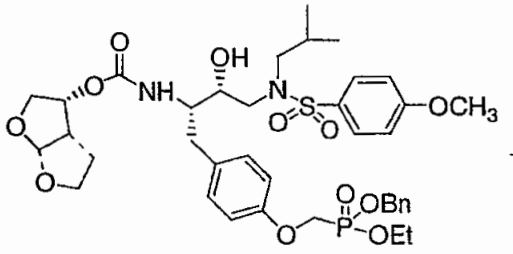
Synthesis of P1-Phosphonic ester



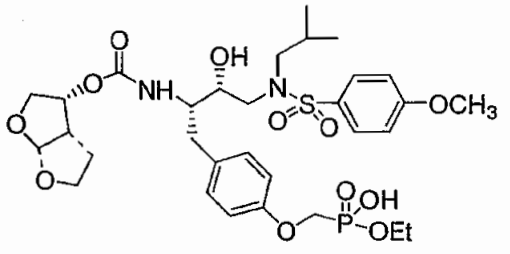
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2



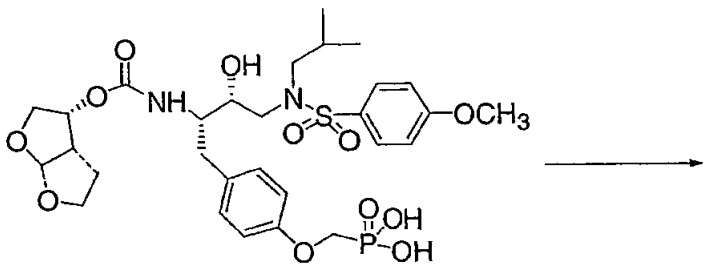
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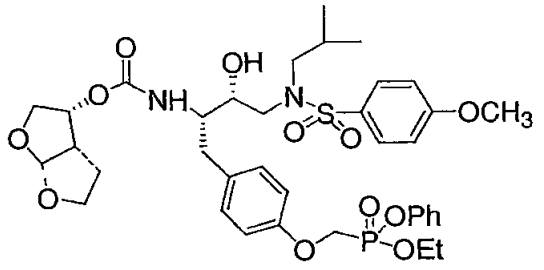
4

5

Scheme 2



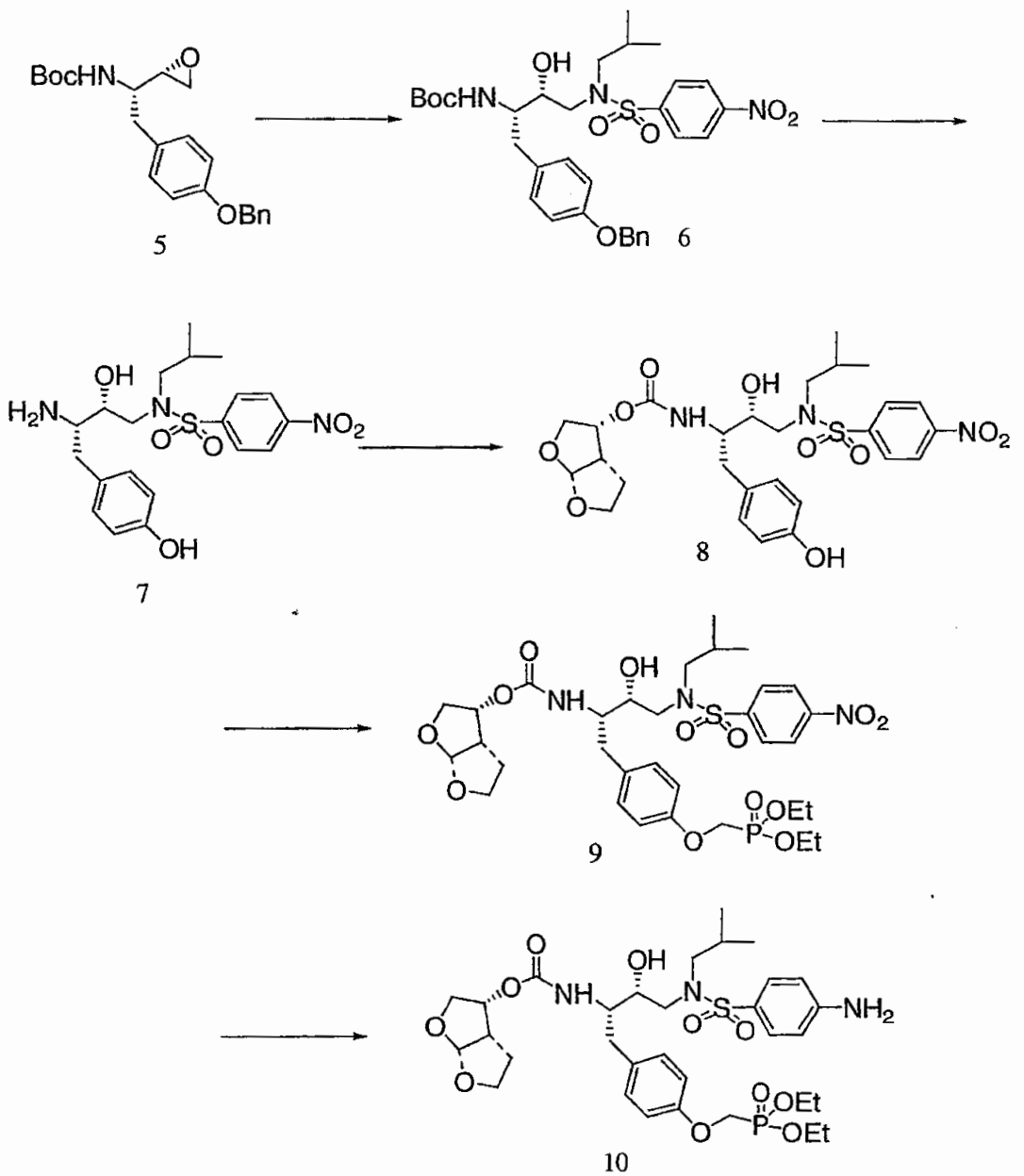
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5

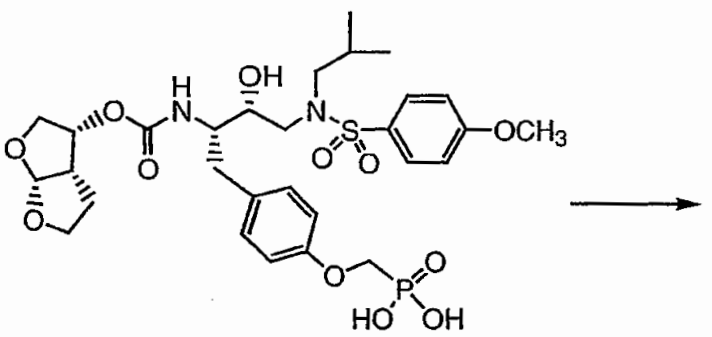
Scheme 3

Synthesis of P2'-Amino-P1-Phosphonic ester

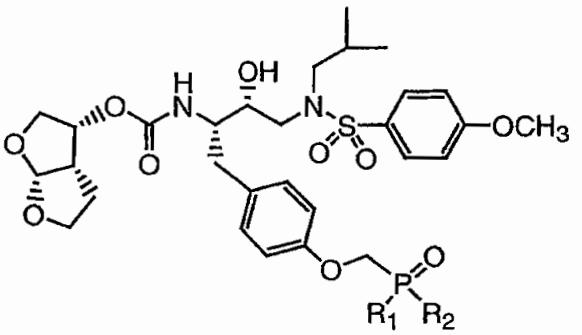


Scheme 4

Synthesis of Bisamidates



11



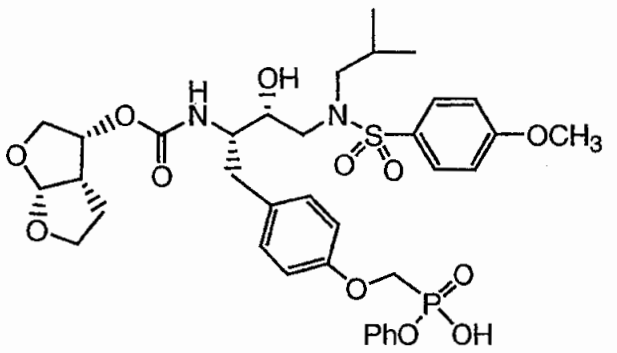
16 a,b,j and k

5

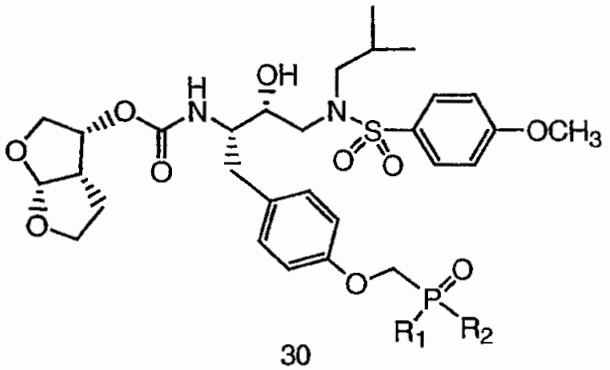
Compound	R_1	R_2
16a	Gly-Et	Gly-Et
16b	Gly-Bu	Gly-Bu
16j	Phe-Bu	Phe-Bu
16k	NHEt	NHEt

Scheme 5

Synthesis of Monoamidates



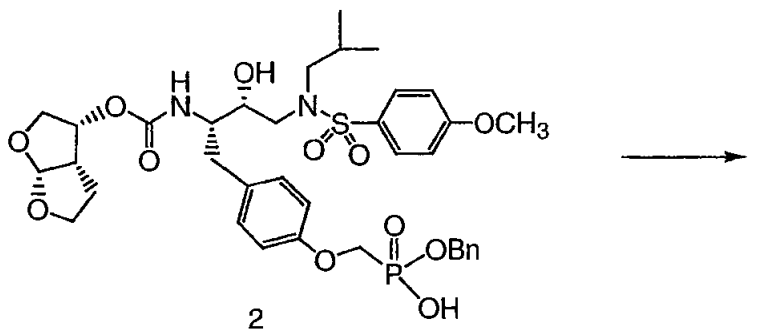
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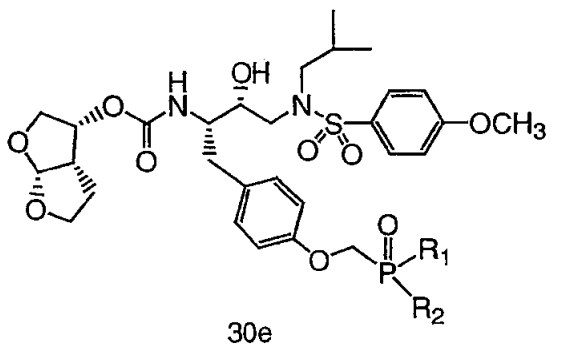
30

Compound	R_1	R_2
30a	OPh	Ala-Me
30b	OPh	Ala-Et
30c	OPh	(D)-Ala-iPr
30d	OPh	Ala-Bu
30e	OBn	Ala-Et

Scheme 6



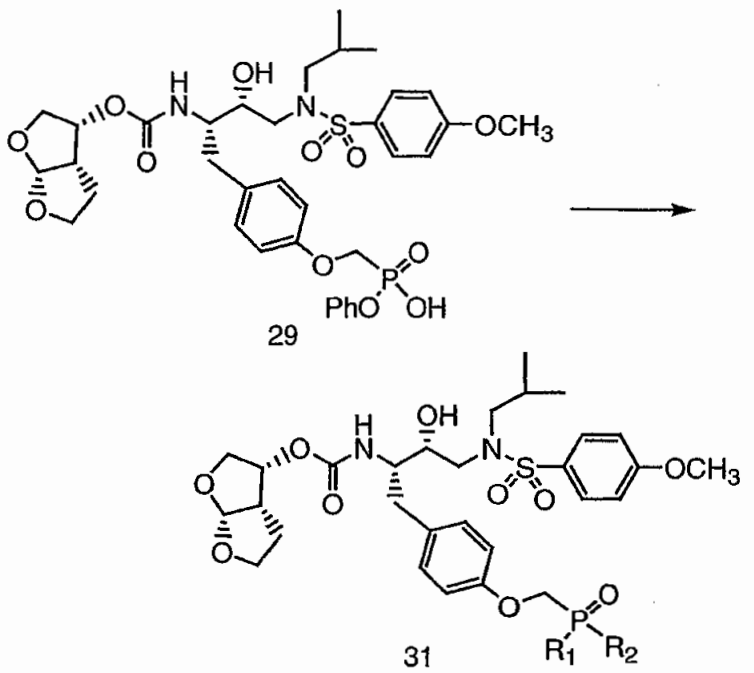
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30e

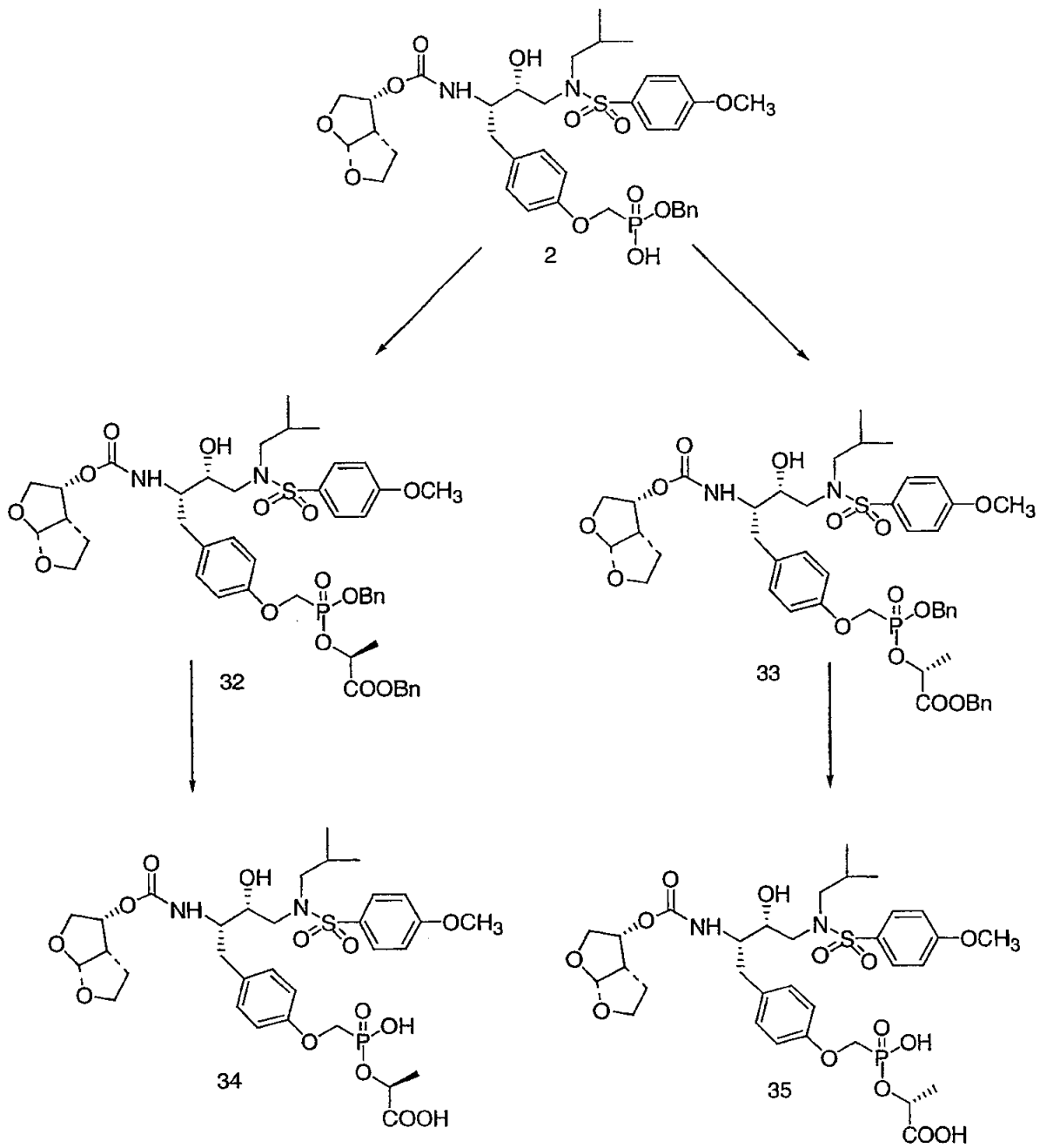
Scheme 7

Synthesis of Lactates



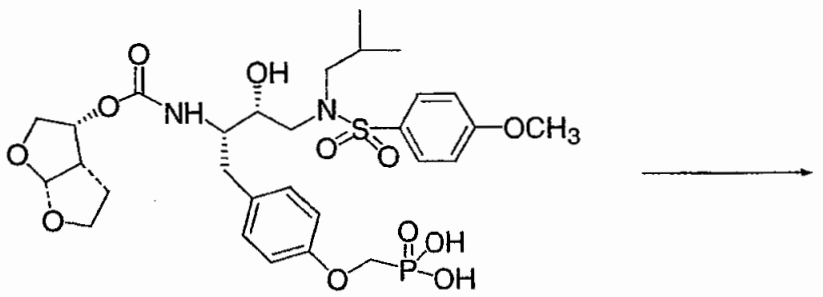
Compound	R_1	R_2
31a	OPh	Lac-iPr
31b	OPh	Lac-Et
31c	OPh	Lac-Bu
31d	OPh	(R)-Lac-Me
31e	OPh	(R)-Lac-Et

Scheme 8

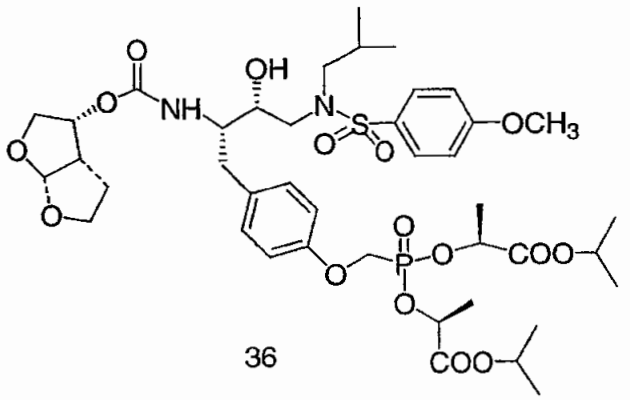


Scheme 9

Synthesis of Bislactate



11



36

5

Examples

The following Examples refer to the Schemes.

Some Examples have been performed multiple times. In repeated Examples, reaction conditions such as time, temperature, concentration and the like, and yields were within normal experimental ranges. In repeated Examples where significant modifications were made, these have been noted where the results varied significantly from those described. In Examples where different starting materials were used, these are noted. When the repeated Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl ester", this intends that an otherwise present group, in this case typically a methyl ester, is taken to be the same group modified as indicated.

Example Section A

Example 1

Diazo ketone 1: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-tyrosine (11 g, 30 mmol, Fluka) in dry THF (55 mL) at -25-30°C (external bath temperature) was added isobutylchloroformate (3.9 mL, 30 mmol) followed by the slow addition of N.methylmorpholine (3.3 mL, 30 mmol). The mixture was stirred for 25 min, filtered while cold, and the filter cake was rinsed with cold (0°C) THF (50 mL). The filtrate was cooled to - 25°C and diazomethane (~50 mmol, generated from 15 g Diazald according to Aldrichimica Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min and was then placed in an icebath at 0°C, allowing the bath to warm to room temperature while stirring overnight for 15 h. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc, washed with water, saturated $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered and evaporated to a pale yellow solid. The crude solid was slurried in hexane, filtered, and dried to afford the diazo ketone (10.9 g, 92%) which was used directly in the next step.

Example 2

Chloroketone 2: To a suspension of diazoketone 1 (10.8 g, 27 mmol) in ether (600 mL) at 0°C was added 4M HCl in dioxane (7.5 mL, 30 mmol). The solution was removed from the cooling bath, and allowed to warm to room temperature at which time the reaction was stirred 1 h. The reaction solvent was evaporated under reduced pressure to give a solid residue that

was dissolved in ether and passed through a short column of silica gel. The solvent was evaporated to afford the chloroketone (10.7 g, 97%) as a solid.

Example 3

Chloroalcohol 3: To a solution of chloroketone 2 (10.6 g, 26 mmol) in THF (90 mL) was added water (10 mL) and the solution was cooled to 3-4°C (internal temperature). A solution of $NaBH_4$ (1.5 g, 39 mmol) in water (5 mL) was added dropwise over a period of 10 min. The mixture was stirred for 1h at 0°C and saturated $KHSO_4$ was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried ($MgSO_4$) filtered and evaporated under reduced pressure. The crude product consisted of a 70:30 mixture of diastereomers by HPLC analysis (mobile phase, 77:25-CH_3CN:H_2O; flow rate: 1 mL/min; detection: 254 nm; sample volume: 20 µL; column: 5µ C18, 4.6X250 mm, Varian; retention times: major diastereomer 3, 5.4 min, minor diastereomer 4, 6.1 min). The residue was recrystallized from EtOAc/hexane twice to afford the chloro alcohol 3 (4.86g, >99% diastereomeric purity by HPLC analysis) as a white solid.

Example 4

Epoxide 5: A solution of chloroalcohol 3 (4.32 g, 10.6 mmol) in EtOH (250 mL) and THF (100 mL) was treated with K_2CO_3 (4.4g, 325 mesh, 31.9 mmol) and the mixture was stirred for at room temperature for 20h. The reaction mixture was filtered and was evaporated under reduced pressure. The residue was partitioned between EtOAc and water and the organic phase was washed with saturated NaCl, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel to afford the epoxide (3.68 g, 94%) as a white solid.

Example 5

Sulfonamide 6: To a suspension of epoxide 5 (2.08 g, 5.6 mmol) in 2-propanol (20 mL) was added isobutylamine (10.7 mL, 108 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C. N,N'-diisopropylethylamine (1.96 mL, 11.3 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (1.45 g, 7 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred for 40 min at 0°C, warmed to room temperature and

evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide (2.79 g, 81%) as a small white needles: mp 122-124°C (uncorrected).

Example 6

Carbamate 7: A solution of sulfonamide 6 (500 mg, 0.82 mmol) in CH_2Cl_2 (5 mL) at 0°C was treated with trifluoroacetic acid (5 mL). The solution was stirred at 0°C for 30 min and was removed from the cold bath stirring for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic extracts were washed with saturated NaCl, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was dissolved in CH_3CN (5 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (263 mg, 0.89 mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and N,N-dimethylaminopyridine (197 mg, 1.62 mmol). After stirring for 1.5h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 5% citric acid. The organic phase was washed twice with 1% K_2CO_3, and then was washed with saturated NaCl, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (1/1 - EtOAc/hexane) affording the carbamate (454 mg, 83%) as a solid: mp 128-129°C (MeOH, uncorrected).

Example 7

Phenol 8: A solution of carbamate 7 (1.15 g, 1.7 mmol) in EtOH (50 mL) and EtOAc (20 mL) was treated with 10% Pd/C (115 mg) and was stirred under H_2 atmosphere (balloon) for 18h. The reaction solution was purged with N_2, filtered through a 0.45 μM filter and was evaporated under reduced pressure to afford the phenol as a solid that contained residual solvent: mp 131-134°C (EtOAc/hexane, uncorrected).

Example 8

Dibenzylphosphonate 10: To a solution of dibenzylhydroxymethyl phosphonate (527 mg, 1.8 mmol) in CH_2Cl_2 (5 mL) was treated with 2,6-lutidine (300 μL, 2.6 mmol) and the reaction flask was cooled to -50°C (external temperature). Trifluoromethanesulfonic anhydride (360 μL, 2.1 mmol) was added and the reaction mixture was stirred for 15 min and then the cooling bath was allowed to warm to 0°C over 45 min. The reaction mixture was partitioned between ether and ice-cold water. The organic phase was washed with cold 1M H_3PO_4, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford triflate 9 (697 mg, 91%) as an oil which was used directly without any further purification. To a solution of phenol 8 (775 mg, 1.3 mmol) in THF (5 mL) was added Cs_2CO_3 (423 mg, 1.3 mmol) and triflate 9 (710 mg, 1.7 mmol) in THF (2 mL). After stirring the reaction mixture for 30 min at room temperature additional Cs_2CO_3 (423 mg, 1.3 mmol) and triflate (178 mg, 0.33 mmol) were added and the mixture was stirred for 3.5h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel eluting (5% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate as an oil that solidified upon standing. The solid was dissolved in EtOAc, ether was added, and the solid was precipitated at room temperature overnight. After cooling to 0°C, the solid was filtered and washed with cold ether to afford the dibenzylphosphonate (836 mg, 76%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.66 (d, 2H), 7.31 (s, 10H), 7.08 (d, 2H), 6.94 (d, 2H), 6.76 (d, 2H), 5.59 (d, 1H), 5.15-4.89 (m, 6H), 4.15 (d, 2H), 3.94-3.62 (m, 10H), 3.13-2.69 (m, 7H), 1.78 (m, 1H), 1.70-1.44 (m, 2H), 0.89-0.82 (2d, 6H); ^{31}P NMR ($CDCl_3$) δ 18.7; MS (ESI) 853 (M+H).

Example 9

Phosphonic acid 11: A solution of dibenzylphosphonate 10 (0.81 g) was dissolved in EtOH/ EtOAc (30mL/10 mL), treated with 10% Pd/C (80 mg) and was stirred under H_2 atmosphere (balloon) for 1.5h. The reaction was purged with N_2, and the catalyst was removed by filtration through celite. The filtrate was evaporated under reduced pressure and the residue was dissolved in MeOH and filtered with a 0.45 μM filter. After evaporation of the filtrate, the residue was triturated with ether and the solid was collected by filtration to afford the phosphonic acid (634 mg, 99%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 2H), 7.19 (d, 2H), 7.09 (d, 2H), 6.92 (d, 2H), 5.60 (d, 1H), 4.95 (m, 1H), 4.17 (d, 2H), 3.94 (m, 1H), 3.89

(s, 3H), 3.85-3.68 (m, 5H), 3.42 (dd, 1H), 3.16-3.06 (m, 2H), 2.96-2.84 (m, 3H), 2.50 (m, 1H), 2.02 (m, 1H), 1.58 (m, 1H), 1.40 (dd, 1H), 0.94 (d, 3H), 0.89 (d, 3H); ^{31}P NMR ($CDCl_3$) δ 16.2; MS (ESI) 671 (M-H).

Example 10

Diethylphosphonate 13: Triflate 12 was prepared from diethyl hydroxymethylphosphonate (2g, 11.9 mmol), 2,6-lutidine (2.1 mL, 17.9 mmol), and trifluoromethanesulfonic anhydride (2.5 mL, 14.9 mmol) as described for compound 9. To a solution of phenol 8 (60 mg, 0.10 mmol) in THF (2 mL) was added Cs_2CO_3 (65mg, 0.20 mmol) and triflate 12 (45 mg, 0.15 mmol) in THF (0.25 mL). The mixture was stirred at room temperature for 2h and additional triflate (0.15 mmol) in THF (0.25 mL) was added. After 2h the reaction mixture was partitioned between EtOAc and saturated NaCl. The organic phase was dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (EtOAc) to give a residue that was purified by chromatography on silica gel (5% 2-propanol /CH_2Cl_2) to afford the diethylphosphonate as a foam: ^{1}H NMR ($CDCl_3$) δ 7.66 (d, 2H), 7.10 (d, 2H), 6.94 (d, 2H), 6.82 (d, 2H), 5.60 (d, 1H), 4.97 (d, 2H), 4.23-4.13 (m, 6H), 3.93-3.62 (m, 10H), 3.12-2.68 (m, 7H), 1.84-1.44 (m, 3H), 1.31 (t, 6H), 0.88-0.82 (2d, 6H); ^{31}P NMR ($CDCl_3$) δ 17.7; MS (ESI) 729 (M+H).

Example 11

Diphenylphosphonate 14: To a solution of 11 (100mg, 0.15 mmol) and phenol (141 mg, 1.5 mmol) in pyridine (1.5 mL) was added N, N-diisopropylcarbodiimide (50 µL, 0.38 mmol). The solution was stirred for 31h at room temperature and for 20h at 50°C. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel eluting (EtOAc) to provide diphenylphosphonate 14 (16 mg) as a foam: ^{31}P NMR ($CDCl_3$) δ 10.9; MS (ESI) 847 (M+Na).

Example 12

Bis-Poc-phosphonate 15: To a solution of 11 (50 mg, 0.74 mmol) and isopropylchloromethyl carbonate (29 mg, 0.19 mmol) in DMF (0.5 mL) was added triethylamine (26 µL, 0.19 mmol) and the solution was heated at 70°C (bath temperature) for 4.5h. The reaction was concentrated under reduced pressure and the residue was purified by preparative layer

chromatography (2% 2-propanol/ CH_2Cl_2) to afford 15 (7 mg): ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H), 7.15 (d, 2H); 7.01 (d, 2H), 6.93 (d, 2H), 5.80-5.71 (m, 4H), 5.67 (d, 1H), 5.07-4.87 (m, 4H), 4.35 (d, 2H), 4.04-3.68 (m, 10H), 3.13 (dd, 1H), 3.04-2.90 (m, 5H), 2.79 (dd, 1H), 1.88-1.50 (m, 3H+H_2O peak), 1.30 (m, 12H), 0.93 (d, 3H), 0.88 (d, 3H); ^{31}P NMR ($CDCl_3$) δ 19.6.

Example 13

Synthesis of Bisamidates 16a-j. Representative Procedure, Bisamidate 16f: A solution of phosphonic acid 11 (100 mg, 0.15 mmol) and (S)-2-aminobutyric acid butyl ester hydrochloride (116 mg, 0.59 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (117 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (98 mg, 0.45 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH_2Cl_2). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16f (106 mg, 75%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H), 7.15 (d, 2H), 7.01 (d, 2H), 6.87 (d, 2H), 5.67 (d, 1H), 5.05 (m, 1H), 4.96 (d, 1H), 4.19-3.71 (m overlapping s, 18H,), 3.42 (t, 1H), 3.30 (t, 1H), 3.20 (dd, 1H), 3.20-2.97 (m, 4H), 2.80 (dd, 2H), 1.87-1.54 (m, 19H), 1.42-1.35 (4H), 0.97-0.88 (m, 18H); ^{31}P NMR ($CDCl_3$) δ 20.3; MS (ESI) 955 (M+H).

Compound	R_1	R_2	Amino Acid
16a	H	Et	Gly
16b	H	Bu	Gly
16c	Me	Et	Ala
16d	Me	Bu	Ala
16e	Et	Et	Aba[1]
16f	Et	Bu	Aba[1]
16g	iBu	Et	Leu
16h	iBu	Bu	Leu
16i	Bn	Et	Phe
16j	Bn	Bu	Phe

[1] Aba, 2-aminobutyric acid

Example 14

Diazo ketone 17: To a solution of N-tert-Butoxycarbonyl-p-bromo-L-phenylalanine (9.9 g, 28.8 mmol, Synthetech) in dry THF (55 mL) at -25-30°C (external bath temperature) was added isobutylchloroformate (3.74 mL, 28.8 mmol) followed by the slow addition of N-

methylmorpholine (3.16 mL, 28.8 mmol). The mixture was stirred for 25 min, filtered while cold, and the filter cake was rinsed with cold (0°C) THF (50 mL). The filtrate was cooled to - 25°C and diazomethane (~50 mmol, generated from 15 g diazald according to Aldrichimica Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min and was then placed in an icebath at 0°C, allowing the bath to warm to room temperature while stirring overnight for 15 h. The solvent was evaporated under reduced pressure and the residue was suspended in ether, washed with water, saturated $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered and evaporated to a pale yellow solid. The crude solid was slurried in hexane, filtered, and dried to afford diazo ketone 17 (9.73 g, 90%) which was used directly in the next step.

Example 15

Chloroketone 18: To a solution of diazoketone 17 (9.73 g, 26 mmol) in ether (500 mL) at 0°C was added 4M HCl in dioxane (6.6 mL, 26 mmol). The solution was stirred for 1 h at 0°C and 4M HCl in dioxane (1 mL) was added. After 1h, the reaction solvent was evaporated under reduced pressure to afford the chloroketone 18 (9.79 g, 98%) as a white solid.

Example 16

Chloroalcohol 19: A solution of chloroketone 18 (9.79g, 26 mmol) in THF (180 mL) and water (16 mL) was cooled to 0°C (internal temperature). Solid $NaBH_4$ (2.5 g, 66 mmol) was added in several portions over a period of 15 min while maintaining the internal temperature below 5°C. The mixture was stirred for 45 min and saturated $KHSO_4$ was slowly added until the pH<3. The mixture was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with brine, dried ($MgSO_4$) filtered and evaporated under reduced pressure. The residue was dissolved in EtOAc, and was passed through a short column of silica gel, and the solvent was evaporated. The solid residue was recrystallized from EtOAc/hexane to afford the chloroalcohol 19 (3.84g) as a white solid.

Example 17

Epoxide 21: A partial suspension of chloroalcohol 19 (1.16g, 3.1 mmol) in EtOH (50 mL) was treated with K_2CO_3 (2g, 14.5 mmol) and the mixture was stirred for 4 h at room

temperature. The reaction mixture was diluted with EtOAc, filtered, and the solvents were evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl, and the organic phase was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford epoxide 21 (1.05g, 92%) as a white crystalline solid.

Example 18

Sulfonamide 22: To a solution of epoxide 21 (1.05g, 3.1 mmol) in 2-propanol (40 mL) was added isobutylamine (6 mL, 61 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C. Triethylamine (642 µL, 4.6 mmol) was added followed by the addition of (634 mg, 3.4 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred for 2h at 0°C at which time the reaction solution was treated with additional triethylamine (1.5 mmol) and 4-methoxybenzenesulfonyl chloride (0.31 mmol). After 1.5 h, the reaction solution was evaporated under reduced pressure. The residue was partitioned between EtOAc and cold 1M H_3PO_4. The organic phase was washed with saturated $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The crude product was purified on silica gel (15/1 - CH_2Cl_2/EtOAc) to afford 1.67g of a solid which was recrystallized from EtOAc/hexane to give sulfonamide 22 (1.54g, 86%) as a white crystalline solid.

Example 19

Silyl ether 23: To a solution of the sulfonamide 22 (1.53g, 2.6 mmol) in CH_2Cl_2 (12 mL) at 0°C was added N,N-diisopropylethylamine (0.68 mL, 3.9 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (0.75 mL, 3.3 mmol). The reaction solution was stirred for 1 h at 0°C and was warmed to room temperature, stirring for 17 h. Additional N,N-diisopropylethylamine (3.9 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (1.6 mmol) was added, stirred for 2.5h, then heated to reflux for 3h and stirred at room temperature for 12 h. The reaction mixture was partitioned between EtOAc and cold 1M H_3PO_4. The organic phase was washed with saturated $NaHCO_3$, saturated NaCl, and was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified on silica gel (2/1 - hexane/ether) to afford silyl ether 23 (780 mg, 43%) as an oil.

Example 20

Phosphonate 24: A solution of 23 (260 mg, 0.37 mmol), triethylamine (0.52 mL, 3.7 mmol), and diethylphosphite (0.24 mmol, 1.85 mmol) in toluene (2 mL) was purged with argon and to the solution was added $(Ph_3P)_4Pd$ (43 mg, 10 mol%). The reaction mixture was heated at 110°C (bath temperature) for 6 h, and was then allowed to stir at room temperature for 12h. The solvent was evaporated under reduced pressure and the residue was partitioned between ether and water. The aqueous phase was extracted with ether and the combined organic extracts were washed with saturated NaCl, dried ($MgSO_4$), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (2/1 - ethyl acetate/hexane) to afford diethylphosphonate 24 (153 mg, 55%).

Example 21

Phosphonic acid 26: To a solution of 24 (143 mg) in MeOH (5 mL) was added 4N HCl (2 mL). The solution was stirred at room temperature for 9h and was evaporated under reduced pressure. The residue was triturated with ether and the solid was collected by filtration to provide hydrochloride salt 25 (100 mg, 92%) as a white powder. To a solution of X (47 mg, 0.87 mmol) in CH_3CN (1 mL) at 0°C was added TMSBr (130 µL, 0.97 mmol). The reaction was warmed to room temperature and stirred for 6.5h at which time TMSBr (0.87 mmol) was added and stirring was continued for 16h. The solution was cooled to 0°C and was quenched with several drops of ice-cold water. The solvents were evaporated under reduced pressure and the residue was dissolved in several milliters of MeOH and treated with propylene oxide (2 mL). The mixture was heated to gentle boiling and evaporated. The residue was triturated with acetone and the solid was collected by filtration to give phosphonic acid 26 (32 mg, 76%) as a white solid.

Example 22

Phosphonate 27: To a suspension of 26 (32 mg, 0.66 mmol) in CH_3CN (1 mL) was added bis(trimethylsilyl)acetamide (100 µL, 0.40 mmol) and the solution was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in CH_3CN (1 mL). To this solution was added (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (20 mg, 0.069 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.), N,N-diisopropylethylamine (35 µL, 0.20 mmol), and N,N-dimethylaminopyridine (catalytic amount). The solution was stirred for 22h at room temperature, diluted with water (0.5 mL) and was stirred with IR 120 ion exchange resin (325

mg, H^+ form) until the pH was <2. The resin was removed by filtration, washed with methanol and the filtrate was concentrated under reduced pressure. The residue was dissolved water, treated with solid $NaHCO_3$ until pH=8 and was evaporated to dryness. The residue was dissolved in water and was purified on C18 reverse phase chromatography eluting with water followed by 5%, 10% and 20% MeOH in water to give the disodium salt 27 (24 mg) as a pale yellow solid: ^1H NMR (D_2O) δ 7.72 (d, 2H), 7.52 (dd, 2H), 7.13 (dd, 2H), 7.05 (d, 2H), 5.58 (d, 1H), 4.87 (m, 1H), 3.86-3.53 (m overlapping s, 10H), 3.22 (dd, 1H), 3.12-2.85 (6H), 2.44 (m, 1H), 1.83 (m, 1H), 1.61 (m, 1H)1.12 (dd, 1H), 0.77 (m, 6H); ^{31}P NMR (D_2O) δ 11.23 ; MS (ESI) 641 (M-H).

Example 23

Diethylphosphonate 28: To a solution of 25 (16 mg, 0.028 mmol) in CH_3CN (0.5 mL) was added (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (9 mg, 0.031 mmol), N,N-diisopropylethylamine (20 µL, 0.11 mmol), and N,N-dimethylaminopyridine (catalytic amount). The solution was stirred at room temperature for 48 h and was then concentrated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated $NaHCO_3$, saturated NaCl, and was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (2.5-5% 2-propanol/CH_2Cl_2). The residue obtained was further purified by preparative layer chromatography (5% MeOH/CH_2Cl_2) followed by column chromatography on silica gel (10% 2-propanol/CH_2Cl_2) to afford diethylphosphonate 28 (7 mg) as a foam: ^1H NMR ($CDCl_3$) δ 7.72-7.66 (m, 4H), 7.32-7.28 (2H), 6.96 (d, 2H), 5.60 (d, 1H), 4.97 (m, 2H), 4.18-4.01 (m, 4H), 3.94-3.60 (m overlapping s, 10H), 3.15-2.72 (m, 7H), 1.78 (m, 1H), 1.61 (m+H_2O, ~3H), 1.28 (t; 6H), 0.86 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 18.6 ; MS (ESI) 699 (M+H).

Prospective Example 24

Diphenyl phosphonate 14 is treated with aqueous sodium hydroxide to provide monophenyl phosphonate 29 according to the method found in J. Med. Chem. 1994, 37, 1857. Monophenyl phosphonate 29 is then converted to the monoamidate 30 by reaction with an amino acid ester in the presence of Ph_3 and 2,2'-dipyridyl disulfide as described in the synthesis of bisamidate 16f. Alteratively, monoamidate 30 is prepared by treating 29 with an

amino acid ester and DCC. Coupling conditions of this type are found in Bull. Chem. Soc. Jpn. 1988, 61, 4491.

Example 25

Diazo ketone 1: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-tyrosine (25 g, 67 mmol, Fluka) in dry THF (150 mL) at -25-30°C (external bath temperature) was added isobutylchloroformate (8.9 mL, 69 mmol) followed by the slow addition of N.methylmorpholine (37.5 mL, 69 mmol). The mixture was stirred for 40 min, and diazomethane (170 mmol, generated from 25 g 1-methyl-3-nitro-1-nitroso-guanidine according to Aldrichimica Acta 1983, 16, 3) in ether (400 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min allowing the bath to warm to room temperature while stirring overnight for 4 h. The mixture was bubbled with N_2 for 30 min., washed with water, saturated $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered and evaporated to a pale yellow solid. The crude solid was slurried in hexane, filtered, and dried to afford the diazo ketone (26.8 g, 99%) which was used directly in the next step.

Example 26

Chloroketone 2: To a suspension of diazoketone 1 (26.8 g, 67 mmol) in ether/THF (750 mL, 3/2) at 0°C was added 4M HCl in dioxane (16.9 mL, 67 mmol). The solution was stirred at 0°C for 2 hr. The reaction solvent was evaporated under reduced pressure to give the chloroketone (27.7 g, 97%) as a solid.

Example 27

Chloroalcohol 3: To a solution of chloroketone 2 (127.1 g, 67 mmol) in THF (350 mL) was added water (40 mL) and the solution was cooled to 3-4°C (internal temperature). $NaBH_4$ (6.3 g, 168 mmol) was added in portions. The mixture was stirred for 1h at 0°C and the solvents were removed. The mixture was diluted with ethyl acetate and saturated $KHSO_4$ was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried ($MgSO_4$) filtered and evaporated under reduced pressure. The crude product consisted of a 70:30 mixture of diastereomers by HPLC analysis (mobile phase, 77:25-CH_3CN:H_2O; flow rate: 1 mL/min; detection: 254 nm; sample volume: 20 µL; column: 5µ C18, 4.6X250 mm, Varian; retention times: major diastereomer 3, 5.4 min, minor

diastereomer 4, 6.1 min). The residue was recrystallized from EtOAc/hexane twice to afford the chloro alcohol 3 (12.2g, >96% diastereomeric purity by HPLC analysis) as a white solid.

Example 28

Epoxide 5: To a solution of chloroalcohol 3 (12.17 g, 130 mmol) in EtOH (300 mL) was added KOH/EtOH solution (0.71N, 51 mL, 36 mmol). The mixture was stirred for at room temperature for 1.5h. The reaction mixture was evaporated under reduced pressure. The residue was partitioned between EtOAc and water and the organic phase was washed with saturated NH_4Cl, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford the epoxide (10.8 g, 97%) as a white solid.

Example 29

Sulfonamide 6: To a suspension of epoxide 5 (10.8 g, 30 mmol) in 2-propanol (100 mL) was added isobutylamine (129.8 mL, 300 mmol) and the solution was refluxed for 1 hr. The solution was evaporated under reduced pressure to give a crude solid. The solid (42 mmol) was dissolved in CH_2Cl_2 (200 mL) and cooled to 0°C. Triethylamine (11.7 mL, 84 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (8.68 g, 42 mmol) and the solution was stirred for 40 min at 0°C, warmed to room temperature and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide (23.4 g, 91%) as a small white needles: mp 122-124°C (uncorrected).

Example 30

Carbamate 7: A solution of sulfonamide 6 (6.29 mg, 10.1 mmol) in CH_2Cl_2 (20 mL) was treated with trifluoroacetic acid (10 mL). The solution was stirred for 3 hr. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase were washed with 0.5 N NaOH (2x), water (2x) and saturated NaCl, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was dissolved in CH_3CN (60 mL), cooled to 0°C and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (298.5 g, 10 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.) and N,N-dimethylaminopyridine (2.4 g, 20 mmol). After stirring for 1h at 0°C, the reaction solvent was evaporated under

reduced pressure and the residue was partitioned between EtOAc and 5% citric acid. The organic phase was washed twice with 1% K_2CO_3, and then was washed with saturated NaCl, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (1/1 - EtOAc/hexane) affording the carbamate (5.4 g, 83%) as a solid: mp 128-129°C (MeOH, uncorrected).

Example 31

Phenol 8: A solution of carbamate 7 (5.4 g, 8.0 mmol) in EtOH (260 mL) and EtOAc (130 mL) was treated with 10% Pd/C (540 mg) and was stirred under H_2 atmosphere (balloon) for 3h. The reaction solution stirred with celite for 10 min, and passed through a pad of celite. The filtrate was evaporated under reduced pressure to afford the phenol as a solid (4.9 g) that contained residual solvent: mp 131-134°C (EtOAc/hexane, uncorrected).

Example 32

Dibenzylphosphonate 10: To a solution of dibenzylhydroxymethyl phosphonate (3.1 g, 10.6 mmol) in CH_2Cl_2 (30 mL) was treated with 2,6-lutidine (1.8 mL, 15.6 mmol) and the reaction flask was cooled to -50°C (external temperature). Trifluoromethanesulfonic anhydride (2.11 mL, 12.6 mmol) was added and the reaction mixture was stirred for 15 min and then the cooling bath was allowed to warm to 0°C over 45 min. The reaction mixture was partitioned between ether and ice-cold water. The organic phase was washed with cold 1M H_3PO_4, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford triflate 9 (3.6 g, 80%) as an oil which was used directly without any further purification. To a solution of phenol 8 (3.61 g, 6.3 mmol) in THF (90 mL) was added Cs_2CO_3 (4.1 g, 12.6 mmol) and triflate 9 (4.1 g, 9.5 mmol) in THF (10 mL). After stirring the reaction mixture for 30 min at room temperature additional Cs_2CO_3 (6.96 g, 3 mmol) and triflate (1.26 g, 3 mmol) were added and the mixture was stirred for 3.5h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel eluting (5% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate as an oil that solidified upon standing. The solid was dissolved in EtOAc, ether was added, and the solid was precipitated at room temperature overnight. After cooling to 0°C the solid was filtered and washed with cold ether to afford the dibenzylphosphonate (3.43 g, 64%) as a white solid: ^1H NMR ($CDCl_3$) δ 7.66

(d, 2H), 7.31 (s, 10H), 7.08 (d, 2H), 6.94 (d, 2H), 6.76 (d, 2H), 5.59 (d, 1H), 5.15-4.89 (m, 6H), 4.15 (d, 2H), 3.94-3.62 (m, 10H), 3.13-2.69 (m, 7H), 1.78 (m, 1H), 1.70-1.44 (m, 2H), 0.89-0.82 (2d, 6H); ^{31}P NMR ($CDCl_3$) δ 18.7; MS (ESI) 853 (M+H).

Example 33

Phosphonic acid 11: A solution of dibenzylphosphonate 10 (3.43 g) was dissolved in EtOH/ EtOAc (150 mL/50 mL), treated with 10% Pd/C (350 mg) and was stirred under H_2 atmosphere (balloon) for 3 h. The reaction mixture was stirred with celite, and the catalyst was removed by filtration through celite. The filtrate was evaporated under reduced pressure and the residue was dissolved in MeOH and filtered with a 0.45 μM filter. After evaporation of the filtrate, the residue was triturated with ether and the solid was collected by filtration to afford the phosphonic acid (2.6 g, 94%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 2H), 7.19 (d, 2H), 7.09 (d, 2H), 6.92 (d, 2H), 5.60 (d, 1H), 4.95 (m, 1H), 4.17 (d, 2H), 3.94 (m, 1H), 3.89 (s, 3H), 3.85-3.68 (m, 5H), 3.42 (dd, 1H), 3.16-3.06 (m, 2H), 2.96-2.84 (m, 3H), 2.50 (m, 1H), 2.02 (m, 1H), 1.58 (m, 1H), 1.40 (dd, 1H), 0.94 (d, 3H), 0.89 (d, 3H); ^{31}P NMR ($CDCl_3$) δ 16.2; MS (ESI) 671 (M-H).

Example Section B

There is no Section B in this application.

Example Section C

Example 1

Diphenyl phosphonate **31**: To a solution of phosphonic acid **30** (11 g, 16.4 mmol) and phenol (11 g, 117 mmol) in pyridine (100 mL) was added 1, 3-dicyclohexylcarbodiimide (13.5 g, 65.5 mmol). The solution was stirred at room temperature for 5 min and then at 70°C for 2h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL) and filtered. The filtrate was evaporated under reduced pressure to remove pyridine. The residue was dissolved in ethyl acetate (250 mL) and acidified to pH = 4 by addition of HCl (0.5 N) at 0°C. The mixture was stirred at 0°C for 0.5 h, filtered and the organic phase was separated and washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified on silica gel to give diphenyl phosphonate **31** (9 g, 67%) as a solid. ^{31}P NMR ($CDCl_3$) d 12.5.

Example 2

Monophenyl phosphonate **32**: To a solution of diphenylphosphonate **31** (9.0 g, 10.9 mmol) in acetonitrile (400 mL) was added NaOH (1N, 27 mL) at 0°C. The reaction mixture was stirred at 0°C for 1 h, and then treated with Dowex (50WX8-200, 12 g). The mixture was stirred for 0.5 h at 0°C, and then filtered. The filtrate was concentrated under reduced pressure and co-evaporated with toluene. The residue was dissolved in ethyl acetate and hexane was added to precipitate out the monophenyl phosphonate **32** (8.1 g, 100%). ^{31}P NMR ($CDCl_3$) d 18.3.

Example 3

Monoamidate **33a** (R_1 = Me, R_2 = n-Bu): To a flask charged with monophenyl phosphonate **32** (4.0 g, 5.35 mmol) , was added L-alanine n-butyl ester hydrochloride (4.0 g, 22 mmol), 1, 3-dicyclohexylcarbodiimide (6.6 g, 32 mmol), and finally pyridine (30 mL) under nitrogen. The resultant mixture was stirred at 60 – 70°C for 1 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2 N) and the organic layer was separated. The ethyl acetate phase was washed with water, saturated $NaHCO_3$, dried over MgSO4 , filtered and concentrated under reduced pressure. The residue was purified on silica gel (pre-treated with 10% MeOH / CH_3CO_2Et, eluting with 40% CH_2Cl_2 / CH_3CO_2Et and CH_3CO_2Et) to give two isomers of **33a** in a total yield of 51%.

Isomer A (1.1 g): 1H NMR (CDCl3) d 0.88 (m, 9H), 1.3 (m, 2H), 1.35 (d, J = 7 Hz, 3H), 1.55 (m, 2H), 1.55-1.7 (m, 2H), 1.8 (m, 1H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 9H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR ($CDCl_3$) d 20.5. Isomer B (1.3 g) 1H NMR (CDCl3) d 0.88 (m, 9H), 1.3 (m, 2H), 1.35 (d, J = 7 Hz, 3H), 1.55 (m, 2H), 1.55-1.7 (m, 2H), 1.8 (m, 1H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 9H), 3.85 (s, 3H), 4.2-4.35 (m, 3H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR ($CDCl_3$) d 19.4.

Example 4

Monoamidate **33b** (R_1 = Me, R_2 = i-Pr) was synthesized in the same manner as **33a** in 77% yield. Isomer A : 1H NMR (CDCl3) d 0.9 (2d, J = 6.3Hz, 6H), 1.2 (d, J = 7 Hz, 6H), 1.38 (d, J = 7 Hz, 3H), 1.55-1.9 (m, 3H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 8H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR ($CDCl_3$) d 20.4. Isomer B: 1H NMR (CDCl3) d 0.9 (2d, J = 6.3Hz, 6H), 1.2 (d, J = 7 Hz, 6H), 1.38 (d, J = 7 Hz, 3H), 1.55-1.9 (m, 3H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 8H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR ($CDCl_3$) d 19.5.

Example Section D

Example 1

Cyclic Anhydride 1 (6.57 g, 51.3 mmol) was treated according to the procedure of Brown et al., J. Amer. Chem. Soc. 1955, 77, 1089 -1091 to afford amino alcohol 3 (2.00g, 33%). *for intermediate 2* : ^{1}H NMR (CD_3OD) δ 2.40 (S, 2H), 1.20 (s, 6H).

Example 2

Amino alcohol 3 (2.0 g, 17 mmol) was stirred in 30 mL 1:1 THF: water. Sodium Bicarbonate (7.2 g, 86 mmol) was added, followed by Boc Anhydride (4.1 g, 19 mmol). The reaction was stirred for 1 hour, at which time TLC in 5% methanol/DCM with ninhydrin stain showed completion. The reaction was partitioned between water and ethyl acetate. The organic layer was dried and concentrated, and the resulting mixture was chromatographed on silica in 1:1 hexane: ethyl acetate to afford two fractions, "upper" and "lower" each having the correct mass. By NMR the correct product 4 was "lower" (0.56 g, 14%) ^{1}H NMR ($CDCl_3$) δ 3.7 (t, 2H), 3.0 (d,2H), 1.45 (t, 2H) 1.4 (s, 9H), 0.85 (s, 6H),
MS (ESI): 240 (M + 23).

Example 3

Sodium Hydride (60% emulsion in oil) was added to a solution of the alcohol 4 (1.1g, 5.2 mmol) in dry DMF in a 3-neck flask under dry nitrogen. Shortly afterward triflate 35 (2.4 g, 5.7 mmol) was added with stirring for 1.5 hrs. Mass spectrometry showed the presence of the starting material (240, M+23), thus 100 mg more 60% sodium hydride emulsion as well as ~1 g more triflate were added with an additional hour of stirring. The reaction was quenched by the addition of saturated $NaHCO_3$ then partitioned between ethyl acetate and water. The organic layer was dried with brine and $MgSO_4$ and eluted on silica with 1:1 hexane:ethyl acetate to afford 5 (0.445 g, 15%). NMR showed some contamination with alcohol 4 starting material. ^{1}H NMR ($CDCl_3$): δ 7.28 (s, 10H), 5.00 (m, 4H), 3.70 (t, 2H), 2.94, (d, 2H), 1.44 (t, 2H), 1.40 (s, 9H), 0.83 (s, 6H) MS (ESI): 514 (M+23).

Example 4

Phosphonate ester 5 (0.445 g, 0.906 mmol) was stirred with with 20% TFA in DCM. (5 mL) TLC showed completion in 1 hr time. The reaction was azeotroped with toluene then run on

a silica gel column with 10% methanol in DCM. Subsequently, the product was dissolved in ethyl acetate and shaken with saturated sodium bicarbonate: water (1:1), dried with brine and magnesium sulfate to afford the free amine 6 (30mg, 8.5%). ^{1}H NMR ($CDCl_3$): δ 7.30 (s, 10H), 5.00 (m, 4H), 3.67 (d, 2H), 3.47, (t, 2H), 2.4-2.6 (brs) 1.45 (t, 2H), 0.82 (s, 6H), MS (ESI): 393 (M+1).

Example 5

Amine 6 (30 mg, 0.08 mmol) and epoxide 7 (21 mg, 0.08 mmol) were dissolved in 2 mL IprOH and heated to reflux for 1 hr then monitored by TLC in 10% MeOH/DCM. Added ~20 mg more epoxide 7 and continued reflux for 1 hr. Cool to room temperature, dilute with ethyl acetate, shake with water and brine, dry with magnesium sulfate. Silica gel chromatography using first 5% then 10% MeOH in EtOAc yielded amine 8 (18 mg, 36%). ^{1}H NMR ($CDCl_3$): δ 7.30 (s, 10H), 7.20-7-14 (m, 5H), 5.25-4.91 (m, 4H), 3.83, (m, 1H), 3.71 (d, 2H) 3.64 (m, 1H), 3.54 (t, 2H), 3.02-2.61 (m, 5H), 2.65-2.36 (dd, 2H) (t, 2H), 1.30 (s, 9H) 0.93 (s, 9H) 0.83 (t, 2H) MS (ESI) 655 (M+1).

Example 6

Amine 8 (18 mg, 0.027 mmol) was dissolved in 1 mL DCM then acid chloride 9 (6 mg, 0.2 mmol) followed by triethylamine (0.004 mL, 0.029 mmol). The reaction was monitored by TLC. Upon completion the reaction was diluted with DCM shaken with 5% citric acid, saturated sodium bicarbonate, brine, and dried with $MgSO_4$. Purification on silica (1:1 Hexane:EtOAc) afforded sulfonamide 10 (10.5 mg, 46%). ^{1}H NMR ($CDCl_3$): δ 7.69 (d, 2H), 7.30 (s, 10H), 7.24-7-18 (m, 5H), 5.00 (m, 4H), 4.73, (d, 1H), 4.19 (s, 1H) 3.81 (m, 1H), 3.80 (s, 3H), 3.71 (d,2H), 3.57 (t, 2H), 3.11-2.95 (m, 5H) 2.75 (m,1H)1.25 (s, 1H), 0.90 (s, 6H) MS (ESI) 847 ($M+Na^+$).

Example 7

Sulfonamide 10 (10.5 mg, 0.013 mmol) was stirred at room temperature in 20% TFA/DCM. Once Boc deprotection was complete by TLC (1:1 Hexane:EtOAc) and MS, the reaction was azeotroped with toluene. The TFA salt of the amine was dissolved in acetonitrile (0.5 mg) and to this were added carbonate 11 (4.3 mg, 0.014 mmol) followed by DMAP (4.6 mg, 0.038 mg). Stir at room temp until TLC (1:1 Hexane:EtOAc) shows completion. Solvent was evaporated and the residue was redissolved in EtOAc then shaken

with saturated $NaHCO_3$. The organic layer was washed with water and brine, then dried with $MgSO_4$ Purification on silica with Hexane: EtOAc afforded compound 12 (7.1 mg, 50%). ^1H NMR ($CDCl_3$): δ 7.75 (d, 2H) 7.24-7.35 (15H) 6.98 (d, 2H), 5.62 (d, 1H) 5.04 (m, 4H) 4.98 (m, 1H) 4.03 (m, 1H), 3.85 (s, 3H), 3.61-3.91 (9H), 3.23-3.04 (5H) 2.85 (m, 1H), 2.74 (m,1H) 1.61 (d, 2H), 1.55 (m, 1H) 1.36 (m, 1H) 0.96 (d, 6H) MS (ESI): 903 (M+23).

Example 8

Compound 12 (6.1 mg, 0.007 mmol) was dissolved in 1 mL 3:1 EtOH:EtoAc. Palladium catalyst (10% on C, 1mg) was added and the mixture was purged three times to vacuum with 1 atmosphere hydrogen gas using a balloon. The reaction was stirred for 2 hrs, when MS and TLC showed completion. The reaction was filtered through Celite with EtOH washing and all solvent to was evaporated to afford final compound 13 (5mg, 100%). ^1H NMR (CD_3OD): δ 7.79 (d, 2H) 7.16-7.24 (5H) 7.09 (d, 2H) 5.58 (d, 1H) 4.92 (m, 1H) 3.97 (m, 1H), 3.92 (dd,1H) 3.89 (s, 3H) 3.66-3.78 (8H) 3.40 (d,1H), 3.37 (dd, 1H), 3.15 (m, 1H) 3.12 (dd,1H) 2.96 (d, 1H), 2.87 (m, 1H), 2.74 (m,1H) 2.53 (m, 1H) 1.70 (m, 2H), 1.53 (m, 1H) 1.32 (m, 1H) 1.04 (d, 6H) MS (ESI): 723 (M+23).

Example 9

Amino Alcohol 14 (2.67g, 25.9 mmol) was dissolved in THF with stirring and Boc Anhydride (6.78g, 31.1 mmol) was added. Heat and gas evolution ensued. TEA (3.97 mL, 28.5 mmol) was added and the reaction was stirred overnight. In the morning, the reaction was quenched by the addition of saturated $NaHCO_3$. The organic layer was separated out and shaken with water, dried with brine and $MgSO_4$ to afford 15 which was used without further purification. (100% yield) (some contamination): ^1H NMR ($CDCl_3$): δ 3.76 (t ,1H) 3.20, (d,2H), 2.97 (d, 2H), 1.44 (s, 9H), 0.85 (s, 6H).

Example 10

A solution of the alcohol 15 (500 mg, 2.45 mmol) in dry THF was cooled under dry N_2 with stirring. To this was added n-butyl lithium (1.29 mL, 2.71 mmol) as a solution in hexane in a manner similar to that described in Tetrahedron. 1995, 51 #35, 9737-9746. Triflate 35 (1.15 g, 2.71 mmol) was added neat with a tared syringe. The reaction was stirred for four hours, then quenched with saturated $NaHCO_3$. The mixture was then partitioned between water and EtOAc. The organic layer was dried with brine and $MgSO_4$, then chromatographed on silica

in 1:1 Hexane:EtOAc to afford phosphonate 16 (445mg, 38%) ^{1}H NMR ($CDCl_3$): δ 7.37 (m, 10H), 5.09 (m, 4H), 3.73-3.75 (m, 2H), 3.24 (s,2H), 3.02 (d, 2H), 1.43 (s, 9H), 0.86 (s, 6H).

Example 11

Phosphonate 16 (249 mg, 0.522 mmol) was stirred in 20% TFA/DCM for 1 hr. The reaction was then azeotroped with toluene. The residue was re-dissolved in EtOAc, then shaken with water: saturated $NaHCO_3$ (1:1). The organic layer was dried with brine and $MgSO_4$ and solvent was removed to afford amine 17 (143 mg, 73%) ^{1}H NMR ($CDCl_3$): δ 7.30 (s, 10H), 5.05-4.99 (m, 4H), 3.73 (d, 2H), 3.23 (s, 2H), 2.46 (brs, 2H), 0.80 (s, 6H) ^{31}P NMR ($CDCl_3$): δ 23.77 (s).

Example 12

Amine 17 (143 mg, 0.379 mmol) and epoxide 7 (95 mg, 0.360 mmol) were dissolved in 3 mL IprOH and heated to 85°C for 1 hr. The reaction was cooled to room temperature overnight then heated to 85°C for 1 hr more in the morning. The reaction was then diluted with EtOAc, shaken with water, dried with brine $MgSO_4$ and concentrated. The residue was eluted on silica in a gradient from 5% to 10% MeOH in DCM to afford compound 18 (33 mg, 14%).

Example 13

Mix compound 18 (33 mg, 0.051 mmol) and chlorosulfonyl compound 9 (11 mg, 0.054 mmol) in 2 mL DCM then add TEA (0.0075 mL, 0.054 mmol), stir for 5 hrs. TLC in 1:1 EtOAc: hexane shows reaction not complete. Place in freezer overnight. In the morning, take out of freezer, stir for 2 hrs, TLC shows completion. Workup done with 5% citric acid, saturated $NaHCO_3$, then dry with brine and $MgSO_4$. The reaction mixture was concentrated and chromatographed on a Monster Pipette column in 1:1 hexane: EtOAc then 7:3 hexane: EtOAc to avail compound 19 (28 mg , 67%) ^{1}H NMR ($CDCl_3$): δ 7.37 (d, 2H), 7.20 (m, 15H), 6.90 (d, 2H), 5.07-4.93 (m, 4H), 4.16 (brs, 1H), 3.80 (s, 3H), 3.75-3.37 (m, 4H), 3.36 (d, 1H), 3.20-2.93 (m, 6H), 2.80- 2.75 (dd, 1H).

Example 14

Compound 19 (28 mg, 0.35 mmol) was stirred in 4 mL DCM with addition of 1 mL TFA. Stir for 45 minutes, at which time complete deprotection was noted by TLC as well as MS. Azeotrope with toluene. The residue was dissolved in 1 mL CH_3CN, cooled to 0°C. Bis-

Furan *para*-Nitro phenol carbonate 11 (12 mg, 0.038 mmol), dimethyl amino pyridine (~ 1 mg, 0.008 mmol) and diisopropylethylamine (0.018 mL, 0.103 mmol) were added. The mixture was stirred and allowed to come to room temperature and stirred until TLC in 1:1 hexane:EtOAc showed completion. The reaction mixture was concentrated and the residue was partitioned between saturated $NaHCO_3$ and EtOAc. The organic layer was dried with brine and $MgSO_4$, then chromatographed on silica with hexane:EtOAc to afford compound 20 (20 mg, 67%). ^{1}NMR ($CDCl_3$): δ 7.76 (d, 2H), 7.34–7.16 (m, 15 H), 7.07 (d, 2H), 5.56 (d, 1H), 5.09 (m, 4H), 4.87 (m, 1H), 4.01 (m, 1H), 3.91 (m, 2H), 3.87 (s, 3H), 3.86 (m, 1H), 3.69 (m, 1H), 3.67 (m, 1H) 3.60 (d, 2H) 3.28 (m, 1H) 3.25 (d, 2H), 3.32 (d, 1H), 3.13 (m, 1H), 3.02 (m, 1H) 2.85 (d, 1H), 2.83 (m, 1H) 2.52 (m, 1H) 1.47 (m, 1H), 1.31 (m, 1H) 0.98 (s, 3H), 0.95 (s,3H).

Example 15

Compound 20 (7 mg, 0.008 mmol) was treated in a manner identical to example 8 to afford compound 21 (5 mg, 90%) ^{1}H NMR ($CDCl_3$): δ 7.80 (d, 2H), 7.25–7.16 (m, 5H), 7.09 (d, 2H), 5.58 (d, 1H), 4.92 (m, 1H), 3.99 (m, 1H), 3.92 (m, 1H), 3.88 (s, 3H), 3.86 (m, 1H), 3.77 (m, 1H), 3.75 (m, 1H), 3.73 (m, 1H), 3.71 (m, 1H) 3.71 (m, 1H), 3.68 (m, 1H), 3.57 (d,1H), 3.41 (d, 1H), 3.36 (m, 1H), 3.29 (d, 1H), 3.25 (d, 2H), 3.18 (m, 1H), 3.12 (m, 1H), 3.01 (d, 1H) 2.86 (m, 1H), 2.53 (m, 1H) 1.50 (m, 1H), 1.33 (m, 1H), 1.02 (s, 3H), 0.99 (s, 3H).

Example 16

Compound 15 (1.86 g, 9.20 mmol) was treated with triflate 22 in a manner identical to example 10 to afford compound 23 (0.71 g, 21.8%) ^{1}H NMR ($CDCl_3$): δ 5.21 (brs, 1H) 4.16-4.07 (m, 4H), 3.71-3.69 (d, 2H), 3.24 (s, 2H), 1.43 (s, 9H), 1.34-1.28 (m, 6H) 0.86 (s, 6H).

Example 17

Compound 23 (151 mg, 0.427 mmol) was dissolved in 10 mL DCM and 1.0 mL TFA was added. The reaction was stirred until completion. The reaction was azeotroped with toluene and the residue was then dissolved in THF and treated with basic Dowex resin beads. Afterwards, the beads were filtered away and solvent was removed to avail compound 24 (100 mg, 92%) ^{1}H NMR ($CDCl_3$): δ 4.15-4.05 (m, 4H), 3.72-3.69 (d, 2H), 3.27 (s, 2H), 1.30-1.26 (m, 6H) 0.81 (s, 6H).

Example 18

Compound 24 (100 mg, 0.395 mmol) was treated in a manner identical to example 12 to avail compound 25 (123 mg, 60%). ^{1}H NMR ($CDCl_3$): δ 7.26–7.13 (m, 5H), 4.48-4.83 (d, 1H) 4.17-4.06 (m, 4H), 3.75 (d, 2H) 3.56 (brs, 1H), 3.33 (s, 2H), 2.93-2.69 (m, 4H), 2.44-2.55 (dd, 2H) 1.32 (m, 6H), 0.916 (s, 6H).

Example 19

Compound 25 (88 mg, 0.171 mmol) was treated in a manner identical to example 13 to afford compound 26 (65 mg, 55%) ^{1}H NMR ($CDCl_3$): δ 7.26–7.13 (m, 5H), 4.48-4.83 (d, 1H) 4.17-4.06 (m, 4H), 3.75 (d, 2H) 3.56 (brs, 1H), 3.33 (s, 2H), 2.93-2.69 (m, 4H), 2.44-2.55 (dd, 2H) 1.32 (m, 6H), 0.916 (s, 6H).

Example 20

Compound 26 (65 mg, 0.171 mmol) was treated in a manner identical to example 14 to afford compound 27 (49 mg, 70%) ^{1}H NMR:
($CDCl_3$):δ 7.75 (d, 2H), 7.25–7.24 (m,4 H), 7.18 (m, 1H) 6.99 (d, 2H), 5.63 (d, 1H), 5.01 (m, 1H), 4.16 (m, 4H), 3.94 (m, 1H), 3.88 (m, 1H), 3.88 (s, 3H), 3.84 (m, 1H), 3.81 (m, 1H), 3.74 (m, 2H),), 3.70 (m, 1H), 3.69 (m, 1H) 3.43 (m, 1H), 3.24 (m, 1H), 3.22 (m, 2H) 3.21 (m, 2H) 3.12 (m, 1H), 3.02 (m, 1H) 2.86 (m, 1H), 2.72 (m, 1H), 1.54 (m, 1H), 1.38 (m, 1H) 1.35 (m, 6H) 1.00 (s, 3H), 0.96 (s,3H).

Example 21

Boc protected amine 28 (103 mg, 0.153 mmol) was dissolved in DCM (5 mL). The stirred solution was cooled to 0°C. BBr_3 as a 1.0 M solution in DCM (0.92 mL, 0.92 mmol) was added dropwise over 10 min, and the reaction was allowed to continue stirring at 0°C for 20 min. The reaction was warmed to room temperature and stirring was continued for 2 hours. The reaction was then cooled to 0°C and quenched by dropwise addition of MeOH (1 mL). The reaction mixture was evaporated and the residue suspended in methanol which was removed under reduced pressure. The procedure was repeated for EtOAc and finally toluene to afford free amine HBr salt 29 (107 mg, >100%) which was used without further purification.

Example 22

Amine HBr salt 29 (50 mg, 0.102 mmol) was suspended in 2 mL CH_3CN with stirring then cooled to 0°C. DMAP (25 mg, 0.205 mmol) was added, followed by Carbonate11. The reaction was stirred at 0°C for 1.5 hrs then allowed to warm to room temperature. The reaction was stirred overnight. A few drops Acetic acid were added to the reaction mixture, which was concentrated and re-diluted with ethyl acetate, shaken with 10% citric acid then saturated $NaHCO_3$. The organic layer was dried with brine and $MgSO_4$ and eluted on silica to afford di-phenol 30 (16 mg, 28%) ^1H NMR (CD_3OD): δ 7.61, (d, 2H), 7.01 (d, 2H), 6.87 (d, 2H), 6.62 (d, 2H), 5.55 (d, 1H), 4.93 (m, 1H), 3.92 (m, 2H), 3.79 (m, 5H), 3.35 (m, 1H), 3.07 (m, 2H), 2.88 (m, 3H), 2.41 (m, 1H), 2.00 (m, 1H), 1.54 (m, 1H), 1.31 (dd, 1H) 0.89-0.82 (dd, 6H).

Example 23

A solution of di-phenol 30 (100 mg, 0.177 mmol) was made in CH_3CN that had been dried over K_2CO_3. To this, the triflate (0.084 mL, 0.23 mmol) was added, followed by Cs_2CO_3 (173 mg, 0.531 mmol). The reaction was stirred for 1 hr. TLC (5% IprOH/DCM) showed 2 spots with no starting materials left. Solvent was evaporated and the residue was partitioned between EtOAc and water. The organic layer was washed with saturated $NaHCO_3$, then dried with brine and $MgSO_4$. The mixture was separated by column chromatography on silica with 3% IprOH in DCM. The upper spot 31 (90 mg, 46%) was confirmed to be the *bis* alkylation product. The lower spot required further purification on silica gel plates to afford a single *mono* alkylation product 32 (37 mg, 26%). The other possible alkylation product was not observed. NMR : ^1H NMR ($CDCl_3$): *for 31:* δ 7.57 (d, 2H), 7.37 (m, 10H) 7.03 (d, 2H), 6.99 (d, 2H), 6.73 (d, 2H), 5.69 (d, 1H), 5.15-5.09 (m, 4H), 5.10 (m, 1H), 4.32 (d, 2H), 4.02 (d, 1H), 3.82 (m, 1H) 3.81 (m, 1H), 3.93-3.81 (m, 2H), 3.74 (d, 1H), 3.06 (m, 1H), 3.00 (m, 1H), 2.96 (m, 1H), 2.91 (m, 1H) 2.77 (m, 1H) 2.64 (m, 1H) 2.47 (m, 1H) 1.82 (m, 2H) 1.79 (m, 1H), 0.94-0.86 (dd, 6H) *for 32:* δ 7.68 (d, 2H), 7.33-7.35 (m, 20H), 7.11 (d, 2H), 6.96 (d, 2H), 6.80 (d, 2H), 5.26 (d, 1H), 5.11(m, 8H), 5.00 (m, 1H) 4.23 (d, 2H), 4.19 (d, 2H), 3.93 (m, 1H), 3.82-3.83 (m, 3H), 3.68-3.69 (m, 2H) 3.12-2.75 (m, 7H), 1.82 (m, 1H), 1.62-1.52 (d, 2H), 0.89-0.86 (dd, 6H).

Example 24

Ref: J. Med. Chem. 1992, 35 10,1681-1701

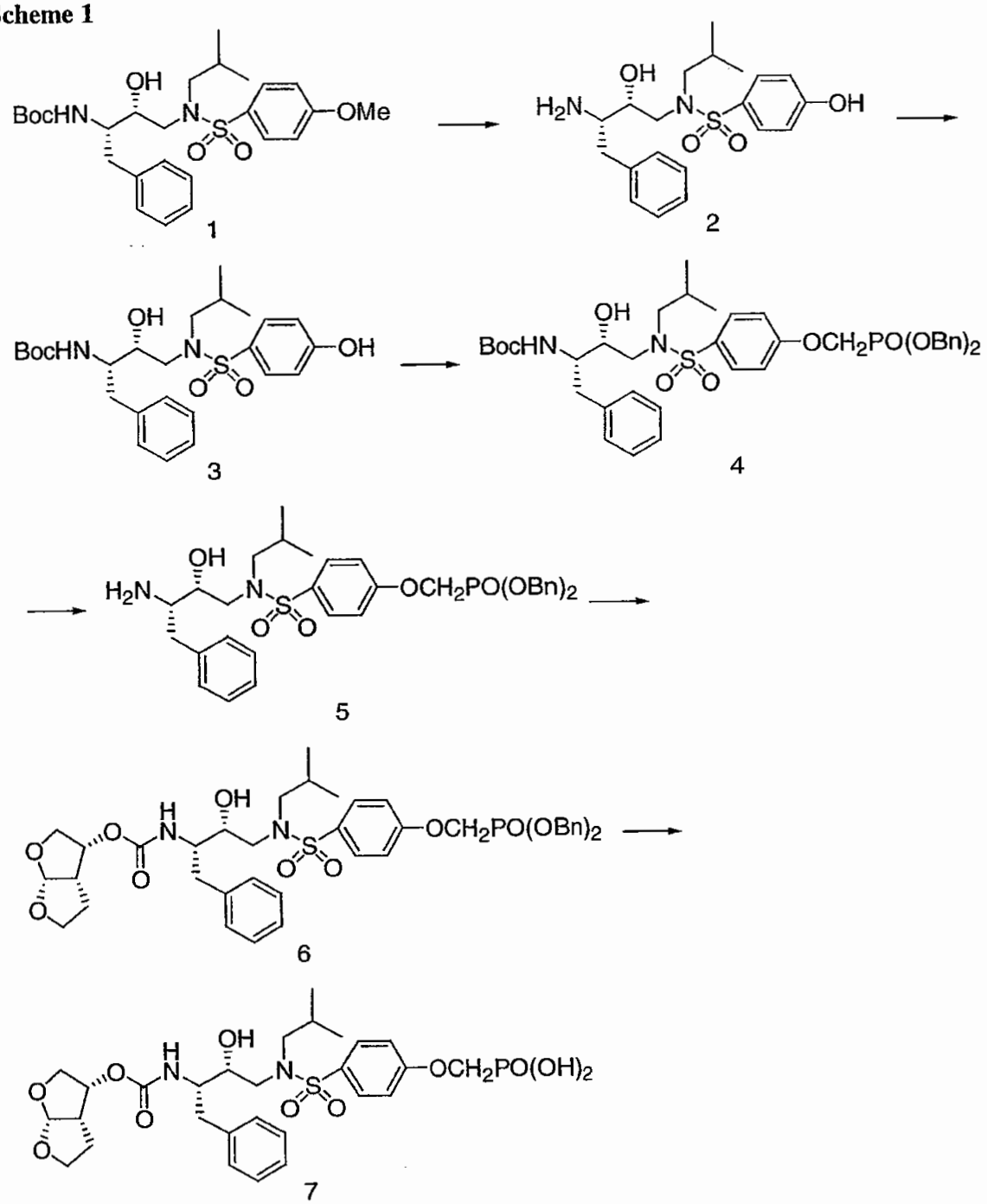
To a solution of phosphonate 32 (100 mg, 0.119 mmol) in dry dioxane was added Cs_2CO_3 (233 mg, 0.715 mmol), followed by 2-(dimethylamino) ethyl chloride hydrochloride salt (69 mg, 0.48 mmol). The reaction was stirred at room temperature and monitored by TLC. When it was determined that starting material remained, additional Cs_2CO_3 (233 mg, 0.715 mmol) as well as amine salt (69 mg, 0.48 mmol) were added and the reaction was stirred overnight at 60°C. In the morning when TLC showed completion the reaction was cooled to room temperature, filtered, and concentrated. The product amine 33 (40 mg, 37%) was purified on silica. Decomposition was noted as lower spots were seen to emerge with time using 15% MeOH in DCM on silica.

Example 25:

Amine 33 (19 mg, 0.021 mmol) was dissolved in 1.5 mL DCM. This solution was stirred in an icebath. Methane sulfonic acid (0.0015 mL, 0.023 mmol) was added and the reaction was stirred for 20 minutes. The reaction was warmed to room temperature and stirred for 1 hour. The product, amine mesylate salt 34 (20 mg, 95%) was precipitated out by addition of hexane. ^{1}H NMR (CD_3OD): δ 7.69 (d, 2H), 7.35 (m, 10H), 7.15 (m, 4H) 6.85 (m, 2H), 5.49 (d, 1H), 5.10 (m, 4H), 4.83 (m, 1H), 4.62 (d, 2H), 4.22 (m, 2H), 3.82 (m, 1H), 3.56 (m, 1H), 3.48 (m, 2H), 3.35 (m, 1H), 2.99 (m, 1H), 2.95 (m, 1H), 2.84 (s, 6H), 2.78 (m, 1H), 2.75 (m, 1H), 2.70 (m, 1H), 2.40 (m, 1H) 1.94 (m, 1H), 1,43 (m, 1H), 1.27 (m, 1H), 0.77 (dd, 6H).

Example Section E

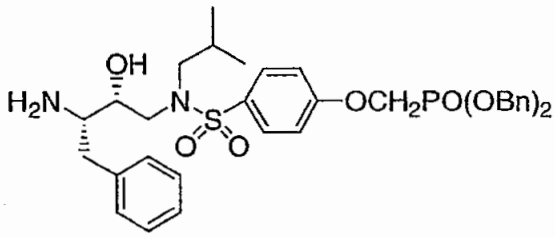
Scheme 1



Example 1

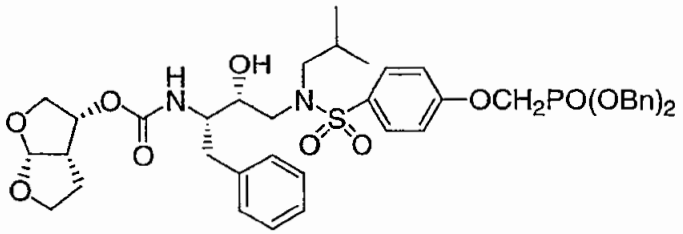
To a solution of phenol **3** (336 mg, 0.68 mmol) in THF (10 mL) was added Cs_2CO_3 (717 mg, 2.2 mmol) and triflate (636 mg, 1.5 mmol) in THF (3 mL). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 40-50% EtOAc/hexane) to give dibenzylphosphonate **4** (420 mg, 80%) as a colorless oil.

Example 2



To a solution of dibenzylphosphonate **4** (420 mg, 0.548 mmol) in CH_2Cl_2 (10 mL) was added TFA (0.21 mL, 2.74 mmol). After the reaction mixture was stirred for 2 h at room temperature, additional TFA (0.84 mL, 11 mmol) was added and the mixture was stirred for 3 h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and 1M $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give amine **5** (325 mg, 89%).

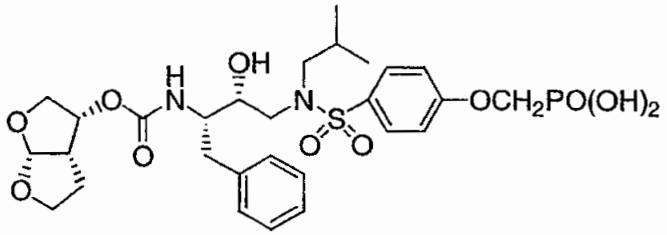
Example 3



To a solution of carbonate (79 mg, 0.27 mmol), amine **5** (178 mg, 0.27 mmol), and CH_3CN (10 mL) was added DMAP (66 mg, 0.54 mmol) at 0°C. After the reaction mixture was warmed to room temperature and stirred for 16 hours, the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (eluting 60-90% EtOAc/hexane) to give a mixture of carbamate **6** and starting carbonate. The mixture was further purified by HPLC on C18 reverse phase chromatography (eluting 60% CH_3CN/water)

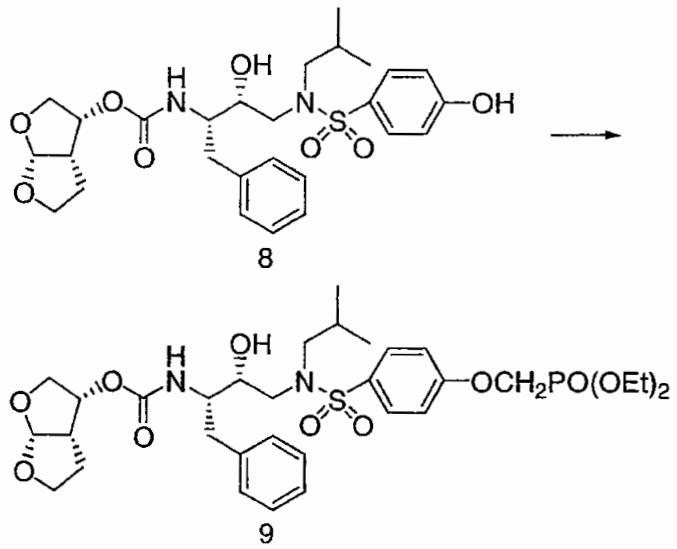
to give carbamate **6** (49 mg, 22%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 2H), 7.22 (m, 15 H), 6.95 (d, 2H), 5.62 (d, 1H), 5.15 (dt, 4H), 5.00 (m, 2H), 4.21 (d, 2H), 3.88 (m, 4H), 3.67 (m, 3H), 3.15 (m, 2H), 2.98 (m, 3H), 2.80 (m, 2H), 1.82 (m, 1H), 1.61 (m, 1H), 0.93 (d, 3H), 0.88 (d, 3H).

Example 4

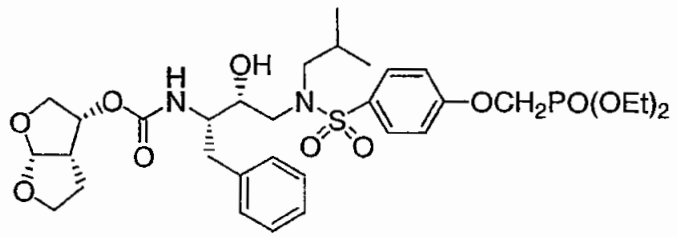


To a solution of carbamate **6** (21 mg, 0.026 mmol) in EtOH / EtOAc (2 mL/1 mL) was added 10% Pd/C (11 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 2 hours, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give phosphonic acid **7** (17 mg, 100%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.73 (d, 2H), 7.19 (m, 5H), 7.13 (d, 2H), 5.53 (d, 1H), 4.26 (d, 2H), 3.86 (m, 1H), 3.64 (m, 5H), 3.38 (d, 1H), 3.13 (d, 1H), 3.03 (dd, 1H), 2.86 (m, 3H), 2.48 (m, 1H), 1.97 (m, 1H), 1.47 (m, 1H), 1.28 (m, 2H), 1.13 (t, 1H), 0.88 (d, 3H), 0.83 (d, 3H).

Scheme 2

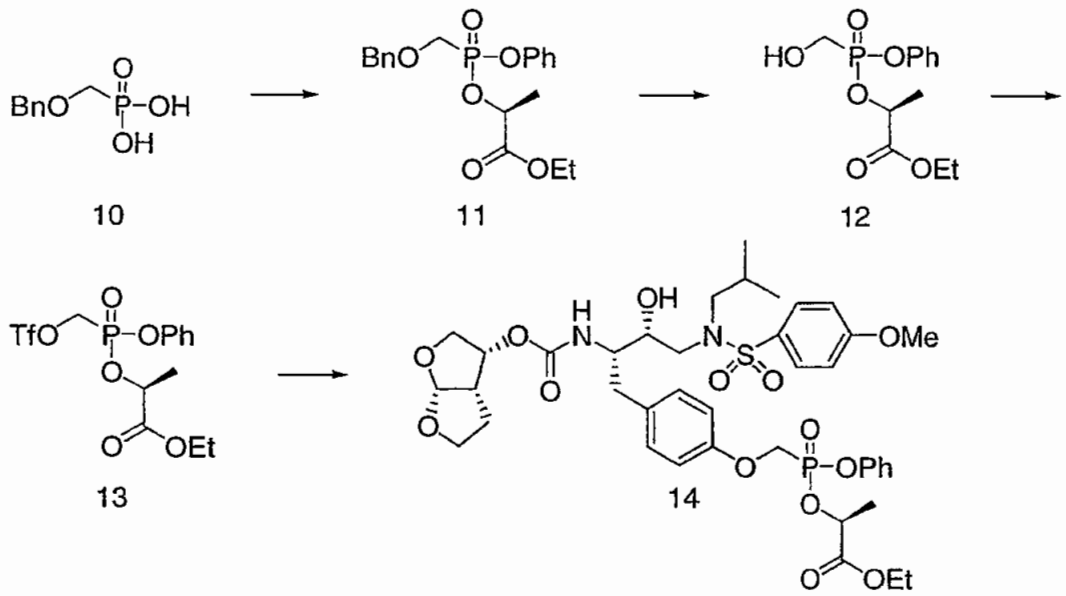


Example 5

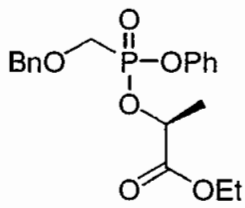


To a solution of phenol **8** (20 mg, 0.036 mmol) and triflate (22 mg, 0.073 mmol) in THF (2 mL) was added Cs_2CO_3 (29 mg, 0.090 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 80% EtOAc/hexane) to give diethylphosphonate **9** (21 mg, 83%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, 2H), 7.25 (m, 5H), 7.07 (d, 2H), 5.64 (d, 1H), 5.01 (m, 2H), 4.25 (m, 6H), 3.88 (m, 4H), 3.70 (m, 3H), 2.97 (m, 6H), 1.70 (m, 4H), 1.38 (t, 6H), 0.92 (d, 3H), 0.88 (d, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 18.1.

Scheme 3

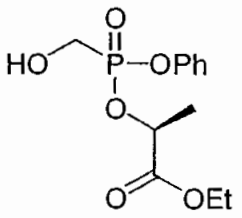


Example 6



To a solution of phosphonic acid **10** (520 mg, 2.57 mmol) in CH_3CN (5 mL) was added thionyl chloride (0.75 mL, 10.3 mmol) and heated to 70°C in an oil bath. After the reaction mixture was stirred for 2 h at 70°C, the mixture was concentrated and azeotroped with toluene. To a solution of the crude chloridate in toluene (5 mL) was added tetrazole (18 mg, 0.26 mmol) at 0°C. To this mixture was added phenol (121 mg, 1.28 mmol) and triethylamine (0.18 mL, 1.28 mmol) in toluene (3 mL) at 0°C. After the reaction mixture was warmed to room temperature and stirred for 2 h, ethyl lactate (0.29 mL, 2.57 mmol) and triethylamine (0.36 mL, 2.57 mmol) in toluene (2.5 mL) were added. The reaction mixture was stirred for 16 hours at room temperature, at which time the mixture was partitioned between EtOAc and sat. NH_4Cl. The organic phase was washed with sat. NH_4Cl, 1M $NaHCO_3$, and brine, then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 20-40% EtOAc/hexane) to give two diastereomers of phosphonate **11** (66 mg, 109 mg, 18% total) as colorless oils.

Example 7A

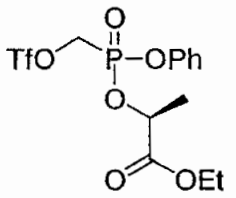


To a solution of phosphonate **11** isomer A (66 mg, 0.174 mmol) in EtOH (2 mL) was added 10% Pd/C (13 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 6 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give alcohol **12** isomer A (49 mg, 98%) as a colorless oil.

Example 7B

To a solution of phosphonate **11** isomer B (110 mg, 0.291 mmol) in EtOH (3 mL) was added 10% Pd/C (22 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 6 h, it was filtered through Celite. The filtrate was evaporated under reduced pressure to give alcohol **12** isomer B (80 mg, 95%) as a colorless oil.

Example 8A

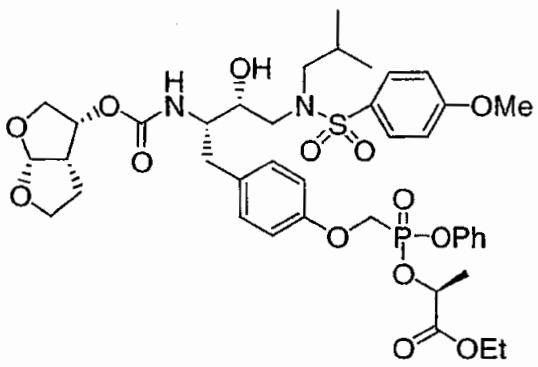


To a solution of alcohol **12** isomer A (48 mg, 0.167 mmol) in CH_2Cl_2 (2 mL) was added 2,6-lutidine (0.03 mL, 0.250 mmol) and trifluoromethanesulfonic anhydride (0.04 mL, 0.217 mmol) at -40°C (dry ice-CH_3CN bath). After the reaction mixture was stirred for 15 min at -40°C, the mixture was warmed to 0°C and partitioned between Et_2O and 1M H_3PO_4. The organic phase was washed with 1M H_3PO_4 (3 times), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give triflate **13** isomer A (70 mg, 100%) as a pale yellow oil.

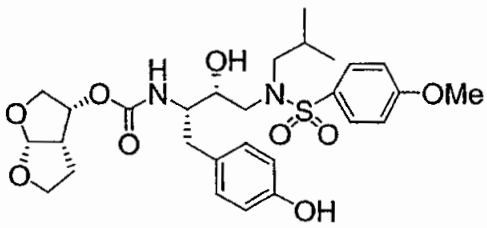
Example 8B

To a solution of alcohol **12** isomer B (80 mg, 0.278 mmol) in CH_2Cl_2 (3 mL) was added 2,6-lutidine (0.05 mL, 0.417 mmol) and trifluoromethanesulfonic anhydride (0.06 mL, 0.361 mmol) at -40°C (dry ice-CH_3CN bath). After the reaction mixture was stirred for 15 min at -40°C, the mixture was warmed to 0°C and partitioned between Et_2O and 1M H_3PO_4. The organic phase was washed with 1M H_3PO_4 (3 times), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give triflate **13** isomer B (115 mg, 98%) as a pale yellow oil.

Example 9A



To a solution of phenol (64 mg, 0.111 mmol):

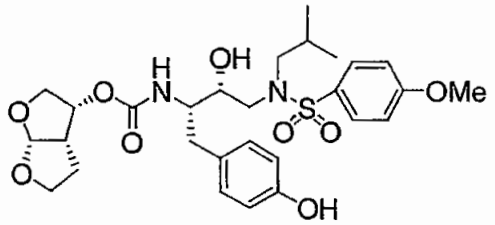


and triflate **13** isomer A (70 mg, 0.167 mmol) in THF (2 mL) was added Cs_2CO_3 (72 mg, 0.222 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 60-80% EtOAc/hexane) to give a mixture. The mixture was further purified by HPLC on C18 reverse phase chromatography (eluting 55% CH_3CN/water) to give phosphonate **14** isomer A (30 mg, 32%) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 2H), 7.26 (m, 6H), 7.00 (m, 5H), 5.65 (d, 1H), 5.14 (m, 1H), 5.00 (m, 2H), 4.54 (dd, 1H), 4.44 (dd, 1H), 4.17 (m, 2H), 3.96 (dd, 1H), 3.86 (m, 5H), 3.72

(m, 3H), 3.14 (m, 1H), 2.97 (m, 4H), 2.79 (m, 2H), 1.83 (m, 1H), 1.62 (m, 3H), 1.50 (d, 3H), 1.25 (m, 3H), 0.93 (d, 3H), 0.88 (d, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 17.4.

Example 9B

To a solution of phenol (106 mg, 0.183 mmol):



and triflate **13** isomer B (115 mg, 0.274 mmol) in THF (2 mL) was added Cs_2CO_3 (119 mg, 0.366 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 60-80% EtOAc/hexane) to give a mixture. The mixture was further purified by HPLC on C18 reverse phase chromatography (eluting 55% CH_3CN/water) to give phosphonate **14** isomer B (28 mg, 18%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 2H), 7.26 (m, 6H), 6.94 (m, 5H), 5.66 (d, 1H), 5.17 (m, 1H), 4.99 (m, 2H), 4.55 (m, 1H), 4.42 (m, 1H), 4.16 (m, 2H), 3.97 (m, 1H), 3.85 (m, 5H), 3.72 (m, 3H), 3.13 (m, 1H), 2.97 (m, 4H), 2.80 (m, 2H), 1.83 (m, 1H), 1.60 (m, 6H), 1.22 (m, 3H), 0.93 (d, 3H), 0.88 (d, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 15.3.

Resolution of Compound 14 **Diastereomers**

Analysis was performed on an analytical Alltech Econosil column, conditions described below, with a total of about 0.5 mg **14** injected onto the column. This lot was a mixture of major and minor diastereomers where the lactate ester carbon is a mix of R and S configurations. Up to 2 mg could be resolved on the analytical column. Larger scale injections (up to 50 mg **14**) were performed on an Alltech Econosil semi-preparative column, conditions described below.

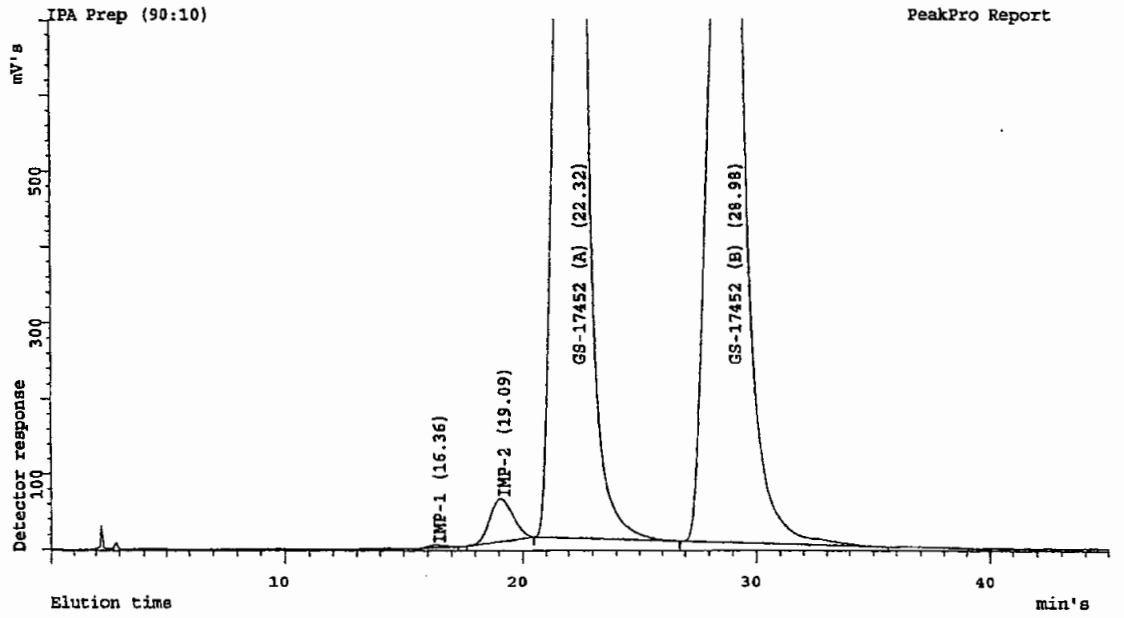
The isolated diastereomer fractions were stripped to dryness on a rotary evaporator under house vacuum, followed by a final high vacuum strip on a vacuum pump. The

chromatographic solvents were displaced by two portions of dichloromethane before the final high vacuum strip to aid in removal of trace solvents, and to yield a friable foam.

The bulk of the diastereomer resolution was performed with *n*-heptane substituted for hexanes for safety considerations.

Sample Dissolution: While a fairly polar solvent mixture is described below, the sample may be dissolved in mobile phase with a minimal quantity of ethyl alcohol added to dissolve the sample.

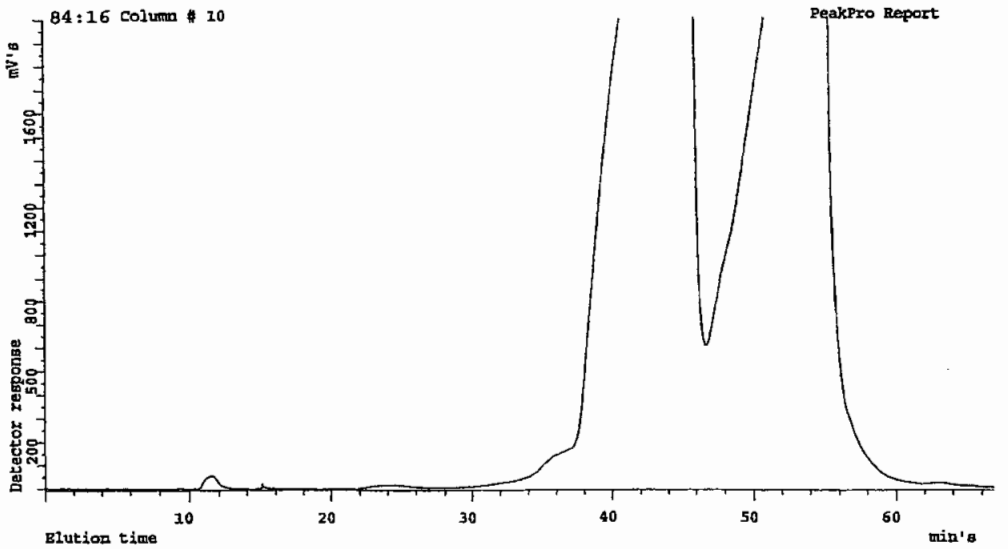
Analytical Column, 0.45 mg Injection, Hexanes – IPA (90:10)



HPLC CONDITIONS

Column	: Alltech Econosil, 5 µm, 4.6 x 250 mm
Mobile Phase	: Hexanes – Isopropyl Alcohol (90:10)
Flow Rate	: 1.5 mL/min
Run Time	: 50 min
Detection	: UV at 242 nm
Temperature	: Ambient
Injection Size	: 100 µL
Sample Prep.	: ~ 5 mg/mL, dissolved in hexanes – ethyl alcohol (75:25)
Retention Times	: **14** ~ 22 min
	: **14** ~ 29 min
	: Less Polar Impurity ~ 19 min

Semi-Preparative Column, 50 mg Injection, *n*-Heptane – IPA (84:16)



HPLC CONDITIONS

Column	: Alltech Econosil, 10 μm, 22 x 250 mm
Mobile Phase	: *n*-Heptane – Isopropyl Alcohol (84:16)
Flow Rate	: 10 mL/min
Run Time	: 65 min
Detection	: UV at 257 nm
Temperature	: Ambient
Injection Size	: ~50 mg
Dissolution	: 2 mL mobile phase plus ~ 0.75 mL ethyl alcohol
Retention Times	: **14** ~ 41 min
	: **14** ~ 54 min
	: Less Polar Impurity ~ Not resolved

Example Section F

Example 1

Phosphonic acid 2: To a solution of compound 1 (A. Flohr et al, J. Med. Chem., 42, 12, 1999; 2633-2640) (4.45 g, 17 mmol) in CH_2Cl_2 (50 mL) at room temperature was added bromotrimethylsilane (1.16 mL, 98.6 mmol). The solution was stirred for 19 h. The volatiles were evaporated under reduced pressure to give the oily phosphonic acid 2 (3.44 g, 100%). ^1H NMR ($CDCl_3$) δ 7.30 (m, 5H), 4.61 (s, 2 H), 3.69 (d, 2H).

Example 2

Compound 3: To a solution of phosphonic acid 2 (0.67 g, 3.3 mmol) in CH_3CN (5 mL) was added thionyl chloride (1 mL, 13.7 mmol) and the solution was heated at 70°C for 2.5 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily phophonyl dichloride. The crude chloride intermediate was dissolved in CH_2Cl_2 (20 mL) and cooled in an ice/water bath. Ethyl lactate (1.5 mL, 13.2 mmol) and triethyl amine (1.8 mL, 13.2 mmol) were added dropwise. The mixture was stirred for 4 h at room temperature and dilluted with more CH_2Cl_2 (100 mL). The organic solution was washed with 0.1N HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$) filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel to afford oily compound 3 (0.548 g, 41%). ^1H NMR ($CDCl_3$) δ 7.30 (m, 5H), 5.00-5.20 (m, 2H), 4.65 (m, 2H), 4.20 (m, 4H), 3.90 (d, 2H), 1.52 (t, 6H), 1.20 (t, 6H).

Example 3

Alcohol 4: A solution of compound 3 (0.54 g, 1.34 mmol) in EtOH (15 mL) was treated with 10% Pd/C (0.1 g) under H_2 (100 psi) for 4 h. The mixture was filtered and the filtrate was treated with fresh 10% PD/C (0.1 g) under H_2 (1 atmosphere) for 18 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 4 (0.395 g, 94%) as an oil. ^1H NMR ($CDCl_3$) δ 4.90-5.17 (m, 2H), 4.65 (q, 2H), 4.22 (m, 4H), 4.01 (m, 2H), 1.55 (t, 6H), 1.21 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 22.8.

Example 4

Triflate 5: To a solution of alcohol 4 (122.8 mg, 0.393 mmol) in CH_2Cl_2 (5 mL) at -40°C were added 2,6-lutidine (0.069 mL, 0.59 mmol) and trifluoromethansulfonic anhydride

(0.086 mL, 0.51 mmol). Stirring was continued at 0°C for 2 h. and the mixture partitioned in CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product 5 (150 mg, 87%) was used for the next step without further purification. ^1H NMR ($CDCl_3$) δ 5.0-5.20 (m, 2H), 4.93 (d, 2H), 4.22 (m, 4H), 1.59 (m, 6H), 1.29 (t, 6H).

Example 5

Phosphonate 6: A solution of phenol 8 (see Scheme Section A, Scheme 1 and 2) (32 mg, 0.055 mmol) and triflate 5 (50 mg, 0.11 mmol) in THF (1.5 mL) at room temperature was treated with Cs_2CO_3 (45.6 mg, 0.14 mmol). The mixture was stirred for 2.5 h and partitioned in EtOAc and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30-70% EtOAc/hexane) affording the phosphonate 6 (41 mg, 84%) as a solid. ^1H NMR ($CDCl_3$) δ 7.71 (d, 2H), 7.13 (d, 2H), 7.00 (d, 2H), 6.90 (d, 2H), 5.65 (d, 1H), 4.90-5.22 (m, 3H), 4.40 (m, 2H), 4.20 (m, 4H), 3.90 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 1.52-1.87 (m, 12H), 1.25 (m, 6H), 0.85-0.90 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 20.0.

Example 6

Compound 7: To a solution of phosphonic acid 2 (0.48 g, 2.37 mmol) in CH_3CN (4 mL) was added thionyl chloride (0.65 mL, 9.48 mmol) and the solution was heated at 70°C for 2.5 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily phophonyl dichloride. The crude chloride intermediate was dissolved in CH_2Cl_2 (5 mL) and cooled in an ice/water bath. Ethyl glycolate (0.9 mL, 9.5 mmol) and triethyl amine (1.3 mL, 9.5 mmol) were added dropwise. The mixture was stirred for 2 h at room temperature and dilluted with more CH_2Cl_2 (100 mL). The organic solution was washed with 0.1N HCl, saturated aqueous $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$) filtered and concentrated under reduced pressure. The crude product was chromatographed on silica gel to afford oily compound 7 (0.223 g, 27%). ^1H NMR ($CDCl_3$) δ 7.30 (m, 5H), 4.65 (m, 6H), 4.25 (q, 4H), 3.96 (d, 2H), 1.27 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 24.0.

Example 7

Alcohol 8: A solution of compound 7 (0.22 g, 0.65 mmol) in EtOH (8 mL) was treated with 10% Pd/C (0.04 g) under H_2 (1 atmosphere) for 4 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 8 (0.156 g, 96%) as an oil. ^{1}H NMR ($CDCl_3$) δ 4.66 (m, 4H), 4.23 (q, 4H), 4.06 (d, 2H), 1.55 (t, 6H), 1.26 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 26.8.

Example 8

Triflate 9: To a solution of alcohol 8 (156 mg, 0.62 mmol) in CH_2Cl_2 (5 mL) at -40°C were added 2,6-lutidine (0.11 mL, 0.93 mmol) and trifluoromethansulfonic anhydride (0.136 mL, 0.8 mmol). Stirring was continued at 0°C for 2 h. and the mixture partitioned in CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product 9 (210 mg, 88%) was used for the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 4.90 (d, 2H), 4.76 (d, 4H), 4.27 (q, 4H), 1.30 (t, 6H).

Example 9

Phosphonate 10: A solution of phenol 8 (30 mg, 0.052 mmol) and triflate 9 (30 mg, 0.078 mmol) in THF (1.5 mL) at room temperature was treated with Cs_2CO_3 (34 mg, 0.1 mmol). The mixture was stirred for 2.5 h and partitioned in EtOAc and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30-70% EtOAc/hexane) affording the unreacted phenol (xx) (12 mg, 40%) and the phosphonate 10 (16.6 mg, 38%) as a solid. ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H), 7.13 (d, 2H), 7.00 (d, 2H), 6.90 (d, 2H), 5.65 (d, 1H), 5.00 (m, 2H), 4.75 (m, 4H), 4.48 (d, 2H), 4.23 (q, 4H), 3.90 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 2.23 (b.s., 2H), 1.52-1.87 (m, 4H), 1.25 (t, 6H), 0.85-0.90 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 22.0.

Example 10

Compound 11: To a solution of phosphonic acid 2 (0.512 g, 2.533 mmol) in CH_3CN (5 mL) was added thionyl chloride (0.74 mL, 10 mmol) and the solution was heated at 70°C for 2.5 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily phophonyl dichloride. The crude chloride intermediate was dissolved in toluene (8 mL) and cooled in an ice/water bath. A catalytic amount of tetrazol (16 mg, 0.21 mmol) was added followed by the addition of a solution of triethylamine (0.35 mL, 2.53 mmol) and phenol (238

mg, 2.53 mmol) in toluene (5 mL). The mixture was stirred at room temperature for 3 h. A solution of ethyl glycolate (0.36 mL, 3.8 mmol) and triethyl amine (0.53 mL, 3.8 mmol) in toluent (3 mL) was added dropwise. The mixture was stirred for 18 h at room temperature and partitioned in EtOAc and 0.1N HCl. The organic solution was washed with saturated aqueous $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$) filtered and concentrated under reduced pressure. The crude product was chromatographed on silica gel to afford diphenyl phophonate as a byproduct (130 mg) and compound 11 (0.16 g, 18%). ^1H NMR ($CDCl_3$) δ 7.15-7.40 (m, 10H), 4.58-4.83 (m, 4H), 4.22 (q, 2H), 4.04 (dd, 2H), 1.24 (t, 3H).

Example 11

Alcohol 12: A solution of compound 11 (0.16 g, 0.44 mmol) in EtOH (5 mL) was treated with 10% Pd/C (0.036 g) under H_2 (1 atmosphere) for 22 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 12 (0.112 g, 93%) as an oil. ^1H NMR ($CDCl_3$) δ 7.15-7.36 (m, 5H), 4.81 (dd, 1H), 4.55 (dd, 1H), 4.22 (q, 2H), 4.12 (m, 2H), 3.78 (b.s., 1H), 1.26 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 22.9

Example 12

Triflate 13: To a solution of alcohol 12 (112 mg, 0.41 mmol) in CH_2Cl_2 (5 mL) at -40°C were added 2,6-lutidine (0.072 mL, 0.62 mmol) and trifluoromethansulfonic anhydride (0.09 mL, 0.53 mmol). Stirring was continued at 0°C for 3 h. and the mixture partitioned in CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30% EtOAc/hexane) affording triflate 13 (106 mg, 64%). ^1H NMR ($CDCl_3$) δ 7.36 (m, 2H), 7.25 (m, 3H), 4.80-5.10 (m, 3H), 4.60 (dd, 1H), 4.27 (q, 2H), 1.28 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 11.1

Example 13

Phosphonate 14: A solution of phenol 8 (32 mg, 0.052 mmol) and triflate 13 (32 mg, 0.079 mmol) in CH_3CN (1.5 mL) at room temperature was treated with Cs_2CO_3 (34 mg, 0.1 mmol). The mixture was stirred for 1 h and partitioned in EtOAc and saturated $NaHCO_3$. The organic layer was washed with saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (70%

EtOAc/hexane) affording phosphonate 14 (18 mg, 40%). ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H), 6.75-7.35 (m, 11H, 5.65 (d, 1H), 5.00 (m, 2H), 4.50-4.88 (m, 3H), 4.20 (q, 2H), 3.84 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 1.52-1.87 (m, 6H), 1.25 (t, 3H), 0.85-0.90 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 17.9, 17.7.

Example 14

Piperidine 16: A solution of compound 15 (3.1 g, 3.673 mmol) in MeOH (100 mL) was treated with 10% Pd/C (0.35 g) under H_2 (1 atmosphere) for 18 h. The mixture was filtered and the filtrate was evaporated to afford phenol 16 (2 g, 88%). ^{1}H NMR (CD_3OD) δ 7.76 (d, 2H), 7.08 (d, 2H), 7.04 (d, 2H), 6.65 (d, 2H), 5.59 (d, 1H), 4.95 (m, 1H), 3.98 (s, 3H), 3.65-4.00 (m, 5H), 3.30-3.50 (m, 3H), 2.80-3.26 (m, 5H), 2.40-2.70 (m, 3H), 1.35-2.00 (m, 7H), 1.16 (m, 2H); MS (ESI) 620 (M+H).

Example 15

Formamide 17: Piperidine 16 obtained above (193 mg, 0.3118 mmol) in DMF (4 mL) was treated with formic acid (0.035 mL, 0.936 mmol), triethylamine (0.173 mL, 1.25 mmol) and EDCI (179 mg, 0.936 mmol) at room temperature. The mixture was stirred for 18 h and partitioned in EtOAc and saturated $NaHCO_3$. The organic layer was washed with saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAC/hexane) affording formamide 17 (162 mg, 80%). ^{1}H NMR ($CDCl_3$) δ 7.96 (s, 1H), 7.68 (d, 2H), 7.04 (d, 2H), 6.97 (d, 2H), 6.76 (d, 2H), 5.63 (d, 1H), 5.37 (bs, 1H), 5.04 (m, 1H), 4.36 (m, 1H), 3.93 (s, 3H), 3.52-3.95 (m, 7H), 2.70-3.20 (m, 8H), 1.48-2.00 (m, 7H), 1.02 (m, 2H).

Example 16

Dibenzyl phosphonate 18: A solution of phenol 17 (123 mg, 0.19 mmol) and dibenzyl trifluoromethansulfonyloxymethanphosphonate YY (120 mg, 0.28 mmol) in CH_3CN (1.5 mL) at room temperature was treated Cs_2CO_3 (124 mg, 0.38 mmol). The mixture was stirred for 3 h and partitioned in CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% MeOH/CH_2Cl_2) affording phosphonate 18 (154 mg, 88%). ^{1}H NMR ($CDCl_3$) δ 7.96 (s, 1H), 7.68 (d, 2H), 7.35 (m, 10H), 7.10 (d, 2H), 6.97 (d, 2H), 6.80 (d, 2H), 5.63 (d, 1H), 4.96-5.24 (m, 6H), 4.37

(m, 1H), 4.20 (d, 2H), 3.84 (s, 3H), 3.52-3.95 (m, 7H), 2.55-3.20 (m, 8H), 1.48-2.00 (m, 7H), 1.02 (m, 2H). ^{31}P NMR ($CDCl_3$) δ 20.3.

Example 17

Phosphonic acid 19: A solution of phosphonate 18 (24 mg, 0.026 mmol) in MeOH (3 mL) was treated with 10% Pd/C (5 mg) under H_2 (1 atmosphere) for 4 h. The mixture was filtered and the filtrate was evaporated to afford phosphonic acid 19 as a solid (18 mg, 93%). ^{1}H NMR (CD_3OD) δ 8.00 (s, 1H), 7.67 (d, 2H), 7.18 (d, 2H), 7.09 (d, 2H), 6.90 (d, 2H), 5.60 (d, 1H), 4.30 (m, 1H), 4.16 (d, 2H), 3.88 (s, 3H), 3.60-4.00 (m, 7H), 3.04-3.58 (m, 5H), 2.44-2.92 (m, 5H), 1.28-2.15 (m, 5H), 1.08 (m, 2H). ^{31}P NMR ($CDCl_3$) δ 16.3.

Example 18

Diethyl phosphonate 20: A solution of phenol 17 (66 mg, 0.1 mmol) and diethyl trifluoromethansulfonyloxymethanphosphonate XY (46 mg, 0.15mmol) in CH_3CN (1.5 mL) at room temperature was treated Cs_2CO_3 (66 mg, 0.2 mmol). The mixture was stirred for 3 h and partitioned in CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% MeOH/CH_2Cl_2) affording the unreacted 17 (17 mg, 26%) and diethyl phosphonate 20 (24.5 mg, 41%). ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.70 (d, 2H), 7.16 (d, 2H), 7.00(d, 2H), 6.88 (d, 2H), 5.66 (d, 1H), 4.98-5.10 (m, 2H), 4.39 (m, 1H), 4.24 (m, 5H), 3.89 (s, 3H), 3.602-3.98 (m, 7H), 2.55-3.16 (m, 8H), 1.50-2.00 (m, 7H), 1.36 (t, 6H), 1.08 (m, 2H). ^{31}P NMR ($CDCl_3$) δ 19.2

Example 19

N-methyl pepiridine diethyl phosphonate 21: A solution of compound 20 (22.2 mg, 0.0278 mmol) in THF (1.5 mL) at 0°C was treated with a solution of borane in THF (1M, 0.083 mL). The mixture was stirred for 2 h at room temperature and the starting material was consumed completely as monitored by TLC. The reaction mixture was cooled in an ice/water bath and excess methanol (1 mL) was added to quench the reaction. The solution was concentrated in vacuo and the crude product was chromatographed on silica gel with MeOH/EtOAc to afford compound 21 (7 mg, 32%). ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 2H), 7.16 (d, 2H), 7.00(d, 2H), 6.88

(d, 2H), 5.66 (d, 1H), 4.98-5.10 (m, 2H), 4.24 (m, 4H), 3.89 (s, 3H), 3.602-3.98 (m, 7H), 2.62-3.15 (m, 9H), 2.26 (s, 3H), 1.52-2.15 (m, 10H), 1.36 (t, 6H). ^{31}P NMR ($CDCl_3$) δ 19.3

Example Section G

Example 1

Compound 1: To a solution of 4-nitrobenzyl bromide (21.6 g, 100 mmol) in toluene (100 mL) was added triethyl phosphite (17.15 mL, 100 mL). The mixture was heated at 120°C for 14 hrs. The evaporation under reduced pressure gave a brown oil, which was purified by flash column chromatography (hexane/EtOAc= 2/1 to 100 % EtOAc) to afford compound 1.

Example 2

Compound 2: To a solution of compound 1 (1.0 g) in ethanol (60 mL) was added 10% Pd-C (300 mg). The mixture was hydrogenated for 14 hrs. Celite was added and the mixture was stirred for 5 mins. The mixture was filtered through a pad of celite, and washed with ethanol. Concentration gave compound 2.

Example 3

Compound 3: To a solution of compound 3 (292 mg, 1.2 mmol) and aldehyde (111 mg, 0.2 mmol) in methanol (3 mL) was added acetic acid (48 μL, 0.8 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (25 mg, 0.4 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 3.

Example 4

Compound 4: To a solution of compound 3 (79 mg , 0.1 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred for 2 hrs, and solvents were evaporated under reduced pressure. Coevaporation with EtOAc and CH_2Cl_2 gave an oil. The oil was dissolved in THF (1mL) and tetrabutylamonium fluoride (0.9 mL, 0.9 mmol) was added. The mixture was stirred for 1 hr, and solvent was removed. Purification by flash column chromotogaphy (CH_2Cl_2/MeOH = 100/7) gave compound 4.

Example 5

Compound 5: To a solution of compound 4 (0.1 mmol) in acetonitrile (1 mL) at 0°C was added DMAP (22 mg, 0.18 mmol), followed by bisfurancarbonate (27 mg, 0.09 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed

with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Purification by flash column chromotography (CH_2Cl_2/MeOH = 100/3 to 100/5) afford compound 5 (50 mg): ^1H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.9 Hz), 7.11 (2 H, d, J = 8.5 Hz), 6.98 (2 H, d, J = 8.9 Hz), 6.61 (2 H, d, J = 8.5 Hz), 5.71 (1 H, d, J = 5.2 Hz), 5.45 (1 H, m), 5.13 (1 H, m), 4.0 (6 H, m), 3.98-3.70 (4 H, m), 3.86 (3 H, s), 3.38 (2 H, m), 3.22 (1 H, m), 3.02 (5 H, m), 2.8 (1 H, m), 2.0-1.8 (3 H, m), 1.26 (6 H, t, J = 7.0 Hz), 0.95 (3 H, d, J = 6.7 Hz), 0.89 (3 H, d, J = 6.7 Hz).

Example 6

Compound 6: To a solution of compound 5 (30 mg, 0.04 mmol) in MeOH (0.8 mL) was added 37% fomaldehyde (30 μL, 0.4 mmol), followed by acetic acid (23 μL, 0.4 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (25 mg, 0.4 mmol) was added. The reaction mixture was stirred for 14 hrs, and diluted with EtOAc. The organic phase was washed 0.5 N NaOH solution (2x), water (2x), and brine, and dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 6 (11 mg): ^1H NMR ($CDCl_3$) δ 7.60 (2 H, d, J = 8.9 Hz), 7.17 (2 H, m), 6.95 (2 H, d, J = 8.9 Hz), 6.77 (2 H, d, J = 8.5 Hz), 5.68 (1 H, d, J = 5.2 Hz), 5.21 (1 H, m), 5.09 (1 H, m), 4.01 (6 H, m), 3.87 (3 H, s), 3.8-3.3 (4 H, m), 3.1-2.6 (7 H, m), 2.90 (3 H, s), 1.8 (3 H, m), 1.25 (6 H, m), 0.91 (6 H, m).

Example 7

Compound 7: To a solution of compound 1 (24.6 g, 89.8 mmol) in acetonitrile (500 mL) was added TMSBr (36 mL, 269 mmol). The reaction mixture was stirred for 14 hrs, and evaporated under reduced pressure. The mixture was coevaporated with MeOH (2x), toluene (2x), EtOAc (2x), and CH_2Cl_2 to give a yellow solid (20 g). To the suspension of above yellow solid (15.8 g, 72.5 mmol) in toluene (140 mL) was added DMF (1.9 mL), followed by thionyl chloride (53 mL, 725 mmol). The reaction mixture was heated at 60°C for 5 hrs, and evaporated under reduced pressure. The mixture was coevaporated with toluene (2x), EtOAc, and CH_2Cl_2 (2x) to afford a brown solid. To the solution of the brown solid in CH_2Cl_2 at 0°C was added benzyl alcohol (29 mL, 290 mmol), followed by slow addition of pyridine (35 mL, 435 mmol). The reaction mixture was allowed to warm to 25°C and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Concentration

gave a dark oil, which was purified by flash column chromatography (hexanes/EtOAc = 2/1 to 1/1) to afford compound 7.

Example 8

Compound 8: To a solution of compound 7 (15.3 g) in acetic acid (190 mL) was added Zinc dust (20 g). The mixture was stirred for 14 hrs, and celite was added. The suspension was filtered through a pad of celite, and washed with EtOAc. The solution was concentrated under reduced pressure to dryness. The mixture was diluted with EtOAc, and was washed with 2N NaOH (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Concentration under reduced pressure gave compound 8 as an oil (15 g).

Example 9

Compound 9: To a solution of compound 8 (13.5 g, 36.8 mmol) and aldehyde (3.9 g, 7.0 mmol) in methanol (105 mL) was added acetic acid (1.68 mL, 28 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (882 mg, 14 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 9 (6.0 g).

Example 10

Compound 10: To a solution of compound 9 (6.2 g , 6.8 mmol) in CH_2Cl_2 (100 mL) was added trifluoroacetic acid (20 mL). The mixture was stirred for 2 hrs, and solvents were evaporated under reduced pressure. Coevaporation with EtOAc and CH_2Cl_2 gave an oil. The oil was dissolved in THF (1mL) and tetrabutylamonium fluoride (0.9 mL, 0.9 mmol) was added. The mixture was stirred for 1 hr, and solvent was removed. Purification by flash column chromotogaphy (CH_2Cl_2/MeOH = 100/7) gave compound 10.

Example 11

Compound 11: To a solution of compound 10 (5.6 mmol) in acetonitrile (60 mL) at 0°C was added DMAP (1.36g, 11.1 mmol), followed by bisfurancarbonate (1.65 g, 5.6 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$.

Purification by flash column chromotography (CH_2Cl_2/MeOH = 100/3 to 100/5) afford compound 11 (3.6 g): ^{1}H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.9 Hz), 7.30 (10 H, m), 7.07 (2 H, m), 6.97 (2 H, d, J = 8.9 Hz), 6.58 (2 H, d, J = 8.2 Hz), 5.70 (1 H, d, J = 5.2 Hz), 5.42 (1 H, m), 5.12 (1 H, m), 4.91 (4 H, m), 4.0-3.7 (6 H, m), 3.85 (3 H, s), 3.4 (2 H, m), 3.25 (1 H, m), 3.06 (2 H, d, J = 21 Hz), 3.0 (3 H, m), 2.8 (1 H, m), 1.95 (1 H, m), 1.82 (2 H, m), 0.91 (6 H, m).

Example 12

Compound 12: To a solution of compound 11 (3.6 g) in ethanol (175 mL) was added 10% Pd-C (1.5 g). The reaction mixture was hydrogenated for 14 hrs. The mixture was stirred with celite for 5 mins, and filtered through a pad of celite. Concentration under reduced pressure gave compound 12 as a white solid (2.8 g): ^{1}H NMR (DMSO-d_6) δ 7.68 (2 H, m), 7.08 (2 H, m), 6.93 (2 H, m), 6.48 (2 H, m), 5.95 (1 H, m), 5.0 (2 H, m), 3.9-3.6 (6 H, m), 3.82 (3 H, s), 3.25 (3 H, m), 3.05 (4 H, m), 2.72 (2 H, d, J = 20.1 Hz), 2.0-1.6 (3 H, m), 0.81 (6 H, m).

Example 13

Compound 13: Compound 12 (2.6 g, 3.9 mmol) and L-alanine ethyl ester hydrochloride (3.575 g, 23 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (20 mL) and diisopropylethylamine (4.1 mL, 23 mmol) was added. To above mixture was added a solution of Aldrithiol (3.46 g, 15.6 mmol) and triphenylphosphine (4.08 g, 15.6 g) in pyridine (20 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with 0.5 N NaOH solution (2x), water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a yellow oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/10) to afford compound 13 (750 mg): ^{1}H NMR ($CDCl_3$) δ 7.71 (2 H, d, J = 8.8 Hz), 7.13 (2 H, m), 6.98 (2 H, d, J = 8.8 Hz), 6.61 (2 H, d, J = 8.0 Hz), 5.71 (1 H, d, J = 5.2 Hz), 5.54 (1 H, m), 5.16 (1 H, m), 4.15 (6 H, m), 4.1-3.6 (6 H, m), 3.86 (3 H, s), 3.4-3.2 (3 H, m), 3.1-2.8 (8 H, m), 2.0 (1 H, m), 1.82 (2 H, m), 1.3 (12 H, m), 0.92 (6 H, m).

Example 14

Compound 14: To a solution of 4-hydroxypiperidine (19.5 g, 193 mmol) in THF at 0°C was

added sodium hydroxide solution (160 mL, 8.10 g, 203 mmol), followed by di-tert-butyl dicarbonate (42.1 g, 193 mmol). The mixture was warmed to 25°C, and stirred for 12 hours. THF was removed under reduced pressure, and the aqueous phase was extracted with EtOAc (2x). The combined organic layer was washed with water (2x) and brine, and dried over MgSO4. Concentration gave a compound 14 as a white solid (35 g).

Example 15

Compound 15: To a solution of alcohol 14 (5.25 g, 25 mmol) in THF (100 mL) was added sodium hydride (1.2 g, 30 mmol, 60%). The suspension was stirred for 30 mins, and chloromethyl methyl sulfide (2.3 mL, 27.5 mmol) was added. Starting material alcohol 14 still existed after 12 hrs. Dimethy sulfoxide (50 mL) and additional chloromethyl methyl sulfide (2.3 mL, 27.5 mmol) were added. The mixture was stirred for additional 3 hrs, and THF was removed under reduced pressure. The reaction was quenched with water, and extracted with ethyl acetate. The organic phase was washed with water and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 8/1) gave compound 15 (1.24 g).

Example 16

Compound 16: To a solution of compound 15 (693 mg, 2.7 mmol) in CH_2Cl_2 (50 mL) at –78°C was added a solution of sulfuryl chloride (214 µL, 2.7 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was kept at –78°C for 3 hrs, and solvents were removed to give a white solid. The white solid was dissolved in toluene (7 mL), and triethyl phosphite (4.5 mL, 26.6 mmol) was added. The reaction mixture was heated at 120°C for 12 hrs. Solvent and excess reagent was removed under reduced pressure to give compound 16.

Example 17

Compound 17: To a solution of compound 17 (600 mg) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 2 hrs, and was concentrated under reduced pressure to give an oil. The oil was diluted with methylene chloride and base resin was added. The suspension was filtered and the organic phase was concentrated to give compound 17.

Example 18

Compound 18: To a solution of compound 17 (350 mg, 1.4 mmol) and aldehyde (100 mg, 0.2 mmol) in methanol (4 mL) was added acetic acid (156 μL, 2.6 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (164 mg, 2.6 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 18 (62 mg).

Example 19

Compound 19: To a solution of compound 18 (62 mg, 0.08 mmol) in THF (3 mL) were added acetic acid (9 μL, 0.15 mmol) and tetrabutylamonium fluoride (0.45 mL, 1.0 N, 0.45mmol). The mixture was stirred for 3 hr, and solvent was removed. Purification by flash column chromotogaphy (CH_2Cl_2/MeOH = 100/5) gave an oil. To a solution of above oil in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 1 hrs, and was concentrated under reduced pressure. Coevaporation with EtOAc and CH_2Cl_2 gave compound 19.

Example 20

Compound 20: To a solution of compound 19 (55 mg 0.08 mmol) in acetonitrile (1 mL) at 0°C was added DMAP (20 mg, 0.16 mmol), followed by bisfurancarbonate (24 mg, 0.08 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Purification by flash column chromotography (CH_2Cl_2/MeOH = 100/3 to 100/5) afford compound 20 (46 mg): ^{1}H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.9 Hz), 7.01 (2 H, d, J = 8.9 Hz), 5.73 (1 H, d, J = 5.1 Hz), 5.51 (1 H, m), 5.14 (1 H, m), 4.16 (1 H, m), 4.06 (1 H, m), 3.94 (3 H, m), 3.86 (3 H, s), 3.80 (1 H, m), 3.75 (2 H, d, J = 9.1 Hz), 3.58 (1 H, m), 3.47 (1 H, m), 3.30 (1 H, m), 3.1-2.6 (8 H, m), 2.3 (2 H, m), 2.1-1.8 (5 H, m), 1.40 (2 H, m), 1.36 (6 H, t, J = 7.0 Hz), 0.93 (3 H, d, J = 6.7 Hz), 0.86 (3 h, d, J = 6.7 Hz).

Example 21

Compound 21: Compound 21 was made from Boc-4-Nitro-L-Phenylalanine (Fluka) following the procedure for Compound 2 in Scheme Section A, Scheme 1.

Example 22

Compound 22: To a solution of chloroketone 21 (2.76 g, 8 mmol) in THF (50 mL) and water (6 mL) at 0°C (internal temperature) was added solid $NaBH_4$ (766 mg, 20 mmol) in several portions over a period of 15 min while maintaining the internal temperature below 5°C. The mixture was stirred for 1.5 hrs at 0°C and solvent was removed under reduced pressure. The mixture was quenched with saturated $KHSO_3$ and extracted with EtOAc. The organic phase was washed with waster and brine, and dried over$MgSO_4$. Concentration gave a solid, which was recrystalized from EtOAc/hexane (1/1) to afford the chloroalcohol 22 (1.72 g).

Example 23

Compound 23: To a suspension of chloroalcohol 22 (1.8 g, 5.2 mmol) in EtOH (50 mL) was added a solution of KOH in ethanol (8.8 mL, 0.71 N, 6.2 mmol). The mixture was stirred for 2 h at room temperature and ethanol was removed under reduced pressure. The reaction mixture was diluted with EtOAc, and washed with water (2x), saturated NH_4Cl (2x), water, and brine, and dried over $MgSO_4$. Concentration under reduced pressure afforded epoxide 23 (1.57g) as a white crystalline solid.

Example 24

Compound 24: To a solution of epoxide 23 (20 g, 65 mmol) in 2-propanol (250 mL) was added isobutylamine (65 mL) and the solution was refluxed for 90 min. The reaction mixture was concentrated under reduced pressure and was coevaporated with MeOH, CH_3CN, and CH_2Cl_2 to give a white solid. To a solution of the white solid in CH_2Cl_2 (300 mL) at 0°C was added triethylamine (19 mL, 136 mmol), followed by the addition of 4-methoxybenzenesulfonyl chloride (14.1 g, 65 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at 0°C for 30 min, and warmed to room temperature and stirred for additional 2 hrs. The reaction solution was concentrated under reduced pressure and was diluted with EtOAc. The organic phase was washed with saturated $NaHCO_3$, water and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave compound 24 as a white solid (37.5 g).

Example 25

Compound 25: To a solution of compound 24 (37.5 g, 68 mmol) in CH_2Cl_2 (100 mL) at 0°C was added a solution of tribromoborane in CH_2Cl_2 (340 mL, 1.0 N, 340 mmol). The reaction

mixture was kept at 0°C for 1 hr, and warmed to room temperature and stirred for additional 3 hrs. The mixture was cooled to 0°C, and methanol (200 mL) was added slowly. The mixture was stirred for 1 hr and solvents were removed under reduced pressure to give a brown oil. The brown oil was coevaporated with EtOAc and toluene to afford compound 25 as a brown solid, which was dried under vacuum for 48 hrs.

Example 26

Compound 26: To a solution of compound 25 in THF (80 mL) was added a saturated sodium bicarbonate solution (25 mL), followed by a solution of Boc2O (982 mg, 4.5 mmol) in THF (20 mL). The reaction mixture was stirred for 5 hrs. THF was removed under reduced pressure, and aqueous phase was extracted with EtOAc. The organic phase was washed with water (2x) and Brine (1x), and dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 1/1) gave compound 26 (467 mg).

Example 27

Compound 27: To a solution of compound 26 (300 mg, 0.56 mmol) in THF (6 mL) was added Cs_2CO_3 (546 mg, 1.68 mmol), followed by a solution of triflate (420 mg, 1.39 mmol) in THF (2 mL). The reaction mixture was stirred for 1.5 hrs. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 1/1 to 1/3) gave compound 27 (300 mg).

Example 28

Compound 28: To a solution of compound 27 (300 mg, 0.38 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 2.5 hrs, and was concentrated under reduced pressure. The mixture was diluted with EtOAc and was washed with 0.5 N NaOH solution (3x), water (2x), and brine (1x), and dried over $MgSO_4$. Concentration gave a white solid. To the solution of above white solid in acetonitrile (3 mL) at 0°C was added DMAP (93 mg, 0.76 mmol), followed by bisfurancarbonate (112 mg, 0.38 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Purification by flash column chromotography (CH_2Cl_2/MeOH = 100/3 to 100/5) afford compound 28 (230 mg): ^{1}H NMR ($CDCl_3$) δ 8.16 (2 H, d, J = 8.5 Hz), 7.73 (2 H, d, J = 9.2 Hz), 7.42 (2 H, d, J = 8.5 Hz), 7.10 (2 H, d, J = 9.2 Hz), 5.65 (1 H,d, J = 4.8 Hz), 5.0 (2 H,

m), 4.34 (2 H, d, J = 10 Hz), 4.25 (4 H, m), 4.0-3.6 (6 H, m), 3.2-2.8 (7 H, m), 1.82 (1 H, m), 1.6 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.95 (6 H, m).

Example 29

Compound 29: To a solution of compound 28 (50 mg) in ethanol (5 mL) was added 10% Pd-C (20 mg). The mixture was hydrogenated for 5 hrs. Celite was added, and the mixture was stirred for 5 mins. The reaction mixture was filtered through a pad of celite. Concentration under reduced pressure gave compound 29 (50 mg): ^{1}H NMR ($CDCl_3$) δ 7.72 (2 H, d, J = 8.8 Hz), 7.07 (2 H, 2 H, d, J = 8.8 Hz), 7.00 (2 H, d, J = 8.5 Hz), 6.61 (2 H, d, J = 8.5 Hz), 5.67 (1 H, d, J = 5.2 Hz), 5.05 (1 H, m), 4.90 (1 H, m), 4.34 (2 H, d, J = 10.3 Hz), 4.26 (2 H, m), 4.0-3.7 (6 H, m), 3.17 (1 H, m), 2.95 (4 H, m), 2.75 (2 H, m), 1.82 (1 H, m), 1.65 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.93 (3 h, d, J = 6.4 Hz), 0.87 (3 h, d, J = 6.4 Hz).

Example 30

Compound 30: To a solution of compound 29 (50 mg, 0.07 mmol) and formaldehyde (52 μL, 37%, 0.7 mmol) in methanol (1 mL) was added acetic acid (40 μL, 0.7 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (44 mg, 0.7 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 30 (40 mg): ^{1}H NMR ($CDCl_3$) δ 7.73 (2 H, d, J = 8.9 Hz), 7.10 (4 H, m), 6.66 (2 H, d, J = 8.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.02 (1 H, m), 4.88 (1 H, m), 4.32 (2 H, d, J = 10.1 Hz), 4.26 (4 H, m), 3.98 (1 H, m), 3.85 (3 H, m), 3.75 (2 H, m), 3.19 (1 H, m), 2.98 (4 H, m), 2.93 (6 H, s), 2.80 (2 H, m), 1.82 (1 H, m), 1.62 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.90 (6 H, m).

Example 31

Compound 31: To a suspension of compound 25 (2.55 g, 5 mmol) in CH_2Cl_2 (20 mL) at 0°C was added triehtylamine (2.8 mL, 20 mmol), followed by TMSCl (1.26 mL, 10 mmol). The mixture was stirred at 0°C for 30 mins, and warmed to 25°C and stirred for additional 1 hr. Concentration gave a yellow solid. The yellow solid was dissolved in acetonitrile (30 mL) and cooled to 0°C. To this solution was added DMAP (1.22 g, 10 mmol) and Bisfurancarbonate (1.48 g, 5 mmol). The reaction mixture was stirred at 0°C for 2 hrs and for

additional 1 hr at 25°C. Acetonitrile was removed under reduced pressure. The mixture was diluted with EtOAc, and washed with 5% citric acid (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Concentration gave a yellow solid. The yellow solid was dissolved in THF (40 mL), and acetic acid (1.3 mL, 20 mmol) and tetrabutylammonium fluoride (8mL, 1.0 N, 8mmol) were added. The mixture was stirred for 20 mins, and THF was removed under reduced pressure. Purification by flash column chromatography (hexenes/EtOAc = 1/1) gave compound 31 (1.5 g).

Example 32

Compound 32: To a solution of compound 31 (3.04 g, 5.1 mmol) in THF (75 mL) was added Cs_2CO_3 (3.31 g, 10.2 mmol), followed by a solution of triflate (3.24 g, 7.65 mmol) in THF (2 mL). The reaction mixture was stirred for 1.5 hrs, and THF was removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 1/1 to 1/3) gave compound 32 (2.4 g): ^{1}H NMR ($CDCl_3$) δ 8.17 (2 H, d, J = 8.5 Hz), 7.70 (2 H, J = 9.2 Hz), 7.43 (2 H, d, J = 8.5 Hz), 7.37 (10 H, m), 6.99 (2 H, d, J =9.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.15 (4 H, m), 5.05 (2 H, m), 4.26 (2 H, d, J = 10.2 Hz), 3.9-3.8 (4 H, m), 3.75 (2 H, m), 3.2-2.8 (7 H, m), 1.82 (1 H, m), 1.62 (2 H, m), 0.92 (6 H, m).

Example 33

Compound 33: To a solution of compound 32 (45 mg) in acetic acid (3 mL) was added zinc (200 mg). The mixture was stirred for 5 hrs. Celite was added, and the mixture was filtered and washed with EtOAc. The solution was concentrated to dryness and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution, water, and brine, and dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/isoproanol = 100/5) gave compound 33 (25 mg): ^{1}H NMR ($CDCl_3$) δ 7.67 (2 H, d, J = 8.8 Hz), 7.36 (10 H, m), 6.98 (4 H, m), 6.60 (2 H, d, J = 8.0 Hz), 5.67 (1 H, d, J = 4.9 Hz), 5.12 (4 H, m), 5.05 (1 H, m), 4.90 (1 H, m), 4.24 (2 H, d, J = 10.4 Hz), 4.0-3.6 (6 H, m), 3.12 (1 H, m), 3.95 (4 H, m), 2.75 (2 H, m), 1.80 (1 H, m), 1.2 (2 H, m), 0.9 (6 H, m).

Example 34

Compound 34: To a solution of compound 32 (2.4 g) in ethanol (140 mL) was added 10% Pd-C (1.0 g). The mixture was hydrogenated for 14 hrs. Celite was added, and the mixture

was stirred for 5 mins. The slurry was filtered through a pad of celite, and washed with pyridine. Concentration under reduced pressure gave compound 34: ^{1}H NMR (DMSO-d_6) δ 7.67 (2 H, d, J = 8.9 Hz), 7.14 (2 H, d, J = 8.9 Hz), 6.83 (2 H, d, J = 8.0 Hz), 6.41 (2 H, d, J = 8.0 Hz), 5.51 (1 H, d, J = 5.2 Hz), 5.0-4.8 (2 H, m), 4.15 (2 H, d, J = 10.0 Hz), 3.9-3.2 (8 H, m), 3.0 (2 H, m), 2.8 (4 H, m), 2.25 (1 H, m), 1.4 (2 H, m), 0.8 (6 H, m).

Example 35

Compound 35: Compound 34 (1.62 g, 2.47 mmol) and L-alanine butyl ester hydrochloride (2.69 g, 14.8 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (12 mL) and diisopropylethylamine (2.6 mL, 14.8 mmol) was added. To above mixture was added a solution of Aldrithiol (3.29 g, 14.8 mmol) and triphenylphosphine (3.88 g, 14.8 g) in pyridine (12 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with 0.5 N NaOH solution (2x), water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a yellow oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/15) to afford compound 35 (1.17 g): ^{1}H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.6 Hz), 7.05 (2 H, d, J =8.6 Hz), 6.99 (2 H, d, J = 8.0 Hz), 6.61 (2 H, d, J = 8.0 Hz), 5.67 (1 H, d, J = 5.2 Hz), 5.05 (1 H, m), 4.96 (1 H, m), 4.28 (2 H, m), 4.10 (6 H, m), 4.0-3.6 (6 H, m), 3.12 (2 H, m), 2.92 (3 H, m), 2.72 (2 H, m), 1.82 (1 H, m), 1.75-1.65 (2 H, m), 1.60 (4 H, m), 1.43 (6 H, m), 1.35 (4 H, m), 0.91 (12 H, m).

Example 36

Compound 37: Compound 36 (100 mg, 0.15 mmol) and L-alanine butyl ester hydrochloride (109 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (105 µL, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/15) to afford compound 37 (21 mg): ^{1}H NMR ($CDCl_3$) δ 7.71 (2 H, d, J = 8.8 Hz), 7.15 (2 H, d, J = 8.2 Hz), 7.01 (2 H, d, J = 8.8 Hz), 6.87 (2 H, d, J = 8.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.03 (1 H, m), 4.95 (1 H, m),4.2-4.0 (8 H, m), 3.98 (1 H, m), 3.89 (3 H, s),

3.88-3.65 (5 H, m), 3.15 (1 H, m), 2.98 (4 H, m), 2.82 (2 H, m), 1.83 (1 H, m), 1.63 (4 H, m), 1.42 (6 H, m), 1.35 (4 H, m), 0.95 (12 H, m).

Example 37

Compound 38: Compound 36 (100 mg, 0.15 mmol) and L-leucine ethyl ester hydrochloride (117 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (105 μL, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/15) to afford compound 38 (12 mg): ^{1}H NMR ($CDCl_3$) δ 7.72 (2 H, d, J = 8.5 Hz), 7.14 (2 H, d, J = 8.0 Hz), 7.00 (2 H, d, J = 8.5 Hz), 6.86 (2 H, d, J = 8.0 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.05 (1 H, m), 4.95 (1 H, m), 4.2-4.0 (8 H, m), 4.0-3.68 (6 H, m), 3.88 (3 H, s), 3.2-2.9 (5 H, m), 2.80 (2 H, m), 1.80 (1 H, m), 1.65 (4 H, m), 1.65-1.50 (4 H, m), 1.24 (6 H, m), 0.94 (18 H, m).

Example 38

Compound 39: Compound 36 (100 mg, 0.15 mmol) and L-leucine butyl ester hydrochloride (117 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (105 μL, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/15) to afford compound 39 (32 mg): ^{1}H NMR ($CDCl_3$) δ 7.72 (2 H, d, J = 8.8 Hz), 7.15 (2 H, d, J = 8.0 Hz), 7.0 (2 H, d, J = 8.8 Hz), 6.89 (2 H, d, J = 8.0 Hz), 5.66 (1 H, d, J = 4.3 Hz), 5.07 (1 H, m), 4.94 (1 H, m), 4.2-4.0 (8 H, m), 3.89 (3 H, s), 4.0-3.6 (6 H, m), 3.2-2.9 (5 H, m), 2.8 (2 H, m), 1.81 (1 H, m), 1.78-1.44 (10 H, m), 1.35 (4 H, m), 0.95 (24 H, m).

Example 39

Compound 41: Compound 40 (82 mg, 0.1 mmol) and L-alanine isopropyl ester hydrochloride (92 mg, 0.53 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (136 µL, 0.78 mmol) was added. To above mixture was added a solution of Aldrithiol (72 mg, 0.33 mmol) and triphenylphosphine (87 mg, 0.33 mmol) in pyridine (1 mL). The reaction mixture was stirred at 75°C for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/1 to100/3) to afford compound 41 (19 mg): ^{1}H NMR ($CDCl_3$) δ 7.71 (2 H, d, J = 8.9 Hz), 7.2-7.35 (5 H, m), 7.15 (2 H, m), 7.01 (2 H, d, J = 8.9 Hz), 6.87 (2 H, m), 5.65 (1 H, d, J = 5.4 Hz), 5.05-4.93 (2 H, m), 4.3 (2 H, m), 4.19 (1 H, m), 3.98 (1 H, m), 3.88 (3 H, s), 3.80 (2 H, m), 3.70 (3 H, m), 3.18 (1 H, m), 2.95 (4 H, m), 2.78 (2 H, m), 1.82 (1 H, m), 1.62 (2 H, m), 1.35 (3 H, m), 1.25-1.17 (6 H, m), 0.93 (3 H, d, J = 6.4 Hz), 0.88 (3 H, d, J = 6.4 Hz).

Example 40

Compound 42: Compound 40 (100 mg, 0.13 mmol) and L-glycine butyl ester hydrochloride (88 mg, 0.53 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (136 µL, 0.78 mmol) was added. To above mixture was added a solution of Aldrithiol (72 mg, 0.33 mmol) and triphenylphosphine (87 mg, 0.33 mmol) in pyridine (1 mL). The reaction mixture was stirred at 75°C for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/1 to100/3) to afford compound 42 (18 mg): ^{1}H NMR ($CDCl_3$) δ 7.71 (2 H, d, J = 9.2 Hz), 7.35-7.24 (5 H, m), 7.14 (2 H, m), 7.00 (2 H, d, J = 8.8 Hz), 6.87 (2 H, m), 5.65 (1 H, d, J = 5.2 Hz), 5.04 (1 H, m), 4.92 (1 H, m), 4.36 (2 H, m), 4.08 (2 H, m), 3.95 (3 H, m), 3.88 (3 H, s), 3.80 (2 H, m), 3.76 (3 H, m), 3.54 (1 H, m), 3.15 (1 H, m), 2.97 (4 H, m), 2.80 (2 H, m), 1.82 (1 H, m), 1.62 (4 H, m), 1.35 (2 H, m), 0.9 (9 H, m).

Example Section H

Example 1

Sulfonamide 1: To a suspension of epoxide (20 g, 54.13 mmol) in 2-propanol (250 mL) was added isobutylamine (54 mL, 541 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (250 mL) and cooled to 0°C. Triethylamine (15.1 mL, 108.26 mmol) was added followed by the addition of 4-nitrobenzenesulfonyl chloride (12 g, 54.13 mmol) and the solution was stirred for 40 min at 0°C, warmed to room temperature for 2 h, and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide (30.59 g, 90%) as an off-white solid.

Example 2

Phenol 2: A solution of sulfonamide 1 (15.58 g, 24.82 mmol) in EtOH (450 mL) and CH_2Cl_2 (60 mL) was treated with 10% Pd/C (6 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 24 h. The reaction mixture was filtered through a plug of celite and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (6% MeOH/CH_2Cl_2) to give the phenol (11.34 g, 90%) as a white solid.

Example 3

Dibenzylphosphonate 3: To a solution of phenol 2 (18.25 g, 35.95 mmol) in CH_3CN (200 mL) was added Cs_2CO_3 (23.43 g, 71.90 mmol) and triflate (19.83 g, 46.74 mmol). The reaction mixture was stirred at room temperature for 1 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane) to give the dibenzylphosphonate (16.87 g, 60%) as a white solid.

Example 4

Amine 4: A solution of dibenzylphosphonate (16.87 g, 21.56 mmol) in CH_2Cl_2 (60 mL) at 0°C was treated with trifluoroacetic acid (30 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure to give the amine (12.94 g, 88%) as a white solid.

Example 5

Carbonate 5: To a solution of (S)-(+)-3-hydroxytetrahydrofuran (5.00 g, 56.75 mmol) in CH_2Cl_2 (80 mL) was added triethylamine (11.86 mL, 85.12 mmol) and bis(4-nitrophenyl)carbonate (25.90 g, 85.12 mmol). The reaction mixture was stirred at room temperature for 24 h and partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The CH_2Cl_2 layer was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane) to give the carbonate (8.62 g, 60%) as a pale yellow oil which solidified upon refrigerating.

Example 6

Carbamate 6: Two methods have been used.

Method 1: To a solution of 4 (6.8 g, 9.97 mmol) and 5 (2.65 g, 10.47 mmol) in CH_3CN (70 mL) at 0 °C was added 4-(dimethylamino)pyridine (2.44 g, 19.95 mmol). The reaction mixture was stirred at 0°C for 3 h and concentrated. The residue was dissolved in EtOAc and washed with 0.5 N NaOH, saturated $NaHCO_3$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the carbamate (3.97 g, 50%) as a pale yellow solid.

Method 2: To a solution of 4 (6.0 g, 8.80 mmol) and 5 (2.34 g, 9.24 mmol) in CH_3CN (60 mL) at 0°C was added 4-(dimethylamino)pyridine (0.22 g, 1.76 mmol) and N, N-diisopropylethylamine (3.07 mL, 17.60 mmol). The reaction mixture was stirred at 0°C for 1 h and warmed to room temperature overnight. The solvent was evaporated under reduced pressure. The crude product was dissolved in EtOAc and washed with 0.5 N NaOH, saturated $NaHCO_3$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product

was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the carbamate (3.85 g, 55%) as a pale yellow solid.

Example 7

Phosphonic Acid 7: To a solution of 6 (7.52 g, 9.45 mmol) in MeOH (350 mL) was added 10% Pd/C (3 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 48 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (5.24 g, 90%) as a white solid.

Example 8

Cbz Amide 8: To a solution of 7 (5.23 g, 8.50 mmol) in CH_3CN (50 mL) was added N, O-bis(trimethylsilyl)acetamide (16.54 mL, 68 mmol) and then heated to 70°C for 3 h. The reaction mixture was cooled to room temperature and concentrated. The residue was co-evaporated with toluene and dried under vacuum to afford the silylated intermediate which was used directly without any further purification. To a solution of the silylated intermediate in CH_2Cl_2 (40 mL) at 0°C was added pyridine (1.72 mL, 21.25 mmol) and benzyl chloroformate (1.33 mL, 9.35 mmol). The reaction mixture was stirred at 0°C for 1 h and warmed to room temperature overnight. A solution of MeOH (50 mL) and 1% aqueous HCl (150 mL) was added at 0°C and stirred for 30 min. CH_2Cl_2 was added and two layers were separated. The organic layer was dried with Na_2SO_4, filtered, concentrated, co-evaporated with toluene, and dried under vacuum to give the Cbz amide (4.46 g, 70%) as an off-white solid.

Example 9

Diphenylphosphonate 9: A solution of 8 (4.454 g, 5.94 mmol) and phenol (5.591 g, 59.4 mmol) in pyridine (40 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (4.903 g, 23.76 mmol) was added. The reaction mixture was stirred at 70°C for 4 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off. The filtrate was concentrated and dissolved in CH_3CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated. The crude product was purified by

column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the diphenylphosphonate (2.947 g, 55%) as a white solid.

Example 10

Monophosphonic Acid 10: To a solution of 9 (2.945 g, 3.27 mmol) in CH_3CN (25 mL) at 0°C was added 1N NaOH (8.2 mL, 8.2 mmol). The reaction mixture was stirred at 0°C for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (2.427 g, 90%) as a white solid.

Example 11

Cbz Protected Monophosphoamidate 11: A solution of 10 (2.421 g, 2.93 mmol) and L-alanine isopropyl ester hydrochloride (1.969 g, 11.73 mmol) in pyridine (20 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (3.629 g, 17.58 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H_2O, saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the monoamidate (1.569 g, 57%) as a white solid.

Example 12

Monophosphoamidate12: To a solution of 11 (1.569 g, 1.67 mmol) in EtOAc (80 mL) was added 10% Pd/C (0.47 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel (CH_2Cl_2 to 1-8% 2-propanol/CH_2Cl_2) to give the monophosphoamidate 12a (1.12 g, 83%, **GS 108577**, 1:1 diastereomeric mixture A/B) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.45 (dd, 2H), 7.41-7.17 (m, 7H), 6.88 (dd, 2H), 6.67 (d, J = 8.4 Hz, 2H), 5.16 (broad s, 1H), 4.95 (m, 1H), 4.37-4.22 (m, 5H), 3.82-3.67 (m, 7H), 2.99-2.70 (m, 6H), 2.11-1.69 (m, 3H), 1.38 (m, 3H), 1.19 (m, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.5, 19.6. 12b (29 mg, 2%, **GS108578**, diastereomer A) as a white solid: ^{1}H NMR ($CDCl_3$)

δ 7.43 (d, J = 7.8 Hz, 2H), 7.35-7.17 (m, 7H), 6.89 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 5.16 (broad s, 1H), 4.96 (m, 1H), 4.38-4.32 (m, 4H), 4.20 (m, 1H), 3.82-3.69 (m, 7H), 2.99-2.61 (m, 6H), 2.10 (m, 1H), 1.98 (m, 1H), 1.80 (m, 1H), 1.38 (d, J = 7.2 Hz, 3H), 1.20 (d, J = 6.3 Hz, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.5. 12c (22 mg, 1.6%, **GS 108579**, diastereomer B) as a white solid : ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 8.1 Hz, 2H), 7.36-7.20 (m, 7H), 6.87 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 5.15 (broad s, 1H), 4.95 (m, 1H), 4.34-4.22 (m, 5H), 3.83-3.67 (m, 7H), 2.99-2.64 (m, 6H), 2.11-1.68 (m, 3H), 1.33 (d, J = 6.9 Hz, 3H), 1.20 (d, J = 6.0 Hz, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 19.6.

Example 13

Sulfonamide 13: To a suspension of epoxide (1.67 g, 4.52 mmol) in 2-propanol (25 mL) was added isobutylamine (4.5 mL, 45.2 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C. Triethylamine (1.26 mL, 9.04 mmol) was added followed by the treatment of 3-nitrobenzenesulfonyl chloride (1.00 g, 4.52 mmol). The solution was stirred for 40 min at 0°C, warmed to room temperature for 2 h, and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the sulfonamide (1.99 g, 70%) as a white solid.

Example 14

Phenol 14: Sulfonamide 13 (1.50 g, 2.39 mmol) was suspended in HOAc (40 mL) and concentrated HCl (20 mL) and heated to reflux for 3 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was partitioned between 10% MeOH/CH_2Cl_2 and saturated $NaHCO_3$. The organic layers were washed with $NaHCO_3$, H_2O, dried with Na_2SO_4, filtered, and concentrated to give a yellow solid. The crude product was dissolved in $CHCl_3$ (20 mL) and treated with triethylamine (0.9 mL, 6.45 mmol) followed by the addition of Boc_2O (0.61 g, 2.79 mmol). The reaction mixture was stirred at room temperature for 6 h. The product was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ layer was washed with $NaHCO_3$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1-5%

MeOH/CH_2Cl_2) to give the phenol (0.52 g, 45%) as a pale yellow solid.

Example 15

Dibenzylphosphonate 15: To a solution of phenol 14 (0.51 g, 0.95 mmol) in CH_3CN (8 mL) was added Cs_2CO_3 (0.77 g, 2.37 mmol) and triflate (0.8 g, 1.90 mmol). The reaction mixture was stirred at room temperature for 1.5 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the dibenzylphosphonate (0.62 g, 80%) as a white solid.

Example 16

Amine 16: A solution of dibenzylphosphonate 15 (0.61 g, 0.75 mmol) in CH_2Cl_2 (8 mL) at 0°C was treated with trifluoroacetic acid (2 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give the amine (0.48 g, 90%) which was used directly without any further purification.

Example 17

Carbamate 17: To a solution of amine 16 (0.48 g, 0.67 mmol) in CH_3CN (8 mL) at 0°C was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (0.2 g, 0.67 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, *39*, 3278.) and 4-(dimethylamino)pyridine (0.17 g, 1.34 mmol). After stirring for 2 h at 0°C, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric acid (2 x), saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the carbamate (0.234 g, 40%) as a white solid.

Example 18

Analine 18: To a solution of carbamate 17 (78 mg, 0.09 mmol) in 2 mL HOAc was added zinc powder. The reaction mixture was stirred at room temperature for 1.5 h and filtered through a small plug of celite. The filtrate was concentrated and co-evaporated with toluene. The crude product was purified by column chromatography on silica gel (5% 2-propanaol/CH_2Cl_2) to give the analine (50 mg, 66%) as a white solid.

Example 19

Phosphonic Acid 19: To a solution of analine (28 mg, 0.033mmol) in MeOH (1 mL) and HOAc (0.5 mL) was added 10% Pd/C (14 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a small plug of celite. The filtrate was concentrated, co-evaporated with toluene, and dried under vacuum to give the phosphonic acid (15 mg, 68%, **GS 17424**) as a white solid: ^1H NMR (DMSO-d_6) δ 7.16-6.82 (m, 8H), 5.50 (d, 1H), 4.84 (m, 1H), 3.86-3.37 (m, 9H), 2.95-2.40 (m, 6H), 1.98 (m, 1H), 1.42-1.23 (m, 2H), 0.84 (d, J = 6.3 Hz, 3H), 0.79 (d, J = 6.3 Hz,3H). MS (ESI) 657 (M-H).

Example 20

Phenol 21: A suspension of aminohydrobromide salt 20 (22.75 g, 44 mmol) in CH_2Cl_2 (200 mL) at 0°C was treated with triethylamine (24.6 mL, 176 mmol) followed by slow addition of chlorotrimethylsilane (11.1 mL, 88 mmol). The reaction mixture was stirred at 0°C for 30 min and warmed to room temperature for 1 h. The solvent was removed under reduced pressure to give a yellow solid. The crude product was dissolved in CH_2Cl_2 (300 mL) and treated with triethylamine (18.4 mL, 132 mmol) and Boc_2O (12 g, 55 mmol). The reaction mixture was stirred at room temperature overnight. The product was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was washed with $NaHCO_3$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was dissolved in THF (200 mL) and treated with 1.0 M TBAF (102 mL, 102 mmol) and HOAc (13 mL). The reaction mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1-3% 2-propanol/CH_2Cl_2) to give the phenol (13.75 g, 58%) as a white solid.

Example 21

Dibenzylphosphonate 22: To a solution of phenol 21 (13.70 g, 25.48 mmol) in THF (200 mL) was added Cs_2CO_3 (16.61 g, 56.96 mmol) and triflate (16.22 g, 38.22 mmol). The reaction mixture was stirred at room temperature for 1 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the dibenzylphosphonate (17.59 g, 85%) as a white solid.

Example 22

Amine 23: A solution of dibenzylphosphonate 22 (17.58 g, 21.65 mmol) in CH_2Cl_2 (60 mL) at 0°C was treated with trifluoroacetic acid (30 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 1.5 h. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure to give the amine (14.64 g, 95%) which was used directly without any further purification.

Example 23

Carbamate 24: To a solution of amine 23 (14.64 g, 20.57 mmol) in CH_3CN (200 mL) at 0°C was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (6.07 g, 20.57 mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and 4-(dimethylamino)pyridine (5.03 g, 41.14mmol). After stirring for 2 h at 0°C, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric acid (2 x), saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the carbamate (10 g, 56%) as a white solid.

Example 24

Phosphonic Acid 25: To a solution of carbamate 24 (8 g, 9.22 mmol) in EtOH (500 mL was added 10% Pd/C (4 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 30 h. The reaction mixture was filtered through a plug of celite. The celite paste was suspended in pyridine and stirred for 30 min and filtered. This process was

repeated twice. The combined solution was concentrated under reduced pressure to give the phosphonic acid (5.46 g, 90%) as an off-white solid.

Example 25

Cbz Amide 26: To a solution of 25 (5.26 g, 7.99 mmol) in CH_3CN (50 mL) was added N, O-bis(trimethylsilyl)acetamide (15.6 mL, 63.92 mmol) and then heated to 70°C for 3 h. The reaction mixture was cooled to room temperature and concentrated. The residue was co-evaporated with toluene and dried under vacuum to afford the silylated intermediate which was used directly without any further purification. To a solution of the silylated intermediate in CH_2Cl_2 (40 mL) at 0°C was added pyridine (1.49 mL, 18.38 mmol) and benzyl chloroformate (1.25mL, 8.79 mmol). The reaction mixture was stirred at 0°C for 1 h and warmed to room temperature overnight. A solution of MeOH (50 mL) and 1% aqueous HCl (150 mL) was added at 0°C and stirred for 30 min. CH_2Cl_2 was added and two layers were separated. The organic layer was dried with Na_2SO_4, filtered, concentrated, co-evaporated with toluene, and dried under vacuum to give the Cbz amide (4.43 g, 70%) as an off-white solid.

Example 26

Diphenylphosphonate 27: A solution of 26 (4.43 g, 5.59 mmol) and phenol (4.21 g, 44.72 mmol) in pyridine (40 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (4.62 g, 22.36 mmol) was added. The reaction mixture was stirred at 70°C for 36 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off. The filtrate was concentrated and dissolved in CH_3CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane to EtOAc) to give the diphenylphosphonate (2.11 g, 40%) as a pale yellow solid.

Example 27

Monophosphonic Acid 28: To a solution of 27 (2.11 g, 2.24 mmol) in CH_3CN (15 mL) at 0°C was added 1N NaOH (5.59 mL, 5.59 mmol). The reaction mixture was stirred at 0°C for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-

evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (1.75 g, 90%) as a white solid.

Example 28

Cbz Protected Monophosphoamidate 29: A solution of 28 (1.54 g, 1.77 mmol) and L-alanine isopropyl ester hydrochloride (2.38 g, 14.16 mmol) in pyridine (15 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (2.20 g, 10.62 mmol) was added. The reaction mixture was stirred at 70°C overnight and cooled to room temperature. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H_2O, saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the monophosphoamidate (0.70g, 40%) as an off-white solid.

Example 29

Monophosphoamidate 30a-b: To a solution of 29 (0.70 g, 0.71 mmol) in EtOH (10 mL) was added 10% Pd/C (0.3 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a small plug of celite. The filtrate was concentrated and the crude products were purified by column chromatography on silica gel (7-10% MeOH/CH_2Cl_2) to give the monoamidates 30a (0.106 g, 18%, **GS 77369**, 1/1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.73-7.16 (m, 5H), 7.10-6.98 9m, 4H), 6.61 (d, J = 8.1 Hz, 2H), 5.67 (d, J = 4.8 Hz, 1H), 5.31-4.91 (m, 2H), 4.44 (m, 2H), 4.20 (m, 1H), 4.00-3.61 (m, 6H), 3.18-2.74 (m, 7H), 1.86-1.64 (m, 3H), 1.38 (m, 3H), 1.20 (m, 6H), 0.93 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) □ 19.1, 18; MS(ESI) 869 (M+Na). 30b (0.200 g, 33%, **GS 77425**, 1/1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.73 (dd, J = 8.7 Hz, J = 1.5 Hz, 2H), 7.36-7.16 (m, 5H), 7.09-7.00 (m, 4H), 6.53 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.4 Hz, 1H), 5.06-4.91 (m, 2H), 4.40 (m, 2H), 4.20 (m, 1H), 4.00-3.60 (m, 6H), 3.14 (m, 3H), 3.00-2.65 (m, 6H), 1.86-1.60 (m, 3H), 1.35 (m, 3H), 1.20 (m, 9H), 0.92 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31} P NMR ($CDCl_3$) □ 19.0, 17.9. MS (ESI) 897 (M+Na).

Example 30

Synthesis of Bisamidates 32: A solution of phosphonic acid 31 (100 mg, 0.15 mmol) and L-valine ethyl ester hydrochloride (108 mg, 0.60 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (117 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (98 mg, 0.45 mmol) in pyridine (1 mL) followed by addition of N,N-diisopropylethylamine (0.1 mL, 0.60 mmol). The reaction mixture was stirred at room temperature for two days. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to give the bisamidate (73 mg, 53%, **GS 17389**) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.1 Hz, 2H), 5.66 (d, J = 4.8 Hz, 1H), 5.05 (m, 1H), 4.95 (d, J = 8.7 Hz, 1H), 4.23-4.00 (m ,4H,), 3.97-3.68 (m, 11H), 3.39-2.77 (m, 9H), 2.16 (m, 2H), 1.82-1.60 (m, 3H), 1.31-1.18 (m, 6H), 1.01-0.87 (m, 18H); ^{31}P NMR ($CDCl_3$) δ 21.3; MS (ESI) 950 (M+Na).

Example 31

Triflate 34: To a solution of phenol 33 (2.00 g, 3.46 mmol) in THF (15 mL) and CH_2Cl_2 (5 mL) was added N-phenyltrifluoromethanesulfonimide (1.40 g, 3.92 mmol) and cesium carbonate (1.40 g, 3.92 mmol). The reaction mixture was stirred at room temperature overnight and concentrated. The crude product was partitioned between CH_2Cl_2 and saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the triflate (2.09 g, 85%) as a white solid.

Example 32

Aldehyde 35: To a suspension of triflate 34 (1.45 g, 2.05 mmol), palladium (II) acetate (46 mg, 0.20 mmol) and 1,3-bis(diphenylphosphino)propane (84 mg, 0.2 mmol) in DMF (8 mL) under CO atmosphere (balloon) was slowly added triethylamine (1.65 mL, 11.87 mmol) and triethylsilane (1.90 mL, 11.87 mmol). The reaction mixture was heated to 70°C under CO atmosphere (balloon) and stirred overnight. The solvent was concentrated under reduced pressure and partitioned between CH_2Cl_2 and H_2O. The organic phase was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the aldehyde (0.80 g, 66%) as a white solid.

Example 33

Substituted Benzyl Alcohol 36: To a solution of aldehyde 35 (0.80g, 1.35 mmol) in THF (9 mL) and H_2O (1 mL) at –10°C was added $NaBH_4$ (0.13 g, 3.39 mmol). The reaction mixture was stirred for 1 h at –10°C and the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with $NaHSO_4$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (6% 2-propanol/CH_2Cl_2) to give the alcohol (0.56 g, 70%) as a white solid.

Example 34

Substituted Benzyl Bromide 37: To a solution of alcohol 36 (77 mg, 0.13 mmol) in THF (1 mL) and CH_2Cl_2 (1 mL) at 0°C was added triethylamine (0.027 mL, 0.20 mmol) and methanesulfonyl chloride (0.011 mL, 0.14 mmol). The reaction mixture was stirred at 0°C for 30 min and warmed to room temperature for 3 h. Lithium bromide (60 mg, 0.69 mmol) was added and stirred for 45 min. The reaction mixture was concentrated and the residue was partitioned between CH_2Cl_2 and H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2% MeOH/CH_2Cl_2) to give the bromide (60 mg, 70%).

Example 35

Diethylphosphonate 38: A solution of bromide 37 (49 mg, 0.075 mmol) and triethylphosphite (0.13 mL, 0.75 mmol) in toluene (1.5 mL) was heated to 120°C and stirred overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (6% MeOH/CH_2Cl_2) to give the diethylphosphonate (35 mg, 66%, **GS 191338**) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.27-7.16 (m, 4H), 7.00 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.1 Hz, 1H), 5.00 (m, 2H), 4.04-3.73 (m, 13H), 3.13-2.80 (m, 9H), 1.82-1.64 (m, 3H), 1.25 (t, J = 6.9 Hz, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) □ 26.4; MS (ESI) 735 (M+Na).

Example 36

N-tert-Butoxycarbonyl-O-benzyl-L-serine 39: To a solution of Boc-L-serine (15 g, 73.09 mmol) in DMF (300 mL) at 0°C was added NaH (6.43 g, 160.80 mmol, 60% in mineral oil) and stirred for 1.5 h at 0°C. After the addition of benzyl bromide (13.75 g, 80.40 mmol), the

reaction mixture was warmed to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in H_2O. The crude product was partitioned between H_2O and Et_2O. The aqueous phase was acidified to pH<4 with 3 N HCl and extracted with EtOAc three times. The combined EtOAc solution was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated to give the N-tert-butoxycarbonyl-O-benzyl-L-serine (17.27 g, 80%).

Example 37

Diazo Ketone 40: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-serine 39 (10 g, 33.86 mmol) in dry THF (120 mL) at –15°C was added 4-methylmorpholine (3.8 mL, 34.54 mmol) followed by the slow addition of isobutylchloroformate (4.40 mL, 33.86 mmol). The reaction mixture was stirred for 30 min and diazomethane (~50 mmol, generated from 15 g Diazald according to Aldrichimica Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min and was then placed in an ice bath at 0°C and stirred for 1 h. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc, washed with water, saturated $NaHCO_3$, saturated NaCl, dried with Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography (EtOAc/hexane) to afford the diazo ketone (7.50 g, 69%) as a yellow oil.

Example 38

Chloroketone 41: To a suspension of diazoketone 40 (7.50 g, 23.48 mmol) in ether (160 mL) at 0°C was added 4N HCl in dioxane (5.87 mL, 23.48 mmol). The reaction mixture was stirred at 0°C for 1 h. The reaction solvent was evaporated under reduced pressure to give the chloroketone which was used directly without any further purification.

Example 39

Chloroalcohol 42: To a solution of chloroketone 41 (7.70 g, 23.48 mmol) in THF (90 mL) was added water (10 mL) and the solution was cooled to 0°C. A solution of $NaBH_4$ (2.67 g, 70.45 mmol) in water (4 mL) was added dropwise over a period of 10 min. The mixture was stirred for 1 h at 0°C and saturated $KHSO_4$ was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column

chromatography on silica gel (1/4 EtOAc/hexane) to give the chloroalcohol (6.20 g, 80%) as a diastereomeric mixture.

Example 40

Epoxide 43: A solution of chloroalcohol 42 (6.20 g, 18.79 mmol) in EtOH (150 mL) was treated with 0.71 M KOH (1.27 g, 22.55 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (1/6 EtOAc/hexane) to afford the desired epoxide 43 (2.79 g, 45%) and a mixture of diastereomers 44 (1.43 g, 23%).

Example 41

Sulfonamide 45: To a suspension of epoxide 43 (2.79 g, 8.46 mmol) in 2-propanol (30 mL) was added isobutylamine (8.40 mL, 84.60 mmol) and the solution was refluxed for 1 h. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (40 mL) and cooled to 0°C. Triethylamine (2.36 mL, 16.92 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (1.75 g, 8.46 mmol). The solution was stirred for 40 min at 0°C, warmed to room temperature, and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was directly used without any further purification.

Example 42

Silyl Ether 46: A solution of sulfonamide 45 (5.10 g, 8.46 mmol) in CH_2Cl_2 (50 mL) was treated with triethylamine (4.7 mL, 33.82 mmol) and TMSOTf (3.88 mL, 16.91 mmol). The reaction mixture was stirred at room temperature for 1 h and partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic extracts were washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (1/6 EtOAc/hexane) to give the silyl ether (4.50 g, 84%) as a thick oil.

Example 43

Alcohol 47: To a solution of silyl ether 46 (4.5 g, 7.14 mmol) in MeOH (50 mL) was added 10% Pd/C (0.5 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 2 h. The reaction mixture was filtered through a plug of celite and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the alcohol (3.40 g, 85%) as a white solid.

Example 44

Aldehyde 48: To a solution of alcohol 47 (0.60 g, 1.07 mmol) in CH_2Cl_2 (6 mL) at 0°C was added Dess Martin reagent (0.77 g, 1.82 mmol). The reaction mixture was stirred at 0°C for 3 h and partitioned between CH_2Cl_2 and $NaHCO_3$. The organic phase was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1/4 EtOAc/hexane) to give the aldehyde (0.45 g, 75%) as a pale yellow solid.

Example 45

Sulfonamide 50: To a suspension of epoxide (2.00 g, 5.41 mmol) in 2-propanol (20 mL) was added amine 49 (4.03 g, 16.23 mmol) (prepared in 3 steps starting from 4-(aminomethyl)piperidine according to Bioorg. Med. Chem. Lett., 2001, 11, 1261.). The reaction mixture was heated to 80°C and stirred for 1 h. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C. Triethylamine (4.53 mL, 32.46 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (3.36 g, 16.23 mmol). The solution was stirred for 40 min at 0°C, warmed to room temperature for 1.5 h, and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (2.50 g, 59%).

Example 46

Amine 51: A solution of sulfonamide 50 (2.50 g, 3.17 mmol) in CH_2Cl_2 (6 mL) at 0°C was treated with trifluoroacetic acid (3 mL). The solution was stirred for 30 min at 0°C and then

warmed to room temperature for an additional 1.5 h. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x) and saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure to give the amine (1.96 g, 90%) which was used directly without any further purification.

Example 47

Carbamate 52: To a solution of amine 51 (1.96 g, 2.85 mmol) in CH_3CN (15mL) at 0°C was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (0.84g, 2.85mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and 4-(dimethylamino)pyridine (0.70 g, 5.70 mmol). After stirring for 2 h at 0°C, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric acid (2 x), saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the carbamate (1.44 g, 60%) as a white solid.

Example Section I

Example 1

Carbonate 2: To a solution of (R)-(+)-3-hydroxytetrahydrofuran (1.23 g, 14 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (2.9 mL, 21 mmol) and bis(4-nitrophenyl)carbonate (4.7 g, 15.4 mmol). The reaction mixture was stirred at room temperature for 24 h and partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The CH_2Cl_2 layer was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane) to give the carbonate (2.3 g, 65%) as a pale yellow oil which solidified upon standing.

Example 2

Carbamate 3: To a solution of 1 (0.385 g, 0.75 mmol) and 2 (0.210 g, 0.83 mmol) in CH_3CN (7 mL) at room temperature was added N, N-diisopropylethylamine (0.16 mL, 0.90 mmol). The reaction mixture was stirred at room temperature for 44 h. The solvent was evaporated under reduced pressure. The crude product was dissolved in EtOAc and washed with saturated $NaHCO_3$, brine, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the carbamate (0.322 g, 69%) as a white solid: mp 98-100°C (uncorrected).

Example 3

Phenol 4: To a solution of 3 (0.31 g, 0.49 mmol) in EtOH (10 mL) and EtOAc (5 mL) was added 10% Pd/C (30 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 15 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phenol (0.265 g) in quantitative yield.

Example 4

Diethylphosphonate 5: To a solution of phenol 4 (100 mg, 0.19 mmol) in THF (3 mL) was added Cs_2CO_3 (124 mg, 0.38 mmol) and triflate (85 mg, 0.29 mmol). The reaction mixture was stirred at room temperature for 4 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH_2Cl_2) to

give the diethylphosphonate (63 mg, 49%, **GS 16573**) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 8.7Hz, 2H), 7.21 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 9 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.06 (broad, s, 1H), 4.80 (d, J = 7.5 Hz, 1H), 4.19 (m, 6H), 3.83 (s, 3H), 3.80-3.70 (m, 6H), 3.09-2.72 (m, 6H), 2.00 (m, 1H), 1.79 (m, 2H), 1.32 (t, J = 7.5 Hz, 6H), 0.86 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{31}P NMR δ 17.8.

Example 5

Dibenzylphosphonate 6: To a solution of phenol 4 (100 mg, 0.19 mmol) in THF (3 mL) was added Cs_2CO_3 (137 mg, 0.42 mmol) and triflate (165 mg, 0.39 mmol). The reaction mixture was stirred at room temperature for 6 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate (130 mg, 84%, **GS 16574**) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 9 Hz, 2H), 7.30 (m, 10H), 7.08 (d, J = 8.4Hz, 2H), 6.94 (d, J = 9 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 5.16-5.04 (m, 5H), 4.80 (d, J = 8.1 Hz, 1H), 4.16 (d, J = 10.2 Hz, 2H), 3.82 (s, 3H), 3.75-3.71 (m, 6H), 3.10-2.72 (m, 6H), 2.00 (m, 1H), 1.79 (m, 2H), 0.86 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{31} P NMR ($CDCl_3$) δ 18.8.

Example 6

Phosphonic Acid 7: To a solution of 6 (66 mg, 0.08 mmol) in EtOH (3 mL) was added 10% Pd/C (12 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 15 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated under reduced pressure and triturated with EtOAc to give the phosphonic acid (40 mg, 78%, **GS 16575**) as a white solid.

Example 7

Carbonate 8: To a solution of (S)-(+)-3-hydroxytetrahydrofuran (2 g, 22.7 mmol) in CH_3CN (50 mL) was added triethylamine (6.75 mL, 48.4 mmol) and N,N'-disuccinimidyl carbonate (6.4 g, 25 mmol). The reaction mixture was stirred at room temperature for 5 h and concentrated under reduced pressure. The residue was partitioned between EtOAc and H_2O. The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc as eluant)

followed by recrystallization (EtOAc/hexane) to give the carbonate (2.3 g, 44%) as a white solid.

Example 8

Carbamate 9: To a solution of 1 (0.218 g, 0.42 mmol) and 8 (0.12 g, 0.53 mmol) in CH_3CN (3 mL) at room temperature was added N, N-diisopropylethylamine (0.11 mL, 0.63 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the carbamate (0.176 g, 66%) as a white solid.

Example 9

Phenol 10: To a solution of 9 (0.176 g, 0.28 mmol) in EtOH (10 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phenol (0.151 g, **GS 10**) in quantitative yield.

Example 10

Diethylphosphonate 11: To a solution of phenol 10 (60 mg, 0.11 mmol) in THF (3 mL) was added Cs_2CO_3 (72 mg, 0.22 mmol) and triflate (66 mg, 0.22 mmol). The reaction mixture was stirred at room temperature for 4 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH_2Cl_2) to give the diethylphosphonate (38 mg, 49%, **GS 11**) as a white solid.

Example Section J

Example 1

Triflate 1: To a solution of A (4 g, 6.9 mmol) in THF (30 mL) and CH_2Cl_2 (10 mL) was added Cs_2CO_3 (2.7 g, 8 mmol) and N-phenyltrifluoromethanesulfonimide (2.8 g, 8.0 mmol) and stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure. The residue wsa partitioned between CH_2Cl_2 and saturated brine twice. The organic phase was dried over sodium sulfate and used for next reaction without further purification.

Example 2

Aldehyde 2: A solution of crude above triflate 1 (~6.9 mmol) in DMF (20 mL) was degassed (high vacumn for 5 min, argon purge, repeat 3 times). To this solution were quickly added $Pd(OAc)_2$ (120 mg, 266 μmol) and bis(diphenylphosphino-propane (dppp ,220 mg, 266 μmol), and heated to 70°C. To this reaction mixture was rapidly introduced carbon monoxide, and stirred at room temperature under an atmopheric pressure of carbon monoxide, followed by slow addition of TEA (5.4 mL, 38 mmol) and triethylsilane (3 mL, 18 mmol). The resultant mixture was stirred at 70°C for 16 h, then cooled to room temperature, concentrated under reduced pressure, partitioned between CH_2Cl_2 and saturated brine. The organic phase was concentrated under reduced pressure and purified on silica gel column to afford aldehyde 2 (2.1 g, 51%) as white solid.

Example 3

Compounds 3a-3e: Respresentative Procedure, 3c: A solution of aldehyde 2 (0.35 g, 0.59 mmol), L-alanine isopropyl ester hydrochloride (0.2 g, 1.18 mmol), glacial acetic acid (0.21 g, 3.5 mmol) in 1,2-dichloroethane (10 mL) was stirred at room temperature for 16 h, followed by addition of sodium cyanoborohydride (0.22 g, 3.5 mmol) and methanol (0.5 mL). The resulting solution was stirred at room temperature for one h. The reaction mixture was washed with sodium bicarbonate solution, saturated brine, and chromatographed on silica gel to afford 3c (0.17 g, 40%). ^{1}H NMR ($CDCl_3$): δ 7.72 (d, 2H), 7.26 (d, 2H), 7.20 (d, 2H), 7.0 (d, 2H), 5.65 (d, 1H), 4.90-5.30 (m, 3H), 3.53-4.0 (m overlapping s, 13H), 3.31 (q, 1H), 2.70-3.20 (m, 7H), 1.50-1.85 (m, 3H), 1.25-1.31 (m, 9H), 0.92 (d, 3H), 0.88 (d, 3H). MS: 706 (M + 1).

Compound	R_1	R_2	Amino Acid
3a	Me	Me	Ala
3b	Me	Et	Ala
3c	Me	iPr	Ala
3d	Me	Bn	Ala
3e	iPr	Et	Val

Example 4

Sulfonamide 1: To a solution of crude amine A (1 g, 3 mmol) in CH_2Cl_2 was added TEA (0.6 g, 5.9 mmol) and 3-methoxybenzenesulfonyl chloride (0.6 g, 3 mmol). The resulting solution was stirred at room temperature for 5 h, and evaporated under reduced pressure. The residue was chromatographed on silica gel to afford sulfonamide 1 (1.0 g, 67%).

Example 5

Amine 2: To a 0°C cold solution of sulfonamide 1 (0.85 g, 1.6 mmol) in CH_2Cl_2 (40 mL) was treated with BBr_3 in CH_2Cl_2 (10 mL of 1 M solution, 10 mmol). The solution was stirred at 0°C 10 min and then warmed to room temperature and stirred for 1.5 h. The reaction mixture was quenched with CH_3OH, concentrated under reduced pressure, azeotroped with CH_3CN three times. The crude amine 2 was used for next reaction without further purification.

Example 6

Carbamate 3: A solution of crude amine 2 (0.83 mmol) in CH_3CN (20 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (245 mg, 0.83 mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and N,N-dimethylaminopyridine (202 mg, 1.7 mmol). After stirring for 16 h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ three times. The organic phase was evaporated under reduced pressure. The residue was purified by chromatography on silica gel affording the carbamate 3 (150 mg, 33%) as a solid.

Example 7

Diethylphosphonate 4: To a solution of carbamate 3(30 mg, 54 μmol) in THF (5 mL) was added Cs_2CO_3 (54 mg, 164 μmol) and triflate # (33 mg, 109 μmol). After stirring the reaction mixture for 30 min at room temperature, additional Cs_2CO_3 (20 mg, 61 μmol) and triflate (15 mg, 50 μmol) were added and the mixture was stirred for 1 more hour. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and water. The organic phase was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel and repurified by HPLC (50% CH_3CN-50% H_2O on C18 column) to give the diethylphosphonate 4 (15 mg, 39%). ^1H NMR ($CDCl_3$): δ 7.45 (m, 3H), 7.17-7.30 (m, 6H), 5.64 (d, 1H), 5.10 (d, 1H), 5.02 (q, 1H), 4.36 (d, 2H), 4.18-4.29 (2 q overlap, 4H), 3.60-3.98 (m, 7H), 2.70-3.10 (m, 7H), 1.80-1.90 (m, 1H), 1.44-1.70 (m, 2H + H2O), 1.38 (t, 6H), 0.94 (d, 3H), 0.90 (d, 3H). ^{31}P NMR ($CDCl_3$): 18.7 ppm; MS (ESI) 699 (M + H).

Example 8

Dibenzylphosphonate 5: To a solution of carbamate 3 (100 mg, 182 μmol) in THF (10 mL) was added Cs_2CO_3 (180 mg, 550 μmol) and dibenzylhydroxymethyl phosphonate triflate, Section A, Scheme 2, Compound 9, (150 mg, 360 μmol). After stirring the reaction mixture for 1 h at room temperature, the reaction mixture was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and water. The organic phase was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by HPLC (50% CH_3CN-50% H_2O on C18 column) to give the dibenzylphosphonate 5 (110 mg, 72%). ^1H NMR ($CDCl_3$): δ 7.41 (d, 2H), 7.35 (s, 10 H), 7.17-7.30 (m, 6H), 7.09-7.11 (m, 1H), 5.64 (d, 1H), 4.90-5.15 (m, 6H), 4.26 (d, 2H), 3.81-3.95 (m, 4H), 3.64-3.70 (m, 2H), 2.85-3.25 (m, 7H), 1.80-1.95 (m, 1H), 1.35-1.50 (m, 1H), 0.94 (d, 3H), 0.91 (d, 3H). ^{31}P NMR ($CDCl_3$) δ 19.4 ppm; MS (ESI): 845 (M + Na), 1666 (2M + Na).

Example 9

Phosphonic acid 6: A solution of dibenzylphosphonate 5 (85 mg, 0.1 mmol) was dissolved in MeOH (10 mL) treated with 10% Pd/C (40 mg) and stirred under H_2 atmosphere (balloon) overnight. The reaction was purged with N_2, and the catalyst was removed by filtration through celite. The filtrate was evaporated under reduced pressure to afford phosphonic acid 6 (67 mg, quantitatively). ^1H NMR (CD_3OD): δ 7.40-7.55 (m, 3H), 7.10-7.35 (m, 6H), 5.57

(d, 1H), 4.32 (d, 2H), 3.90-3.95 (m, 1H), 3.64-3.78 (m, 5H), 3.47 (m, 1H), 2.85-3.31 (m, 5H), 2.50-2.60 (m, 1H), 2.00-2.06 (m, 1H), 1.46-1.60 (m, 1H), 1.30-1.34 (m, 1H), 0.9 (d, 3H), 0.90 (d, 3H). ^{31}P NMR (CD_3OD): 16.60 ppm; MS (ESI): 641 (M – H).

Example 10

Sulfonamide 1: To a solution of crude amine A (0.67 g, 2 mmol) in CH_2Cl_2 (50 mL) was added TEA (0.24 g, 24 mmol) and crude 3-acetoxy-4-methoxybenzenesulfonyl chloride (0.58 g, 2.1 mmol, was prepared according to Kratzl et al., Monatsh. Chem.1952, 83, 1042-1043), and the solution was stirred at room temperature for 4 h, and evaporated under reduced pressure. The residue was chromatographed on silica gel to afford sulfonamide 1 (0.64 g, 54%). MS: 587 (M + Na), 1150 (2M + Na)

Phenol 2: Sulfonamide 1 (0.64 g, 1.1 mmol) was treated with saturated NH_3 in MeOH (15 mL) at room temperature for 15 min., then evaporated under reduced pressure. The residue was purified on silica gel column to afford phenol 2 (0.57 g, 96%).

Example 11

Dibenzylphosphonate 3a: To a solution of phenol 2 (0.3 g, 0.57 mmol) in THF (8 mL) was added Cs_2CO_3 (0.55 g, 1.7 mmol)) and dibenzylhydroxymethyl phosphonate triflate (0.5 g, 1.1 mmol). After stirring the reaction mixture for 1 h at room temperature, the reaction mixture was quenched with water and partitioned between CH_2Cl_2 and saturated ammonium chloride aqueous solution. The organic phase was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel (40% EtOAc/ 60% hexane) to give the dibenzylphosphonate 3a (0.36 g, 82%). ^{1}H NMR ($CDCl_3$): δ 7.20-7.40 (m, 17H), 6.91 (d, 1H), 5.10-5.25 (2 q(ab) overlap, 4H), 4.58-4.70 (m, 1H), 4.34 (d, 2H), 3.66-3.87 (m + s, 5H), 2.85-3.25 (m, 6H), 1.80-1.95 (m, 1H), 1.58 (s, 9H), 0.86-0.92 (2d, 6H).

Example 12

Diethylphosphonate 3b: To a solution of phenol 2 (0.15 g, 0.28 mmol) in THF (4 mL) was added Cs_2CO_3 (0.3 g, 0.92 mmol)) and diethylhydroxymethyl phosphonate triflate (0.4 g, 1.3 mmol). After stirring the reaction mixture for 1 h at room temperature, the reaction mixture was quenched with water and partitioned between CH_2Cl_2 and saturated $NaHCO_3$ aqueous

solution. The organic phase was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel (1% CH_3OH-CH_2Cl_2) to give the diethylphosphonate 3b (0.14 g, 73%).

Example 13

Amine 4a: To a solution of 3a (0.35 g, 0.44 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (0.75 g, 6.6 mmol) at room temperature for 2 h. The reaction was evaporated under reduced pressure, azeotroped with CH_3CN twice, dried to afford crude amine 4a. This crude 4a was used for next reaction without further purification.

Example 14

Amine 4b: To a solution of 3b (60 mg, 89 μmol) in CH_2Cl_2 (1 mL) was treated with TFA (0.1 mL, 1.2 mmol) at room temperature for 2 h. The reaction was evaporated under reduced pressure, azeotroped with CH_3CN twice, dried to afford crude amine 4b (68 mg). This crude 4b was used for next reaction without further purification.

Example 15

Carbamate 5a: An ice-cold solution of crude amine 4a (0.44 mmol) in CH_3CN (10 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (120 mg, 0.4 mmol) and N,N-dimethylaminopyridine (DMAP, 110 mg, 0.88 mmol). After 4 h, more DMAP (0.55 g, 4.4 mmol) was added to the reaction mixture. After stirring for 1.5 h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was evaporated under reduced pressure. The residue was purified by chromatography on silica gel affording the crude carbamate 5a (220 mg) containing some p-nitrophenol. The crude 5a was repurified by HPLC (50% CH_3CN /50% H_2O) to afford pure carbamate 5a (176 mg, 46%, 2 steps). ^1H NMR ($CDCl_3$): δ 7.20-7.36 (m, 1H), 6.94 (d, 1H), 5.64 (d, 1H), 5.10-5.25 (2 q(ab) overlap, 4H), 4.90-5.10 (m, 1H), 4.90 (d, 1H), 4.34 (d, 2H), 3.82-3.91 (m + s, 6H), 3.63-3.70 (m, 3H), 2.79-3.30 (m, 7H), 1.80-1.90 (m, 1H), 1.40-1.50 (m, 1H), 0.94 (d, 3H), 0.89 (d, 3H). ^{31}P NMR ($CDCl_3$): 17.2 ppm.

Example 16

Carbamate 5b: An ice-cold solution of crude amine 4b (89 μmol)) in CH_3CN (5 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (26mg, 89 μmol) and N,N-dimethylaminopyridine (DMAP, 22 mg, 0.17 mmol). After 1 h at 0°C, more DMAP (10 mg. 82 μmol) was added to the reaction mixture. After stirring for 2 h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was evaporated under reduced pressure. The residue was purified by HPLC (C18 column, 45% CH_3CN/55% H_2O) to afford pure carbamate 5b (18.8 mg, 29%, 3 steps). ^1H NMR ($CDCl_3$): δ 7.38 (d, 2H), 7.20-7.36 (m, 6H), 7.0 (d, 1H), 5.64 (d, 1H), 4.96-5.03 (m, 2H), 4.39 (d, 2H), 4.20-4.31 (2q overlap, 4H) 3.80-4.00 ((s overlap with m, 7H), 3.60-3.73 (m, 2H), 3.64-3.70 (m, 2H), 2.85-3.30 (m, 7H), 1.80-1.95 (m, 1H), 1.55-1.75 (m, 1H), 1.35-1.50 (s overlap with m, 7H), 0.94 (d, 3H), 0.88 (d, 3H). ^{31}P NMR ($CDCl_3$): 18.1ppm.

Example 17

Phosphonic acid 6: A solution of dibenzylphosphonate 5a (50 mg, 58 μmol) was dissolved in MeOH (5 mL) and EtOAc (3 mL) and treated with 10% Pd/C (25 mg) and was stirred at room temperature under H_2 atmosphere (balloon) for 8 h. The catalyst was filtered off. The filtrate was concentrated and redissolved in MeOH (5 mL), treated with 10% Pd/C (25 mg) and was stirred at room temperature under H_2 atmosphere (balloon) overnight. The catalyst was filtered off. The filtrate was evaporated under reduced pressure to afford phosphonic acid 6 (38 mg, quantitatively). ^1H NMR (CD_3OD): δ 7.42 (m, 1H), 7.36 (s, 1H), 7.10-7.25 (m, 6H), 5.58 7 (d, 1H), 4.32 (d, 2H), 3.90 (s, 3H), 3.60-3.80 (m, 6H), 3.38 (d, 1H), 2.85-3.25 (m, 5H), 2.50-2.60 (m, 1H), 1.95-2.06 (m, 1H), 1.46-1.60 (m, 1H), 1.30-1.40 (m, 1H), 0.93(d, 3H), 0.89 (d, 3H). ^{31}P NMR (CD_3OD): 14.8 ppm; MS (ESI): 671 (M – H).

Example 18

Amine 7: To a 0°C cold solution of diethylphosphonate 3b (80 mg, 0.118 mmol) in CH_2Cl_2 was treated with BBr_3 in CH_2Cl_2 (0.1 mL of 1 M solution, 1 mmol). The solution was stirred at 0°C 10 min and then warmed to room temperature and stirred for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (containing some CH_3OH, concentrated, azeotroped with CH_3CN three times. The crude amine 7 was used for next reaction without further purification.

Example 19

Carbamate 8: An ice-cold solution of crude amine 7 (0.118 mmol) in CH_3CN (5 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (35 mg, 0.118 mmol) and N,N-dimethylaminopyridine (29 mg, 0.24mmol), warmed to room temperature. After stirring for 1 h at room temperature, more DMAP (20 mg, 0.16 mmol) was added to reaction mixture. After 2 h stirred at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was evaporated under reduced pressure. The residue was purified by HPLC on C18 (CH_3CN-55%H_2O) to afford the desired carbamate 8 (11.4 mg, 13.4%) as an off-white solid. ^1H NMR ($CDCl_3$): δ 7.20-7.40 (m, 7H), 7.00 (d, 1H), 5.64 (d, 1H), 5.00-5.31 (m, 2H), 4.35 (d, 2H), 4.19-4.30 (2q overlap, 4H), 3.80-4.00 (m, 4H), 3.68-3.74 (m, 2H), 3.08-3.20 (m, 3H), 2.75-3.00 (m, 4H), 1.80-1.90 (m, 1H), 1.55-1.75 (m, 1H), 1.38 (t, 6H), 0.91 (2d overlap, 6H). ^{31}P NMR (CD_3OD): δ19.5 ppm.

Example Section K

Example 1

Monophenyl-monolactate 3: A mixture of monoacid 1 (0.500 g, 0.7 mmol), alcohol 2 (0.276 g, 2.09 mmol) and dicyclohexylcarbodiimide (0.431 g, 2.09 mmol) in dry pyridine (4 mL) was placed into a 70°C oil bath and heated for two hours. The reaction was monitored by TLC assay (SiO_2, 70% ethyl acetate in hexanes as eluent, product $R_f = 0.68$, visualization by UV). The reaction contents were cooled to ambient temperature with the aid of a cool bath and diluted with dichloromethane (25 mL). TLC assay may show presence of starting material. The diluted reaction mixture was filtered to remove solids. The filtrate was then cooled to 0°C and charged with 0.1 N HCl (10 mL). The pH 4 mixture was stirred for 10 minutes and poured into separatory funnel to allow the layers to separate. The lower organic layer was collected and dried over sodium sulfate. The drying agent was filtered off and the filtrate concentrated to an oil via rotary evaporator (< 30°C warm bath). The crude product oil was purified on pretreated silica gel (deactivated using 10% methanol in dichlorormethane followed by rinse with 60% ethyl acetate in dichloromethane). The product was eluted with 60% ethyl acetate in dichloromethane to afford the product monophenyl-monolactate 3 as a white foam (0.497 g, 86% yield). ^1H NMR ($CDCl_3$) δ 7.75 (d, 2H), 7.40-7.00 (m, 14H), 5.65 (d, 1H), 5.20-4.90 (m, 4H), 4.70 (d, 1H), 4.55-4.50 (m, 1H), 4.00-3.80 (m, 4H), 3.80-3.60 (m, 3H), 3.25-2.75 (m, 7H), 1.50 (d, 3H), 1.30-1.20 (m, 7H), 0.95 (d, 3H), 0.85 (d, 3H). ^{31}P NMR ($CDCl_3$) δ 16.2, 13.9.

Example 2

Monophenyl-monoamidate 5: A mixture of monoacid 1 (0.500 g, 0.70 mmol), amine hydrochloride 4 (0.467 g, 2.78 mmol) and dicyclohexylcarbodiimide (0.862 g, 4.18 mmol) in dry pyridine (8 mL) was placed into a 60°C oil bath, and heated for one hour (at this temperature, product degrades if heating continues beyond this point). The reaction was monitored by TLC assay (SiO_2, 70% ethyl acetate in hexanes as eluent, product $R_f = 0.39$, visualization by UV). The contents were cooled to ambient temperature and diluted with ethyl acetate (15 mL) to precipitate a white solid. The mixture was filtered to remove solids and the filtrate was concentrated via rotary evaporator to an oil. The oil was diluted with dichloromethane (20 mL) and washed with 0.1 N HCl (2 x 20 mL), water (1 x 20 mL) and dilute sodium bicarbonate (1 x 20 mL). The organic layer was dried over sodium sulfate,

filtered, and concentrated to an oil via rotary evaporator. The crude product oil was dissolved in dichloromethane (10 mL). Hexane was slowly charged to the stirring solution until cloudiness persisted. The cloudy mixture was stirred for a few mintues until TLC assay showed that the dichloromethane/hexane layer contained no product. The dichloromethane/hexanes layer was decanted and the solid was further purified on silica gel first pretreated with 10% methanol in ethyl acetate and rinsed with 50% ethyl acetate in hexanes. The product 5 was eluted with 50% ethyl acetate in hexanes to afford a white foam (0.255 g, 44% yield) upon removal of solvents. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 2H), 7.40-7.15 (m, 10H), 7.15-7.00 (t, 2H), 5.65 (d, 1H), 5.10-4.90 (m, 3H), 4.50-4.35 (m, 2H), 4.25-4.10 (m, 1H), 4.00-3.60 (m, 8H), 3.20-2.75 (m, 7H), 1.40-1.20 (m, 11H), 0.95 (d, 3H), 0.85 (d, 3H). ^{31}P NMR ($CDCl_3$) δ 19.1, 18.0.

Example 3

Bisamidate 8: A solution of triphenylphosphine (1.71 g, 6.54 mmol) and aldrithiol (1.44 g, 6.54 mmol) in dry pyridine (5 mL), stirred for at least 20 minutes at room temperature, was charged into a solution of diacid 6 (1.20 g, 1.87 mmol) and amine hydrochloride 7 (1.30 g, 7.47 mmol) in dry pyridine (10 mL). Diisopropylethylamine (0.97 g, 7.48 mmol) was then added to this combined solution and the contents were stirred at room temperature for 20 hours. The reaction was monitored by TLC assay (SiO_2, 5:5:1 ethyl acetate/hexanes/methanol as eluent, product R_f = 0.29, visualization by UV). The reaction mixture was concentrated via rotary evaporator and dissolved in dichloromethane (50 mL). Brine (25 mL) was charged to wash the organic layer. The aqueous layer was back extracted with dichloromethane (1 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated via rotary evaporator to afford an oil. The crude product oil was purified on silica gel using 4% isopropanol in dichloromethane as eluent. The combined fractions containing the product may have residual amine contamination. If so, the fractions were concentrated via rotary evaporator and further purified by silica gel chromatography using a gradient of 1:1 ethyl acetate/hexanes to 5:5:1 ethyl acetate/hexanes/methanol solution as eluent to afford the product 8 as a foam (0.500 g, 30% yield).

Example 4

Diacid 6: A solution of dibenzylphosphonate 9 (8.0 g, 9.72 mmol) in ethanol (160 mL) and ethyl acetate (65 mL) under a nitrogen atmosphere and at room temperature was charged 10%

Pd/C (1.60 g, 20 wt%). The mixture was stirred and evacuated by vacuum and purged with hydrogen several times. The contents were then placed under atmospheric pressure of hydrogen via a balloon. The reaction was monitored by TLC assay (SiO_2, 7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, product $R_f = 0.05$, visualization by UV) and was judged complete in 4 to 5 hours. The reaction mixture was filtered through a pad of celite to remove Pd/C and the filter cake rinsed with ethanol/ethyl acetate mixture (50 mL). The filtrate was concentrated via rotary evaporation followed by several co-evaporations using ethyl acetate (3 x 50 mL) to remove ethanol. The semi-solid diacid 6, free of ethanol, was carried forward to the next step without purification.

Example 5

Diphenylphosphonate 10: To a solution of diacid 6 (5.6 g, 8.71 mmol) in pyridine (58 mL) at room temperature was charged phenol (5.95 g, 63.1 mmol). To this mixture, while stirring, was charged dicyclohexylcarbodiimide (7.45 g, 36.0 mmol). The resulting cloudy, yellow mixture was placed in a 70-80°C oil bath. The reaction was monitored by TLC assay (SiO_2, 7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, diacid $R_f = 0.05$, visualization by UV for the disappearance of starting material. SiO_2, 60% ethyl acetate in hexanes as eluent, diphenyl $R_f = 0.40$, visualization by UV) and was judged complete in 2 hours. To the reaction mixture was charged isopropyl acetate (60 mL) to produce a white precipitation. The slurry was filtered through a pad of celite to remove the white precipitate and the filter cake rinsed with isopropyl acetate (25 mL). The filtrate was concentrated via rotary evaporator. To the resulting yellow oil was charged a premixed solution of water (58 mL) and 1N HCl (55 mL) followed by isopropyl acetate (145 mL). The mixture was stirred for one hour in an ice bath. After separating the layers, the aqueous layer was back extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated via rotary evaporator. The crude product oil was purified by silica gel column chromatography using 50% ethyl acetate in hexanes as eluent to afford the product 10 as a white foam (3.52 g, 51% yield). ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 2H), 7.40-7.20 (m, 15H), 7.10 (d, 2H), 5.65 (d, 1H), 5.10-4.90 (m, 2H), 4.65 (d, 2H), 4.00-3.80 (m, 4H), 3.75-3.65 (m, 3H), 3.25-2.75 (m, 7H), 1.90-1.75 (m, 1H), 1.70-1.60 (m, 1H), 1.50-1.40 (m, 1H), 0.90 (d, 3H), 0.85 (d, 3H). ^{31}P NMR ($CDCl_3$) δ 10.9.

Example 6

Monophenyl 1: To a solution of diphenyl 10 (3.40 g, 4.28 mmol) in acetonitrile (170 mL) at 0°C was charged 1N sodium hydroxide (4.28 mL). The reaction was monitored by TLC assay (SiO_2, 7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, diphenyl $R_f = 0.65$, visualization by UV for the disappearance of starting material. Product monophenyl $R_f = 0.80$, visualization by UV). Additional 1N NaOH was added (if necessary) until the reaction was judged complete. To the reaction contents at 0°C was charged Dowex H^+ (Dowex 50WX8-200) (4.42 g) and stirred for 30 minutes at which time the pH of the mixture reached pH 1 (monitored by pH paper). The mixture was filtered to remove the Dowex resin and the filtrate was concentrated via rotary evaporation (water bath < 40°C). The resulting solution was co-evaporated with toluene to remove water (3 x 50 mL). The white foam was dissolved in ethyl acetate (8 mL) followed by slow addition of hexanes (16 mL) over 30 minutes to induce precipitation. A premixed solution of 2:1 hexnaes/ethyl acetate solution (39 mL) was charged to the precipitated material and stirred. The product 1 was filtered and rinsed with premixed solution of 2:1 hexanes/ethyl acetate solution (75 mL) and dried under vacuum to afford a white powder (2.84 g, 92% yield). ^1H NMR (CD_3OD) δ 7.80 (d, 2H), 7.40-7.30 (m, 2H), 7.20-7.15 (m, 11H), 5.55 (d, 1H), 4.50 (d, 2H), 3.95-3.85 (m, 1H), 3.80-3.60 (m, 5H), 3.45 (bd, 1H), 3.25-3.15 (m, 2H), 3.00-2.80 (m, 3H), 2.60-2.45 (m, 1H), 2.10-1.95 (m, 2H), 1.85-1.60 (m, 2H), 1.50-1.40 (m, 1H), 1.40-1.30 (m, 1H), 0.95 (d, 3H), 0.85 (d, 3H). ^{31}P NMR ($CDCl_3$) δ 13.8. The monophenyl product 1 is sensitive to silica gel. On contact with silica gel 1 converts to an unknown compound possessing ^{31}P NMR chemical shift of 8 ppm. However, the desired monophenyl product 1 can be regenerated by treatment of the unknown compound with 2.5 M NaOH in acetonitrile at 0°C for one hour followed by Dowex H^+ treatment as described above.

Example 7

Dibenzylphosphonate 9: To a solution of phenol 11 (6.45 g, 11.8 mmol) in tetrahydrofuran (161 mL) at room temperature was charged triflate reagent 12 (6.48 g, 15.3 mmol). Cesium carbonate (11.5 g, 35.3 mmol) was added and the mixture was stirred and monitored by TLC assay (SiO_2, 5% methanol in dichloromethane as eluent, dibenzyl product $R_f = 0.26$, visualization by UV or ninhydrin stain and heat). Additional Cs_2CO_3 was added until the reaction was judged complete. To the reaction contents was charged water (160 mL) and the mixture extracted with ethyl acetate (2 x 160 mL). The combined organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporator to afford a viscous oil.

The crude oil was purified by silica gel column chromatography using a gradient of 100% dichloromethane to 1% methanol in dichloromethane to afford product 9 as a white foam (8.68 g, 90% yield). ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 2H), 7.40-7.20 (m, 16H), 6.95 (d, 2H), 5.65 (d, 1H), 5.20-4.90 (m, 6H), 4.25 (d, 2H), 4.00-3.80 (m, 4H), 3.75-3.65 (m, 3H), 3.20-2.75 (m, 7H), 1.90-1.75 (m, 1H), 1.30-1.20 (m, 1H), 0.90 (d, 3H), 0.85 (d, 3H). ^{31}P NMR ($CDCl_3$) δ 19.1.

Example 7a

Hydroxyphenylsulfonamide 14: To a solution of methoxyphenylsulfonamide 13 (35.9 g, 70.8 mmol) in dichloromethane (3.5 L) at 0°C was charged boron tribromide (1M in DCM, 40.1 mL, 425 mmol). The reaction content was allowed to warm to room temperature, stirred over two hours, and monitored by TLC assay (SiO_2, 10% methanol in dichloromethane as eluent, dibenzyl product R_f = 0.16, visualization by UV). To the contents at 0°C was slowly charged propylene oxide (82 g, 1.42 mmol). Methanol (200 mL) was added and the reaction mixture was concentrated via rotary evaporator to afford a viscous oil. The crude product mixture was purified by silica gel column chromatography using 10% methanol in dichloromethane to afford the product 14 as a foam (22 g, 80% yield). ^{1}H NMR (DMSO) δ 7.60 (d, 2H), 7.30-7.20 (m, 5H), 6.95 (d, 2H), 3.90-3.75 (m, 1H), 3.45-3.20 (m, 5H), 3.00-2.55 (m, 5H), 2.50-2.40 (m, 1H), 1.95-1.85 (m, 1H), 0.85 (d, 3H), 0.80 (d, 3H).

Example 8

Cisfuran carbamate 16: To a solution of amine 14 (20.4 g, 52.0 mmol) in acetonitrile (600 mL) at room temperature was charged dimethylaminopyridine (13.4 g, 109 mmol) followed by cisfuran *p*-nitrophenylcarbonate reagent 15 (14.6 g, 49.5 mmol). The resulting solution was stirred at room temperature for at least 48 hours and monitored by TLC assay (SiO_2, 10% methanol in dichloromethane as eluent, cisfuran product R_f = 0.34, visualization by UV). The reaction mixture was concentrated via rotary evaporator. The crude product mixture was purified by silica gel column chromatography using a gradient of 60% ethyl acetate in hexanes to 70% ethyl acetate in hexanes to afford the product 16 as a solid (18.2 g, 64% yield). ^{1}H NMR (DMSO) δ 10.4 (bs, 1H), 7.60 (d, 2H), 7.30-7.10 (m, 6H), 6.95 (d, 2H), 5.50 (d, 1H), 4.85 (m, 1H), 3.85 (m, 1H), 3.70 (m, 1H), 3.65-3.50 (m, 4H), 3.30 (d, 1H), 3.05-2.95 (m, 2H), 2.80-2.65 (m, 3H), 2.50-2.40 (m, 1H), 2.00-1.90 (m, 1H), 1.45-1.20 (m, 2H), 0.85 (d, 3H), 0.80 (d, 3H).

Example Section L

Example 1

Monobenzyl phosphonate 2 A solution of dibenzylphosphonate 1(150 mg, 0.175mmol) was dissolved in toluene (1 mL), treated with DABCO (20 mg, 0.178 mmol) and was refluxed under N2 atmosphere (balloon) for 3 h. The solvent was removed and the residual was dissolved in aqueous HCl (5%). The aqueous layer was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. After evaporation to yield the monobenzyl phosphonate 2 (107 mg, 80%) as a white powder. ^{1}H NMR (CD_3OD) δ 7.75 (d, J = 5.4 Hz, 2H), 7.42-7.31 (m, 5H) 7.16 (d, J = 5.4 Hz, 2H), 7.01 (d, J = 5.4 Hz, 2H), 6.86 (d, J = 5.4 Hz, 2H), 5.55 (d, J = 3.3 Hz, 1H), 5.14 (d, J = 5.1 Hz, 2H), 4.91 (m, 1H), 4.24-3.66 (m overlapping s, 11H), 3.45 (m, 2H), 3.14-2.82 (m, 6H), 2.49 (m, 1H), 2.01 (m, 1H), 1.51-1.34 (m, 2H), 0.92 (d, J = 3.9 Hz, 3H), 0.87 (d, J = 3.9 Hz, 3H); ^{31}P NMR (CD_3OD) δ 20.5; MS (ESI) 761 (M-H).

Example 2

Monobenzyl, ethyl phosphonate 3 To a solution of monobenzyl phosphonate 2 (100 mg, 0.13 mmol) in dry THF (5 mL) at room temperature under N_2 was added Ph_3P (136 mg, 0.52 mmol) and ethanol (30 μL, 0.52 mmol). After cooled to 0°C, DEAD (78μL, 0.52 mmol) was added. The mixture was stirred for 20 h at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by using chromatograph on silica gel (10% to 30% ethyl acetate / hexane) to afford the monobenzyl, ethyl phosphonate 3 (66 mg, 64%) as white solid. ^{1}H NMR ($CDCl_3$) 7.70 (d, J = 8.7 Hz, 2H), 7.43-7.34 (m, 5H) 7.14 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.7Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.56 (d, J = 5.4 Hz, 1H), 5.19 (d, J = 8.7 Hz, 2H), 5.00 (m, 2H), 4.22-3.67 (m overlapping s, 13H), 3.18-2.76 (m, 7H), 1.82-1.54 (m, 3H), 1.33 (t, J = 7.0 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 19.8; MS (ESI) 813 (M+Na).

Example 3

Monoethyl phosphonate 4 A solution of monobenzyl, ethyl phosphonate 3 (60 mg) was dissolved in EtOAc (2 mL), treated with 10% Pd/C (6 mg) and was stirred under H_2 atmosphere (balloon) for 2h. The catalyst was removed by filtration through celite. The filtered was evaporated under reduced pressure, the residue was triturated with ether and the

solid was collected by filtration to afford the monoethyl phosphonate 4 (50 mg, 94%) as white solid. ^{1}H NMR (CD_3OD) 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.7Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 5.58 (d, J = 5.4 Hz, 1H), 5.90 (m, 1H), 4.22-3.67 (m overlapping s, 13H), 3.18-2.50 (m, 7H), 1.98(m, 1H), 1.56 (m, 2H), 1.33 (t, J = 6.9 Hz, 3H), 0.92 (d, J = 6.6Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CD_3OD) δ 18.7; MS (ESI) 700 (M-H).

Example 4

Monophenyl, ethyl phosphonate 5 To a solution of phosphonic acid 11 (800 mg, 1.19 mmol) and phenol (1.12 g, 11.9 mmol) in pyridine (8 mL) was added ethanol (69 μL, 1.19 mmol) and 1, 3-dicyclohexylcarbodiimide (1g, 4.8 mmol). The solution was stirred at 70°C for 2h. The reaction mixture was cooled to room temperature, then diluted with ethyl acetate (10 mL) and filtered. The filtrate was evaporated under reduced pressure to remove pyridine. The residue was dissolved in ethyl acetate and the organic phase was separated and washed with brine, dried over MgSO4, filtered and concentrated. The residue was purified by chromatography on silica gel to give monophenyl, ethyl phosphonate 5 (600 mg, 65%) as white solid. ^{1}H NMR ($CDCl_3$) 7.72 (d, J = 9 Hz, 2H), 7.36-7.18 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 9Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.00 (m, 2H), 4.34 (m, 4H), 3.94-3.67 (m overlapping s, 9H), 3.18-2.77 (m, 7H), 1.82-1.54 (m, 3H), 1.36 (t, J = 7.2 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 16.1; MS (ESI) 799 (M+Na).

Example 5

Sulfonamide 6 To a suspension of epoxide 5 (3 g, 8.12 mmol) in 2-propanol (30 mL) was added isobutylamine (8 mL, 81.2 mmol) and the solution was stirred at 80°C for 1 h. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (40 mL) and cooled to 0°C. TEA (2.3 mL, 16.3mmol) was added followed by the addition of 4-nitrobenzenesulfonyl chloride (1.8 g, 8.13 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred for 30 min at 0°C, warmed to room temperature and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide 6 (4.6 g, 91%) as an off-white solid. MS (ESI) 650 (M+Na).

Example 6

Phenol 7 A solution of sulfonamide 6 (4.5 g, 7.1 mmol) in CH_2Cl_2 (50 mL) at 0°C was treated with BBr_3 (1M in CH_2Cl_2, 50mL). The solution was stirred at 0°C to room temperature for 48h. CH_3OH (10 mL) was carefully added. The solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase washed with saturated NaCl, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% - MeOH/CH_2Cl_2) to give the phenol 7 (2.5 g, 80%) as an off-white solid. MS (ESI) 528 (M+H).

Example 7

Carbamate 8 A solution of sulfonamide 7 (2.5 g, 5.7 mmol) in CH_3CN (100 mL) and was treated with proton-sponge (3 g, 14 mmol) and followed by (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (1.7 g, 5.7 mmol) at 0°C. After stirring for 48h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 10% HCl. The organic phase was washed with saturated NaCl, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% MeOH/CH_2Cl_2) affording the carbamate 8 (2.1g, 62 %) as a white solid. MS (ESI) 616 (M+Na).

Example 8

Diethylphosphonate 9 To a solution of carbamate 8 (2.1 g, 3.5 mmol) in CH_3CN (50 mL) was added Cs_2CO_3 (3.2 g, 9.8 mmol) and diethyltriflate (1.6g, 5.3 mmol). The mixture was stirred at room temperature for 1h. After removed the solvent, the residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (1% to 5% MeOH /CH_2Cl_2) to afford the diethylphosphonate 9 as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.35 (d, J = 9 Hz, 2H), 7.96 (d, J = 9 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.63 (d, J = 5.1 Hz, 1H), 5.18-5.01 (m, 2H), 4.27-4.17 (m, 6H), 3.94-3.67 (m, 7H), 3.20-2.73 (m, 7H), 1.92-1.51 (m, 3H), 1.35 (t, J = 7.2 Hz, 6H), 0.88-0.85 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 19.2; MS (ESI) 756 (M+Na).

Example 9

Amine 10 A solution of diethylphosphonate 9 (1 g) was dissolved in EtOH (100 mL), treated with 10% Pd/C (300 mg) and was stirred under H_2 atmosphere (balloon) for 3h. The reaction was purged with N_2, and the catalyst was removed by filtration through celite. After evaporation of the filtrate, the residue was triturated with ether and the solid was collected by filtration to afford the amine 10 (920 mg, 96%) as a white solid. ^{1}H NMR ($CDCl_3$) ^{1}H NMR ($CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.13-5.05 (m, 2H), 4.42 (s, 2H), 4.29-4.20 (m, 6H), 4.00-3.69 (m, 7H), 3.00-2.66 (m, 7H), 1.80-1.69 (m, 3H), 1.38 (m, 6H), 0.94 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 6H); ^{31}P NMR ($CDCl_3$) δ 19.4; MS (ESI) 736 (M+Na).

Compound	R_1	R_2
16a	Gly-Et	Gly-Et
16b	Gly-Bu	Gly-Bu
16j	Phe-Bu	Phe-Bu
16k	NHEt	NHEt

Example 10

Synthesis of Bisamidates 16a. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-alanine ethyl ester hydrochloride (84 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH_2Cl_2). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16a (90 mg, 72%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz , 2H), 5.68 (d, J = 5.1 Hz,, 1H), 5.05 (m, 1H), 4.25 (d, J = 9.9 Hz, 2H), 4.19 (q, 4H), 3.99-3.65 (m overlapping s, 13H,), 3.41 (m, 1H), 3.20-2.81 (m, 7H), 1.85-1.60 (m, 3H), 1.27 (t, J = 7.2 Hz, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 21.8; MS (ESI) 843 (M+H).

Example 11

Synthesis of Bisamidates 16b. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-alanine n-butyl ester hydrochloride (101 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH_2Cl_2). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16b (100 mg, 74%) as a white solid: ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 2H), 7.01 (d, J = 9 Hz, 2H), 6.87 (d, J = 9 Hz, 2H), 5.67 (d, J = 5.4 Hz, 1H), 5.05 (m, 1H), 4.96 (m, 1H), 4.25 (d, J = 9.9 Hz, 2H), 4.11 (t, J = 6.9 Hz, 4H), 3.99-3.71 (m overlapping s, 13H,), 3.41 (m, 1H), 3.20-2.80 (m, 7H), 1.87-1.60 (m, 7H), 1.42 (m, 4H), 0.96-0.88 (m, 12H); ^{31}P NMR ($CDCl_3$) δ 21.8; MS (ESI) 890 (M+H).

Example 12

Synthesis of Bisamidates 16j. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-phenylalanine n-butyl ester hydrochloride (155 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in pyridine (1 mL) stirring for 36h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH_2Cl_2). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16j (106 mg, 66%) as a white solid. ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.31-7.10 (m, 12H), 7.01 (d, J = 9 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.05 (m, 1H), 4.96 (m, 1H), 4.35-3.98 (m., 7H), 3.90-3.61 (m overlapping s, 10H,), 3.19-2.78 (m, 11H), 1.87-1.25 (m, 11H), 0.96-0.88 (m, 12H); ^{31}P NMR ($CDCl_3$) δ 19.3; MS (ESI) 1080 (M+H).

Example 13

Synthesis of Bisamidates 16k. A solution of phosphonic acid 11 (80 mg, 0.12 mmol), ethylamine (0.3 mL,2M in THF, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (109 mg, 0.42 mmol) and 2,2'-dipyridyl disulfide (93 mg, 0.42 mmol) in pyridine (1 mL) stirring for 48h at room temperature. The solvent was evaporated under reduced

pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH_2Cl_2). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16k (60 mg, 70%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz , 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.05-4.95 (m, 2H), 4.15 (d, J = 9.6 Hz, 2H), 3.99-3.72 (m overlapping s, 9H,), 3.18-2.81 (m, 11H), 2.55 (br, 1H), 1.85-1.65 (m, 3H), 1.18 (t, J = 7.2 Hz, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 21.6; MS (ESI) 749 (M+Na).

Compound	R_1	R_2
30a	OPh	Ala-Me
30b	OPh	Ala-Et
30c	OPh	(D)-Ala-iPr
30d	OPh	Ala-Bu
30e	OBn	Ala-Et

Example 14

Monoamidate 30a (R1 = OPh, R2 = Ala-Me) To a flask was charged with monophenyl phosphonate 29 (75 mg, 0.1 mmol), L-alanine methyl ester hydrochloride (4.0 g, 22 mmol) and 1, 3-dicyclohexylcarbodiimide (84 mg, 0.6 mmol), then pyridine (1 mL) was added under N2. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between ethyl acetate and HCl (0.2 N), the ethyl acetate phase was washed with water and $NaHCO_3$, dried over Na_2SO_4 filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:5) to give 30a (25 mg, 30%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.01 (m, 2H), 4.30 (m, 2H), 3.97-3.51 (m overlapping s, 12H), 3.20-2.77 (m, 7H), 1.81 (m, 1H), 1.58 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.4 and 19.3; MS (ESI) 856 (M+Na).

Example 15

Monoamidate 30b (R1 = OPh, R2 = Ala-Et) was synthesized in the same manner in 35% yield. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.01 (m, 3H), 4.30 -3.67

(m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.22 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.4 and 19.3; MS (ESI) 870 (M+Na).

Example 16

Monoamidate 30c (R1 = OPh, R2 = (D)-Ala-iPr) was synthesized in the same manner in 52% yield. Isomer A ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.66 (m,, 1H), 5.01 (m, 3H), 4.30 -3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.23 (m, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.4; MS (ESI) 884 (M+Na). Isomer B ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.66 (m,, 1H), 5.01 (m, 3H), 4.30 -3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.23 (m, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 19.3; MS (ESI) 884 (M+Na).

Example 17

Monoamidate 30d (R1 = OPh, R2 = Ala-Bu) was synthesized in the same manner in 25% yield. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.01 (m, 3H), 4.30 -3.67 (m overlapping s, 16H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 8H), 1.22 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.4 and 19.4; MS (ESI) 898 (M+Na).

Example 18

Monoamidate 30e (R1 = OBn, R2 = Ala-Et) To a flask was charged with monobenzyl phosphonate 2 (76 mg, 0.1 mmol), L-alanine methyl ester hydrochloride (4.0 g, 22 mmol) and 1, 3-dicyclohexylcarbodiimide (84 mg, 0.6 mmol), then pyridine (1 mL) was added under N2. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between ethyl acetate and HCl (0.2 N), the ethyl acetate phase was washed with water and $NaHCO_3$, dried over Na_2SO_4 filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate / hexane 1:5) to give 30a (25 mg, 30%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.38-7.34 (m, 5H), 7.13

(d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.86-6.80 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.15-5.01 (m, 5H), 4.30 -3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.22 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 23.3 and 22.4; MS (ESI) 884 (M+Na).

Compound	R_1	R_2
31a	OPh	Lac-iPr
31b	OPh	Lac-Et
31c	OPh	Lac-Bu
31d	OPh	(R)-Lac-Me
31e	OPh	(R)-Lac-Et

Example 19

Monolactate 31a (R1 = OPh, R2 = Lac-iPr): To a flask was charged with monophenyl phosphonate 29 (1.5 g, 2 mmol), isopropyl-(s)-lactate (0.88 mL, 6.6 mmol) and 1, 3-dicyclohexylcarbodiimide (1.36 g, 6.6 mmol), then pyridine (15 mL) was added under N_2. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was washed with ethyl acetate and the combined organic phase was washed with NH_4Cl, brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate / CH_2Cl_2 1:5) to give 31a (1.39g, 81%) as a white solid. Isomer A ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.15 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 5.65 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 4H), 4.56-4.44 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.13-2.78 (m, 7H), 1.81-1.23 (m, 6H), 1.22 (m, 6H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.4; MS (ESI) 885 (M+Na). Isomer B ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.64 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 4H), 4.53 -4.41 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.13-2.78 (m, 7H), 1.81-1.23 (m, 6H), 1.22 (m, 6H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 15.3; MS (ESI) 885 (M+Na).

Example 20

Monolactate 31b (R1 = OPh, R2 = Lac-Et) was synthesized in the same manner in 75% yield. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.63 (m, 1H), 5.19-4.95 (m, 3H), 4.44-4.40 (m, 2H), 4.17-4.12 (m,

2H), 3.95 -3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 1.23 (m, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.5 and 15.4; MS (ESI) 872 (M+Na).

Example 21

Monolactate 31c (R1 = OPh, R2 = Lac-Bu) was synthesized in the same manner in 58% yield. Isomer A ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.63 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 3H), 4.56-4.51 (m, 2H), 4.17-4.10 (m, 2H), 3.95 -3.67 (m overlapping s, 9H), 3.10-2.77 (m, 7H), 1.81-1.23 (m, 10H), 1.23 (m, 6H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.3; MS (ESI) 899 (M+Na). Isomer B ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.64 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 3H), 4.44 -4.39 (m, 2H), 4.17-4.10 (m, 2H), 3.95 -3.67 (m overlapping s, 9H), 3.10-2.77 (m, 7H), 1.81-1.23 (m, 10H), 1.23 (m, 6H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 15.3; MS (ESI) 899 (M+Na).

Example 22

Monolactate 31d (R1 = OPh, R2 = (R)-Lac-Me): To a stirred solution of monophenyl phosphonate 29 (100 mg, 0.13 mmol) in 10 mL of THF at room temperature under N_2 was added methyl-(S)-lactate (54 mg, 0.52 mmol) and Ph_3P (136 mg g,, 0.52 mmol), followed by DEAD (82μL, 0.52 mmol). After 2 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 31d (33 mg, 30%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.63 (m, 1H), 5.19-4.95 (m, 3H), 4.44-4.40 (m, 2H), 3.95 -3.64 (m overlapping s, 12H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 4H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.4 and 15.3; MS (ESI) 857 (M+Na).

Example 23

Monolactate 31e (R1 = OPh, R2 = (R)-Lac-Et): To a stirred solution of monophenyl phosphonate 29 (50 mg, 0.065 mmol) in 2.5 mL of THF at room temperature under N_2 was

added ethyl-(s)-lactate (31 mg, 0.52 mmol) and Ph_3P (68 mg g, 0.26 mmol), followed by DEAD (41μL, 0.52 mmol). After 2 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 31e (28 mg, 50%) as a white solid. ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.85(m, 2H), 5.63 (m, 1H), 5.19-4.95 (m, 3H), 4.44-4.40 (m, 2H), 4.17-4.12 (m, 2H), 3.95 -3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 1.23 (m, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.5 and 15.4; MS (ESI) 872 (M+Na).

Example 24

Monolactate 32 (R1 = OBn, R2 = (S)-Lac-Bn): To a stirred solution of monobenzyl phosphonate 2 (76 mg, 0.1 mmol) in 0.5 mL of DMF at room temperature under N_2 was added benzyl-(s)-lactate (27 mg, 0.15 mmol) and PyBOP (78 mg, 0.15mmol), followed by DIEA (70μL, 0.4 mmol). After 3 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 32 (46 mg, 50%) as a white solid. ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.38-7.44 (m, 10H), 7.13 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.81(m, 2H), 5.63 (d, J = 5.1 Hz, 1H), 5.23-4.92 (m, 7H), 4.44-22 (m, 2H), 3.96 -3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.8 and 19.6; MS (ESI) 947 (M+Na).

Example 25

Monolactate 33 (R1 = OBn, R2 = (R)-Lac-Bn): To a stirred solution of monobenzyl phosphonate 2 (76 mg, 0.1 mmol) in 5 mL of THF at room temperature under N_2 was added benzyl-(s)-lactate (72 mg, 0.4 mmol) and Ph_3P (105 mg g, 0.4mmol), followed by DEAD (60μL, 0.4 mmol). After 20 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 33 (44 mg, 45%) as a white solid. ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.38-7.44 (m, 10H), 7.13 (m, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.81(m, 2H), 5.63 (m, 1H), 5.23-4.92 (m, 7H), 4.44-22 (m, 2H), 3.96 -3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.8 and 19.6; MS (ESI) 947 (M+Na).

Example 26

Monophosphonic acid 34: A solution of monobenzyllactate 32 (20 mg) was dissolved in EtOH/ EtOAc (3 mL/1 mL), treated with 10% Pd/C (4 mg) and was stirred under H2 atmosphere (balloon) for 1.5 h. The catalyst was removed by filtration through celite. The filtered was evaporated under reduced pressure, the residue was triturated with ether and the solid was collected by filtration to afford the monophosphonic acid 33 (15 mg, 94%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.69 (d, J = 5.7 Hz, 1H), 5.03-4.95 (m, 2H), 4.20 (m, 2H), 3.90 -3.65 (m overlapping s, 9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 2.00 (m, 1H), 1.61-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 18.0; MS (ESI) 767 (M+Na).

Example 27

Monophosphonic acid 35: A solution of monobenzyllactate 33(20 mg) was dissolved in EtOH (3 mL), treated with 10% Pd/C (4 mg) and was stirred under H2 atmosphere (balloon) for 1h. The catalyst was removed by filtration through celite. The filtered was evaporated under reduced pressure, the residue was triturated with ether and the solid was collected by filtration to afford the monophosphonic acid 35 (15 mg, 94%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.69 (d, J = 5.7 Hz, 1H), 5.03-4.95 (m, 2H), 4.20 (m, 2H), 3.90 -3.65 (m overlapping s, 9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 2.00 (m, 1H), 1.61-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 18.0; MS (ESI) 767 (M+Na).

Example 28

Synthesis of Bislactate 36: A solution of phosphonic acid 11 (100 mg, 0.15 mmol) isopropyl-(S)-lactate (79 mg, 0.66 mmol) was dissolved in pyridine (1 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (137 mg, 0.53 mmol) and 2,2'-dipyridyl disulfide (116 mg, 0.53 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH_2Cl_2). The purified product was suspended in ether and was evaporated under reduced pressure to afford

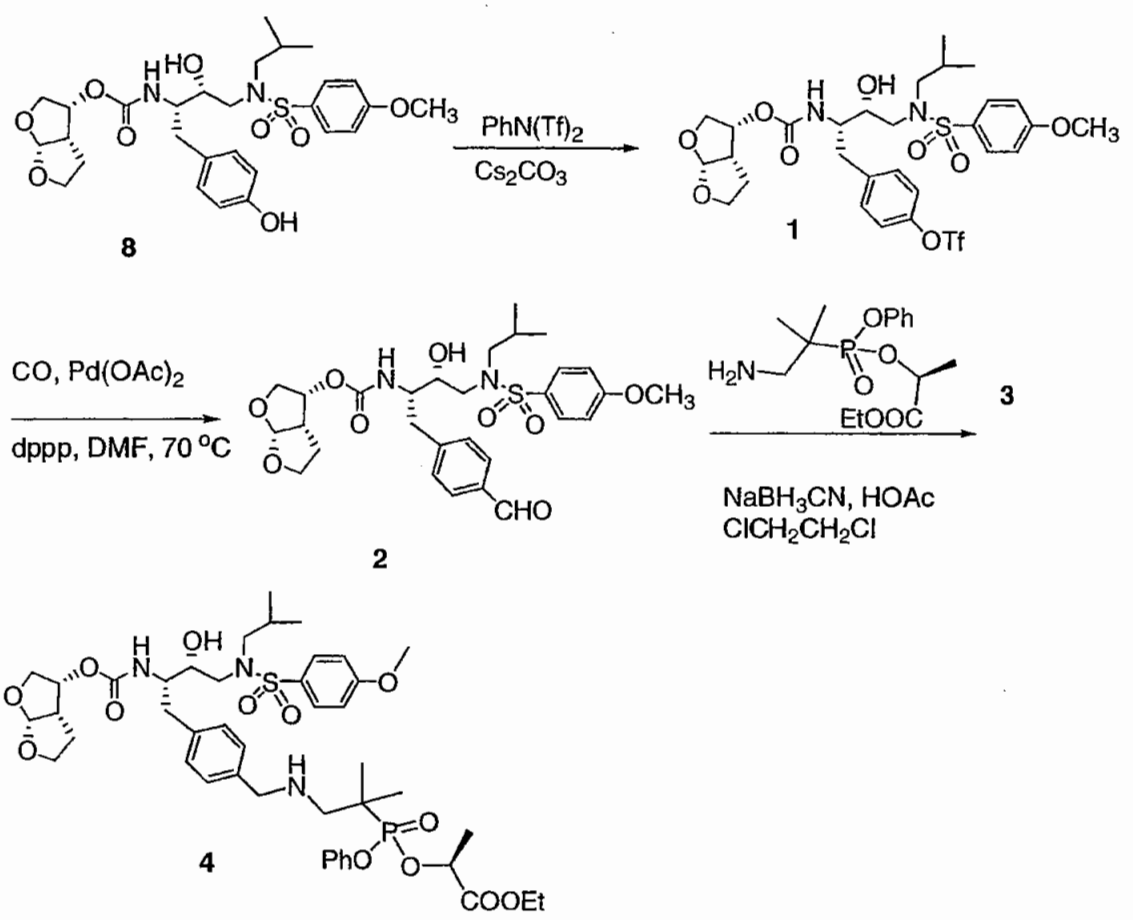
bislactate 36 (42 mg, 32%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.1 Hz, 1H), 5.05 (m, 3H), 4.25 (d, J = 9.9 Hz, 2H), 4.19 (q, 4H), 3.99-3.65 (m overlapping s, 9H,), 3.41 (m, 1H), 3.20-2.81 (m, 7H), 1.85-1.60 (m, 3H),1.58 (m, 6H), 1.26 (m, 12H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 21.1; MS (ESI) 923 (M+Na).

Example 29

Triflate derivative **1**: A THF-CH_2Cl_2 solution (30mL-10 mL) of **8** (4 g, 6.9 mmol), cesium carbonate (2.7 g, 8 mmol), and N-phenyltrifluoromethane sulfonimide (2.8 g, 8 mmol) was reacted overnight. The reaction mixture was worked up, and concentrated to dryness to give crude triflate derivative **1**.

Aldehyde **2**: Crude triflate **1** (4.5 g, 6.9 mmole) was dissolved in DMF (20 mL), and the solution was degassed (high vacuum for 2 min, Ar purge, repeat 3 times). Pd(OAc)2 (0.12 g, 0.27 mmol), and bis(diphenylphosphino)propane (dppp, 0.22 g, 0.27 mmol) were added and the solution was heated to 70°C. Carbon monoxide was rapidly bubbled through the solution, then under 1 atmosphere of carbon monoxide. To this solution were slowly added TEA (5.4 mL, 38 mmol), and triethylsilane (3 mL, 18 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was worked up, and purified on silica gel column chromatograph to afford aldehyde **2** (2.1 g, 51%). (Hostetler, et al. J. Org. Chem., 1999. 64, 178-185).

Lactate prodrug **4**: Compound 4 is prepared as described above procedure for 3a-e by the reductive amination between 2 and 3 with $NaBH_3CN$ in 1,2-dichloroethane in the presence of HOAc.



Example 30

Preparation of compound **3** Diethyl (cyano(dimethyl)methyl) phosphonate **5**: A THF solution (30 mL) of NaH (3.4 g of 60% oil dispersion, 85 mmole) was cooled to –10°C, followed by the addition of diethyl (cyanomethyl)phosphonate (5g, 28.2 mmol) and iodomethane (17 g, 112 mmol). The resulting solution was stirred at –10°C for 2 hr, then 0°C for 1 hr, was worked up, and purified to give dimethyl derivative **5** (5 g, 86%).

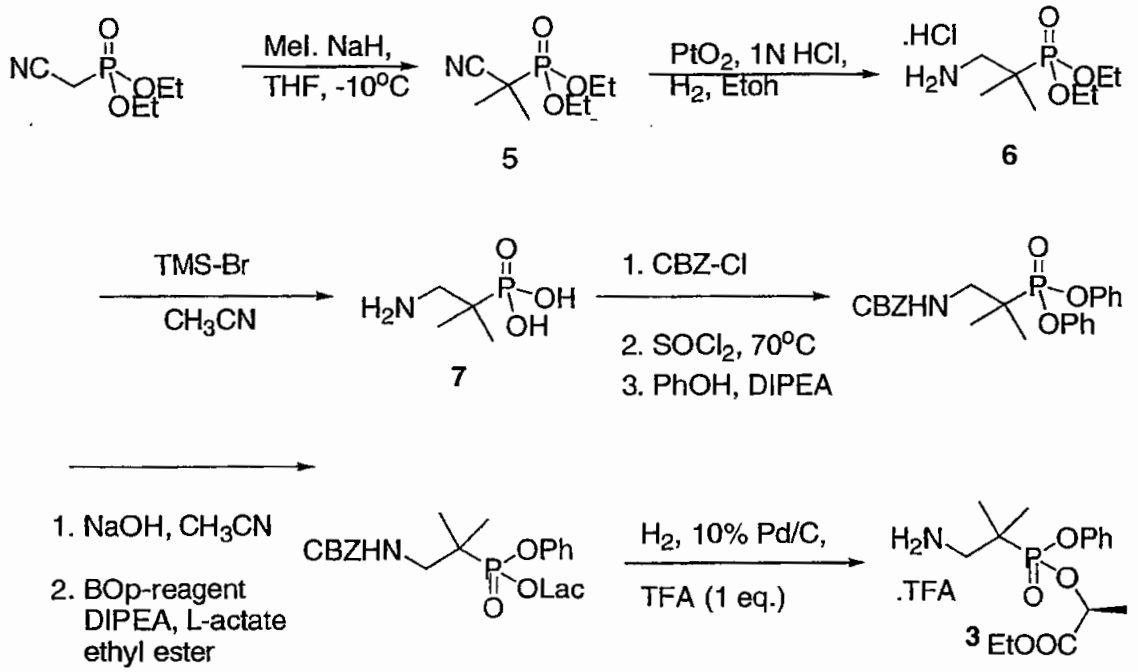
Dietyl (2-amino-1,1-diemthyl-ethyl)phosphonate **6**: Compound **5** was reduced to amine derivative **6** by the described procedure (J. Med. Chem. 1999, 42, 5010-5019).

A ethanol (150 mL) and 1N HCl aqueous solution (22 mL) of 5 (2.2 g, 10.7 mmol) was hydrogenated at 1 atmosphere in the presence of PtO_2 (1.25 g) at room temperature overnight. The catalyst was filtered through a celite pad. The filtrate was concentrated to dryness, to give crude **6** (2.5g, as HCl salt).

2-Amino-1,1-dimethyl-ethyl phosphonic acid **7**: A CH_3CN (30 mL) of crude **6** (2.5 g) was cooled to 0°C, and treated with TMSBr (8 g, 52 mmol) for 5 hr. The reaction mixture was

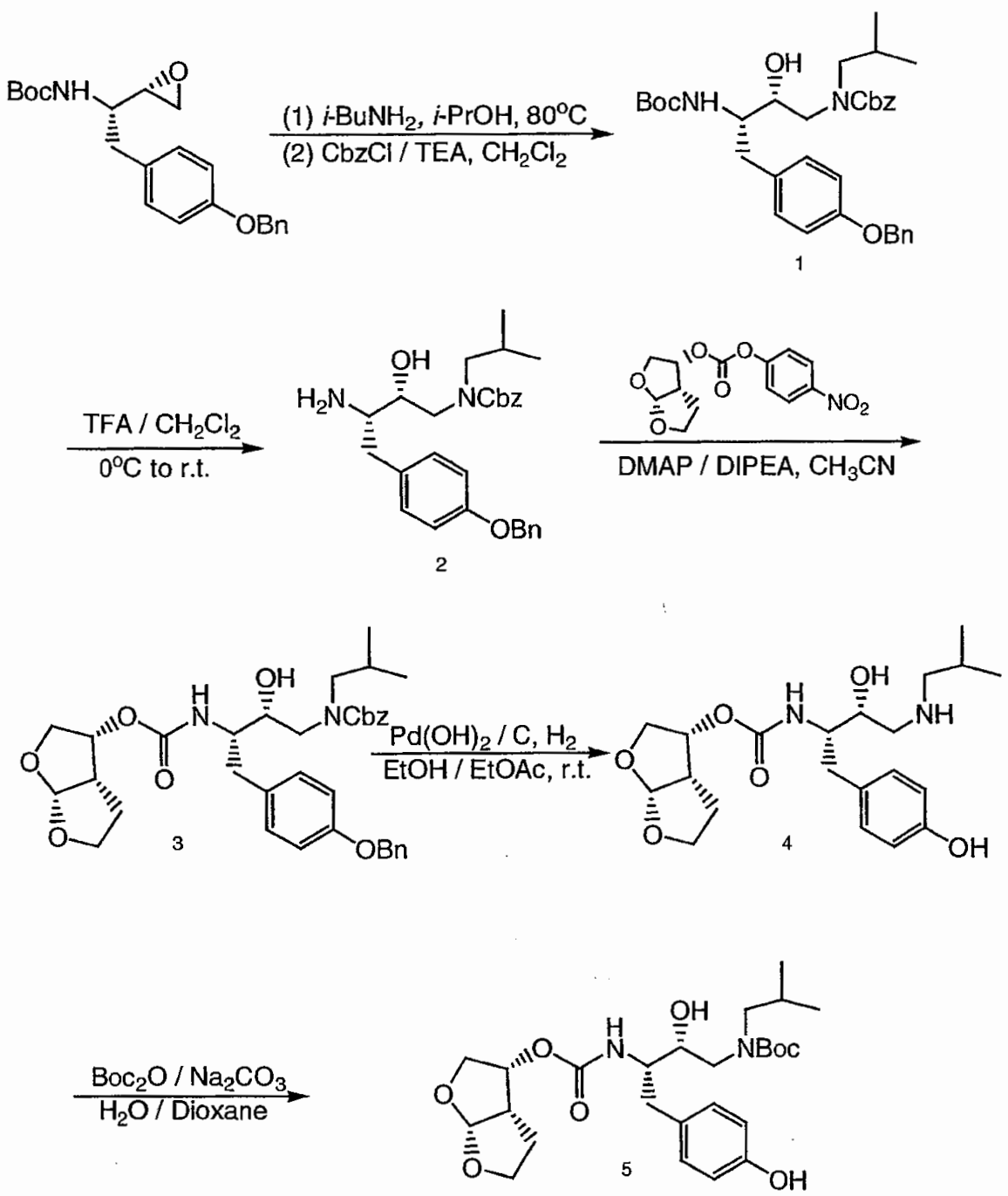
stirred with methanol for 1.5 hr at room temperature, concentrated, recharged with methanol, concentrated to dryness to give crude **7** which was used for next reaction without further purification.

Lactate phenyl (2-amino-1,1-diemthyl-ethyl)phosphonate **3**: Compound **3** is synthesized according to the procedures described in a previous scheme for the preparation of a lactate phenyl 2-aminoethyl phosponate. Compound **7** is protected with CBZ, followed by the reaction with thionyl chloride at 70°C. The CBZ protected dichlorodate is reacted phenol in the presence of DIPEA. Removal of one phenol, follow by coupling with ethyl L-lactate leads N-CBZ-2-amino-1,1-dimethyl-ethyl phosphonated derivative. Hydrogenation of N-CBZ derivative at 1 atmosphere in the presence of 10% Pd/C and 1 equivalent of TFA affords compound **3** as TFA salt.

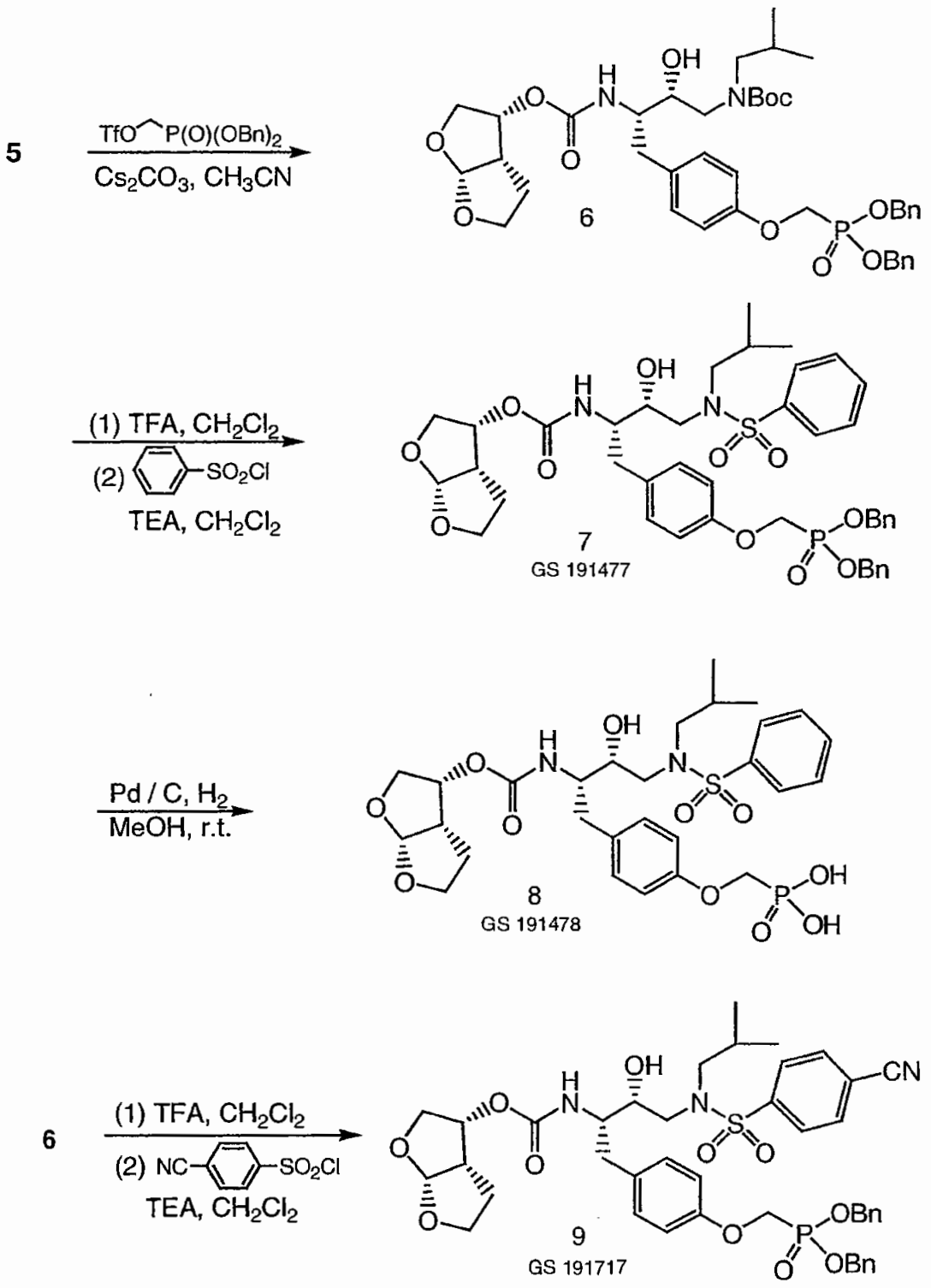


Example Section M

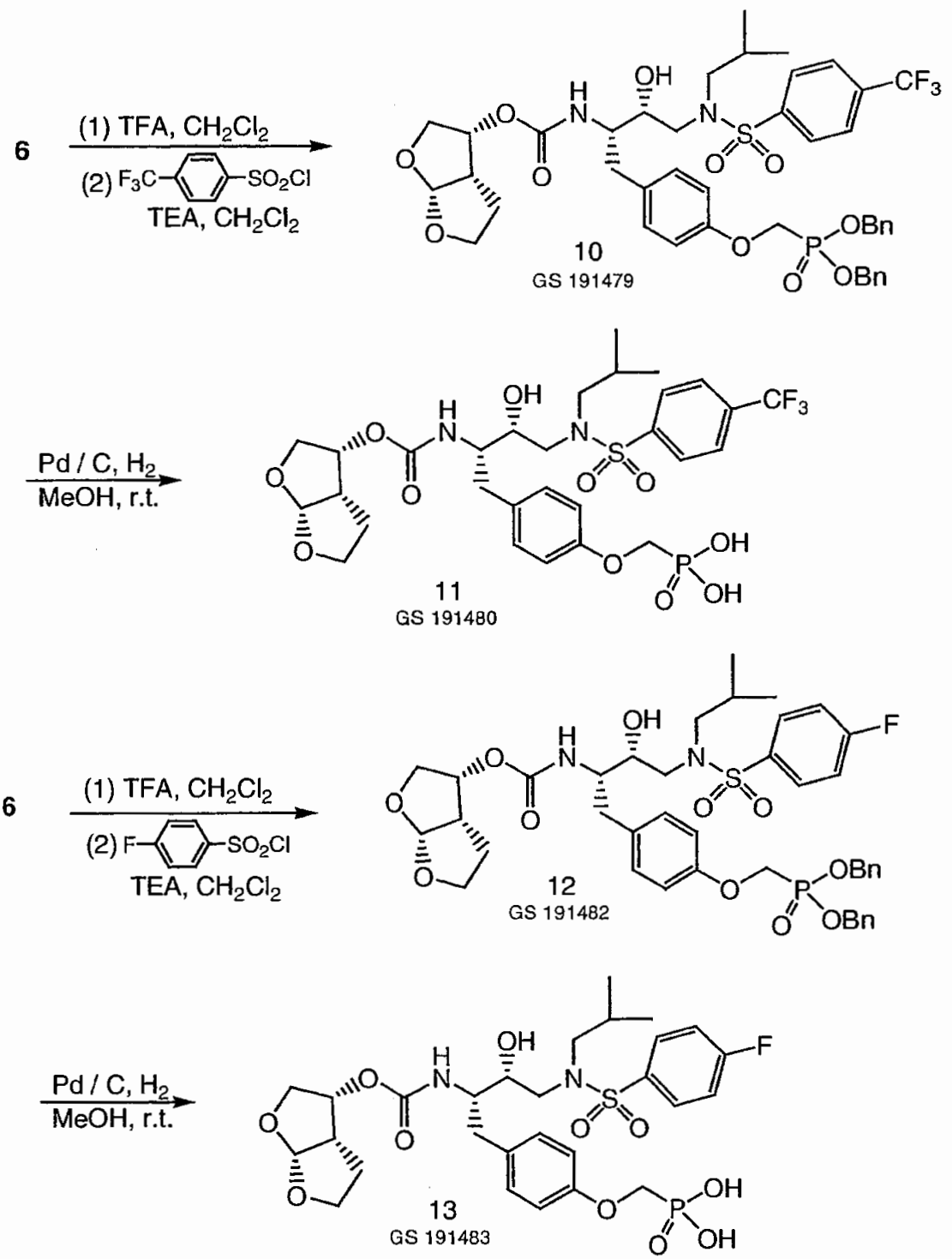
Scheme 1



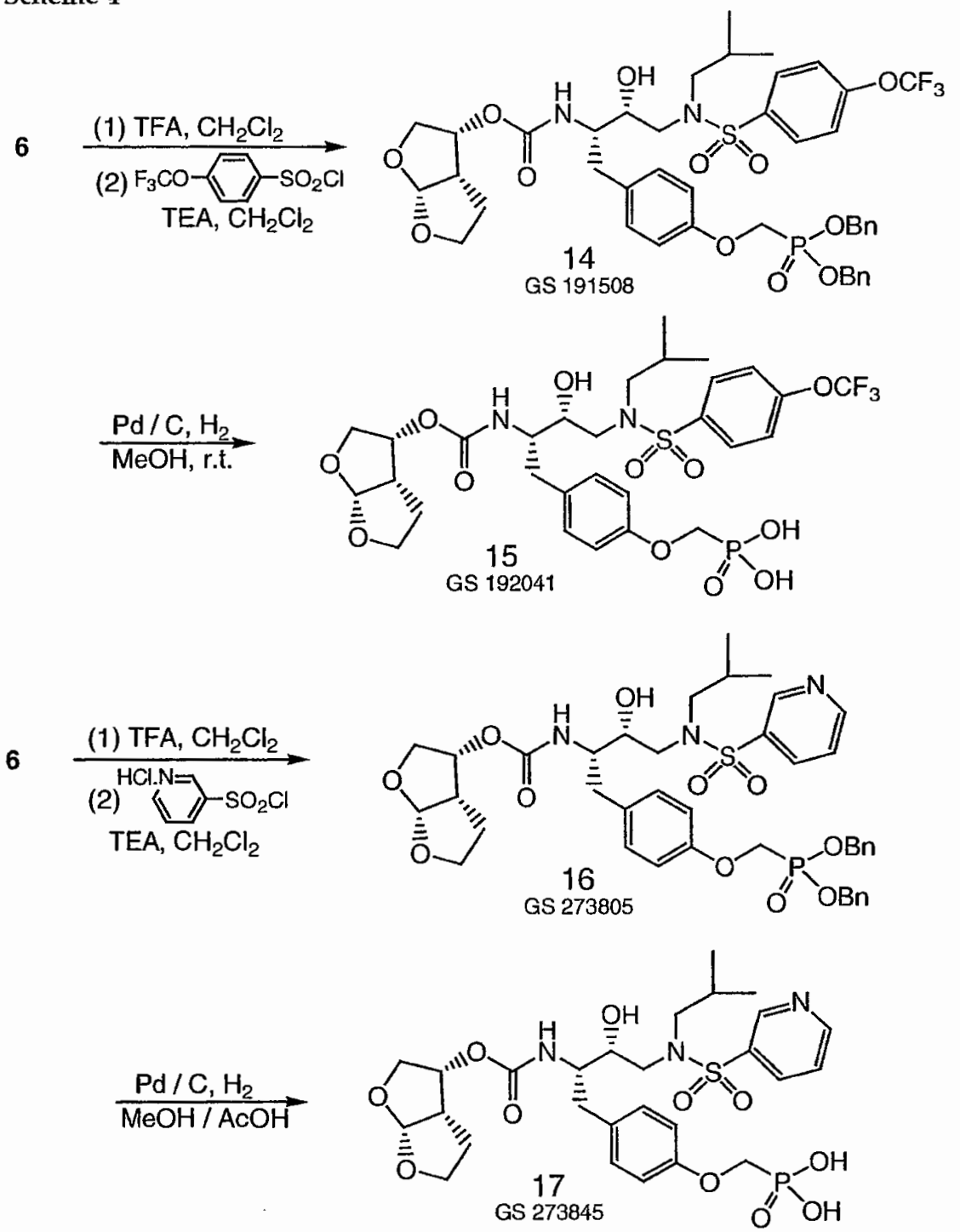
Scheme 2


5
TfO P(O)(OBn)2
Cs2CO3, CH3CN
6
(1) TFA, CH2Cl2
(2) SO2Cl
TEA, CH2Cl2
7
GS 191477
Pd / C, H2
MeOH, r.t.
8
GS 191478
6
(1) TFA, CH2Cl2
(2) NC SO2Cl
TEA, CH2Cl2
9
GS 191717

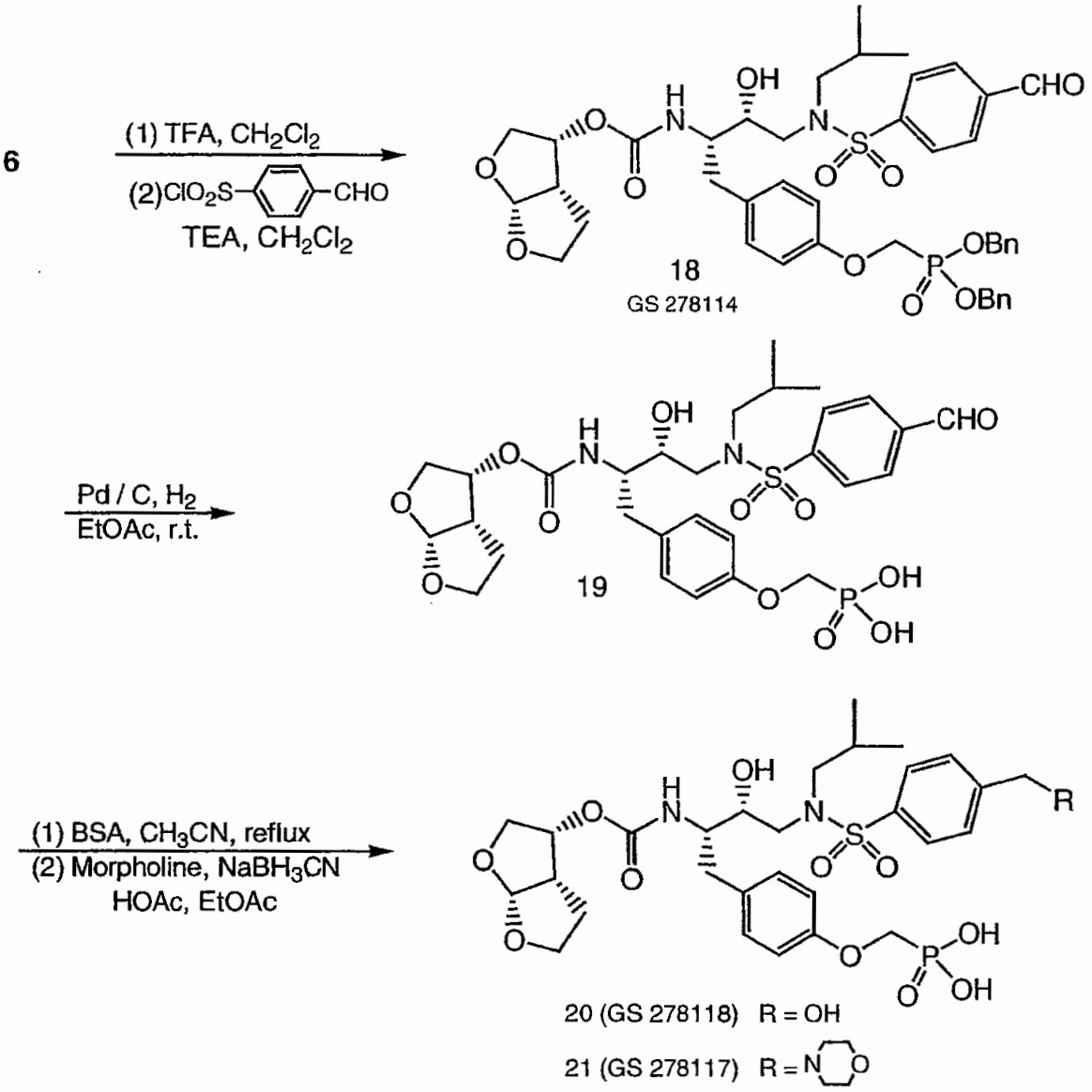
Scheme 3


6
(1) TFA, CH2Cl2
(2) F3C SO2Cl
TEA, CH2Cl2
10
GS 191479
Pd / C, H2
MeOH, r.t.
11
GS 191480
6
(1) TFA, CH2Cl2
(2) F SO2Cl
TEA, CH2Cl2
12
GS 191482
Pd / C, H2
MeOH, r.t.
13
GS 191483

Scheme 4


6
(1) TFA, CH2Cl2
(2) F3CO SO2Cl
TEA, CH2Cl2
14
GS 191508
Pd / C, H2
MeOH, r.t.
15
GS 192041
6
(1) TFA, CH2Cl2
(2) HCl.N SO2Cl
TEA, CH2Cl2
16
GS 273805
Pd / C, H2
MeOH / AcOH
17
GS 273845

Scheme 5



Example 1

Cbz Amide 1: To a suspension of epoxide (34 g, 92.03 mmol) in 2-propanol (300 mL) was added isobutylamine (91.5 mL, 920 mmol) and the solution was refluxed for 1 h. The solution was evaporated under reduced pressure and the crude solid was dried under vacuum to give the amine (38.7 g, 95%) which was dissolved in CH_2Cl_2 (300 mL) and cooled to 0°C. Triethylamine (18.3 mL, 131 mmol) was added followed by the addition of benzyl chloroformate (13.7 mL, 96.14 mmol) and the solution was stirred for 30 min at 0°C, warmed to room temperature overnight, and evaporated under reduced pressure. The residue was partitioned between EtOAc and 0.5 M H_3PO_4. The organic phase was washed with saturated $NaHCO_3$, brine, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The

crude product was purified by column chromatography on silica gel (1/2-EtOAc/hexane) to give the Cbz amide (45.37 g, 90%) as a white solid.

Example 2

Amine 2: A solution of Cbz amide 1 (45.37 g, 78.67 mmol) in CH_2Cl_2 (160 mL) at 0°C was treated with trifluoroacetic acid (80 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2 x), water (2 x), saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure to give the amine (35.62 g, 95%) as a white solid.

Example 3

Carbamate 3: To a solution of amine 2 (20.99 g, 44.03 mmol) in CH_3CN (250 mL) at 0°C was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (13.00 g, 44.03 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, *39*, 3278.), *N,N*-diisopropylethylamine (15.50 mL, 88.06 mmol) and 4-dimethylaminopyridine (1.08 g, 8.81 mmol). The reaction mixture was stirred at 0°C for 30 min and then warmed to room temperature overnight. The reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2 x), 5% citric acid (2 x), saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the carbamate (23.00 g, 83%) as a white solid.

Example 4

Amine 4: To a solution of 3 (23.00 g, 36.35 mmol) in EtOH (200 mL) and EtOAc (50 mL) was added 20% $Pd(OH)_2/C$ (2.30 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 3 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the amine (14.00 g, 94%) as a white solid.

Example 5

Phenol 5: To a solution of amine 4 (14.00 g, 34.27 mmol) in H_2O (80 mL) and 1,4-dioxane (80 mL) at 0°C was added Na_2CO_3 (5.09 g, 47.98 mmol) and di-*tert*-butyl dicarbonate (8.98 g, 41.13 mmol). The reaction mixture was stirred at 0°C for 2 h and then warmed to room temperature for 30 min. The residue was partitioned between EtOAc and H_2O. The organic layer was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the phenol (15.69 g, 90%) as a white solid.

Example 6

Dibenzylphosphonate 6: To a solution of phenol 5 (15.68 g, 30.83 mmol) in CH_3CN (200 mL) was added Cs_2CO_3 (15.07 g, 46.24 mmol) and triflate (17.00 g, 40.08 mmol). The reaction mixture was stirred at room temperature for 1 h, the salt was filtered off, and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate (15.37 g, 73%) as a white solid.

Example 7

Sulfonamide 7: A solution of dibenzylphosphonate 6 (0.21 g, 0.26 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.15 mL, 1.04 mmol) was added followed by the treatment of benzenesulfonyl chloride (47 mg, 0.26 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide 7 (0.12 g, 55%, GS 191477) as a white solid: ^{1}HNMR ($CDCl_3$) δ 7.79 (dd, 2H), 7.61-7.56 (m, 3H), 7.38-7.36 (m, 10H), 7.13 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.18 (m, 4H), 5.05 (m, 1H), 4.93 (d, J = 8.7 Hz, 1H), 4.20 (d, J = 10.2 Hz, 2H), 4.0-3.67 (m, 7H), 3.15-2.8 (m, 7H), 1.84 (m, 1H),

1.65-1.59 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.36.

Example 8

Phosphonic Acid 8: To a solution of 7 (70 mg, 0.09 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (49 mg, 90% GS 191478) as a white solid: ^{1}HNMR (CD_3OD) δ 7.83 (dd, 2H), 7.65-7.56 (m, 3H), 7.18 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 7.8 Hz, 2H), 5.59 (d, J = 5.4 Hz, 1H), 4.96 (m, 1H), 4.15 (d, J = 9.9 Hz, 2H), 3.95-3.68 (m, 6H), 3.44 (dd, 2H), 3.16 (m, 2H), 2.99-2.84 (m, 4H), 2.48 (m, 1H), 2.02 (m, 1H), 1.6 (m, 1H), 1.37 (m, 1H), 0.93 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 17.45.

Example 9

Sulfonamide 9: A solution of dibenzylphosphonate 6 (0.24 g, 0.31 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.17 mL, 1.20 mmol) was added followed by the treatment of 4-cyanobenzenesulfonyl chloride (61.4 mg, 0.30 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide 9 (0.20 g, 77%, GS 191717) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 7.8 Hz, 2H), 7.36 (m, 10H), 7.11 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.2-4.9 (m, 5H), 4.8 (d, 1H), 4.2 (d, J = 9.9 Hz, 2H), 3.99 (m 1H), 3.94 (m, 3H), 3.7 (m, 2H), 3.48 (broad, s, 1H), 3.18-2.78 (m, 7H), 1.87 (m, 1H), 1.66-1.47 (m, 2H), 0.91 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.3..

Example 10

Sulfonamide 10: A solution of dibenzylphosphonate 6 (0.23 g, 0.29 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.16 mL, 1.17 mmol) was added followed by the treatment of 4-trifluoromethyl benzenesulfonyl chloride (72 mg, 0.29 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.13 g, 50%, GS 191479) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.1 Hz, 2H), 7.36 (m, 10H), 7.12 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.20-4.89 (m, 6H), 4.20 (d, J = 9.9 Hz, 2H), 3.95 (m, 1H), 3.86 (m, 3H), 3.71 (m, 2H), 3.19-2.78 (m, 7H), 1.86 (m, 1H), 1.65 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.3.

Example 11

Phosphonic Acid 11: To a solution of 10 (70 mg, 0.079 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (50 mg, 90%, GS 191480) as a white solid: ^{1}H NMR (CD_3OD) δ 8.03 (dd, 2H), 7.90 (dd, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.91 (d, J = 7.8 Hz, 2H), 5.59 (d, J = 5.7 Hz, 1H), 4.94 (m, 1H), 4.15 (d, J = 10.2 Hz, 2H), 3.94-3.72 (m, 6H), 3.48 (m, 1H), 3.2-3.1 (m, 3H), 3.0-2.9 (m, 2H), 2.47 (m, 1H), 2.06 (m, 1H), 1.56 (m, 1H), 1.37 (m, 1H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 17.5.

Example 12

Sulfonamide 12: A solution of dibenzylphosphonate 6 (0.23 g, 0.29 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.16 mL, 1.17 mmol) was added followed by the treatment of 4-fluorobenzenesulfonyl chloride (57 mg, 0.29 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.13 g, 55%, GS 191482) as a white solid: ^1H NMR ($CDCl_3$) δ 7.81 (m, 2H), 7.38 (m, 10H), 7.24 (m, 2H), 7.12 (d, J = 8.1 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.17 (m, 4H), 5.0 (m, 1H), 4.90 (d, 1H), 4.20 (d, J = 9.9 Hz, 2H), 3.97 (m, 1H), 3.86 (m, 3H), 3.73 (m, 2H), 3.6 (broad, s, 1H), 3.13 (m, 1H), 3.03-2.79 (m, 6H), 1.86 (m, 1H), 1.66-1.58 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.3.

Example 13

Phosphonic Acid 13: To a solution of 12 (70 mg, 0.083 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (49 mg, 90%, GS 191483) as a white solid: ^1H NMR (CD_3OD) δ 7.89 (m, 2H), 7.32 (m, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 8.1 Hz, 2H), 5.59 (d, J = 5.1 Hz, 1H), 4.94 (m, 1H), 4.16 (d, J = 9.9 Hz, 2H), 3.94 (m, 1H), 3.85-3.7 (m, 5H), 3.43 (dd, 1H), 3.15-2.87 (m, 5H), 2.48 (m, 1H), 2.03 (m, 1H), 1.59-1.36 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 17.5.

Example 14

Sulfonamide 14: A solution of dibenzylphosphonate 6 (0.21 g, 0.26 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.15 mL, 1.04 mmol) was added followed by the treatment of 4-trifluoromethoxybenzenesulfonyl chloride (69 mg, 0.26 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.17 g, 70%, GS 191508) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 9 Hz, 2H), 7.36 (m, 12H), 7.12 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.16 (m, 4H), 5.03 (m, 1H), 4.89 (d, 1H), 4.2 (d, J = 9.9 Hz, 2H), 3.97 (m, 1H), 3.85 (m, 3H), 3.7 (m, 2H), 3.59 (broad, s, 1H), 3.18 (m, 1H), 3.1-3.0 (m, 3H), 2.96-2.78 (m, 3H), 1.86 (m, 1H), 1.66-1.5 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{1}P NMR ($CDCl_3$) δ 20.3.

Example 15

Phosphonic Acid 15: To a solution of 14 (70 mg, 0.083 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (50 mg, 90%, GS 192041) as a white solid: ^{1}H NMR (CD_3OD) δ 7.95 (dd, 2H), 7.49 (dd, 2H), 7.17 (dd, 2H), 6.92 (dd, 2H), 5.58 (d, J = 5.4 Hz, 1H), 4.89 (m, 1H), 4.17 (d, J = 9 Hz, 2H), 3.9 (m, 1H), 3.82-3.7 (m, 5H), 3.44 (m, 1H), 3.19-2.9 (m, 5H), 2.48 (m, 1H), 2.0 (m, 1H), 1.6 (m, 1H), 1.35 (m, 1H), 0.93 (d, J = 6.0 Hz, 3H), 0.88 (d, J = 6.0 Hz, 3H); ^{31}P NMR (CD_3OD) δ 17.4.

Example 16

Sulfonamide 16: A solution of dibenzylphosphonate 6 (0.59 g, 0.76 mmol) in CH_2Cl_2 (2.0 mL) at 0°C was treated with trifluoroacetic acid (1.0 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction

mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.53 mL, 3.80 mmol) was added followed by the treatment of hydrogen chloride salt of 3-pyridinylsulfonyl chloride (0.17 g, 0.80 mmol, prepared according to Karaman, R. et al. J. Am. Chem. Soc. 1992, 114, 4889). The solution was stirred for 30 min at 0°C and warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.50 g, 80%, GS 273805) as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.0 (d, J = 1.5 Hz, 1H), 8.8 (dd, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.48 (m, 1H), 7.36 (m, 10H), 7.12 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.18 (m, 4H), 5.06 (m, 1H), 4.93 (d, 1H), 4.21 (d, J = 8.4 Hz, 2H), 3.97 (m, 1H), 3.86 (m, 3H), 3.74 (m, 2H), 3.2 (m, 1H), 3.1-2.83 (m, 5H), 2.76 (m, 1H), 1.88 (m, 1H), 1.62 (m, 2H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.3.

Example 17

Phosphonic Acid 17: To a solution of 16 (40 mg, 0.049 mmol) in MeOH (3 mL) and AcOH (1 mL) was added 10% Pd/C (10 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (28 mg, 90%, GS 273845) as a white solid: ^{1}H NMR (CD_3OD) δ 8.98 (s, 1H), 8.77 (broad, s, 1H), 8.25 (dd, 1H), 7.6 (m, 1H), 7.15 (m, 2H), 6.90 (m, 2H), 5.6 (d, J = 5.4 Hz, 1H), 4.98 (m, 1H), 4.15 (d, 2H), 3.97-3.7 (m, 6H), 3.45-2.89 (m, 6H), 2.50 (m, 1H), 2.0 (m, 1H), 1.6-1.35 (m, 2H), 0.9 (m, 6H).

Example 18

Sulfonamide 18: A solution of dibenzylphosphonate 6 (0.15 g, 0.19 mmol) in CH_2Cl_2 (0.60 mL) at 0°C was treated with trifluoroacetic acid (0.30 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the

ammonium triflate salt which was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C. Triethylamine (0.11 mL, 0.76 mmol) was added followed by the treatment of 4-formylbenzenesulfonyl chloride (43 mg, 0.21 mmol). The solution was stirred for 30 min at 0°C and warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.13 g, 80%, GS 278114) as a white solid: ^{1}H NMR ($CDCl_3$) δ 10.1 (s, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.94 (d, J = 8.1 Hz, 2H), 7.35 (m, 10H), 7.13 (m, J = 8.1 Hz, 2H), 6.82 (d, J = 8.1 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.17 (m, 4H), 5.06 (m, 1H), 4.93 (m, 1H), 4.2 (d, J = 9.9 Hz, 2H), 3.94 (m, 1H), 3.85 (m, 3H), 3.7 (m, 2H), 3.18-2.87 (m, 5H), 2.78 (m, 1H), 1.86 (m, 1H), 1.67-1.58 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.3.

Example 19

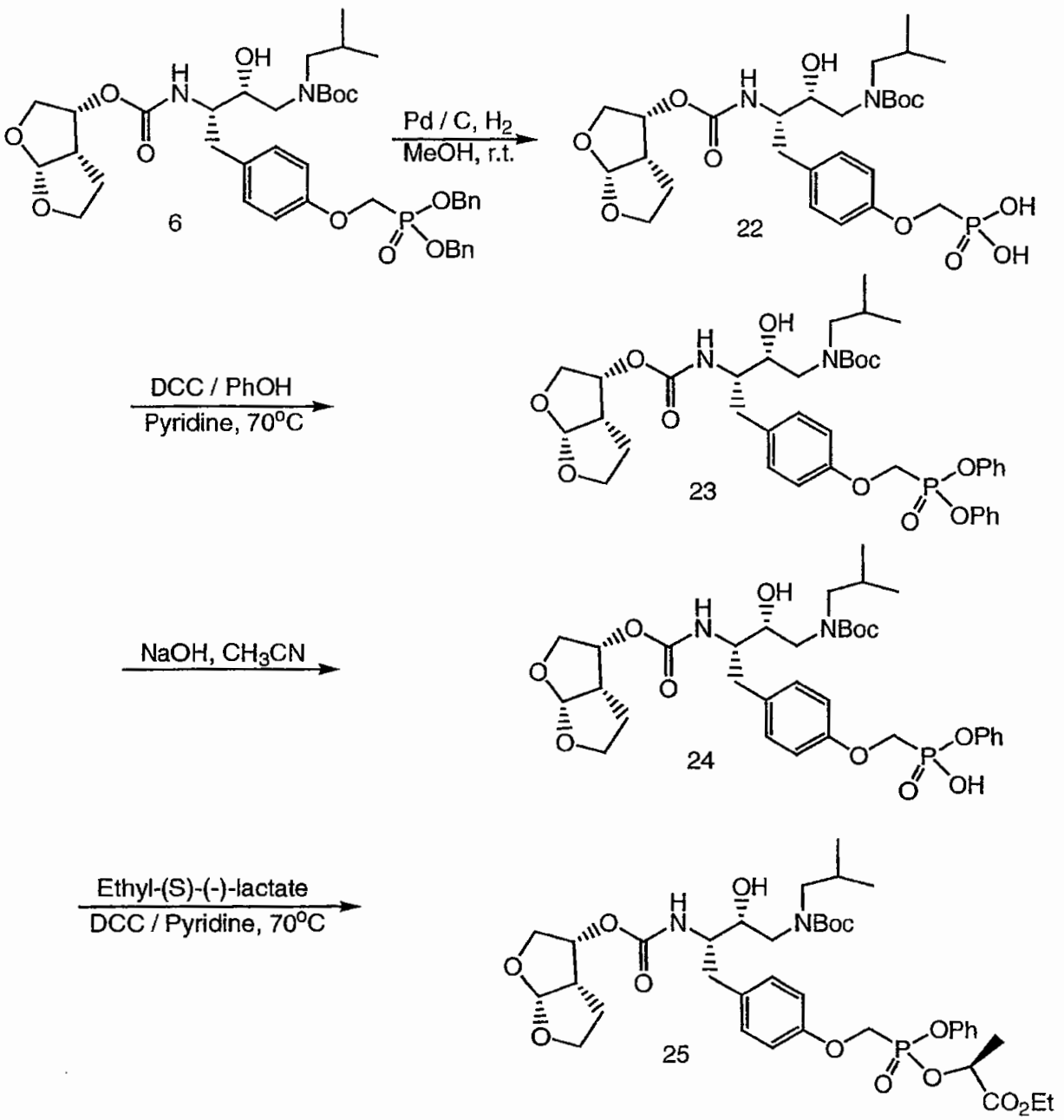
Phosphonic Acid 19: To a solution of 18 (0.12 g, 0.15 mmol) in EtOAc (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (93 mg, 95%) as a white solid.

Example 20

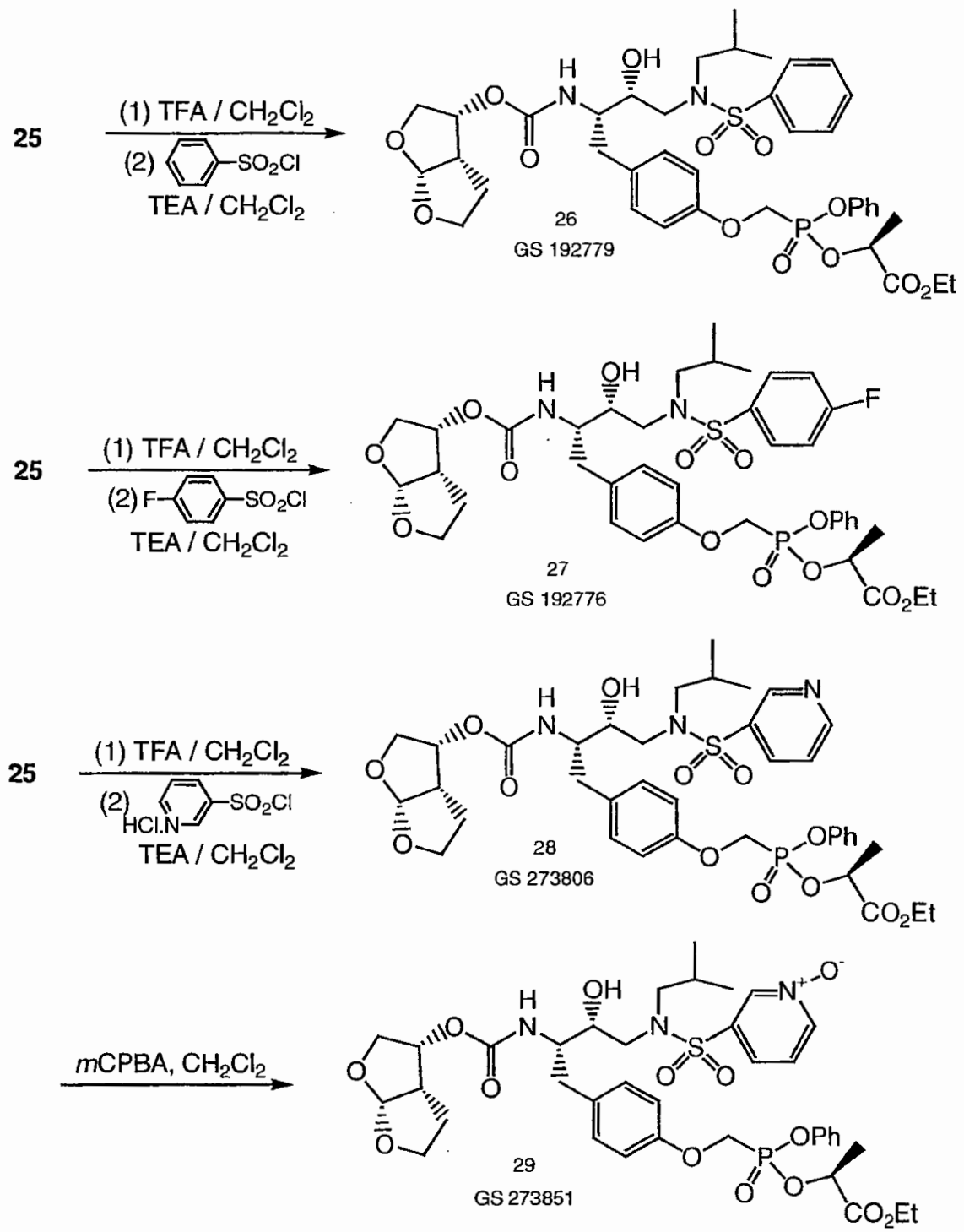
Phosphonic Acids 20 and 21: Compound 19 (93 mg, 0.14 mmol) was dissolved in CH_3CN (2 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 0.28 g, 1.4 mmol) was added. The reaction mixture was heated to reflux for 1 h, cooled to room temperature and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a semi-solid which was dissolved in EtOAc (2 mL). Morpholine (60 µL, 0.9 mmol), AcOH (32 µL, 0.56 mmol), and $NaBH_3CN$ (17 mg, 0.28 mmol) were added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with H_2O, stirred for 2 h, filtered, and concentrated. The crude product was purified by HPLC to give the phosphonic acid 20 (10 mg, GS 278118) as a white solid: ^{1}H NMR (CD_3OD) δ 7.80 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 7.5 Hz, 2H), 7.17 (d, J = 7.8 Hz, 2H), 6.91 (d, J = 7.5 Hz, 2H), 5.59

(d, J = 5.1 Hz, 1H), 5.06 (m, 1H), 4.7 (s, 2H), 4.15 (d, J = 10.2 Hz, 2H), 3.92 (m, 1H), 3.82-3.7 (m, 5H), 3.43 (dd, 1H), 3.11-2.89 (m, 6H), 2.50 (m, 1H), 2.0 (m, 1H), 1.6-1.35 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 17.3. Phosphonic acid 21 (15 mg, GS 278117) as a white solid: ^{1}H NMR (CD_3OD) δ 7.8-7.7 (m, 4H), 7.20 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 5.62 (d, J = 5.1 Hz, 1H), 5.00 (m, 1H), 4.42 (s, 2H), 4.20 (dd, 2H), 3.98-3.68 (m, 9H), 3.3-2.92 (m, 11H), 2.6 (m, 1H), 2.0 (m, 1H), 1.6 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CD_3OD) δ 16.2.

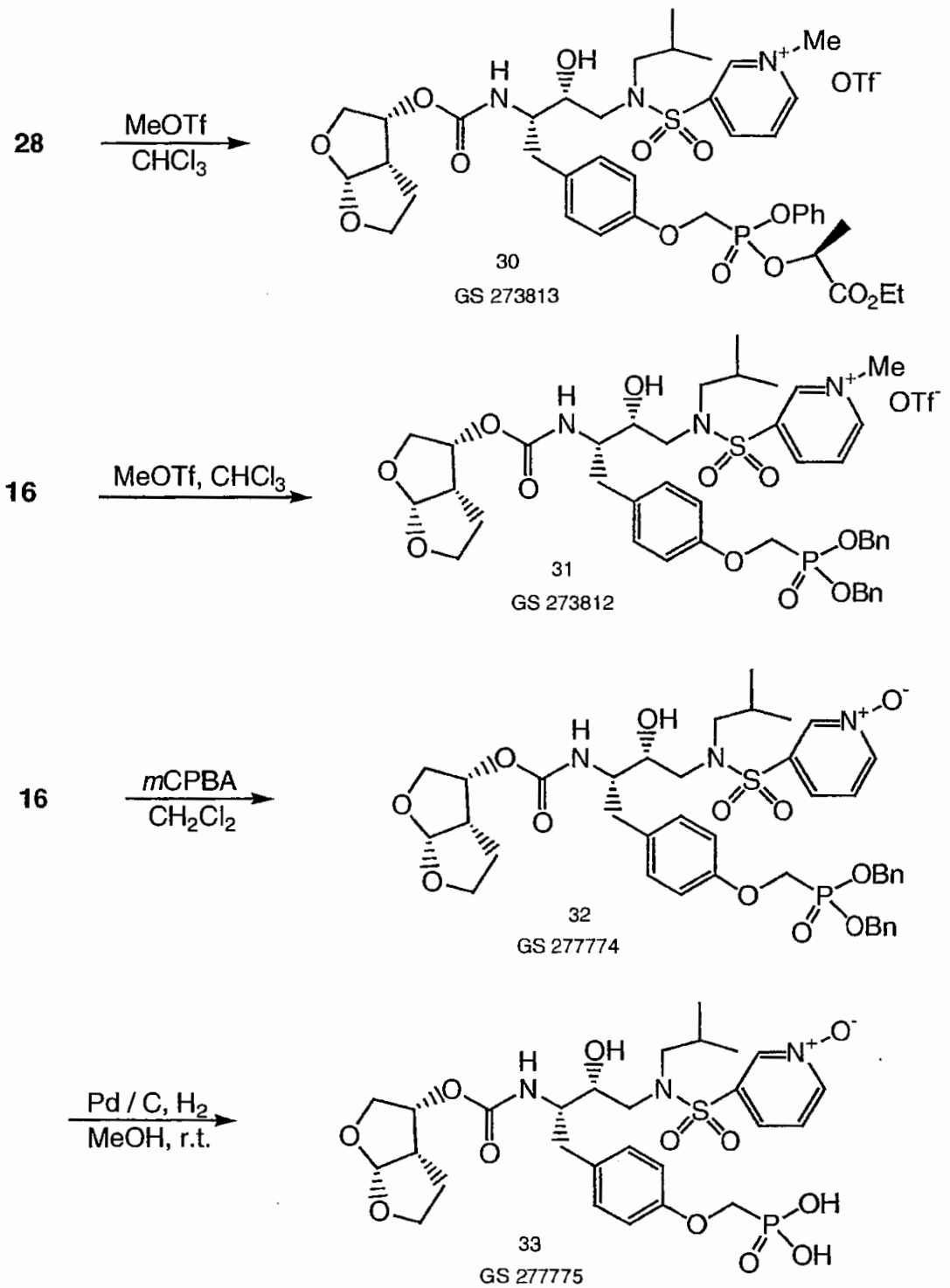
Scheme 6


Pd / C, H2
MeOH, r.t.
DCC / PhOH
Pyridine, 70°C
NaOH, CH3CN
Ethyl-(S)-(-)-lactate
DCC / Pyridine, 70°C
6
22
23
24
25

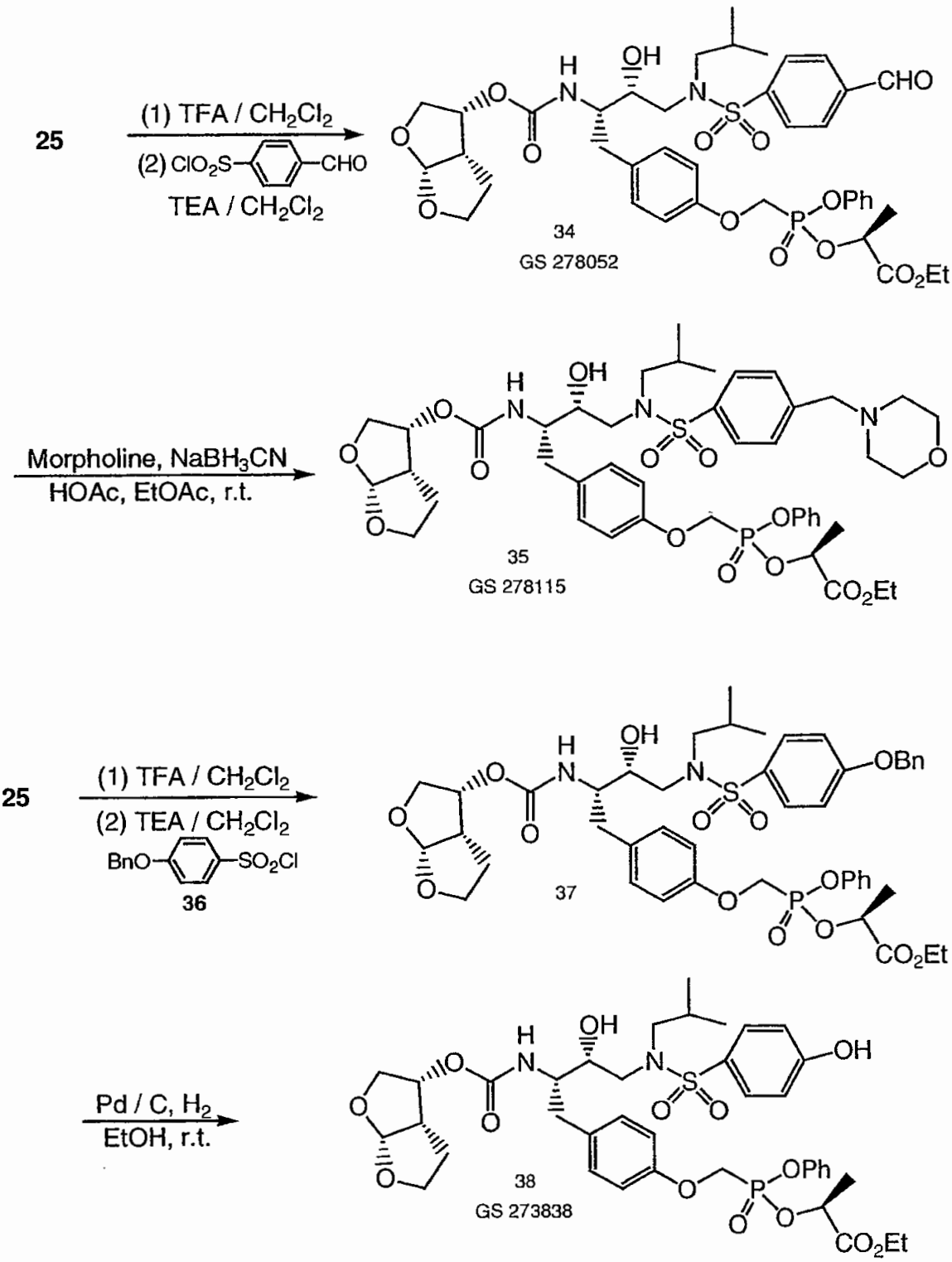
Scheme 7


25
(1) TFA / CH2Cl2
(2) SO2Cl
TEA / CH2Cl2
26
GS 192779
25
(1) TFA / CH2Cl2
(2) F SO2Cl
TEA / CH2Cl2
27
GS 192776
25
(1) TFA / CH2Cl2
(2) HCl.N SO2Cl
TEA / CH2Cl2
28
GS 273806
mCPBA, CH2Cl2
29
GS 273851

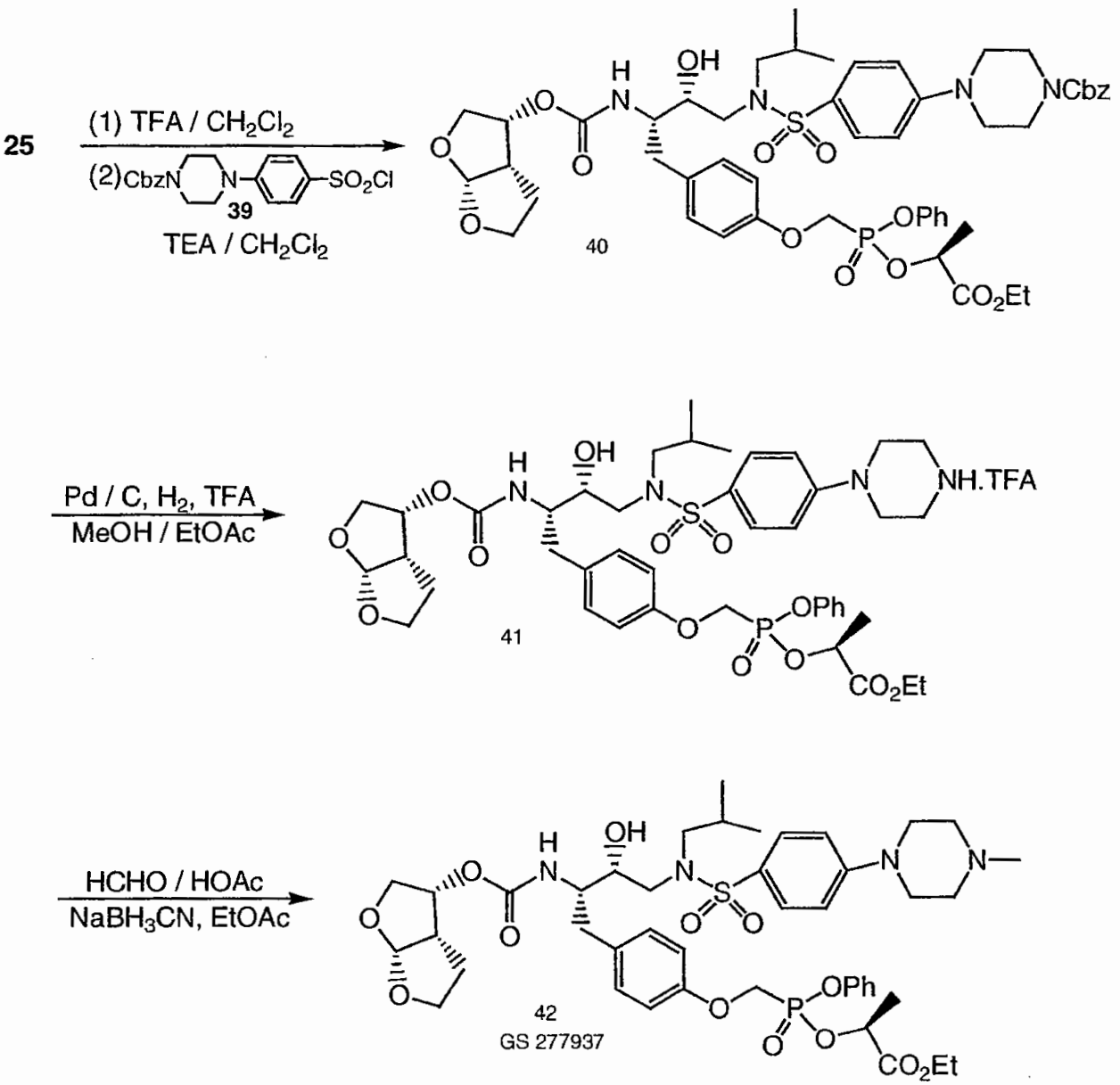
Scheme 8


28
MeOTf
CHCl3
30
GS 273813
16
MeOTf, CHCl3
31
GS 273812
16
mCPBA
CH2Cl2
32
GS 277774
Pd / C, H2
MeOH, r.t.
33
GS 277775

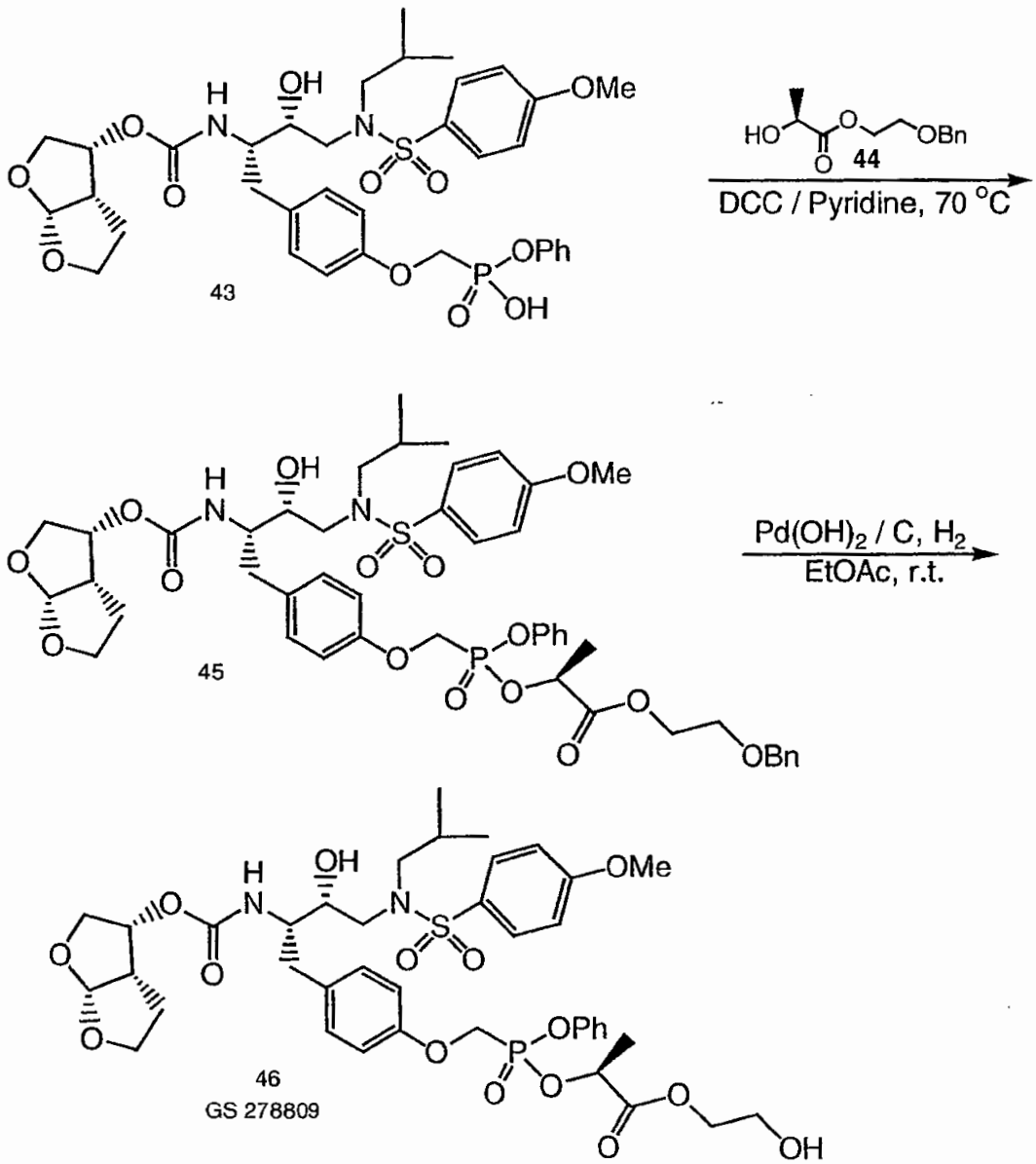
Scheme 9


25
(1) TFA / CH2Cl2
(2) ClO2S-C6H4-CHO
TEA / CH2Cl2
34
GS 278052
Morpholine, NaBH3CN
HOAc, EtOAc, r.t.
35
GS 278115
25
(1) TFA / CH2Cl2
(2) TEA / CH2Cl2
BnO-C6H4-SO2Cl
36
37
Pd / C, H2
EtOH, r.t.
38
GS 273838

Scheme 10


(1) TFA / CH2Cl2
(2)CbzN
SO2Cl
39
TEA / CH2Cl2
40
NCbz
OPh
CO2Et
Pd / C, H2, TFA
MeOH / EtOAc
41
NH.TFA
HCHO / HOAc
NaBH3CN, EtOAc
42
GS 277937

Scheme 11



Example 21

Phosphonic Acid 22: To a solution of dibenzylphosphonate 6 (5.00 g, 6.39 mmol) in EtOH (100 mL) was added 10% Pd/C (1.4 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (3.66 g, 95%) as a white solid.

Example 22

Diphenylphosphonate 23: A solution of 22 (3.65 g, 6.06 mmol) and phenol (5.70 g, 60.6 mmol) in pyridine (30 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (5.00 g, 24.24 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off. The filtrate was concentrated and dissolved in CH_3CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the diphenylphosphonate (2.74 g, 60%) as a white solid.

Example 23

Monophosphonic Acid 24: To a solution of 23 (2.74 g, 3.63 mmol) in CH_3CN (40 mL) at 0°C was added 1 N NaOH (9.07 mL, 9.07 mmol). The reaction mixture was stirred at 0°C for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (2.34 g, 95%) as a white solid.

Example 24

Monophospholactate 25: A solution of 24 (2.00 g, 2.95 mmol) and ethyl-(S)-(-)-lactate (1.34 mL, 11.80 mmol) in pyridine (20 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (2.43 g, 11.80 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H_2O, saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (1.38 g, 60%) as a white solid.

Example 25

Monophospholactate 26: A solution of 25 (0.37 g, 0.48 mmol) in CH_2Cl_2 (0.80 mL) at 0°C was treated with trifluoroacetic acid (0.40 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was

diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.27 mL, 1.92 mmol) was added followed by the treatment of benzenesulfonyl chloride (84 mg, 0.48 mmol). The solution was stirred for 30 min at 0°C and then warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and 0.2 N HCl. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.33 g, 85%, GS 192779, 1:1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.78 (dd, 2H), 7.59 (m, 3H), 7.38-7.18 (m, 7H), 6.93 (dd, 2H), 5.66 (m, 1H), 5.18-4.93 (m, 3H), 4.56-4.4 (m, 2H), 4.2 (m, 2H), 4.1-3.7 (m, 6H), 3.17 (m, 1H), 3.02-2.8 (m, 6H), 1.84 (m, 1H), 1.82-1.5 (m, 5H), 1.27 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.4, 15.3.

Example 26

Monophospholactate 27: A solution of 25 (0.50 g, 0.64 mmol) in CH_2Cl_2 (1.0 mL) at 0°C was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (4 mL) and cooled to 0°C. Triethylamine (0.36 mL, 2.56 mmol) was added followed by the treatment of 4-fluorobenzenesulfonyl chloride (0.13 g, 0.64 mmol). The solution was stirred for 30 min at 0°C and then warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and 0.2 N HCl. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.44 g, 81%, GS 192776, 3/2 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 2H), 7.38-7.15 (m, 9H), 6.92 (m, 2H), 5.66 (m, 1H), 5.2-4.9 (m, 3H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 4.1-3.7 (m, 6H), 3.6 (broad, s, 1H), 3.17 (m, 1H), 3.02-2.75 (m, 6H), 1.85 (m, 1H), 1.7-1.5 (m, 5H), 1.26 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.3, 15.2.

Example 27

Monophospholactate 28: A solution of 25 (0.50 g, 0.64 mmol) in CH_2Cl_2 (1.0 mL) at 0°C was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.45 mL, 3.20 mmol) was added followed by the treatment of hydrogen chloride salt of 3-pyridinylsulfonyl chloride (0.14 g, 0.65 mmol). The solution was stirred for 30 min at 0°C and then warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and H_2O. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.41 g, 79%, GS 273806, 1:1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.0 (s, 1H), 8.83 (dd, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.5 (m, 1H), 7.38-7.15 (m, 7H), 6.92 (m, 2H), 5.66 (m, 1H), 5.18-4.95 (m, 3H), 4.6-4.41 (m, 2H), 4.2 (m, 2H), 4.0 (m, 1H), 3.95-3.76 (m, 6H), 3.23-2.8 (m, 7H), 1.88 (m, 1H), 1.7-1.5 (m, 5H), 1.26 (m, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.3, 15.3.

Example 28

Monophospholactate 29: A solution of compound 28 (0.82 g, 1.00 mmol) in CH_2Cl_2 (8 mL) at 0°C was treated with *m*CPBA (1.25 eq). The solution was stirred for 1 h at 0°C and then warmed to room temperature for an additional 6 h. The reaction mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.59 g, 70%, GS 273851, 1:1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.63 (dd, 1H), 8.3 (dd, 1H), 7.57 (m, 1H), 7.44 (m, 1H), 7.38-7.13 (m, 7H), 6.92 (m, 2H), 5.66 (m, 1H), 5.2-5.05 (m, 2H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 4.0-3.73 (m, 6H), 3.2 (m, 2H), 3.0 (m, 4H), 2.77 (m, 1H), 1.92 (m, 1H), 1.7-1.49 (m, 5H), 1.26 (m, 3H), 0.91 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 17.3, 15.3.

Example 29

Monophospholactate 30: A solution of compound 28 (71 mg, 0.087 mmol) in $CHCl_3$ (1 mL) was treated with MeOTf (18 mg, 0.11 mmol). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated and co-evaporated with toluene (2 x), $CHCl_3$ (2 x) and dried under vacuum to give the monophospholactate (81 mg, 95%, GS 273813, 1:1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.0 (dd, 1H), 8.76 (m, 2H), 8.1 (m, 1H), 7.35-7.1 (m, 7H), 6.89 (m, 2H), 5.64 (m, 1H), 5.25-5.0 (m, 3H), 4.6-4.41 (m, 5H), 4.2 (m, 2H), 3.92-3.72 (m, 6H), 3.28 (m, 2H), 3.04-2.85 (m, 3H), 2.62 (m, 1H), 1.97 (m, 1H), 1.62-1.5 (m, 5H), 1.25 (m, 3H), 0.97 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 17.4, 15.4.

Example 30

Dibenzylphosphonate 31: A solution of compound 16 (0.15 g, 0.18 mmol) in $CHCl_3$ (2 mL) was treated with MeOTf (37 mg, 0.23 mmol). The solution was stirred at room temperature for 2 h. The reaction mixture was concentrated and co-evaporated with toluene (2 x), $CHCl_3$ (2 x) and dried under vacuum to give the dibenzylphosphonate (0.17 g, 95%, GS 273812) as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.0 (dd, 1H), 8.73 (m, 2H), 8.09 (m, 1H), 7.35 (m, 10H), 7.09 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.1 Hz, 2H), 5.61 (d, J = 4.2 Hz, 1H), 5.2-4.96 (m, 6H), 4.54 (s, 3H), 4.2 (dd, 2H), 3.92-3.69 (m, 6H), 3.3 (m, 2H), 3.04-2.6 (m, 5H), 1.97 (m, 1H), 1.6 (m, 2H), 0.98 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 20.4.

Example 31

Dibenzylphosphonate 32: A solution of compound 16 (0.15 g, 0.18 mmol) in CH_2Cl_2 (3 mL) at 0°C was treated with *m*CPBA (1.25 eq). The solution was stirred for 1 h at 0°C and then warmed to room temperature overnight. The reaction mixture was partitioned between 10% 2-propanol/CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate (0.11 g, 70%, **GS 277774**) as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.64 (m, 1H), 8.27 (d, J = 6.9 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.36 (m, 11H), 7.10 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.22-5.02 (m, 6H), 4.21 (dd, 2H), 3.99-3.65 (m, 6H), 3.2 (m, 2H), 3.03-2.73 (m, 5H), 1.90 (m, 1H), 1.66-1.56 (m, 2H), 0.91 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 20.3.

Example 32

Phosphonic Acid 33: To a solution of dibenzylphosphonate 32 (0.1 g, 0.12 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 1 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and purified by HPLC to give the phosphonic acid (17 mg, **GS 277775**) as a white solid: ^{1}H NMR (CD_3OD) δ 8.68 (s, 1H), 8.47 (d, J = 6.0 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.68 (m, 1H), 7.14 (m, 2H), 6.90 (d, J = 7.8 Hz, 2H), 5.58 (d, J = 5.4 Hz, 1H), 5.00 (m, 1H), 4.08 (d, J = 9.9 Hz, 2H), 3.93-3.69 (m, 6H), 3.4-2.9 (m, 7H), 2.5 (m, 1H), 2.04 (m, 1H), 1.6-1.35 (m, 2H), 0.92 (m, 6H); ^{31}P NMR (CD_3OD) δ 15.8.

Example 33

Monophospholactate 34: A solution of 25 (2.50 g, 3.21 mmol) in CH_2Cl_2 (5.0 mL) at 0°C was treated with trifluoroacetic acid (2.5 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (30 mL) and cooled to 0°C. Triethylamine (1.79 mL, 12.84 mmol) was added followed by the treatment of 4-formylbenzenesulfonyl chloride (0.72 g, 3.53 mmol) and the solution was stirred at 0°C for 1 h. The product was partitioned between CH_2Cl_2 and 5% HCl. The organic phase was washed with H_2O, saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (2.11 g, 77%, GS 278052, 1:1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 10.12 (s, 1H), 8.05 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 7.5 Hz, 2H), 7.38-7.15 (m, 7H), 6.94 (m, 2H), 5.67 (m, 1H), 5.18-4.91 (m, 3H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 4.0-3.69 (m, 6H), 3.57 (broad, s, 1H), 3.19-2.8 (m, 7H), 1.87 (m, 1H), 1.69-1.48 (m, 5H), 1.25 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.3, 15.2.

Example 34

Monophospholactate 35: A solution of 34 (0.60 g, 0.71 mmol) and morpholine (0.31 mL, 3.54 mmol) in EtOAc (8 mL) was treated with HOAc (0.16 mL, 2.83 mmol) and $NaBH_3CN$ (89 mg, 1.42 mmol). The reaction mixture was stirred at room temperature for 4 h. The

product was partitioned between EtOAc and H_2O. The organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (6% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.46 g, 70%, GS 278115, 1:1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.38-7.15 (m, 7H), 6.92 (m, 2H), 5.66 (m, 1H), 5.2-5.0 (m, 2H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 3.97-3.57 (m, 12H), 3.2-2.78 (m, 7H), 2.46 (broad, s, 4H), 1.87 (m, 1H), 1.64-1.5 (m, 5H), 1.25 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.3, 15.3.

Example 35

Monophospholactate 37: A solution of 25 (0.50 g, 0.64 mmol) in CH_2Cl_2 (2.0 mL) at 0°C was treated with trifluoroacetic acid (1 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.45 mL, 3.20 mmol) was added followed by the treatment of 4-benzyloxybenzenesulfonyl chloride (0.18 g, 0.64 mmol, prepared according to Toja, E. et al. Eur. J. Med. Chem. 1991, 26, 403). The solution was stirred for 30 min at 0°C and then warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.51 g, 85%) as a white solid.

Example 36

Monophospholactate 38: To a solution of 37 (0.48 g, 0.52 mmol) in EtOH (15 mL) was added 10% Pd/C (0.10 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel (5% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.38 g, 88%, GS 273838, 1:1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.86 (dd, 1H), 7.42-7.25 (m, 9H), 6.91 (m, 4H), 5.73 (d, J = 5.1 Hz, 1H), 5.42 (m, 1H), 5.18 (m, 2H), 4.76-4.31 (m, 2H), 4.22 (m, 2H), 4.12-3.75 (m, 6H), 3.63 (broad, s, 1H), 3.13 (m, 3H), 2.87 (m, 1H), 2.63

(m, 1H), 2.4 (m, 1H), 2.05 (m, 2H), 1.9 (m, 1H), 1.8(m, 1H), 1.6 (m, 3H), 1.25 (m, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.1, 15.7.

Example 37

Monophospholactate 40: A solution of 25 (0.75 g, 0.96 mmol) in CH_2Cl_2 (2.0 mL) at 0°C was treated with trifluoroacetic acid (1 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (4 mL) and cooled to 0°C. Triethylamine (0.67 mL, 4.80 mmol) was added followed by the treatment of 4-(4'-benzyloxycarbonyl piperazinyl)benzenesulfonyl chloride (0.48 g, 1.22 mmol, prepared according to Toja, E. et al. Arzneim. Forsch. 1994, 44, 501). The solution was stirred at 0°C for 1 h and then warmed to room temperature for 30 min. The product was partitioned between 10% 2-propanol/CH_2Cl_2 and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.63 g, 60%) as a white solid.

Example 38

Monophospholactate 41: To a solution of 40 (0.62 g, 0.60 mmol) in MeOH (8 mL) and EtOAc (2 mL) was added 10% Pd/C (0.20 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was treated with 1.2 equivalent of TFA, co-evaporated with $CHCl_3$ and dried under vacuum to give the monophospholactate (0.55 g, 90%) as a white solid.

Example 39

Monophospholactate 42: A solution of 41 (0.54 g, 0.53 mmol) and formaldehyde (0.16 mL, 5.30 mmol) in EtOAc (10 mL) was treated with HOAc (0.30 mL, 5.30 mmol) and $NaBH_3CN$ (0.33 g, 5.30 mmol). The reaction mixture was stirred at room temperature overnight. The product was partitioned between EtOAc and H_2O. The organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column

chromatography on silica gel (6% 2-propanol/CH_2Cl_2) to give the monophospholactate (97.2 mg, 20%, GS 277937, 1:1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 9.0 Hz, 2H), 7.38-7.17 (m, 7H), 6.95-6.88 (m, 4H), 5.67 (m, 1H), 5.2-4.96 (m, 2H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 3.97-3.64 (m, 8H), 3.49-3.37 (m, 4H), 3.05-2.78 (m, 12H), 1.88-1.62 (m, 3H), 1.58 (m, 3H), 1.25 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.3, 15.3.

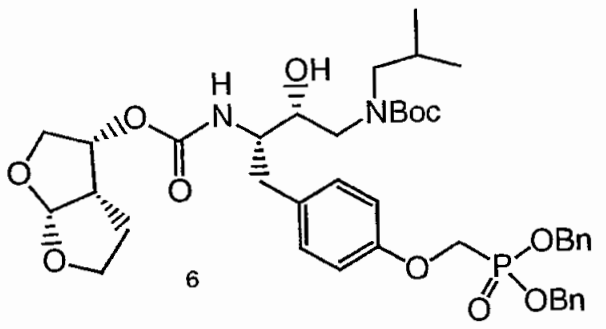
Example 40

Monophospholactate 45: A solution of 43 (0.12 g, 0.16 mmol) and lactate 44 (0.22 g, 1.02 mmol) in pyridine (1 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (0.17 g, 0.83 mmol) was added. The reaction mixture was stirred at 70°C for 4 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H_2O, saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (45 mg, 26%) as a white solid.

Example 41

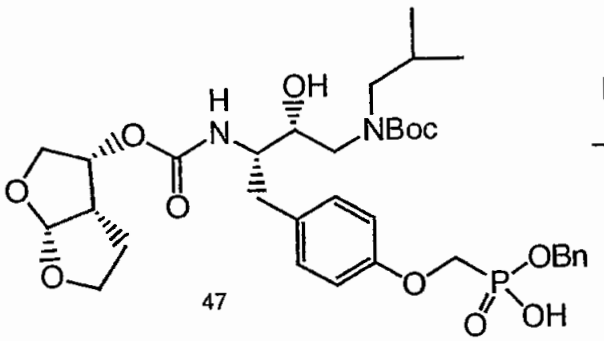
Alcohol 46: To a solution of 45 (40 mg, 0.042 mmol) in EtOAc (2 mL) was added 20% $Pd(OH)_2$/C (10 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 3 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and the product was dried under vacuum to give the alcohol (33 mg, 90%, GS 278809, 3/2 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.39-7.15 (m, 7H), 7.02-6.88 (m, 4H), 5.66 (d, J = 4.5 Hz, 1H), 5.13-5.02 (m, 2H), 4.54-4.10 (m, 4H), 4.00-3.69 (m, 11H), 3.14 (m, 1H), 3.02-2.77 (m, 6H), 1.85-1.6 (m, 6H), 0.94 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.4, 15.9.

Scheme 12



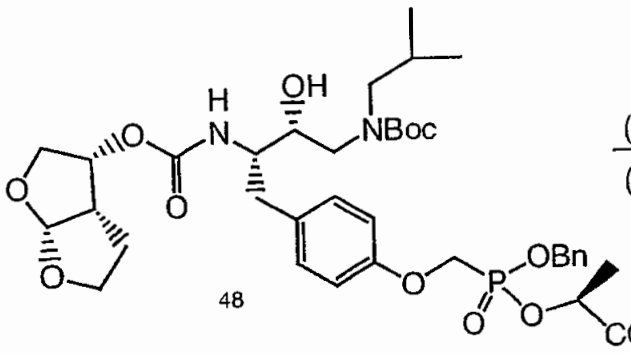
6

DABCO, toluene
reflux, 2 h



47

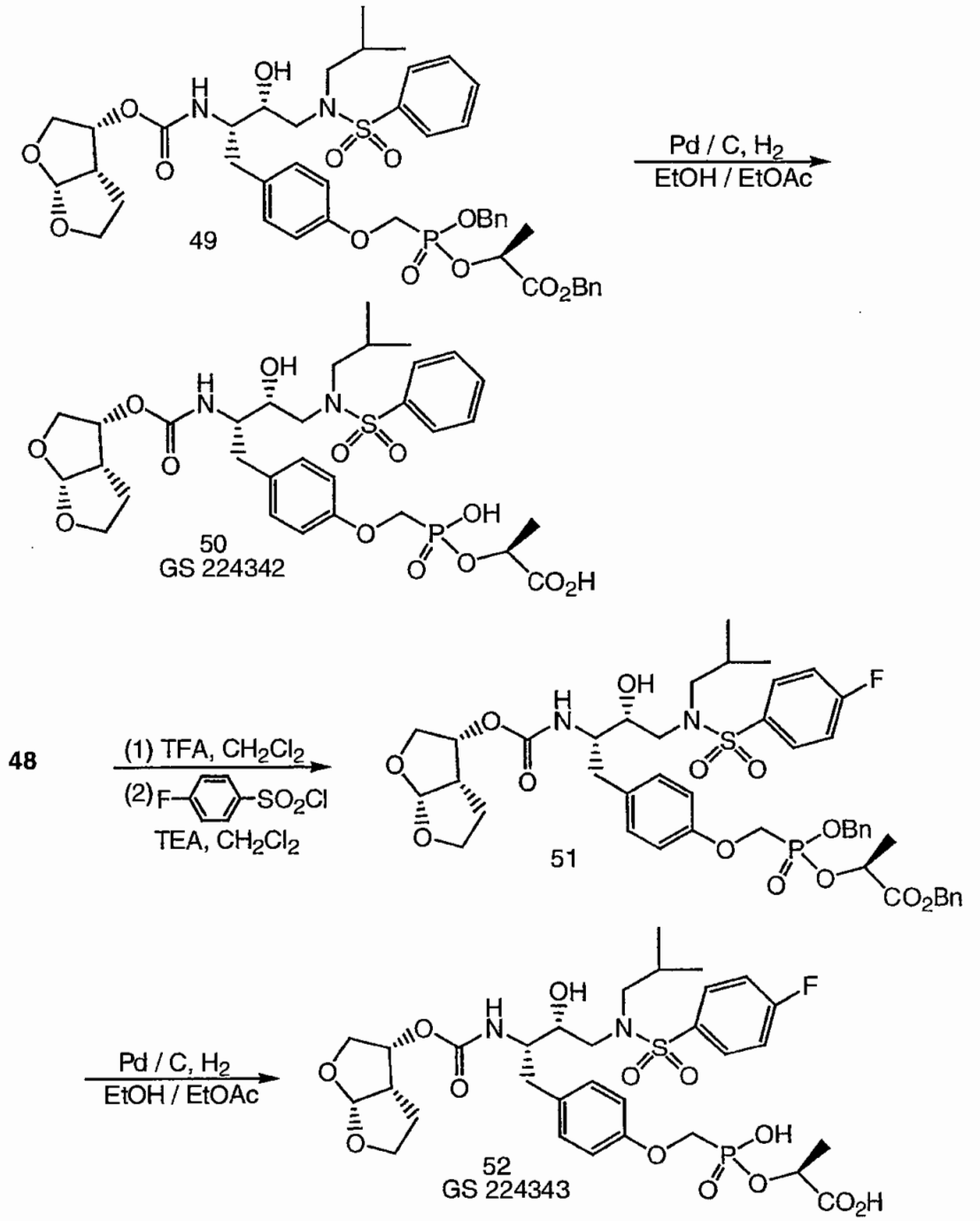
Benzyl-(S)-(-)-lactate
PyBop, DIPEA, DMAP
DMF, r.t.



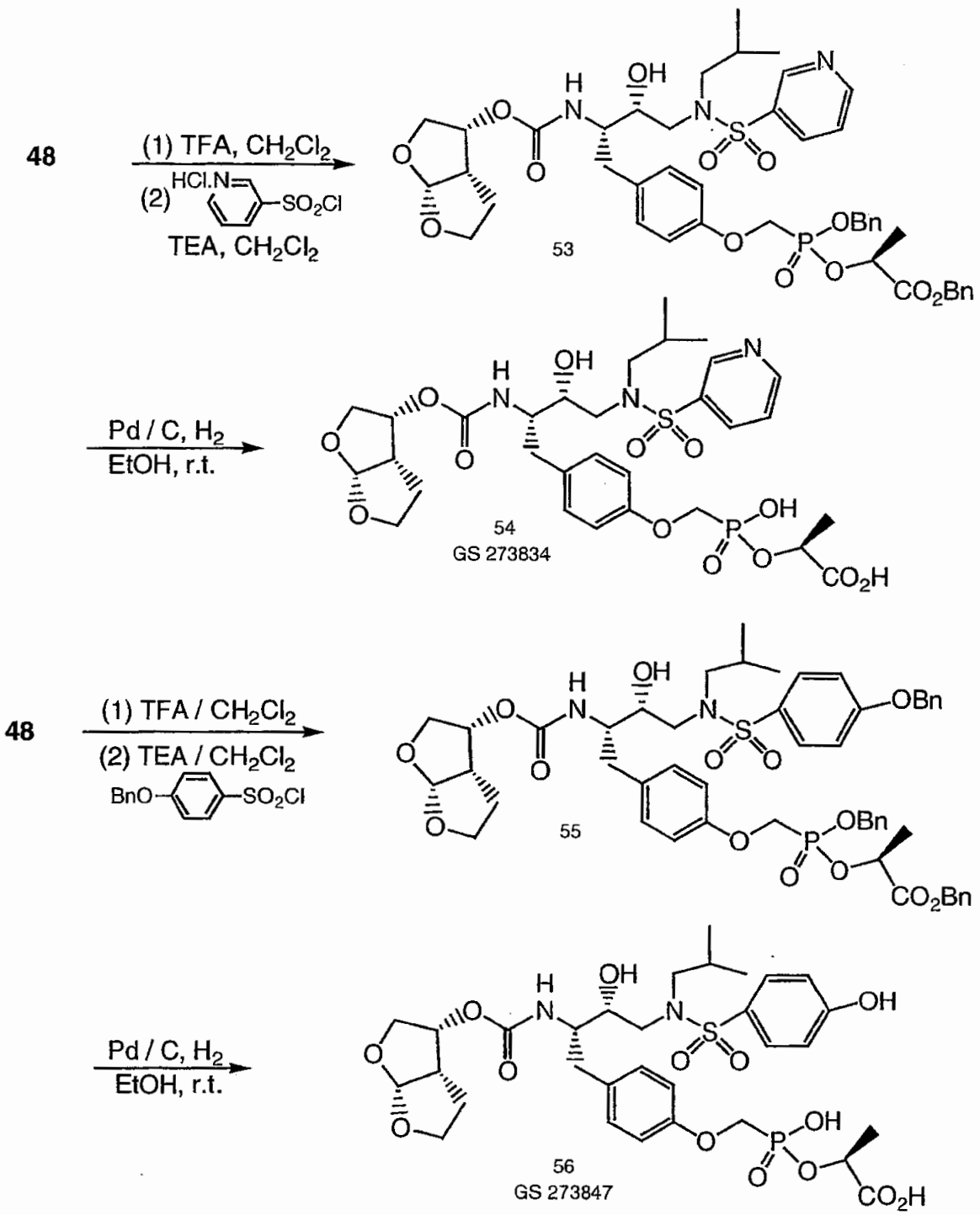
48

(1) TFA, CH_2Cl_2
(2) SO_2Cl
TEA, CH_2Cl_2

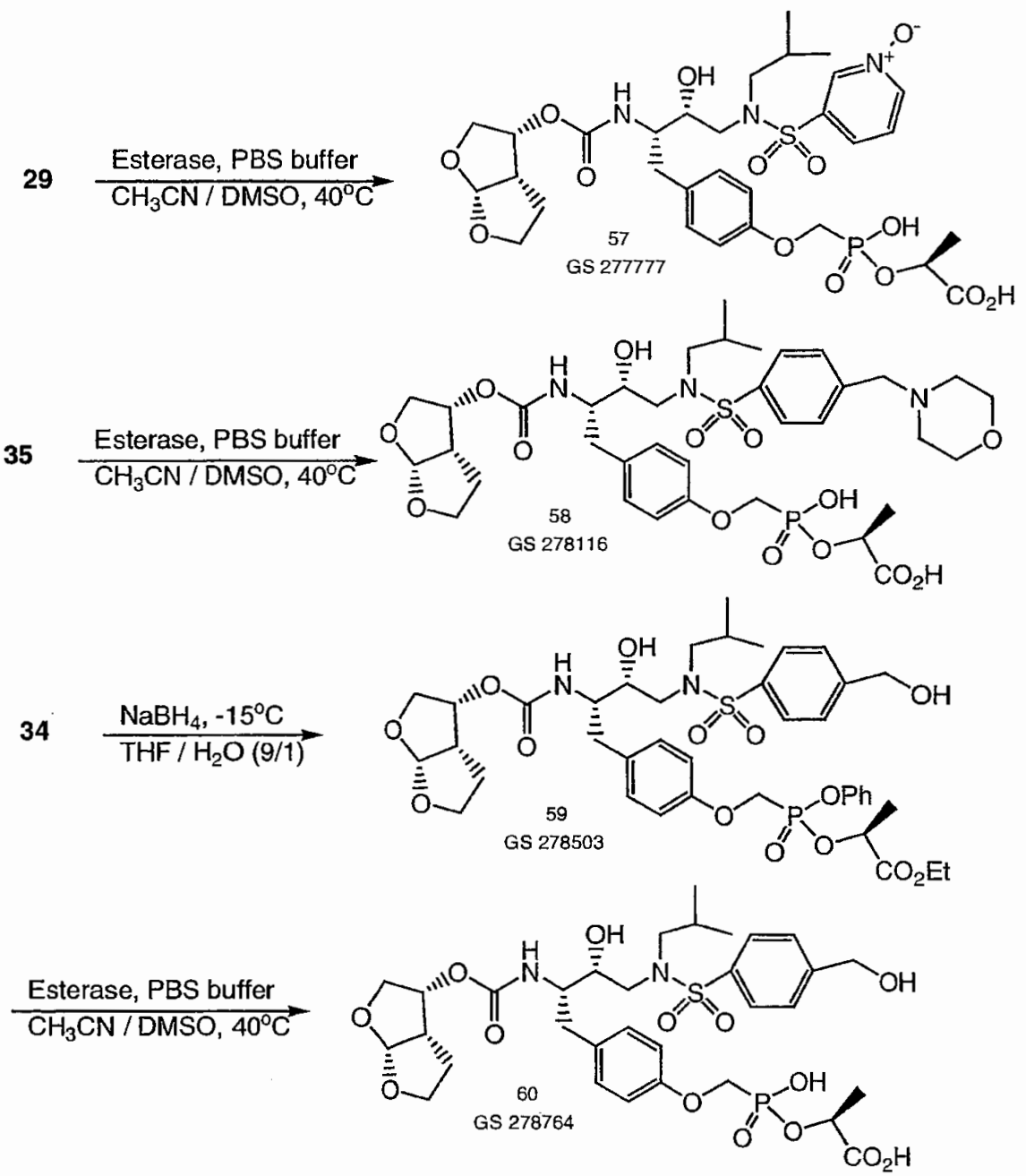
Scheme 13


Pd / C, H2
EtOH / EtOAc
49
50
GS 224342
48
(1) TFA, CH2Cl2
(2) F-SO2Cl
TEA, CH2Cl2
51
Pd / C, H2
EtOH / EtOAc
52
GS 224343

Scheme 14


48
(1) TFA, CH2Cl2
(2) HCl.N SO2Cl
TEA, CH2Cl2
53
Pd / C, H2
EtOH, r.t.
54
GS 273834
48
(1) TFA / CH2Cl2
(2) TEA / CH2Cl2
BnO SO2Cl
55
Pd / C, H2
EtOH, r.t.
56
GS 273847

Scheme 15



Example 42

Monobenzylphosphonate 47: A solution of 6 (2.00 g, 2.55 mmol) and DABCO (0.29 g, 2.55 mmol) in toluene (10 mL) was heated to reflux for 2 h. The solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with H_2O, saturated NaCl, dried with Na_2SO_4, filtered, and concentrated.

The crude product was dried under vacuum to give the monobenzylphosphonate (1.68 g, 95%) as a white solid.

Example 43

Monophospholactate 48: To a solution of 47 (2.5 g, 3.61 mmol) and benzyl-(S)-(-)-lactate (0.87 mL, 5.42 mmol) in DMF (12 mL) was added PyBop (2.82 g, 5.42 mmol) and *N,N*-diisopropylethylamine (2.51 mL, 14.44 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated. The residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with H_2O, saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (1.58 g, 51%) as a white solid.

Example 44

Monophospholactate 49: A solution of 48 (0.30 g, 0.35 mmol) in CH_2Cl_2 (0.6 mL) at 0°C was treated with trifluoroacetic acid (0.3 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C. Triethylamine (0.20 mL, 1.40 mmol) was added followed by the treatment of benzenesulfonyl chloride (62 mg, 0.35 mmol). The solution was stirred at 0°C for 30 min and then warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.17 g, 53%) as a white solid.

Example 45

Metabolite X 50: To a solution of 49 (80 mg, 0.09 mmol) in EtOH (6 mL) and EtOAc (2 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 8 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with $CHCl_3$ and dried under vacuum to give the metabolite X (61 mg, 95%, GS 224342) as a white solid: ^{1}H NMR (CD_3OD) δ 7.83 (d, J = 6.9 Hz, 2H), 7.65-7.58 (m, 3H), 7.18 (d, J = 7.8 Hz, 2H), 6.90 (d, J = 7.8 Hz, 2H), 5.59

(d, J = 4.8 Hz, 1H), 5.0 (m, 1H), 4.27 (d, J = 10.2 Hz, 2H), 3.95-3.68 (m, 6H), 3.45 (dd, 1H), 3.18-2.84 (m, 6H), 2.50 (m, 1H), 2.02 (m, 1H), 1.6-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD), δ 18.0.

Example 46

Monophospholactate 51: A solution of 48 (0.28 g, 0.33 mmol) in CH_2Cl_2 (0.6 mL) at 0°C was treated with trifluoroacetic acid (0.3 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C. Triethylamine (0.18 mL, 1.32 mmol) was added followed by the treatment of 4-fluorobenzenesulfonyl chloride (64 mg, 0.33 mmol). The solution was stirred at 0°C for 30 min and then warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.16 g, 52%) as a white solid.

Example 47

Metabolite X 52: To a solution of 51 (80 mg, 0.09 mmol) in EtOH (6 mL) and EtOAc (2 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 8 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with $CHCl_3$ and dried under vacuum to give the metabolite X (61 mg, 95%, GS 224343) as a white solid: ^{1}H NMR (CD_3OD) δ 7.9 (dd, 2H), 7.32 (m, 2H), 7.18 (dd, 2H), 6.90 (dd, 2H), 5.59 (d, J = 5.4 Hz, 1H), 5.0 (m, 1H), 4.28 (d, J = 10.2 Hz, 2H), 3.95-3.72 (m, 6H), 3.44 (dd, 1H), 3.15-2.85 (m, 6H), 2.5 (m, 1H), 2.02 (m, 1H), 1.55-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H). ^{31}P NMR (CD_3OD) δ 18.2.

Example 48

Monophospholactate 53: A solution of 48 (0.20 g, 0.24 mmol) in CH_2Cl_2 (0.6 mL) at 0°C was treated with trifluoroacetic acid (0.3 mL). The solution was stirred for 30 min at 0°C and

then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C. Triethylamine (0.16 mL, 1.20 mmol) was added followed by the treatment of hydrogen chloride salt of 3-pyridinysulfonyl chloride (50 mg, 0.24 mmol). The solution was stirred at 0°C for 30 min and then warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and H_2O. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.11 g, 53%) as a white solid.

Example 49

Metabolite X 54: To a solution of 53 (70 mg, 0.09 mmol) in EtOH (5 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 5 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with $CHCl_3$ and dried under vacuum to give the metabolite X (53 mg, 95%, GS 273834) as a white solid: ^{1}H NMR (CD_3OD) δ 8.99 (s, 1H), 8.79 (d, J = 4.2 Hz, 1H), 8.29 (d, J = 7.5 Hz, 1H), 7.7 (m, 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 7.8 Hz, 2H), 5.59 (d, J = 5.4 Hz, 1H), 5.0 (m, 1H), 4.28 (d, J = 9.9 Hz, 2H), 3.97-3.70 (m, 6H), 3.44 (dd, 1H), 3.17-2.85 (m, 6H), 2.5 (m, 1H), 2.03 (m, 1H), 1.65-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H). ^{31}P NMR (CD_3OD) δ 17.8.

Example 50

Monophospholactate 55: A solution of 48 (0.15 g, 0.18 mmol) in CH_2Cl_2 (1 mL) at 0°C was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C. Triethylamine (0.12 mL, 0.88 mmol) was added followed by the treatment of 4-benzyloxybenzenesulfonyl chloride (50 mg, 0.18 mmol). The solution was stirred at 0°C for 30 min and then warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and

concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.11 g, 63%) as a white solid.

Example 51

Metabolite X 56: To a solution of 55 (70 mg, 0.07 mmol) in EtOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with $CHCl_3$ and dried under vacuum to give the metabolite X (46 mg, 90%, GS 273847) as a white solid: ^{1}H NMR (CD_3OD), δ 7.91 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.91 (m, 4H), 5.59 (d, J = 5.1 Hz, 1H), 5.0 (m, 1H), 4.27 (d, J = 10.2 Hz, 2H), 3.97-3.74 (m, 6H), 3.4 (dd, 1H), 3.17-2.8 (m, 6H), 2.5 (m, 1H), 2.0 (m, 1H), 1.6-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 17.9.

Example 52

Metabolite X 57: To a suspension of 29 (40 mg, 0.05 mmol) in CH_3CN (1 mL), DMSO (0.5 mL), and 1.0 M PBS buffer (5 mL) was added esterase (200 μL). The suspension was heated to 40°C for 48 h. The reaction mixture was concentrated, suspended in MeOH and filtered. The filtrate was concentrated and purified by HPLC to give the metabolite X (20 mg, 57%, GS 277777) as a white solid: ^{1}H NMR (CD_3OD) δ 8.68 (s, 1H), 8.47 (d, J = 6.0 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.68 (m, 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 8.4 Hz, 2H), 5.59 (d, J = 5.4 Hz, 1H), 5.0 (m, 1H), 4.23 (d, J = 10.5 Hz, 2H), 3.97-3.68 (m, 6H), 3.45 (dd, 1H), 3.15-2.87 (m, 6H), 2.46 (m, 1H), 2.0 (m, 1H), 1.6-1.38 (m, 5H), 0.95 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CD_3OD) δ 17.2.

Example 53

Metabolite X 58: To a suspension of 35 (60 mg, 0.07 mmol) in CH_3CN (1 mL), DMSO (0.5 mL), and 1.0 M PBS buffer (5 mL) was added esterase (400 μL). The suspension was heated to 40°C for 3 days. The reaction mixture was concentrated, suspended in MeOH and filtered. The filtrate was concentrated and purified by HPLC to give the metabolite X (20 mg, 38%, GS 278116) as a white solid: ^{1}H NMR (CD_3OD) δ 7.74 (d, J = 6.9 Hz, 2H), 7.63 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.1 Hz, 2H), 5.64 (d, J = 5.1 Hz, 1H), 5.0 (m,

2H), 4.41 (m, 2H), 4.22 (m, 2H), 3.97-3.65 (m, 12H), 3.15-2.9 (m, 8H), 2.75 (m, 1H), 2.0 (m, 1H), 1.8 (m, 2H), 1.53 (d, J = 6.9 Hz, 3H), 0.88 (m, 6H).

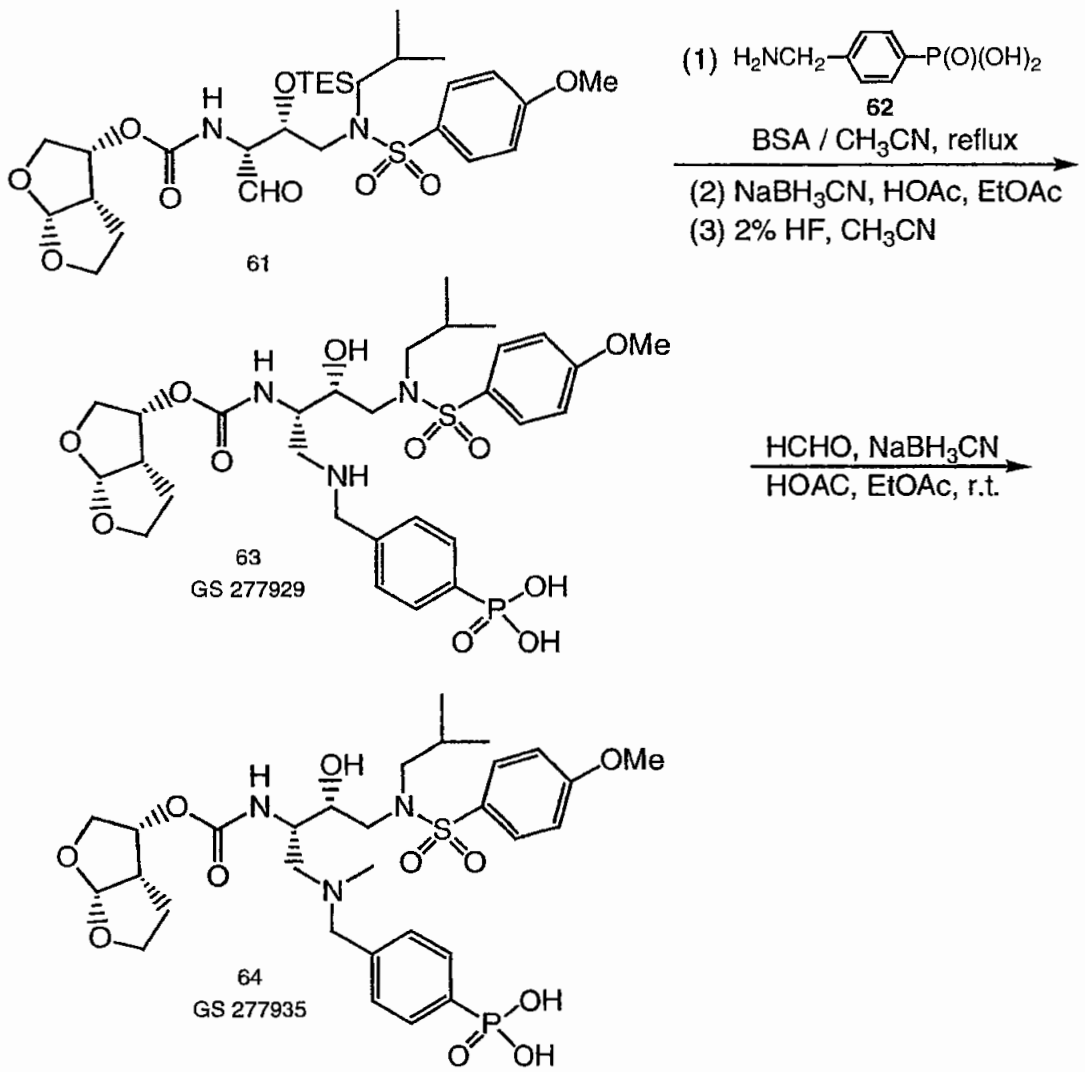
Example 54

Monophospholactate 59: A solution of 34 (2.10 g, 2.48 mmol) in THF (72 mL) and H_2O (8 mL) at -15°C was treated with $NaBH_4$ (0.24 g, 6.20 mmol). The reaction mixture was stirred for 10 min at -15°C. The reaction was quenched with 5% aqueous $NaHSO_3$ and extracted with CH_2Cl_2 (3 x). The combined organic layers were washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH_2Cl_2) to give monophospholactate (1.89 g, 90%, GS 278053, 1:1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.64 (m, 2H), 7.51(m, 2H), 7.38-7.19 (m, 7H), 6.92 (m, 2H), 5.69 (d, J = 4.8 Hz, 1H), 5.15 (m, 2H), 4.76 (s, 2H), 4.54 (d, J = 10.5 Hz, 1H), 4.44 (m, 1H), 4.2 (m, 2H), 4.04-3.68 (m, 6H), 3.06-2.62 (m, 7H), 1.8 (m, 3H), 1.62-1.5 (dd, 3H), 1.25 (m, 3H), 0.94 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.4, 15.4.

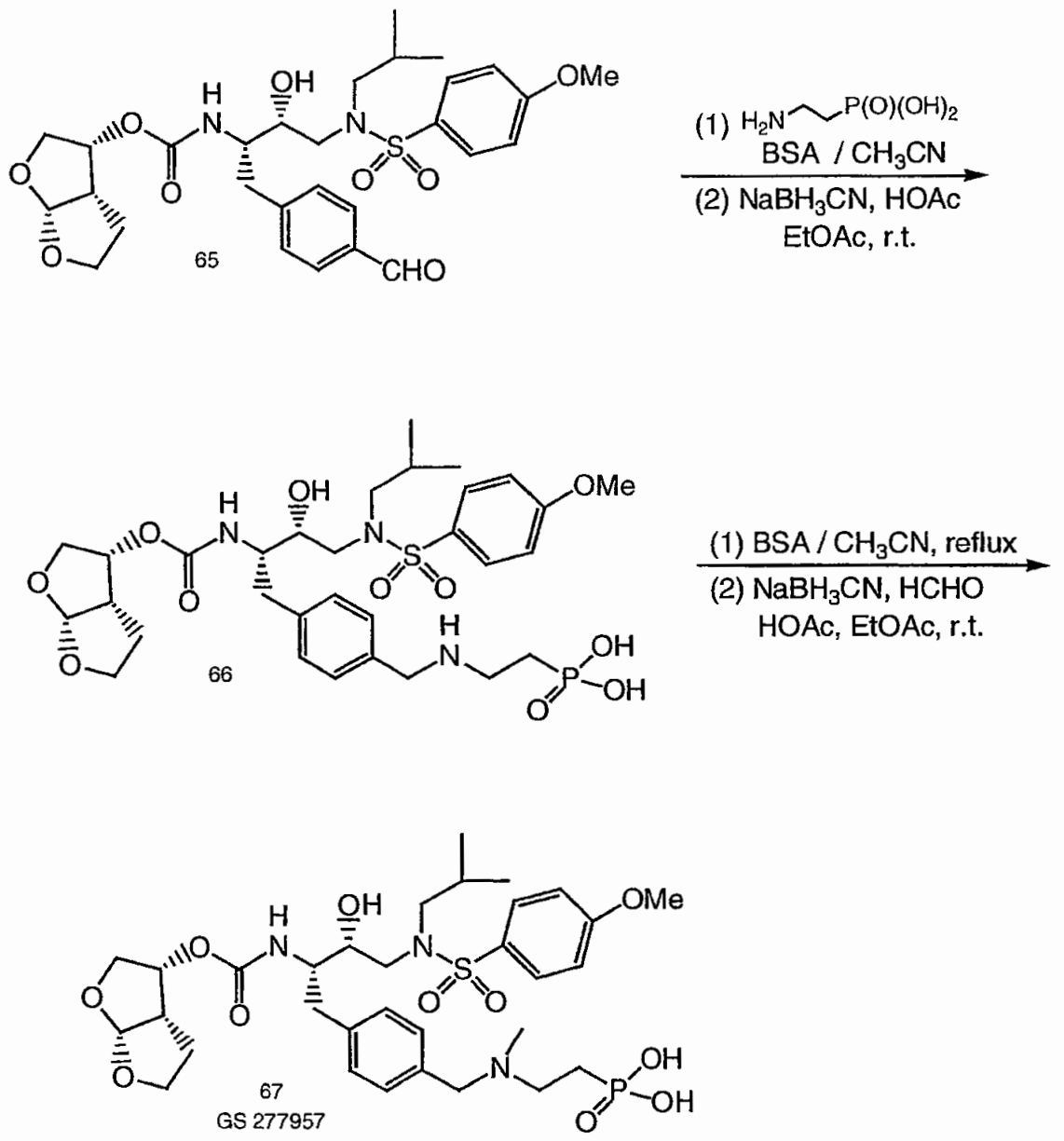
Example 55

Metabolite X 60: To a suspension of 59 (70 mg, 0.08 mmol) in CH_3CN (1 mL), DMSO (0.5 mL), and 1.0 M PBS buffer (5 mL) was added esterase (600 μL). The suspension was heated to 40°C for 36 h. The reaction mixture was concentrated, suspended in MeOH and filtered. The filtrate was concentrated and purified by HPLC to give the metabolite X (22 mg, 36%, GS 278764) as a white solid: ^{1}H NMR (CD_3OD) δ 7.78 (dd, 2H), 7.54 (dd, 2H), 7.15 (m, 2H), 6.9 (m, 2H), 5.57 (d, 1H), 5.0 (m, 2H), 4.65 (m, 4H), 4.2 (m, 2H), 3.9-3.53 (m, 6H), 3.06-2.82 (m, 6H), 2.5 (m, 1H), 2.0 (m, 2H), 1.62-1.35 (m, 3H), 0.94 (m, 6H).

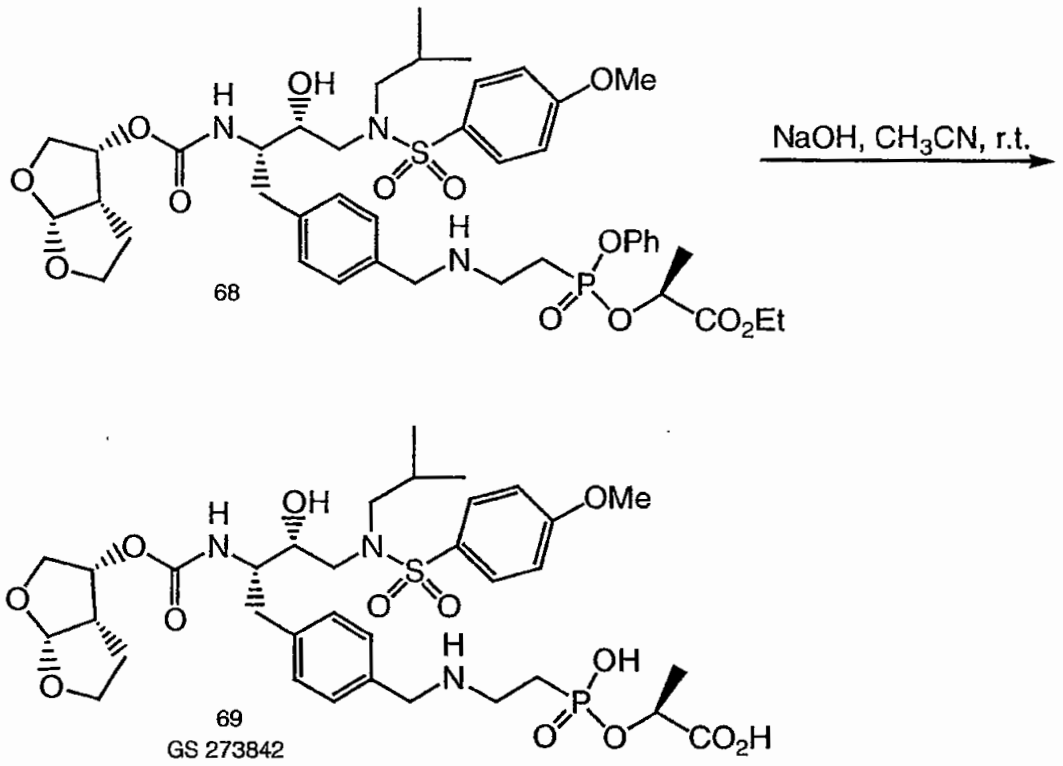
Scheme 16


OTES
OMe
H
N
O
CHO
61
(1) H2NCH2–P(O)(OH)2
62
BSA / CH3CN, reflux
(2) NaBH3CN, HOAc, EtOAc
(3) 2% HF, CH3CN
OH
NH
63
GS 277929
HCHO, NaBH3CN
HOAC, EtOAc, r.t.
N
64
GS 277935

Scheme 17


OMe
OH
H
N
O
N
S
O
O
O
O
O
CHO
65
(1) H_2N $P(O)(OH)_2$
BSA / CH_3CN
(2) $NaBH_3CN$, HOAc
EtOAc, r.t.
OMe
OH
H
N
O
N
S
O
O
O
O
H
N
OH
P
OH
O
66
(1) BSA / CH_3CN, reflux
(2) $NaBH_3CN$, HCHO
HOAc, EtOAc, r.t.
OMe
OH
H
N
O
N
S
O
O
O
O
N
OH
P
OH
O
67
GS 277957

Scheme 18



Example 56

Phosphonic Acid 63: Compound 62 (0.30 g, 1.12 mmol) was dissolved in CH_3CN (5 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 2.2 mL, 8.96 mmol) was added. The reaction mixture was heated to reflux for 2 h, cooled to room temperature, and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a thick oil which was dissolved in EtOAc (4 mL) and cooled to 0°C. Aldehyde 61 (0.20 g, 0.33 mmol), AcOH (0.18 mL, 3.30 mmol), and $NaBH_3CN$ (0.20 g, 3.30 mmol) were added. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with H_2O, stirred for 30 min, filtered, and concentrated. The crude product was dissolved in CH_3CN (13 mL) and 48% aqueous HF (0.5 mL) was added. The reaction mixture was stirred at room temperature for 2 h and concentrated. The crude product was purified by HPLC to give the phosphonic acid (70 mg, 32%, GS 277929) as a white solid: ^1H NMR (CD_3OD) δ 7.92 (dd, 2H), 7.73 (d, J = 8.7 Hz, 2H), 7.63 (dd, 2H), 7.12 (d, J = 8.7 Hz, 2H), 5.68 (d, J = 5.1 Hz, 1H), 5.13 (m, 1H), 4.4 (m, 2H), 4.05-3.89 (m, 8H), 3.75 (m, 1H), 3.5 (m, 1H), 3.37 (m, 1H), 3.23-3.0 (m, 3H), 2.88-2.7 (m, 2H), 2.2 (m, 1H), 1.8 (m, 2H), 0.92 (d, J = 6.3 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 14.5.

Example 57

Phosphonic Acid 64: A solution of 63 (50 mg, 0.07 mmol) and formaldehyde (60 mg, 0.70 mmol) in EtOAc (2 mL) was treated with HOAc (43 μL, 0.70 mmol) and $NaBH_3CN$ (47 mg, 0.7 mmol). The reaction mixture was stirred at room temperature for 26 h. The reaction was quenched with H_2O, stirred for 20 min, and concentrated. The crude product was purified by HPLC to give the phosphonic acid (15 mg, 29%, **GS 277935**) as a white solid: ^1H NMR (CD_3OD) δ 7.93 (m, 2H), 7.75 (m, 2H), 7.62 (m, 2H), 7.11 (m, 2H), 5.66 (m, 1H), 5.13 (m, 1H), 4.4 (m, 2H), 4.05-3.89 (m, 8H), 3.75 (m, 2H), 3.09-2.71 (m, 6H), 2.2 (m, 1H), 1.9 (m, 5H), 0.92 (d, J = 6.3 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 14.0.

Example 58

Phosphonic Acid 66: 2-Aminoethylphosphonic acid (2.60 g, 21.66 mmol) was dissolved in CH_3CN (40 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 40 mL) was added. The reaction mixture was heated to reflux for 2 h and cooled to room temperature and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a thick oil which was dissolved in EtOAc (40 mL). Aldehyde 65 (1.33 g, 2.25 mmol), AcOH (1.30 mL, 22.5 mmol) and $NaBH_3CN$ (1.42 g, 22.5 mmol) were added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with H_2O, stirred for 1 h, filtered, and concentrated. The residue was dissolved in MeOH and filtered. The crude product was purified by HPLC to give the phosphonic acid (1.00 g, 63%) as a white solid.

Example 59

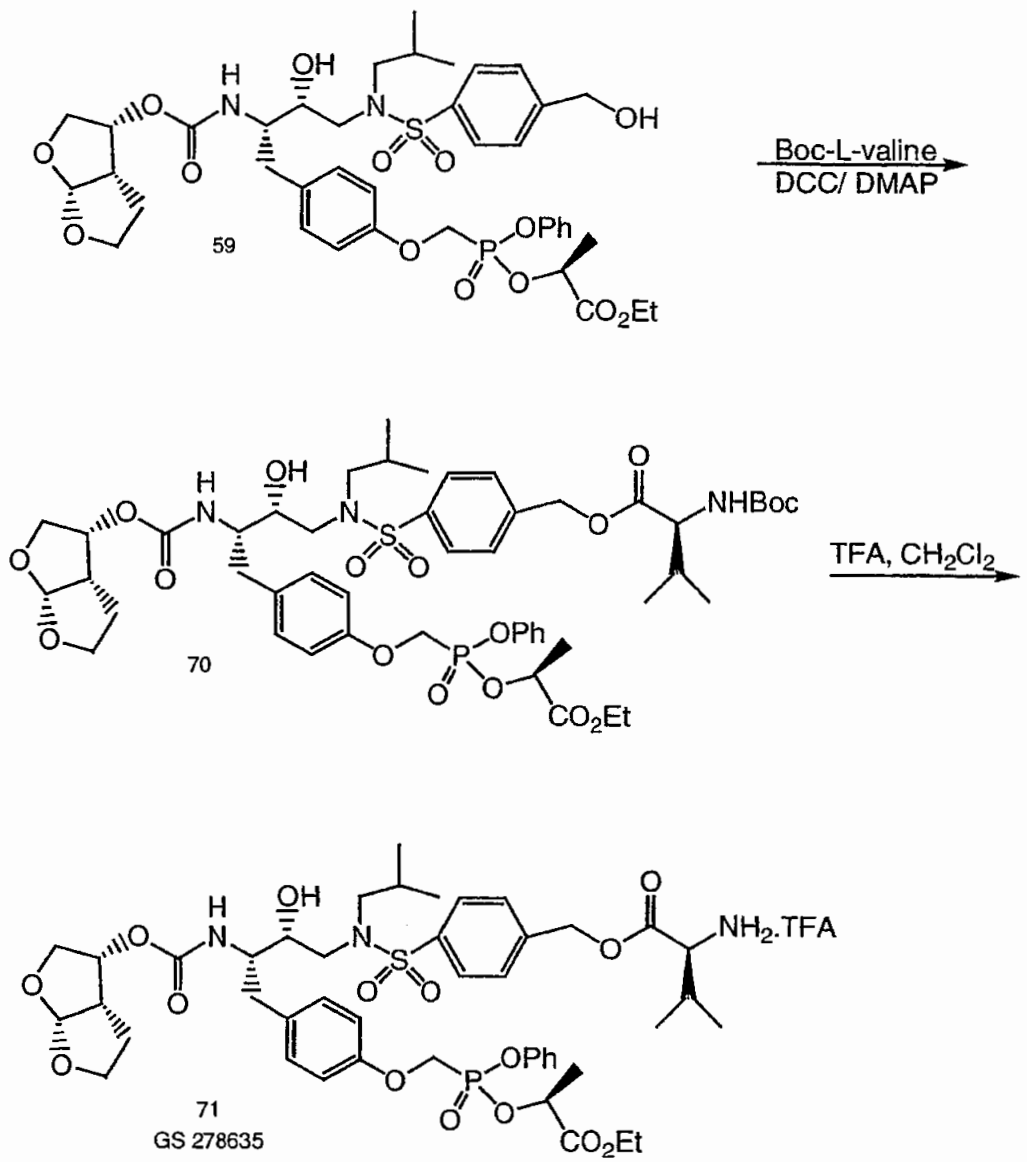
Phosphonic Acid 67: Phosphonic acid 66 (0.13 g, 0.19 mmol) was dissolved in CH_3CN (4 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 0.45 mL, 1.90 mmol) was added. The reaction mixture was heated to reflux for 2 h, cooled to room temperature, and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a thick oil which was dissolved in EtOAc (3 mL). Formaldehyde (0.15 mL, 1.90 mmol), AcOH (0.11 mL, 1.90 mmol) and $NaBH_3CN$ (63 mg, 1.90 mmol) were added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with H_2O, stirred for 6 h, filtered, and concentrated. The residue was dissolved in MeOH and filtered. The crude product was purified by HPLC to give the phosphonic acid (40 mg, 30%, GS

277957) as a white solid: ^{1}H NMR (CD_3OD) δ 7.78 (d, J = 8.4 Hz, 2H), 7.4 (m, 4H), 7.09 (d, J = 8.4 Hz, 2H), 5.6 (d, J = 5.1 Hz, 1H), 4.33 (m, 2H), 3.95-3.65 (m, 9H), 3.5-3.05 (m, 6H), 2.91-2.6 (m, 7H), 2.0 (m, 3H), 1.5 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 19.7.

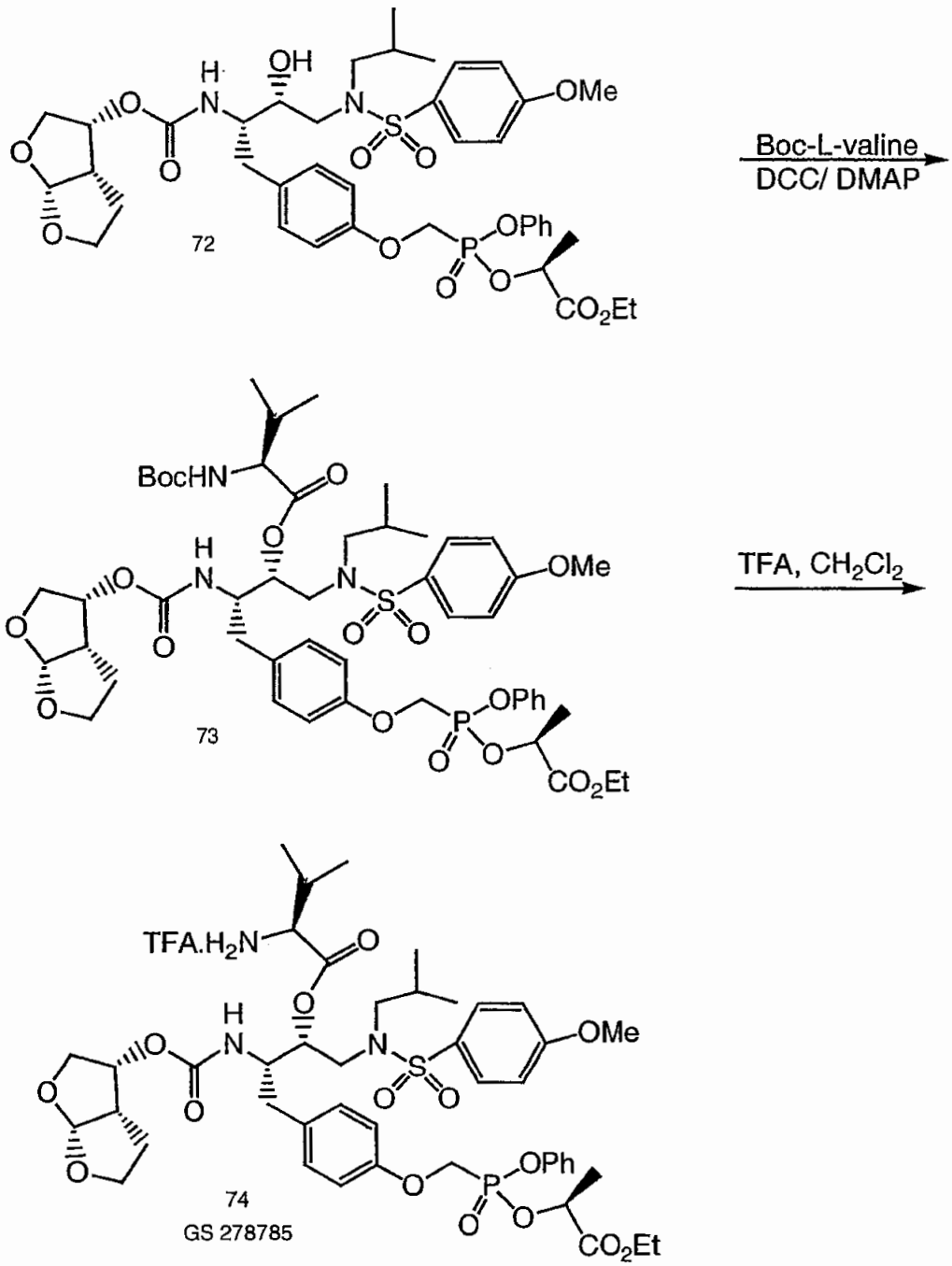
Example 60

Metabolite X 69: Monophospholactate 68 (1.4 g, 1.60 mmol) was dissolved in CH_3CN (20 mL) and H_2O (20 mL). 1.0 N NaOH (3.20 mL, 3.20 mmol) was added. The reaction mixture was stirred at room temperature for 1.5 h and cooled to 0°C. The reaction mixture was acidified to pH = 1-2 with 2 N HCl (1.6 mL, 3.20 mmoL). The solvent was evaporated under reduced pressure. The crude product was purified by HPLC to give the metabolite X (0.60 g, 49%, GS 273842) as a white solid: ^{1}H NMR (DMSO-d_6) δ 7.72 (d, J = 8.7 Hz, 2H), 7.33 (m, 4H), 7.09 (d, J = 9.0 Hz, 2H), 5.52 (d, J = 5.7 Hz, 1H), 5.1 (broad, s, 1H), 4.85 (m, 1H), 4.63 (m, 1H), 4.13 (m, 2H), 3.8 (m, 5H), 3.6 (m, 4H), 3.36 (m, 1H), 3.03 (m, 4H), 2.79 (m, 3H), 2.5 (m, 1H), 2.0 (m, 3H), 1.5-1.3 (m, 5H), 0.85 (d, J = 6.6 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H); ^{31}P NMR (DMSO-d_6) δ 21.9.

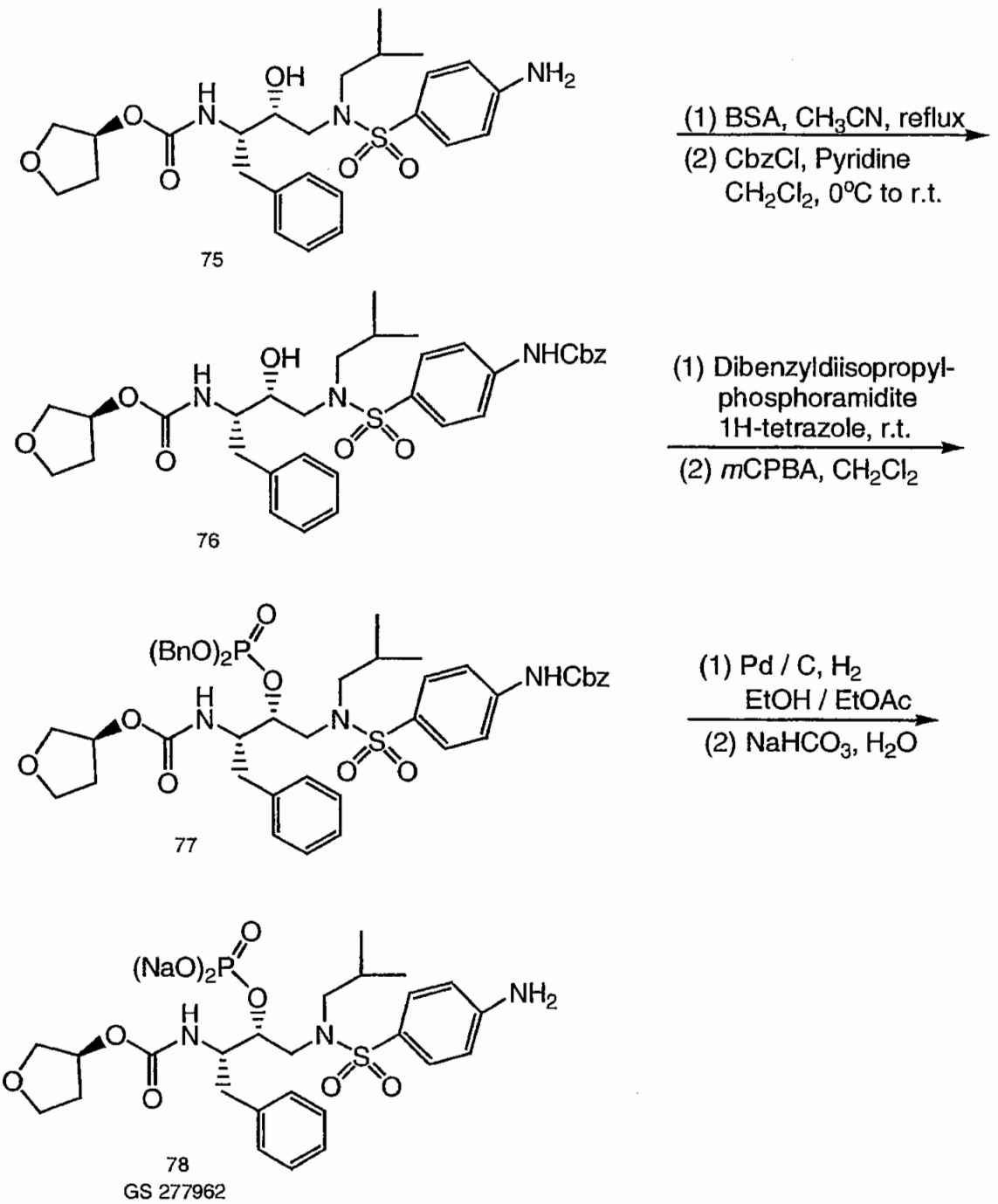
Scheme 19


Boc-L-valine
DCC/ DMAP
TFA, CH2Cl2
59
70
71
GS 278635
NHBoc
NH2.TFA
OPh
CO2Et

Scheme 20



Scheme 21



Example 61

Monophospholactate 70: A solution of 59 (1.48 g, 1.74 mmol) and Boc-L-valine (0.38 g, 1.74 mmol) in CH_2Cl_2 (30 mL) at 0°C was treated with 1,3- dicyclohexylcarbodiimide (0.45 g, 2.18 mmol) and 4-dimethylaminopyridine (26 mg, 0.21 mmol). The reaction mixture was stirred at 0°C for 1 h and then warmed to room temperature for 2 h. The product was

partitioned between CH_2Cl_2 and 0.2 N HCl. The organic layer was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the monophospholactate (1.65 g, 90%) as a white solid.

Example 62

Monophospholactate 71: A solution of 70 (1.65 g, 1.57 mmol) in CH_2Cl_2 (8 mL) at 0°C was treated with trifluoroacetic acid (4 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% 2-propanol/CH_2Cl_2) to give the monophospholactate (1.42 g, 85%, GS 278635, 2/3 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.73 (m, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.4-7.1 (m, 7H), 6.89 (m, 2H), 5.64 (m, 1H), 5.47 (m, 1H), 5.33-5.06 (m, 4H), 4.57-4.41 (m, 2H), 4.2 (m, 2H), 3.96-3.7 (m, 7H), 3.15-2.73 (m, 7H), 2.38 (m, 1H), 1.9 (m, 1H), 1.7 (m, 1H), 1.63-1.5 (m, 4H), 1.24 (m, 3H), 1.19 (m, 6H), 0.91 (d, 3H), 0.88 (d, 3H); ^{31}P NMR ($CDCl_3$) δ 17.3, 15.4.

Example 63

Monophospholactate 73: A solution of 72 (0.43 g, 0.50 mmol) and Boc-L-valine (0.11 g, 0.50 mmol) in CH_2Cl_2 (6 mL) was treated with 1,3-dicyclohexylcarbodiimide (0.13 g, 0.63 mmol) and 4-dimethylaminopyridine (62 mg, 0.5 mmol). The reaction mixture was stirred at room temperature overnight. The product was partitioned between CH_2Cl_2 and 0.2 N HCl. The organic layer was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.45 g, 85%) as a white solid.

Example 64

Monophospholactate 74: A solution of 73 (0.44 g, 0.42 mmol) in CH_2Cl_2 (1 mL) at 0°C was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% 2-propanol/CH_2Cl_2) to give the monophospholactate (0.40 g, 90%, GS 278785, 1:1 diastereomeric mixture) as a white solid:

^{1}H NMR ($CDCl_3$) δ 7.69 (d, J = 8.4 Hz, 2H), 7.34-7.2 (m, 7H), 6.98 (d, J = 8.4 Hz, 2H), 6.88 (m, 2H), 6.16 (m, 1H), 5.64 (m, 1H), 5.46 (m, 1H), 5.2-5.0 (m, 2H), 4.5 (m, 2H), 4.2 (m, 3H), 4.0-3.4 (m, 9H), 3.3 (m, 1H), 3.0-2.8 (m, 5H), 2.5 (m, 1H), 1.83 (m, 1H), 1.6-1.5 (m, 5H), 125 (m, 3H), 1.15 (m, 6H), 0.82 (d, J = 6.0 Hz, 3H), 0.76 (d, J = 6.0 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.3, 15.5.

Example 65

Cbz Amide 76: Compound 75 (0.35 g, 0.69 mmol) was dissolved in CH_3CN (6 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 0.67 mL, 2.76 mmol) was added. The reaction mixture was heated to reflux for 1 h, cooled to room temperature, and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a thick oil which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Pyridine (0.17 mL, 2.07 mmol) and benzyl chloroformate (0.12 mL, 0.83 mmol) were added. The reaction mixture was stirred at 0°C for 1 h and then warmed to room temperature overnight. The reaction was quenched with MeOH (5 mL) and 10% HCl (20 mL) at 0°C and stirred for 1 h. The product was extracted with CH_2Cl_2, washed with brine, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the CBz amide (0.40 g, 90%) as a white solid.

Example 66

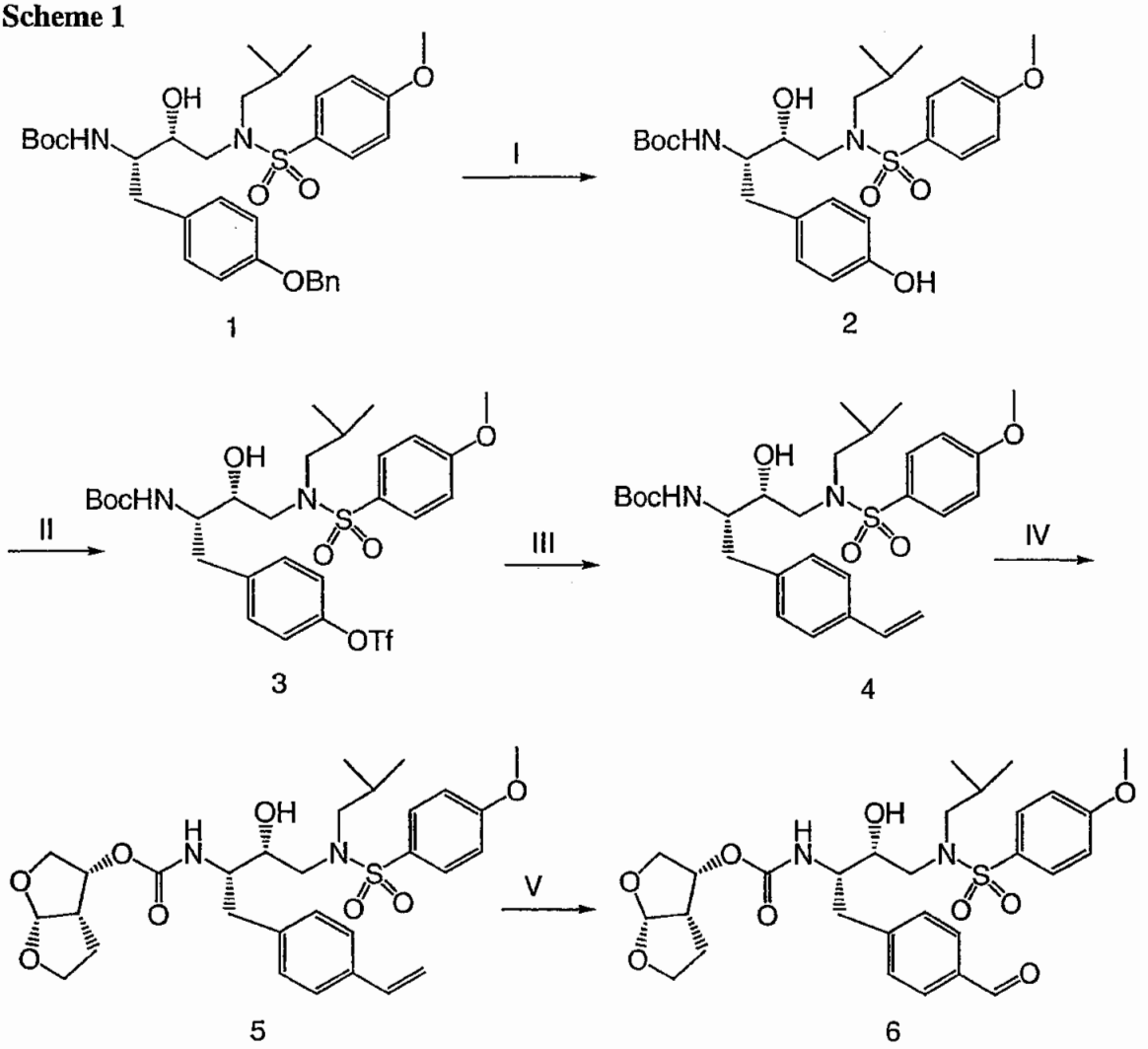
Dibenzylphosphonate 77: A solution of 76 (0.39 g, 0.61 mmol) and 1*H*-tetrazole (54 mg, 0.92 mmol) in CH_2Cl_2 (8 mL) was treated with dibenzyldiisopropylphosphoramidite (0.32 g, 0.92 mmol) and stirred at room temperature overnight. The solution was cooled to 0°C, treated with *m*CPBA, stirred for 1 h at 0°C and then warmed to room temperature for 1 h. The reaction mixture was poured into a mixture of aqueous Na_2SO_3 and $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate (0.42 g, 76%) as a white solid.

Example 67

Disodium Salt of Phosphonic Acid 78: To a solution of 77 (0.18 g, 0.20 mmol) in EtOH (20 mL) and EtOAc (4 mL) was added 10% Pd/C (40 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through

a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (0.11 g, 95%) which was dissolved in H_2O (4 mL) and treated with $NaHCO_3$ (32 mg, 0.38 mmol). The reaction mixture was stirred at room temperature for 1 h and lyopholyzed overnight to give the disodium salt of phosphonic acid (0.12 g, 99%, GS 277962) as a white solid: ^1H NMR (D_2O) δ 7.55 (dd, 2H), 7.2 (m, 5H), 7.77 (dd, 2H), 4.65 (m, 1H), 4.24 (m, 1H), 4.07 (m, 1H), 3.78-2.6 (m, 12H), 1.88-1.6 (m, 3H), 0.75 (m, 6H).

Scheme 1



I. H_2/10%Pd-C/EtOAc-EtOH ; II.Tf_2NPh/Cs_2CO_3;
III. $Bu_3SnCH{=}CH_2/PdCl_2(PPh_3)_2$/LiCl/DMF/90 C;
IV.a. TFA/CH_2Cl_2;b.Bisfurancarbonate/i-Pr_2NEt/DMAP;
V.$NaIO_4/OsO_4$/EtOAc-H_2O

Example 1

Compound 1 was prepared by methods from Examples herein.

Example 2

Compound 2: To a solution of compound 1 (47.3 g) in EtOH/EtOAc (1000 mL/500 mL) was added 10% Pd-C (5 g). The mixture was hydrogenated for 19 hours. Celite was added and

the mixture was stirred for 10 minutes. The mixture was filtered through a pad of celite and was washed with ethyl acetate. Concentration gave compound 2 (42.1 g).

Example 3

Compound 3: To a solution of compound 2 (42.3 g, 81 mmol) in CH_2Cl_2 (833 mL) was added N-phenyltrifluoromethanesulfonimide (31.8 g, 89 mmol), followed by cesium carbonate (28.9 g, 89 mmol). The mixture was stirred for 24 hours. The solvent was removed under reduced pressure, and ethyl acetate was added. The reaction mixture was washed with water (3x) and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/EtOAc = 13/1) gave compound 3 (49.5 g) as a white powder.

Example 4

Compound 4: To a solution of compound 3 (25.2, 38.5 mmol) in DMF (240 mL) was added lithium chloride (11.45 g, 270 mmol), followed by dichlorobis(triphenylphosphine) palladium(II) (540 mg, 0.77 mmol). The mixture was stirred for 3 minutes under high vacuum and recharged with nitrogen. To the above solution was added tributylvinyltin (11.25 mL). The reaction mixture was heated at 90°C for 6 hours and cooled to 25°C. Water was added to the reaction, and the mixture was extracted with ethyl acetate (3X). The combined organic layer was washed with water (6x) and brine, and dried over $MgSO_4$. Concentration gave an oil. The oil was diluted with dichloromethane (40 mL), water (0.693 mL, 38.5 mmol) and DBU (5.76 mL, 38.5 mmol) were added . The mixture was stirred for 5 minutes, and subjected to flash column chromatography (hexanes/EtOAc = 2.5/1). Compound 4 was obtained as white solid (18.4 g).

Example 5

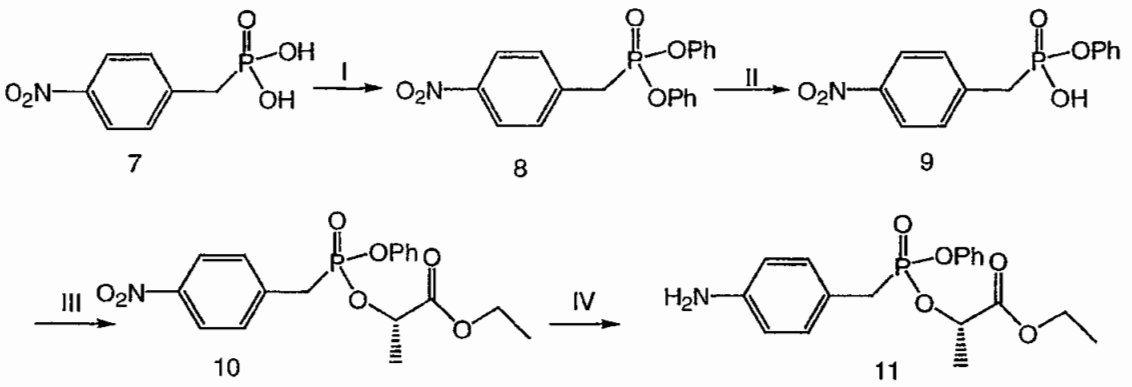
Compound 5: To a solution of compound 4 (18.4 g, 34.5 mmol) in CH_2Cl_2 (70 mL) at 0°C was added trifluoroacetic acid (35 mL). The mixture was stirred at 0°C for 2 hrs, and solvents were evaporated under reduced pressure. The reaction mixture was quenched with saturated sodium carbonate solution, and was extracted with ethyl acetate (3x). The combined organic layer was washed with saturated sodium carbonate solution(1x), water (2x), and brine (1x), and dried over $MgSO_4$. Concentration gave a solid. To a solution of the above solid in acetonitrile (220 mL) at 0°C was added bisfurancarbonate (10.09 g, 34.2

mmol), followed by di-isopropylethylamine (12.0 mL, 69.1 mmol) and DMAP (843 mg, 6.9 mmol). The mixture was warmed to 25°C and stirred for 12 hours. Solvents were removed under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2X), 5% hydrochloric acid (2x), water (2x), 1N sodium hydroxide (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 1/1)) gave compound 5 (13.5 g).

Example 6

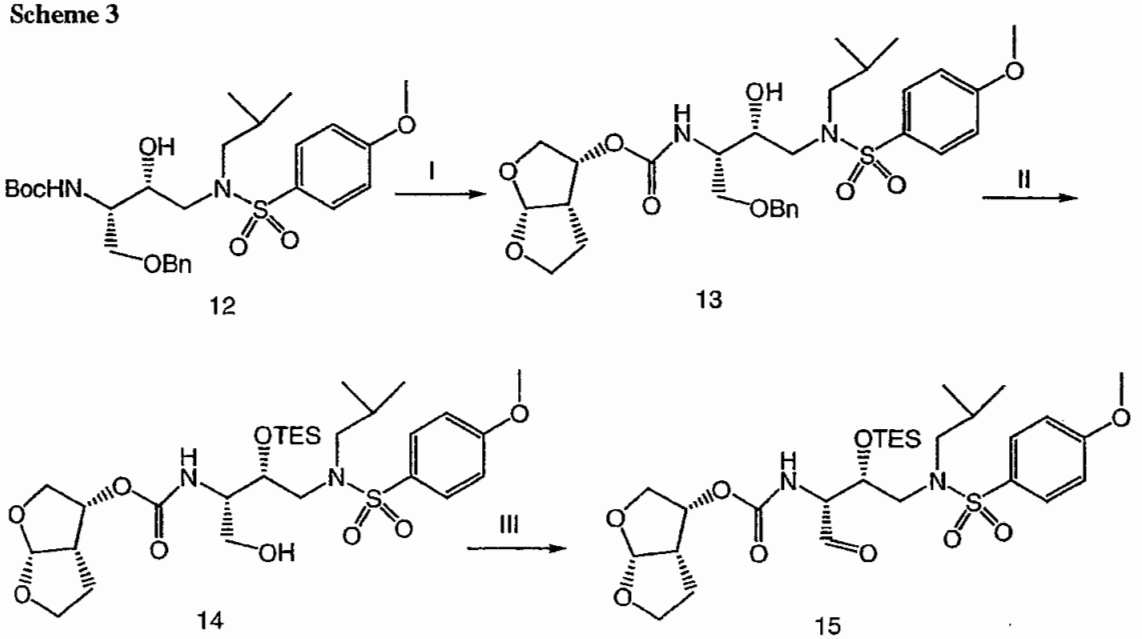
Compound 6: To a solution of compound 5 (13.5 g, 23 mmol) in ethyl acetate (135 mL) was added water (135 mL), followed by 2.5% osmium tetraoxide/tert-butanol (17 mL). Sodium periodate (11.5 g) was added in portions over 2 minutes period. The mixture was stirred for 90 minutes, and was diluted with ethyl acetate. The organic layer was separated and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = ½) gave compound 6 as white powder (12 g): ^{1}H NMR ($CDCl_3$) δ 9.98 (1 H, s), 7.82 (2 H, m), 7.75 (2 H, m), 7.43 (2 H, m), 6.99 (2 H, m), 5.64 (1 H, m), 5.02 (2 H, m), 4.0-3.8 (9 H, m), 3.2-2.7 (7 H, m), 1.9-1.4 (3 H, m), 0.94 (6 H, m).

Scheme 2



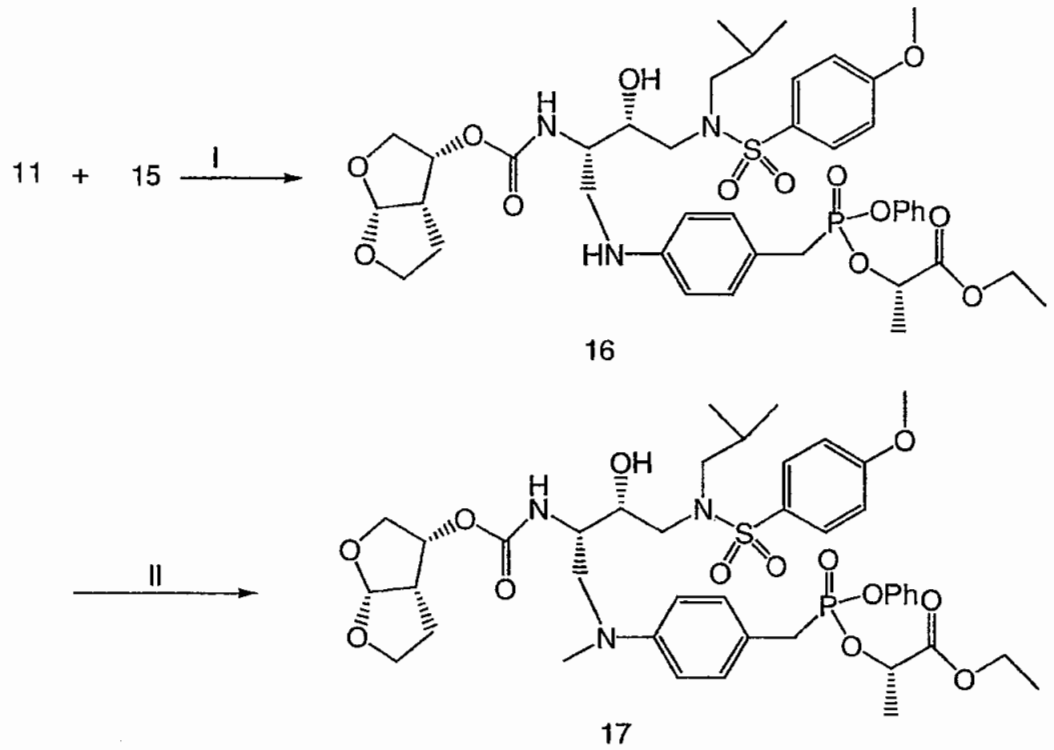
I. a..$SOCl_2$/toluene/60 C; b. PhOH/pyridine; II. a.NaOH/THF/H_2O; b. HCl;
III. b.$SOCl_2$/toluene/60 C; c.ethyl lactate/pyridine; IV. H_2/10%Pd-C/EtOAc

Scheme 3



I. a.TFA/CH_2Cl_2; b. bisfurancarbonate/i-Pr_2NEt/DMAP; II. a.Et_3SiCl/Imidazole/DMF;
b. H_2/20%$Pd(OH)_2$-C/iPrOH; III. Des-Martin reagent/CH_2Cl_2

Scheme 4



I. a. $NaBH_3CN$/HOAc/EtOAc; b. 2%HF/CH_3CN;
II. HCHO/$NaBH_3CN$/HOAc/EtOAc

Example 8

Compound 8: To the suspension of compound 7 (15.8 g, 72.5 mmol) in toluene (140 mL) was added DMF (1.9 mL), followed by thionyl chloride (53 mL, 725 mmol). The reaction mixture was heated at 60°C for 5 hrs, and evaporated under reduced pressure. The mixture was coevaporated with toluene (2x), EtOAc, and CH_2Cl_2 (2x) to afford a brown solid. To the solution of the brown solid in CH_2Cl_2 at 0°C was added phenol (27.2 g, 290 mmol), followed by slow addition of pyridine (35 mL, 435 mmol). The reaction mixture was allowed to warm to 25°C and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Concentration gave a dark oil, which was purified by flash column chromatography (hexanes/EtOAc = 4/1 to 1/1) to afford compound 8 (12.5 g).

Example 9

Compound 9: To a solution of compound 8 (2.21 g, 6 mmol) in THF (30 mL) was added 12 mL of 1.0 N NaOH solution. The mixture was stirred at 25°C for 2 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and acetic acid (343 mL, 6 mmol) was added. The aqueous phase was washed with EtOAc (3x), and then acidified with concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over $MgSO_4$. Concentration under reduced pressure gave compound 9 as a solid (1.1 g).

Example 10

Compound 10: To a suspension of compound 9 (380 mg, 1.3 mmol) in toluene (2.5 mL) was added thionyl chloride (1 mL, 13 mmol), followed by DMF (1 drop). The mixture was heated at 60°C for 2 hours. The solvent and reagent were removed under reduced pressure. The mixture was coevaporated with toluene (2x) and CH_2Cl_2 to give a white solid. To the solution of the above solid in CH_2Cl_2 (5 ml) at –20°C was added ethyl lactate (294 µL, 2.6 mmol), followed by pyridine (420 µL, 5.2 mmol). The mixture was warmed to 25°C and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure to give a yellow solid, which was purified by flash column chromatography to generate compound 10 (427 mg).

Example 11

Compound 11: To a solution of compound 10 (480 mg) in EtOAc (20 mL) was added 10% Pd-C (80 mg). The reaction mixture was hydrogenated for 6 hrs. The mixture was stirred with celite for 5 mins, and filtered through a pad of celite. Concentration under reduced pressure gave compound 11 (460 mg).

Example 12

Compound 12 was prepared by the methods of the Examples herein

Example 13

Compound 13: To a solution of compound 12 (536 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 2 hrs, and was concentrated under reduced pressure. The liquid was coevaporated with CH_2Cl_2 (3x) and EtOAc (3x) to give a brown solid. To the solution of above brown solid in acetonitrile (6.5 mL) at 0°C was

added bisfurancarbonate (295 mg, 1.0 mmol), followed by diisopropylethylamine (350 μL, 2.0 mmol) and DMAP (24 mg). The mixture was warmed to 25°C, and was stirred for 12 hrs. The mixture was diluted with EtOAc, and was washed sequentially with water (2x), 0.5 N HCl (2x), water (2x), 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 1/1) afford compound 13 (540 mg).

Example 14

Compound 14: To a solution of compound 13 (400 mg, 0.67 mmol) in DMF (3 mL) was added imidazole (143 mg, 2.10 mmol), followed by triethylchlorosilane (224 μL, 1.34 mmol). The mixture was stirred for 12 hours. The mixture was diluted with EtOAc, and was washed with water (5x) and brine, and dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 2/1) gave a white solid (427 mg). To the solution of above solid in isopropanol (18 mL) was added 20% palladium(II) hydroxide on carbon (120 mg). The mixture was hydrogenated for 12 hours. The mixture was stirred with celite for 5 mins, and filtered through a pad of celite. Concentration under reduced pressure gave compound 14(360 mg).

Example 15

Compound 15: To a solution of compound 14 (101 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin periodiane (136 mg, 0.36 mmol). The mixture was stirred for 1 hour. Purification by flash column chromatography (hexanes/EtOAc = 2/1) gave compound 15 (98 mg).

Example 16

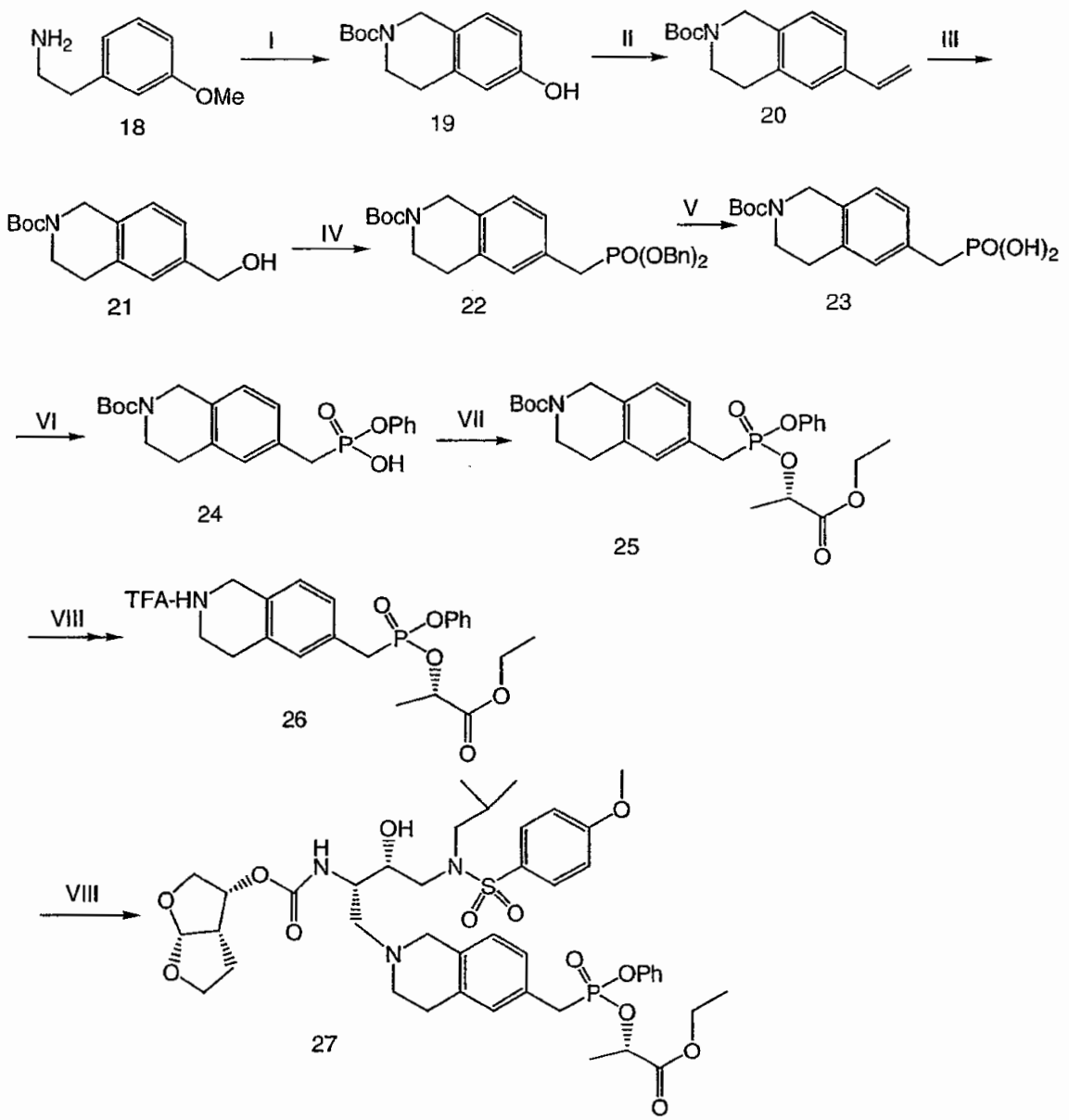
Compound 16: To a solution of compound 15 (50 mg, 0.08 mmol) in EtOAc (0.5 mL) was added compound 11 (150 mg, 0.41 mmol). The mixture was cooled to 0°C, acetic acid (19 μL, 0.32 mmol) was added, followed by sodium cyanoborohydride (10 mg, 0.16 mmol). The mixture was warmed to 25°C, and was stirred for 14 hrs. The mixture was diluted with EtOAc, and was washed with water (3x) and brine, and was dried over $MgSO_4$. Concentration gave a oil. To the solution of above oil in acetonitrile (2.5 mL) was added 48% HF/CH_3CN (0.1 mL). The mixture was stirred for 30 minutes, and was diluted with EtOAc. The organic phase was washed with water (3x) and brine (1x), and was dried over

$MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/3) gave compound 16 (50 mg): ^1H NMR ($CDCl_3$) δ 7.72 (2 H, d, J = 8.9 Hz), 7.15-7.05 (7 H, m), 7.30 (2 H, d, J = 8.9 Hz), 6.64 (2 H, m), 5.73 (1 H, m), 5.45 (1 H, m), 5.13 (1 H, m), 4.93 (1 H, m), 4.22-3.75 (11 H, m), 3.4 (4 H, m), 3.35-2.80 (5 H, m), 2.1-1.8 (3 H, m), 1.40-1.25 (6 H, m), 0.94 (6 H, m).

Example 17

Compound 17: To a solution of compound 16 (30 mg, 0.04 mmol) in EtOAc (0.8 mL) was added 37% formaldehyde (26 μL, 0.4 mmol). The mixture was cooled to 0°C, acetic acid (20 μL, 0.4 mmol) was added, followed by sodium cyanoborohydride (22 mg, 0.4 mmol). The mixture was warmed to 25°C, and was stirred for 14 hrs. The mixture was diluted with EtOAc, and was washed with water (3x) and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/3) gave compound 17 (22 mg): ^1H NMR ($CDCl_3$) δ 7.63 (2 H, m), 7.3-6.9 (9 H, m), 6.79 (2 H, m), 5.68 (1 H, m), 5.2 (1 H, m), 5.10 (1 H, m), 4.95 (1 H, m), 4.22 (2 H, m), 4.2-3.7 (21 H, m), 2.0-1.7 (3 H, m), 1.4-1.2 (6 H, m), 0.93 (6 H, m).

Scheme 5



I. a.HCHO/100 C; b. HCl/100 C; c.HBr/120 C;d. Boc_2O/Na_2CO_3 II. a.Tf_2NPh/Cs_2CO_3;
b. $Bu_3SnCH{=}CH_2/LiCl/PdCl_2(PPh_3)_2$/90 C; III.a. $NaIO_4/OsO_4$; b. $NaBH_4$;
IV. a. CBr_4/PPh_3; b. $(BnO)_2POH/Cs_2CO_3$; V. H_2/10% Pd-C;VI. a. PhOH/DCC; b. NaOH; C. HCl;
VII. Ethyl lactate/BOP; VIII.TFA/CH_2Cl_2; VIII. compound 15/$NaBH_3CN$/HOAc.

Example 18

Compound 18: Compound 18 was purchased from Aldrich.

Example 19

Compound 19: To compound 18 (12.25 g, 81.1 mmol) was added 37% formaldehyde (6.15 mL, 82.7 mmol) slowly. The mixture was heated at 100°C for 1 hour. The mixture was cooled to 25°C, and was diluted with benzene, and was washed with water (2x). Concentration under reduced pressure gave a yellow oil. To above oil was added 20% HCl (16 mL), and the mixture was heated at 100°C for 12 hours. The mixture was basified with 40% KOH solution at 0°C, and was extracted with EtOAc (3x). The combined organic layer was washed with water and brine, and was dried over $MgSO_4$. Concentration gave a oil. To the oil was added 48% HBr (320 mL), and the mixture was heated at 120°C for 3 hours. Water was removed at 100°C under reduced pressure to give a brown solid. To the solution of above solid in water/dioxane (200 mL/200mL) at 0°C was added sodium carbonate (25.7 g, 243 mmol) slowly, followed by di-tert-butyl dicarbonate (19.4 g, 89 mmol). The mixture was warmed to 25°C and stirred for 12 hours. Dioxane was removed under reduced pressure, and the remaining was extracted with EtOAc (3x). The combined organic phase was washed with water (3x) and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 4/1 to 3/1) gave compound 19 as white solid (13.6 g).

Example 20

Compound 20: To a solution of compound 19 (2.49 g, 10 mmol) in CH_2Cl_2 (100 mL) was added N-phenyltrifluoromethanesulfonimide (3.93 g, 11 mmol), followed by cesium carbonate (3.58 g, 11 mmol). The mixture was stirred for 48 hours. The solvent was removed under reduced pressure, and ethyl acetate was added. The reaction mixture was washed with water (3x) and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 6/1) gave a white solid (3.3 g). To the solution of above solid (2.7 g, 7.1 mmol) in DMF (40 mL) was added lithium chloride (2.11 g, 49.7 mmol), followed by dichlorobis(triphenylphosphine) palladium(II) (100 mg, 0.14 mmol). The mixture was stirred for 3 minutes under high vacuum and recharged with nitrogen. To the above solution was added tributylvinyltin (2.07 mL, 7.1 mmol). The reaction mixture was heated at 90°C for 3 hours and cooled to 25°C. Water was added to the reaction, and the mixture was extracted with ethyl acetate (3X). The combined organic layer was washed with water (6x) and brine, and dried over $MgSO_4$. Concentration gave an oil. The oil was diluted with CH_2Cl_2 (5 mL), water (128 μL, 7.1mmol) and DBU (1 mL, 7.1 mmol) were added. The mixture was stirred for 5 minutes, and was subjected to flash column chromatography (hexanes/EtOAc = 9/1). Compound 20 was obtained as white solid (1.43 g).

Example 21

Compound 21: To a solution of compound 20 (1.36 g, 5.25 mmol) in ethyl acetate (16 mL) was added water (16 mL), followed by 2.5% osmium tetraoxide/tert-butanol (2.63 mL). Sodium periodate (2.44 g) was added in portions over 2 minutes period. The mixture was stirred for 45 minutes, and was diluted with ethyl acetate. The organic layer was separated and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Concentration gave a brown solid. To the solution of above solid in methanol (100 mL) at 0°C was added sodium borohydride. The mixture was stirred for 1 hour at 0°C, and was quenched with saturated NH_4Cl (40 mL). Methanol was removed under reduced pressure, and the remaining was extracted with EtOAc (3x). The combined organic layer was washed with water and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 2/1) gave compound 21 (1.0 g).

Example 22

Compound 22: To a solution of compound 21 (657 mg, 2.57 mmol) in CH_2Cl_2 (2 mL) was added a solution of tetrabromocarbon (1.276 g, 3.86 mmol) in CH_2Cl_2 (2 mL). To the above mixture was added a solution of triphenylphsophine (673 mg, 2.57 mmol) in CH_2Cl_2 (2 mL) over 30 minutes period. The mixture was stirred for 2 hours, and was concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc = 9/1) gave the bromide intermediate (549 mg). To the solution of above bromide (548 mg, 1.69 mmol) in acetonitrile (4.8 mL) was added dibenzyl phosphite (0.48 mL, 2.19 mmol), followed by cesium carbonate (828 mg, 2.54 mmol). The mixture was stirred for 48 hours, and was diluted with EtOAc. The mixture was washed with water (3x) and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 3/1 to 100% EtOAc) gave compound 22 (863 mg).

Example 23

Compound 23: To a solution of compound 22 (840 mg) in ethanol (80 mL) was added 10% palladium on carbon (200 mg). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 23 (504 mg).

Example 24

Compound 24: To a solution of compound 23 (504 mg, 1.54 mmol) in pyridine (10.5 mL) was added phenol (1.45 g, 15.4 mmol), followed by DCC (1.28 g, 6.2 mmol). The mixture was heated at 65°C for 3 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc (5 ml), and was filtered and washed with EtOAc (2x5 mL). Concentration gave a oil, which was purified by flash column chromatography (CH_2Cl_2/isopropanol = 100/3) to give diphenylphosphonate intermediate (340 mg). To a solution of above compound (341 mg, 0.71 mmol) in THF (1 mL) was added 0.85 mL of 1.0 N NaOH solution. The mixture was stirred at 25°C for 3 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and was washed with EtOAc (3x), and then acidified with concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over $MgSO_4$. Concentration under reduced pressure gave compound 24 as a solid (270 mg).

Example 25:

Compound 25: To a solution of compound 24 (230 mg, 0.57 mmol) in DMF (2 mL) was added ethyl (s)-lactate (130 µL, 1.14 mmol), followed by diisopropylethylamine (400 µL, 2.28 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (504 mg, 1.14 mmol). The mixture was stirred for 14 hours, was diluted with EtOAc. The organic phase was washed with water (5x) and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/isopropanol = 100/3) gave compound 25 (220 mg).

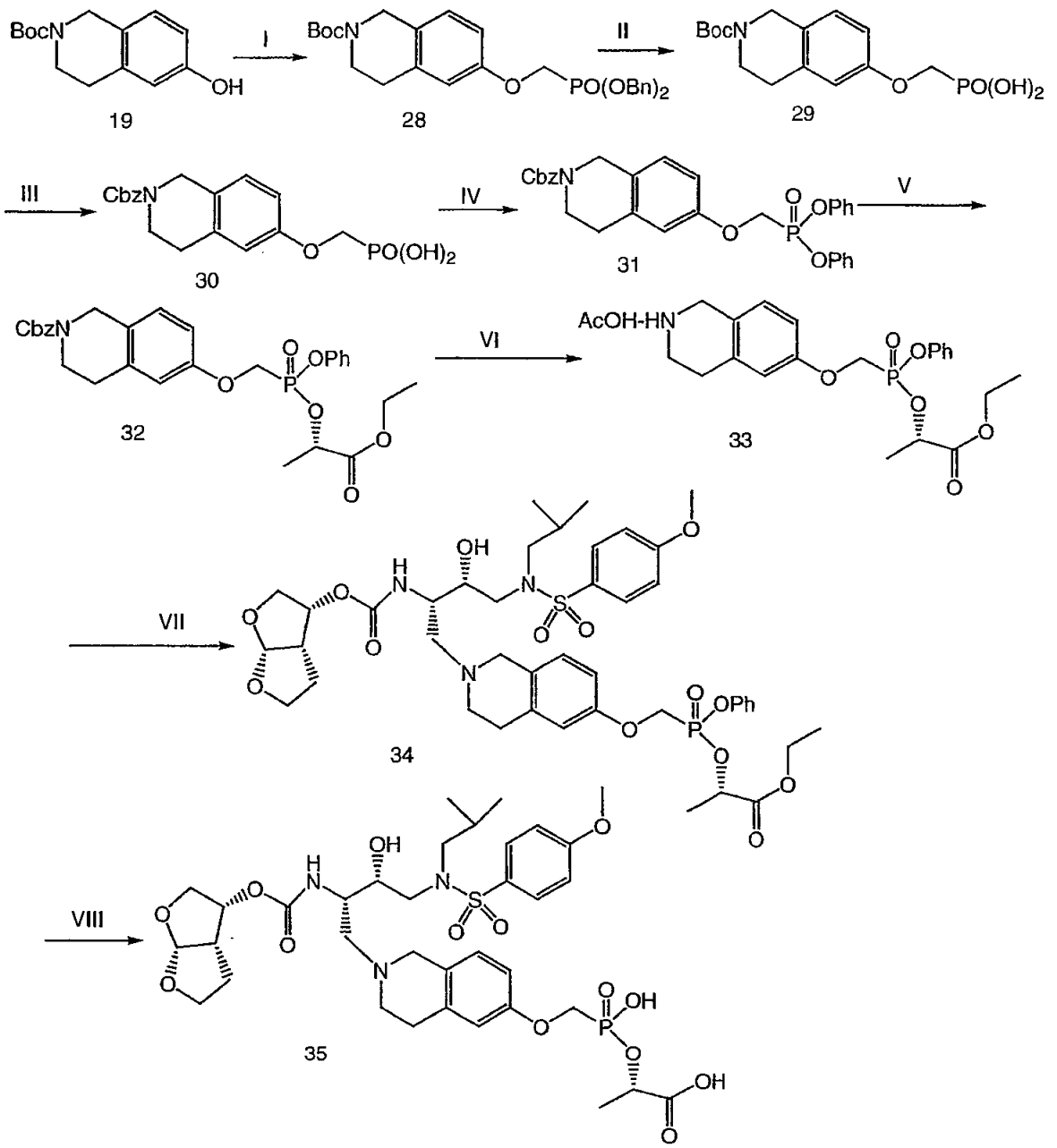
Example 26

Compound 26: To a solution of compound 25 (220 mg) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred for 2 hrs, and was concentrated under reduced pressure. The mixture was diluted with EtOAc, and was washed with saturated sodium carbonate solution, water, and brine, and was dried over $MgSO_4$. Concentration gave compound 26 (170 mg).

Example 27

Compound 27: To a solution of compound 15 (258 mg, 0.42 mmol) in EtOAc (2.6 mL) was added compound 26 (170 mg, 0.42 mmol), followed by acetic acid (75 μL, 1.26 mmol). The mixture was stirred for 5 minutes, and sodium cyanoborohydride (53 mg, 0.84 mmol) was added. The mixture was stirred for 14 hrs. The mixture was diluted with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/4 to 100/6) gave the intermediate (440 mg). To the solution of above compound (440 mg) in acetonitrile (10 mL) was added 48% HF/ CH_3CN (0.4 mL). The mixture was stirred for 2 hours, and acetonitrile was removed under reduced pressure. The remaining was diluted with EtOAc, and was washed with water (3x) and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/5) gave compound 27 (120 mg): ^1H NMR ($CDCl_3$) δ 7.70 (2 H, m), 7.27 (2 H, m), 7.15 (5 H, m), 6.95 (3 H, m), 5.73 (1 H, m), 5.6-5.4 (1 H, m), 5.16 (1 H, m), 4.96 (1 H, m), 4.22-3.60 (13 H, m), 3.42 (2 H, m), 3.4-2.6 (11 H, m), 2.1-3.8 (3 H, m), 1.39 (3 H, m), 1.24 (3 H, m), 0.84 (6 H, m).

Scheme 6



I. $TfOCH_2PO(OBn)_2/Cs_2CO_3$ II.H_2/10% Pd-C; III.a. TFA/CH_2Cl_2;
b.CbzCl/NaOH; IV. a.$SOCl_2$/60 C;b. PhOH/pyridine; V. a. NaOH/THF;
b. HCl; c. $SOCl_2$/60 C; d. Ethyl (s)Lactate/pyridine; VI. H_2/10% Pd-C/HOAc;
VII:a. compound 15/$NaBH_3CN$/HOAc; b. 2%HF/CH_3CN;
VIII. esterase/1.0 PBS buffer/CH_3CN/DMSO

Example 28

Compound 28: To a solution of compound 19 (7.5 g, 30 mmol) in acetonitrile (420 mL) was added dibenzyl triflate (17.8 g, 42 mmol), followed by cesium carbonate (29.4 g, 90 mmol).

The mixture was stirred for 2.5 hours, and was filtered. Acetonitrile was removed under reduced pressure, and the remaining was diluted with EtOAc. The mixture was washed with water (3x) and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 2/1 to 1/1) gave compound 28 (14.3 g).

Example 29

Compound 29: To a solution of compound 28 (14.3 g) in ethanol (500 mL) was added 10% palladium on carbon (1.45 g). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 29 (9.1 g).

Example 30

Compound 30: To a solution of compound 29 (9.1 g) in CH_2Cl_2 (60 mL) was added trifluoroacetic acid (30 mL). The mixture was stirred for 4 hrs, and was concentrated under reduced pressure. The mixture was coevaporated with CH_2Cl_2 (3x) and toluene, and was dried under high vacuum to give a white solid. The white solid was dissolved in 2.0 N NaOH solution (45 mL, 90 mmol), and was cooled to 0°C. To the above solution was added slowly a solution of benzyl chloroformate (6.4 mL, 45 mmol) in toluene (7 mL). The mixture was warmed to 25°C, and was stirred for 6 hours. 2.0 N sodium hydroxide was added to above solution until pH =11. The aqueous was extracted with ethyl ether (3x), and was cooled to 0°C. To the above aqueous phase at 0°C was added concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combine organic layers were washed with brine, and were dried over $MgSO_4$. Concentration gave compound 30 (11.3 g) as a white solid.

Example 31

Compound 31: To the suspension of compound 30 (11.3 g, 30 mmol) in toluene (150 mL) was added thionyl chloride (13 mL, 180 mmol), followed by DMF (a few drops). The reaction mixture was heated at 65°C for 4.5 hrs, and evaporated under reduced pressure. The mixture was coevaporated with toluene (2x) to afford a brown solid. To the solution of the brown solid in CH_2Cl_2 (120 ml) at 0°C was added phenol (11.28 g, 120 mmol), followed by slow addition of pyridine (14.6 mL, 180 mmol). The reaction mixture was allowed to warm to 25°C and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture

was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Concentration gave a dark oil, which was purified by flash column chromatography (hexanes/EtOAc = 3/1 to 1/1) to afford compound 31 (9.8 g).

Example 32

Compound 32: To a solution of compound 31 (9.8 g, 18.5 mmol) in THF (26 mL) was added 20.3 mL of 1.0 N NaOH solution. The mixture was stirred at 25°C for 2.5 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and was washed with EtOAc (3x). The aqueous phase was cooled to 0°C, and was acidified with concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over $MgSO_4$. Concentration under reduced pressure gave a solid (8.2 g). To a suspension of above solid (4.5 g, 10 mmol) in toluene (50 mL) was added thionyl chloride (4.4 mL, 60 mmol), followed by DMF (0.2 mL). The mixture was heated at 70°C for 3.5 hours. The solvent and reagent were removed under reduced pressure. The mixture was coevaporated with toluene (2x) to give a white solid. To the solution of the above solid in CH_2Cl_2 (40 mL) at 0°C was added ethyl (s)-lactate (2.3 mL, 20 mmol), followed by pyridine (3.2 mL, 40 mmol). The mixture was warmed to 25°C and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure, and was diluted with EtOAc. The organic phase was washed with 1 N HCl, water, and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 2/1 to 1/1) gave compound 32 (4.1 g).

Example 33

Compound 33: To a solution of compound 32 (3.8 g, 6.9 mmol) in EtOAc/EtOH (30 mL/30 mL) was added 10% palladium on carbon (380 mg), followed by acetic acid (400 µL, 6.9 mmol). The mixture was hydrogenated for 3 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 33 (3.5 g).

Example 34

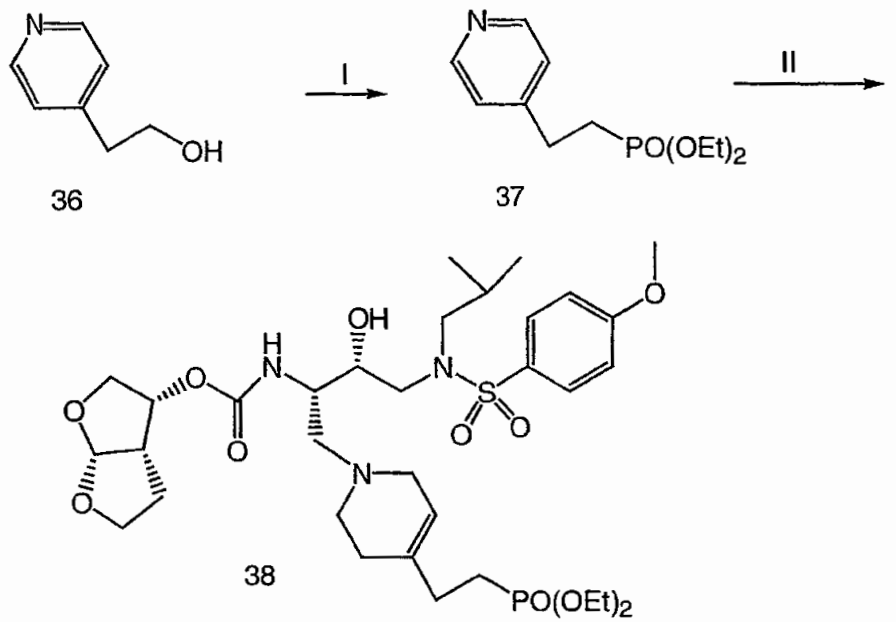
Compound 34: To a solution of compound 15 (1.70 g, 2.76 mmol) in EtOAc (17 mL) was added compound 33 (3.50 g, 6.9 mmol). The mixture was stirred for 5 minutes, and was cooled to 0°C, and sodium cyanoborohydride (347 mg, 5.52 mmol) was added. The mixture

was stirred for 6 hrs. The mixture was diluted with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/6) gave the intermediate (3.4 g). To the solution of above compound (3.4 g) in acetonitrile (100 mL) was added 48% HF/ CH_3CN (4 mL). The mixture was stirred for 2 hours, and acetonitrile was removed under reduced pressure. The remaining was diluted with EtOAc, and was washed with saturated sodium carbonate, water (3x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/5) gave compound 34 (920 mg): ^{1}H NMR ($CDCl_3$) δ 7.71 (2 H, m), 7.38-7.19 (5 H, m), 6.92 (3 H, m), 6.75 (2 H, m), 5.73 (1 H, m), 5.57-5.35 (1 H, m), 5.16 (2 H, m), 4.5 (2 H, m), 4.2-3.6 (13 H, m), 3.25-2.50 (11 H, m), 2.0-1.8 (3 H, m), 1.5 (3 H, m), 1.23 (3 H, m), 0.89 (6 H, m).

Example 35

Compound 35: To a solution of compound 34 (40 mg) in CH_3CN /DMSO (1 mL/0.5 mL) was added 1.0 M PBS buffer (5 mL), followed by esterase (200 μL). The mixture was heated at 40°C for 48 hours. The mixture was purified by reverse phase HPLC to give compound 35 (11 mg).

Scheme 7



I. a.$SOCl_2$/toluene/60 C; b. $P(OEt)_3$/toluene/120 C;
II. a. compound 14/Tf_2O;b. $NaBH_4$/EtOH/HOAc; c. 2% HF/CH_3CN

Example 36

Compound 36: Compound 36 was purchased from Aldrich.

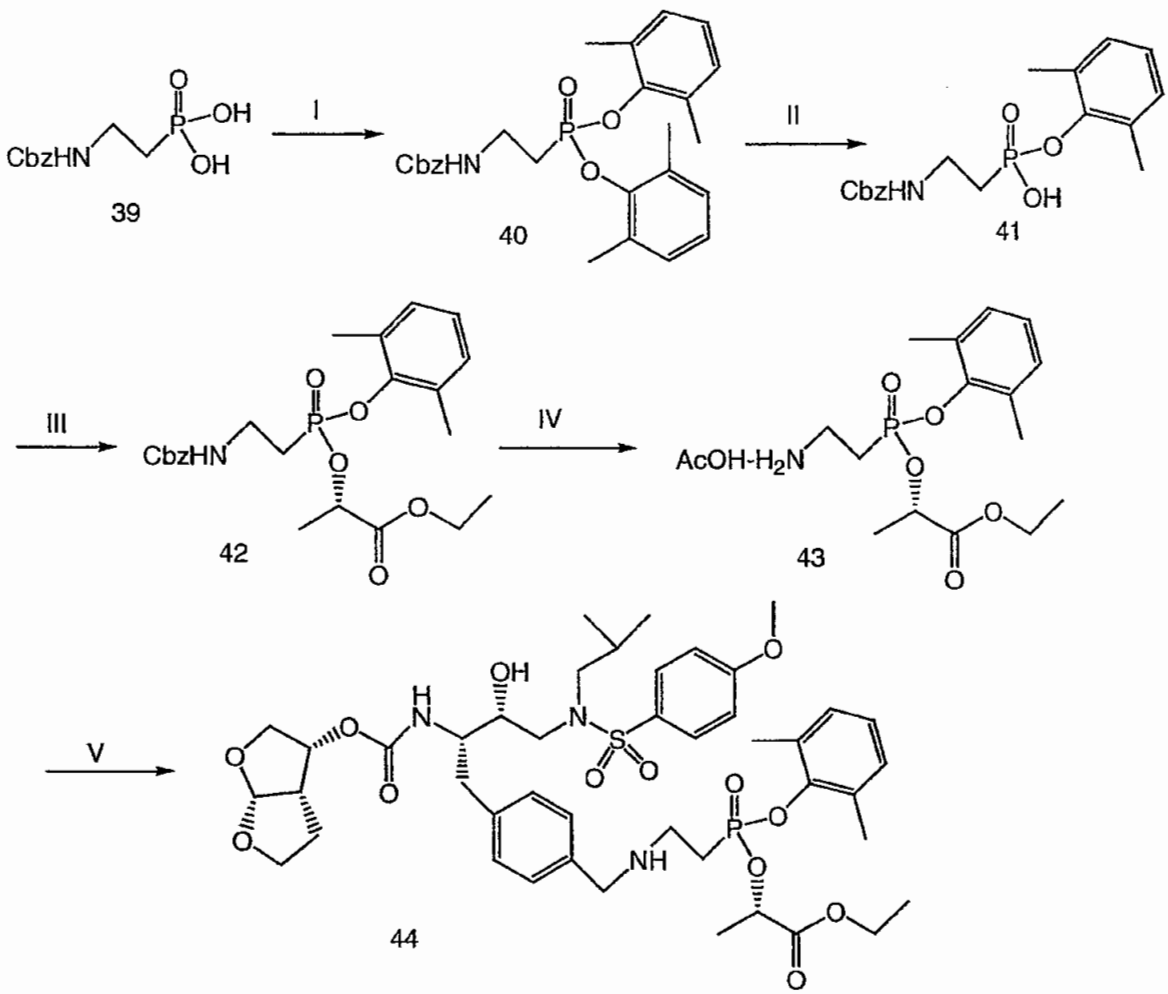
Example 37

Compound 37: To a solution of compound 36 (5.0 g, 40 mmol) in chloroform (50 mL) was added thionyl chloride (12 mL) slowly. The mixture was heated at 60°C for 2.5 hours. The mixture was concentrated under reduced pressure to give a yellow solid. To the suspension of above solid (5.2 g, 37 mmol) in toluene (250 mL) was added triethyl phosphite (19 mL, 370 mmol). The mixture was heated at 120°C for 4 hours, and was concentrated under reduced pressure to give a brown solid. The solid was dissolved in EtOAc, and was basified with 1.0 N NaOH. The organic phase was separated and was washed with water (2x) and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 9/1) gave compound 37 (4.8 g).

Example 38

Compound 38: To a solution of compound 14 (100 mg, 0.16 mmol) and compound 37 (232 mg, 0.74 mmol) in CH_2Cl_2 (1 mL) at –40°C was added triflic anhydride (40 μL, 0.24 mmol) slowly. The mixture was warmed to 25°C slowly, and was stirred for 12 hours. The mixture was concentrated, and was diluted with EtOH/EtOAc (2 mL/0.4 mL). To the above solution at 0°C was added sodium borohydride (91 mg) in portions. The mixture was stirred at 0°C for 3 hours, and was diluted with EtOAc. The mixture was washed with saturated sodium bicarbonate, water, and brine, and was dried over $MgSO_4$. Purification by flash column chromatograph (CH_2Cl_2/iPrOH = 100/5 to 100/10) gave the intermediate (33 mg). To the solution of above intermediate in acetonitrile (2.5 mL) was added 48% HF/ CH_3CN (0.1 mL). The mixture was stirred for 30 minutes, and was diluted with EtOAc. The organic solution was washed with 0.5 N sodium hydroxide, water, and brine, was dried over $MgSO_4$. Purification by reverse HPLC gave compound 38 (12 mg): ^{1}H NMR ($CDCl_3$) δ 7.72 (2 H, d, J = 8.9 Hz), 7.02 (2 H, d, J = 8.9 Hz), 5.70 (1 H, m), 5.45 (1 H, m), 5.05 (1 H, m), 4.2-3.4 (19 H, m), 3.4-2.8 (5 H, m), 2.45-2.20 (4 H, m), 2.15-1.81 (5 H, m), 1.33 (6 H, m), 0.89 (6 H, m).

Scheme 8



I. a..$SOCl_2$/toluene/60 C; b. ArOH/pyridine; II. a.NaOH/THF/H_2O; b. HCl;
III. b.$SOCl_2$/toluene/60 C; c.ethyl lactate/pyridine; IV. H_2/10%Pd-C/EtOAc/HOAc;
V. a. compound 6/$MgSO_4$; b. HOAc/$NaCNBH_3$

Example 39

Compound 39 was prepared by the methods of the previous Examples.

Example 40

Compound 40: To the suspension of compound 39 (4.25 g, 16.4 mmol) in toluene (60 mL) was added thionyl chloride (7.2 mL, 99 mmol), followed by DMF (a few drops). The reaction mixture was heated at 65°C for 5 hrs, and evaporated under reduced pressure. The mixture was coevaporated with toluene (2x) to afford a brown solid. To the solution of the brown solid in CH_2Cl_2 (60 ml) at 0°C was added 2,6-dimethylphenol (8.1 g, 66 mmol),

followed by slow addition of pyridine (8mL, 99 mmol). The reaction mixture was allowed to warm to 25°C and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 3/1 to 1/1) afforded compound 40 (1.38 g).

Example 41

Compound 41: To a solution of compound 40 (1.38 g, 1.96 mmol) in THF (6 mL) was added 3.55 mL of 1.0 N NaOH solution. The mixture was stirred at 25°C for 24 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and was washed with EtOAc (3x). The aqueous phase was cooled to 0°C, and was acidified with concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over $MgSO_4$. Concentration under reduced pressure gave compound 41 as a white solid (860 mg).

Example 42

Compound 42: To a suspension of compound 41 (1.00 g, 2.75 mmol) in toluene (15 mL) was added thionyl chloride (1.20 mL, 16.5 mmol), followed by DMF (3 drops). The mixture was heated at 65°C for 5 hours. The solvent and reagent were removed under reduced pressure. The mixture was coevaporated with toluene (2x) to give a brown solid. To the solution of the above solid in CH_2Cl_2 (11 mL) at 0°C was added ethyl (s)-lactate (1.25, 11 mmol), followed by pyridine (1.33 mL, 16.6 mmol). The mixture was warmed to 25°C and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure, and was diluted with EtOAc. The organic phase was washed with 1 N HCl, water, and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 1.5/1 to 1/1) gave compound 42 (470 mg).

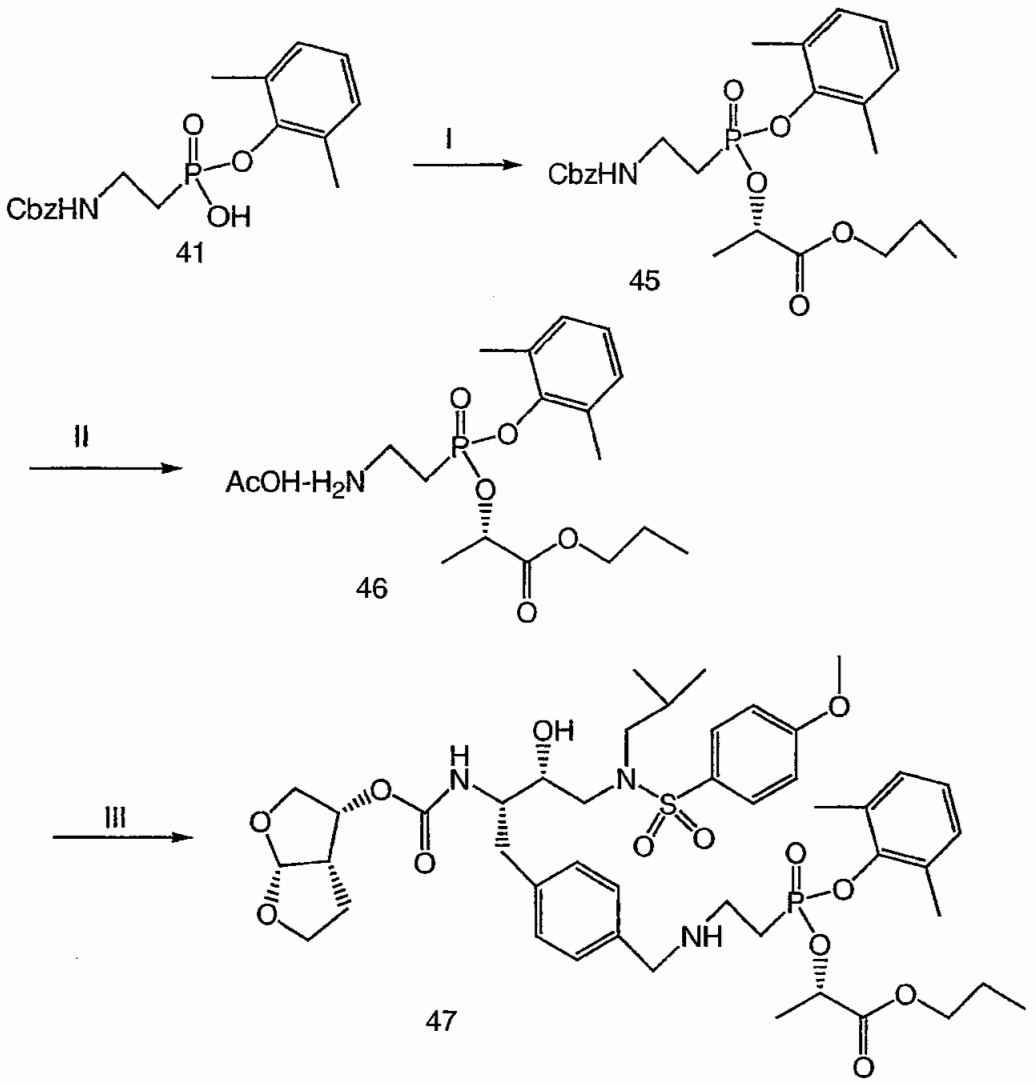
Example 43

Compound 43: To a solution of compound 42 (470 mg) in EtOH (10 mL) was added 10% palladium on carbon (90 mg), followed by acetic acid (150 µL). The mixture was hydrogenated for 6 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 43 (400 mg).

Example 44

Compound 44: To a solution of compound 6 (551 mg, 0.93 mmol) in 1,2-dichloroethane (4 mL) was added compound 43 (400 mg, 1.0 mmol), followed by $MgSO_4$ (1 g). The mixture was stirred for 3 hours, and acetic acid (148 μL) and sodium cyanoborohydride (117 mg, 1.86 mmol) were added sequentially. The mixture was stirred for 1 hour. The mixture was diluted with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (EtOAc to EtOAc/EtOH = 9/1) gave compound 44. Compound 44 was dissolved in CH_2Cl_2 (25 mL), and trifluoroacetic acid (100 μL) was added. The mixture was concentrated to give compound 44 as a TFA salt (560 mg): ^{1}H NMR ($CDCl_3$) δ 7.74 (2 H, m), 7.39 (2 H, m), 7.20 (2 H, m), 7.03 (5 H, m), 5.68 (1 H, m), 5.43 (1 H, m), 5.01 (1 H, m), 4.79 (1 H, m), 4.35-4.20 (4 H, m), 4.18-3.4 (11 H, m), 3.2-2.6 (9 H, m), 2.30 (6 H, m), 1.82 (1 H, m), 1.70 (2 H, m), 1.40-1.18 (6 H, m), 0.91 (6 H, m).

Scheme 9



I. b.$SOCl_2$/toluene/60 C; c.propyl (s)-lactate/pyridine;
II. H_2/10%Pd-C/EtOAc/HOAc;
III. a. compound 6/$MgSO_4$; b. HOAc/$NaCNBH_3$

Example 45

Compound 45: To a suspension of compound 41 (863 mg, 2.4 mmol) in toluene (13 mL) was added thionyl chloride (1.0mL, 14.3 mmol), followed by DMF (3 drops). The mixture was heated at 65°C for 5 hours. The solvent and reagent were removed under reduced pressure. The mixture was coevaporated with toluene (2x) to give a brown solid. To the solution of the above solid in CH_2Cl_2 (10 mL) at 0°C was added propyl (s)-lactate (1.2mL, 9.6 mmol), followed by triethylamine (2.0 mL, 14.4 mmol). The mixture was warmed to 25°C and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure, and was

diluted with EtOAc. The organic phase was washed with water and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 1.5/1 to 1/1) gave compound 45 (800 mg).

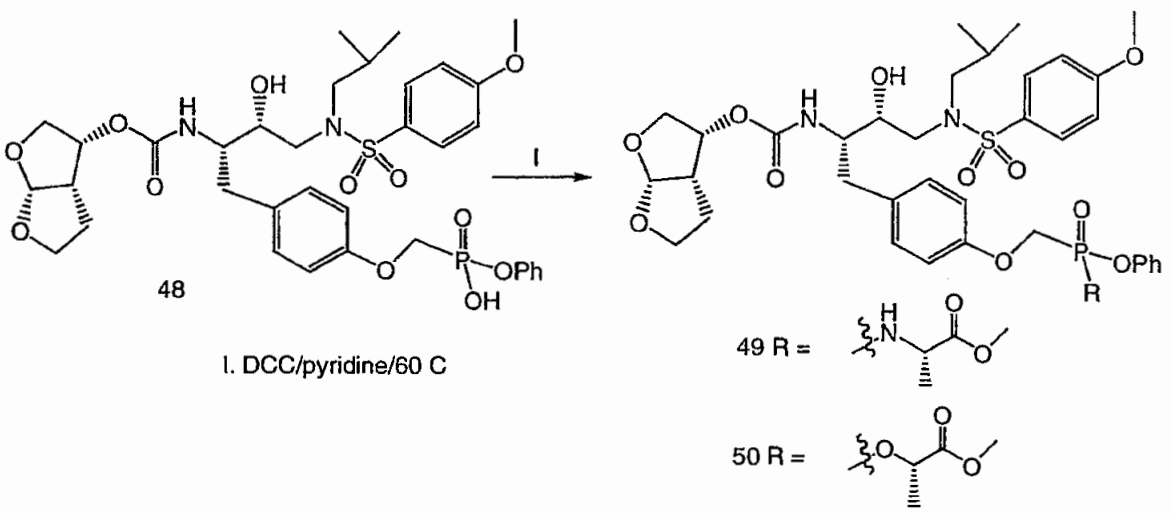
Example 46

Compound 46: To a solution of compound 45 (785 mg) in EtOH (17 mL) was added 10% palladium on carbon (150 mg), followed by acetic acid (250 μL). The mixture was hydrogenated for 16 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 46 (700 mg).

Example 47

Compound 47: To a solution of compound 6 (550 mg, 0.93 mmol) in 1,2-dichloroethane (4 mL) was added compound 43 (404 mg, 1.0 mmol), followed by $MgSO_4$ (1 g). The mixture was stirred for 3 hours, and acetic acid (148 μL) and sodium cyanoborohydride (117 mg, 1.86 mmol) were added sequentially. The mixture was stirred for 1 hour. The mixture was diluted with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (EtOAc to EtOAc/EtOH = 9/1) gave compound 47. Compound 47 was dissolved in CH_2Cl_2 (25 mL), and trifluoroacetic acid (100 μL) was added. The mixture was concentrated to give compound 47 as a TFA salt (650 mg): ^1H NMR ($CDCl_3$) δ 7.74 (2 H, m), 7.41 (2 H, m), 7.25-7.1 (2 H, m), 7.02 (5 H, m), 5.65 (1 H, m), 5.50 (1 H, m), 5.0-4.75 (2 H, m), 4.25-4.05 (4 H, m), 4.0-3.4 (11 H, m), 3.2-2.6 (9 H, m), 2.31 (6 H, m), 1.82-1.51 (3 H, m), 1.45-1.2 (5 H, m), 0.93 (9 H, m).

Scheme 10



Example 48

Compound 48 was made by the methods of the previous Examples.

Example 49

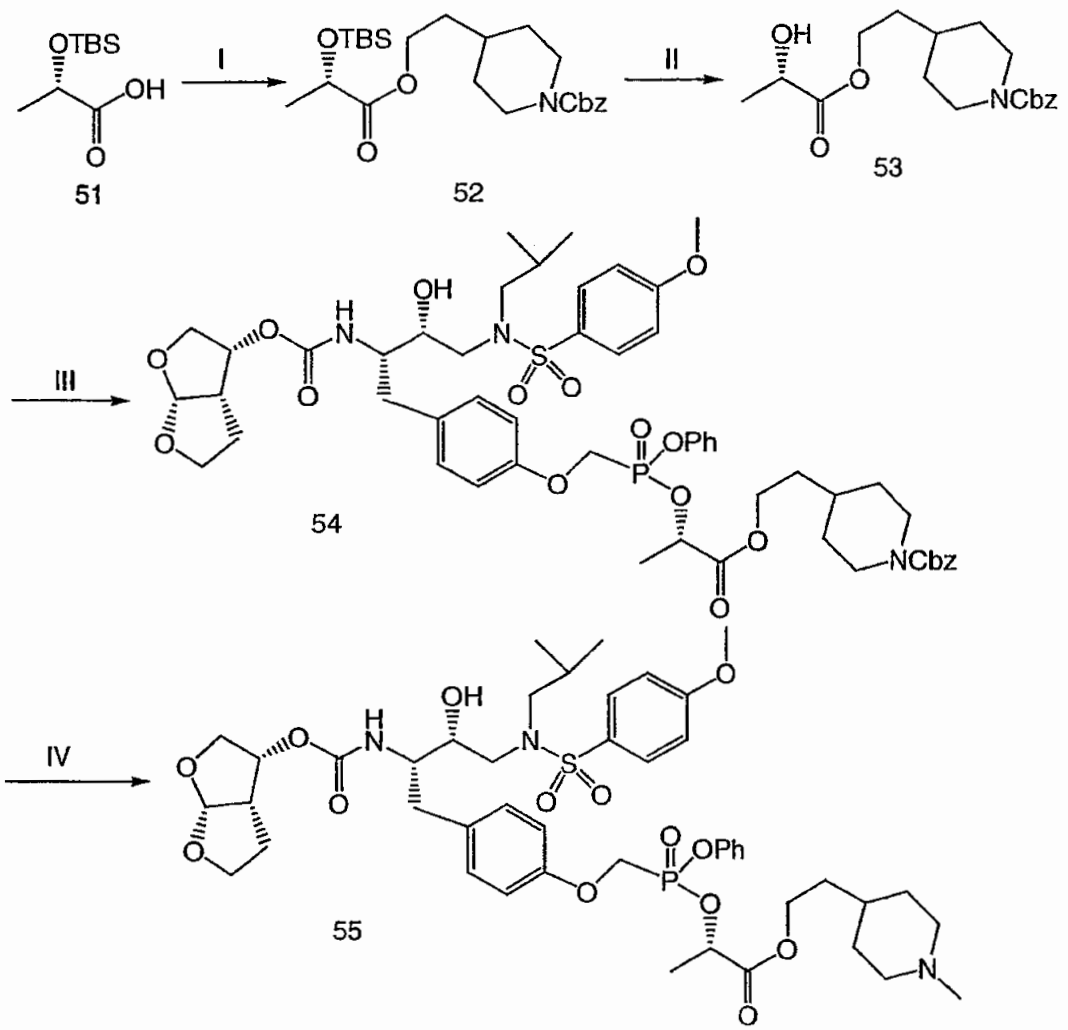
Compound 49: To a solution of compound 48 (100 mg, 0.13 mmol) in pyridine (0.75 mL) was added L-alanine methyl ester hydrochloride (73 mg, 0.52 mmol), followed by DCC (161 mg, 0.78 mmol). The mixture was heated at 60°C for 1 hour. The mixture was diluted with EtOAc, and was washed with 0.2 N HCl, water, 5% sodium bicarbonate, and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/5) gave compound 49 (46 mg): ^{1}H NMR ($CDCl_3$) δ 7.73 (2 H, m), 7.38-7.18 (7 H, m), 7.03 (2 H, m), 6.89 (2 H, m), 5.68 (1 H, m), 5.05 (1 H, m), 4.95 (1 H, m), 4.30 (3 H, m), 4.0-3.6 (12 H, m), 3.2-2.8 (7 H, m), 1.84-1.60 (3 H, m), 1.38 (3 H, m), 0.93 (6 H, m).

Example 50

Compound 50: To a solution of compound 48 (100 mg, 0.13 mmol) in pyridine (0.75 mL) was added methyl (s)-lactate (41 mg, 0.39 mmol), followed by DCC (81 mg, 0.39 mmol). The mixture was heated at 60°C for 2 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc (5 mL), and was filtered. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/5) gave compound 50 (83 mg): ^{1}H NMR ($CDCl_3$) δ 7.74 (2 H, m), 7.38-7.14 (7 H, m), 7.02 (2 H, m), 6.93 (2 H, m), 5.67 (1 H,

m), 5.18 (1 H, m), 5.04 (1 H, m), 4.92 (1 H, m), 4.5 (2 H, m), 4.0-3.68 (12 H, m), 3.2-2.75 (7 H, m), 1.82 (1 H, m), 1.75-1.50 (5 H, m), 0.93 (6 H, m).

Scheme 11



I. Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/ROH/iPr_2NEt;
II.15% HF/CH_3CN; III. Compound 48/DCC/pyridine/60 C; IV. a. H_2/10%Pd-C;
b. $NaBH_3CN$/HCHO/HOAc

Example 51

Compound 51: To a solution of benzyl (s)-lactate (4.0 g, 20 mmol) in DMF (40 mL) was added imidazole (2.7 g, 20 mmol), followed by tert-butyldimethylsilyl chloride (3.3 g, 22 mmol). The mixture was stirred for 14 hours, and diluted with EtOAc. The organic phase was washed with 1.0 N HCl solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$.

Concentration gave the lactate intermediate (6.0 g). To the solution of the above intermediate in EtOAc (200 mL) was added 10% Palladium on carbon (700 mg). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 minutes, and was filtered through a pad of celite. Concentration gave compound 51 (3.8 g).

Example 52

Compound 52: To a solution of compound 51 (1.55 g, 7.6 mmol) in CH_2Cl_2 (20 mL) was added 4-benzyloxycarbonylpiperidineethanol (2.00 g, 7.6 mmol), followed by benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (4.74 g, 9.1 mmol) and diisopropylethylamine (1.58 mL, 9.1 mmol). The mixture was stirred for 14 hours, and dichloromethane was removed. The mixture was diluted with EtOAc, and was washed with brine, and dried with $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 10/1) gave compound 52 (1.50 g).

Example 53

Compound 53: To a solution of compound 52 (1.50 g) in CH_3CN was added 58% HF/ CH_3CN (5 mL). The mixture was stirred for 30 minutes, and acetonitrile was removed under reduced pressure. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 1/1) gave compound 53 (1.00 g).

Example 54

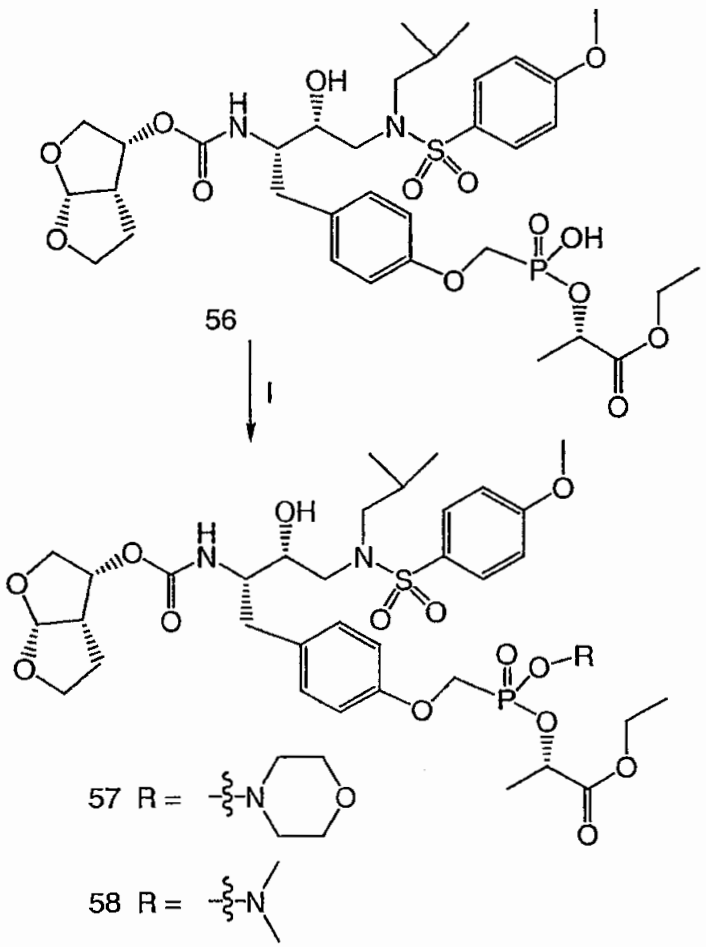
Compound 54: To a solution of compound 48 (769 mg, 1.0 mmol) in pyridine (6.0 mL) was added compound 53 (1.0 g, 3.0 mmol), followed by DCC (618 mg, 3.0 mmol). The mixture was heated at 60°C for 2 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc (5 mL), and was filtered. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/4) gave compound 54 (630 mg).

Example 55

Compound 55: To a solution of compound 54 (630 mg, 0.58 mmol) in EtOAc (30 mL) was added 10% Palladium on carbon (63 mg), followed by acetic acid (80 μL). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 minutes, and was filtered through a pad of celite. Concentration gave the intermediate. To the solution of the above

intermediate in EtOAc (10 mL) was added 37% formaldehyde (88 μL, 1.18 mmol), followed by acetic acid (101 μL, 1.77 mmol). The mixture was cooled to 0°C, and sodium cyanoborohydride (74 mg, 1.18 mmol) was added. The mixture was stirred at 25°C for 80 minutes, and was diluted with EtOAc. The mixture was washed with water and brine, and was dried over $MgSO_4$. Concentration gave compound 55 as a white solid (530 mg): ^1H NMR ($CDCl_3$) δ 7.74 (2 H, m), 7.40-7.15 (7 H, m), 7.03 (2 H, m), 6.92 (2 H, m), 5.66 (1 H, m), 5.20-5.00 (3 H, m), 4.58 –4.41 (2 H, m), 4.16 (2 H, m), 4.0-3.7 (9 H, m), 3.4-2.6 (14 H, m), 1.90-1.50 (13 H, m), 0.92 (6 H, m).

Scheme 12



I. R_2NOH/DCC/pyridine

Example 56

Compound 56 was made by the methods of the previous Examples.

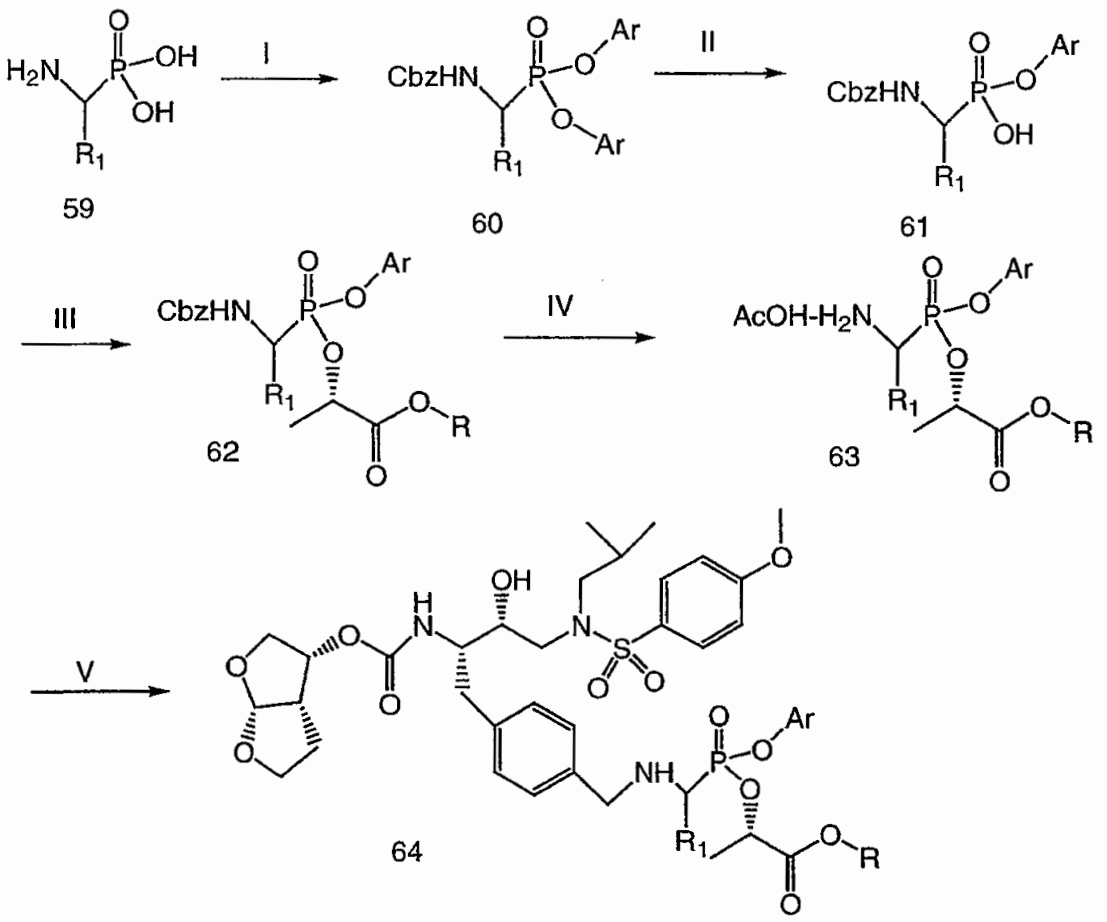
Example 57

Compound 57: To a solution of compound 56 (100 mg, 0.12 mmol) in pyridine (0.6 mL) was added N-hydroxymorpholine (50 mg, 0.48 mmol), followed by DCC (99 mg, 0.48 mmol). The mixture was stirred for 14 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc, and was filtered. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/5) gave compound 57 (53 mg): ^{1}H NMR ($CDCl_3$) δ 7.71 (2 H, d, J = 8.6 Hz), 7.15 (2 H, d, J = 7.6 Hz), 6.99 (2 H, d, J = 8.8 Hz), 6.90 (2 H, m), 5.67 (1 H, m), 5.18 (1 H, m), 5.05 (1 H, m), 4.95 (1 H, m), 4.58-4.38 (2 H, m), 4.21 (2 H, m), 4.02-3.80 (13 H, m), 3.55-3.38 (2 H, m), 3.2-2.78 (9 H, m), 1.9-1.8 (1 H, m), 1.8-0.95 (5 H, m), 1.29 (3 H, m), 0.93 (6 H, m).

Example 58

Compound 58: To a solution of compound 56 (100 mg, 0.12 mmol) in pyridine (0.6 mL) was added N,N-dimethylhydroxylamine hydrochloride (47 mg, 0.48 mmol), followed by DCC (99 mg, 0.48 mmol). The mixture was stirred for 6 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc, and was filtered. Purification by flash column chromatography (CH_2Cl_2/iPrOH = 100/5) gave compound 58 (35 mg). ^{1}H NMR ($CDCl_3$) δ 7.71 (2 H, d, J = 8.9 Hz), 7.15 (2 H, d, J = 8.2 Hz), 6.99 (2 H, d, J =8.4 Hz), 6.89 (2 H, m), 5.65 (1 H, d, J = 5.2 Hz), 5.15 (1 H, m), 4.98 (2 H, m), 4.42 (2 H, m), 4.18 (2 H, m), 4.0-3.6 (9 H, m), 3.2-2.7 (13 H, m), 1.92-1.45 (6 H, m), 1.25 (3 H, m), 0.90 (6 H, m).

Scheme 13



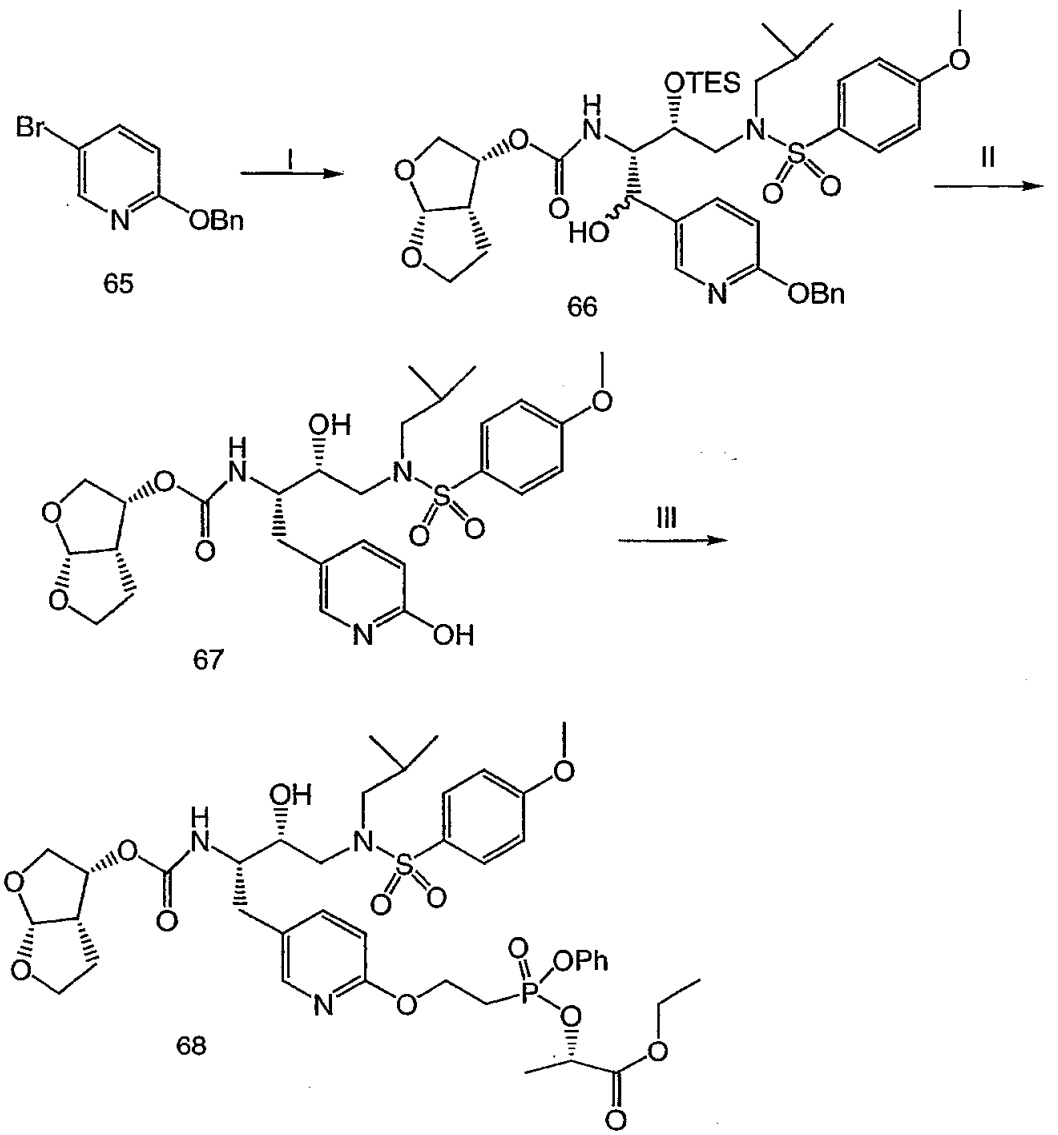
R = Me, Et, Pr, i-Pr; R_1 = H, Me, Et, i-Pr; Ar = phenyl, 2, 6-dimethylphenyl

I. a. CbzCl/NaOH; b..$SOCl_2$/toluene/60 C; c. ArOH/pyridine; II. a.NaOH/THF/H_2O; b. HCl;
III. a.$SOCl_2$/toluene/60 C; b.alkyll lactate/pyridine; IV. H_2/10%Pd-C/EtOAc/HOAc;
V. a. compound 6/$MgSO_4$; b. HOAc/$NaCNBH_3$

Aminomethylphosphonic acid 59 is protected as benzyl carbamate. The phosphonic acid is treated with thionyl chloride to generate dichloridate, which reacts with phenol or 2,6-dimethylphenol to give compound 60. Compound 60 is hydrolyzed with sodium hydroxide, followed by acidification to afford monoacid 61. Monoacid 61 is treated with thionyl chloride to generate monochloridate, which reacts with different alkyl (s)-lactates to form compound 62. Compound 62 is hydrogenated with 10%Pd-C in the presence of acetic acid to

give compound 63. Compound 63 reacts with aldehyde 6 in the presence of $MgSO_4$ to form imine, which is reduced with sodium cyanoborohydride to generate compound 64.

Scheme 14

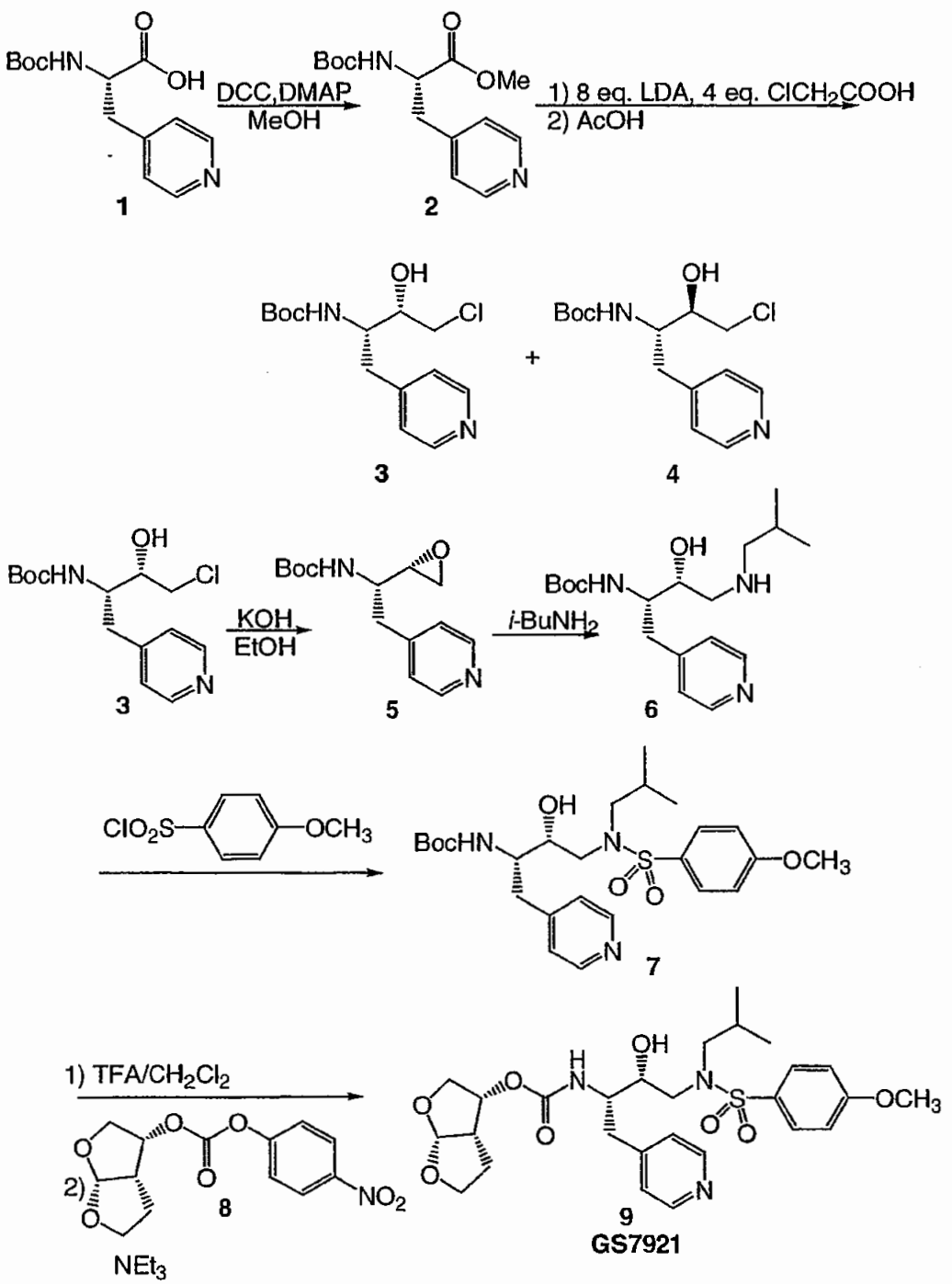


I.a. n-BuLi; b. compound 15; II. H_2/10%Pd-C/HOAc; IV. PPh_3/DEAD

Compound 65 is prepared from 2-hydroxy-5-bromopyridine by alkylation. J. Med. Chem. 1992, 35, 3525. Compound 65 is treated with n-Butyl lithium to generate aryl lithium, which reacts with aldehyde 15 to form compound 66. J. Med. Chem. 1994, 37, 3492. Compound 66 is hydrogenated with 10%Pd-C in the presence of acetic acid to give compound 67. J. Med. Chem. 2000, 43, 721. Compound 68 is prepared from compound 67

with corresponding alcohol under Mitsunobu reaction conditions. Bioorg. Med.Chem. Lett.. 1999, 9, 2747.

Scheme 1



Example 1

Methyl 2-(*S*)-(dimethylethoxycarbonylamino)-3-(4-pyridyl)propanoate (2): A solution of N-tert-Butoxycarbonyl-4-pyridylalanine (**1**, 9.854 g, 37 mmol, Peptech), 4-dimethylaminopyridine (4.52 g, 37 mmol, Aldrich), and dicyclohexylcarbodiimide (15.30 g, 74.2 mmol, Aldrich) in methanol (300 mL) was stirred at 0°C for 2 h and at room temperature for 12 h. After the solids were removed by filtration, the filtrate was concentrated under reduced pressure. More dicyclohexylurea was removed by repeated trituration of the concentrated residue in EtOAc followed by filtration. The residue was chromatographed on silica gel to afford the methyl ester **2** (9.088 g, 88%): ^{1}H NMR ($CDCl_3$) δ 8.53 (d, 2H, J = 5.7 Hz), 7.09 (d, 2H, J = 5.7 Hz), 5.04 (br, 1H), 4.64 (br, 1H), 3.74 (s, 3H), 3.16 (dd, 1H, J = 13.5 and 5.7 Hz), 3.02 (dd, 1H, J = 13.5 and 6.3 Hz), 1.42 (s, 9H); MS (ESI) 281 (M+H).

Example 2

1-Chloro-3-(*S*)-(dimethylethoxycarbonylamino)-4-(4-pyridyl)-2-(*S*)-butanol (3): A solution of diisopropylamine (37.3 mL, 266 mmol, Aldrich) in THF (135 mL) was stirred at –78°C as a solution of *n*-butyllithium (102 mL of 2.3 M solution and 18 mL of 1.4 M solution 260 mmol, Aldrich) in hexane was added. After 10 min, the cold bath was removed and stirred the solution for 10 min at the ambient temperature. The solution was cooled at –78°C again and stirred as a solution of chloroacetic acid (12.255 g, 130 mmol, Aldrich) in THF (50 mL) was added over 20 min. After the solution was stirred for 15 min, this dianion solution was transferred to a stirred solution of the methyl ester **2** (9.087 g, 32.4 mmol) in THF (100 mL) at 0°C over 15 min. The resulting yellow slurry was stirred at 0°C for 10 min and cooled at –78°C. A solution of acetic acid (29 mL, 507 mmol, Aldrich) in THF (29 mL) was added quickly to the slurry and the resulting slurry was stirred at –78°C for 30 min, at 0°C for 30 min, and at room temperature for 15 min. The resulting slurry was dissolved in saturated $NaHCO_3$ solution (750 mL) and EtOAc (500 mL). The separated aqueous layer was extracted with EtOAc (300 mL x 2) and the combined organic fractions were washed with water (750 mL x 2) and saturated NaCl solution (250 mL). The resulting solution was dried ($MgSO_4$) and evaporated under reduced pressure.

A solution of the residue in THF (170 mL) and water (19 mL) was stirred at 0°C as $NaBH_4$ (3.375 g, 89.2 mmol, Aldrich) was added. After 30 min, the solution was evaporated under reduced pressure and the residue was dissolved in EtOAc, acidified with aqueous $NaHSO_4$,

and then neutralized by adding saturated aqueous $NaHCO_3$ solution. The separated aqueous fraction was extracted with EtOAc (100 mL) and the combined organic fractions were washed with water (500 mL) and saturated NaCl solution (100 mL). The solution was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel to afford the chlorohydrin **3** and **4** (4.587 g, 47%) as a mixture of two diastereomers (3~4:1). The obtained mixture was recrystallized from EtOAc-hexane twice to obtain pure desired diastereomer **3** (2.444 g, 25%) as yellow crystals: ^{1}H NMR ($CDCl_3$) δ 8.53 (d, 2H, J = 5.7 Hz), 7.18 (d, 2H, J = 5.7 Hz), 4.58 (br, 1H), 3.94 (m, 1H), 3.87 (br, 1H), 3.75-3.54 (m, 2H), 3.05 (dd, 1H, J = 13.8 and 3.9 Hz), 2.90 (dd, 1H, J = 13.8 and 8.4 Hz), 1.36 (s, 9H); MS (ESI) 301 (M+H).

Example 3

The epoxide **5**: A solution of the chlorohydrin **3** (1.171 g, 3.89 mmol) in ethanol (39 mL) was stirred at room temperature as 0.71 M KOH in ethanol (6.6 mL) was added. After 1.5 h, the mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (60 mL) and water (60 mL). The separated aqueous fraction was extracted with EtOAc (60 mL) and the combined organic fractions were washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated under reduced pressure to obtain the epoxide (1.058 g, quantitative): ^{1}H NMR ($CDCl_3$) δ 8.52 (d, 2H, J = 6.0 Hz), 7.16 (d, 2H, J = 6.0 Hz), 4.57 (d, 1H, J = 7.8 Hz), 3.76 (br, 1H), 3.02-2.92 (m, 2H), 2.85-2.79 (m, 2H), 2.78-2.73 (m, 1H), 1.37 (s, 9H); MS (ESI) 265 (M+H).

Example 4

The hydroxy-amine 6: A solution of the epoxide **5** obtained above and *i*-$BuNH_2$ (3.9 mL, 39.2 mmol, Aldrich) in 58 mL of *i*-PrOH was stirred at 65°C for 2 h and the solution was concentrated under reduced pressure. The residual *i*-PrOH was removed by dissolving the residue in toluene and concentration of the solution twice: ^{1}H NMR ($CDCl_3$) δ 8.51 (d, 2H, J = 6.0 Hz), 7.18 (d, 2H, J = 6.0 Hz), 4.70 (d, 1H, J = 9.6 Hz), 3.86 (br, 1H), 3.46 (q, 1H, J = 5.8 Hz), 3.06 (dd, 1H, J = 14.1 and 3.9 Hz), 2.79 (dd, 1H, J = 14.1 and 9.0 Hz), 2.76-2.63 (m, 3H), 2.43 (m, 2H, J = 6.9 Hz), 1.73 (m, 1H, J = 6.6 Hz), 1.36 (s, 9H), 0.93 (d, 3H, J = 6.6 Hz), 0.92 (d, 3H, J = 6.6 Hz); MS (ESI) 338 (M+H).

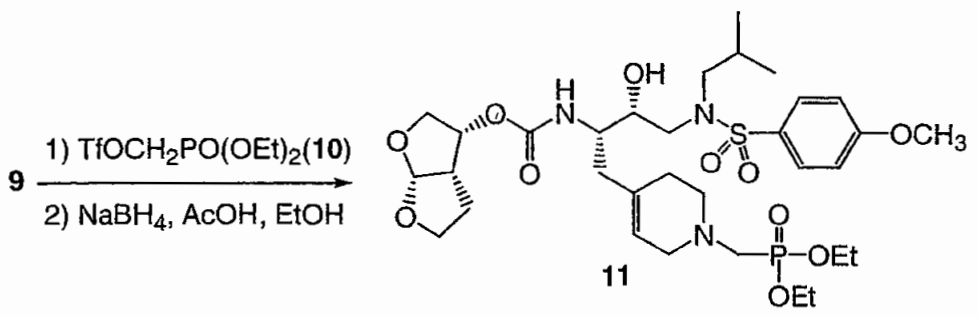
Example 5

The sulfoamide **7**: A solution of the crude **6** and *p*-methoxybenzene sulfonyl chloride (890 mg, 4.31 mmol, Aldrich) in CH_2Cl_2 (24 mL) was stirred at 0°C for 2 h and at room temperature for 13 h. The solution was washed with saturated $NaHCO_3$ solution and the aqueous washing was extracted with CH_2Cl_2 (60 mL). After the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure, the residue was purified by chromatography on silica gel to obtain the sulfoamide **7** (1.484 g, 75%): ^{1}H NMR ($CDCl_3$) δ 8.51 (d, 2H, *J* = 5.7 Hz), 7.73 (d, 2H, *J* = 8.7 Hz), 7.21 (d, 2H, *J* = 5.7 Hz), 7.00 (d, 2H, *J* = 8.7 Hz), 4.68 (d, 1H, *J* = 8.1 Hz), 4.08 (br, 1H), 3.88 (s, 3H), 3.83 (br, 2H), 3.09 (d, 2H, *J* = 5.1 Hz), 3.06-2.80 (m, 4H), 1.85 (m, 1H, *J* = 7.0 Hz), 1.34 (s, 9H), 0.92 (d, 3H, *J* = 6.3 Hz), 0.89 (d, 3H, *J* = 6.6 Hz); MS (ESI) 508 (M+H).

Example 6

The bisfurancarbamate 9: A solution of the sulfoamide **7** (1.484 g, 2.92 mmol) and trifluoroacetic acid (6.8 mL, 88.3 mmol, Aldrich) in CH_2Cl_2 (18 mL) was stirred at room temperature for 2 h. After the solution was evaporated under reduced pressure, the residue was dissolved in acetonitrile (10 mL) and toluene (10 mL), and evaporated to dryness twice to result crude amine as TFA salt. A solution of the crude amine, dimethylaminopyridine (72 mg, 0.59 mmol, Aldrich), diisopropylethylamine (2.55 mL, 14.6 mmol, Aldrich) in acetonitrile was stirred at 0°C as the bisfurancarbonate **8** (907 mg, 3.07 mmol, obtained from Azar) was added in portion. The solution was stirred at 0°C for 1 h and at room temperature for 19 h, and concentrated under reduced pressure. The residue was dissolved in EtOAc (60 mL) and washed with saturated $NaHCO_3$ solution (60 mL). After the aqueous washing was extracted with EtOAc (60 mL), the combined organic fractions were washed with saturated $NaHCO_3$ (60 mL) and saturated NaCl solution (60 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to obtain the carbamate **9** (1.452 g, 88%): ^{1}H NMR ($CDCl_3$) δ 8.50 (d, 2H, *J* = 5.7 Hz), 7.72 (d, 2H, *J* = 8.7 Hz), 7.19 (d, 2H, *J* = 5.7 Hz), 7.01 (d, 2H, *J* = 8.7 Hz), 5.65 (d, 1H, *J* = 5.1 Hz), 5.12 (d, 1H, *J* = 9.3 Hz), 5.02 (q, 1H, *J* = 6.7 Hz), 4.01-3.77 (m, 4H), 3.88 (s, 3H), 3.76-3.63 (m, 2H), 3.18-2.76 (m, 7H), 1.95-1.77 (m, 1H), 1.77-1.56 (m, 2H), 1.56-1.41 (m, 1H), 0.94 (d, 3H, *J* = 6.6 Hz), 0.90 (d, 3H, *J* = 6.9 Hz); MS (ESI) 564 (M+H).

Scheme 2

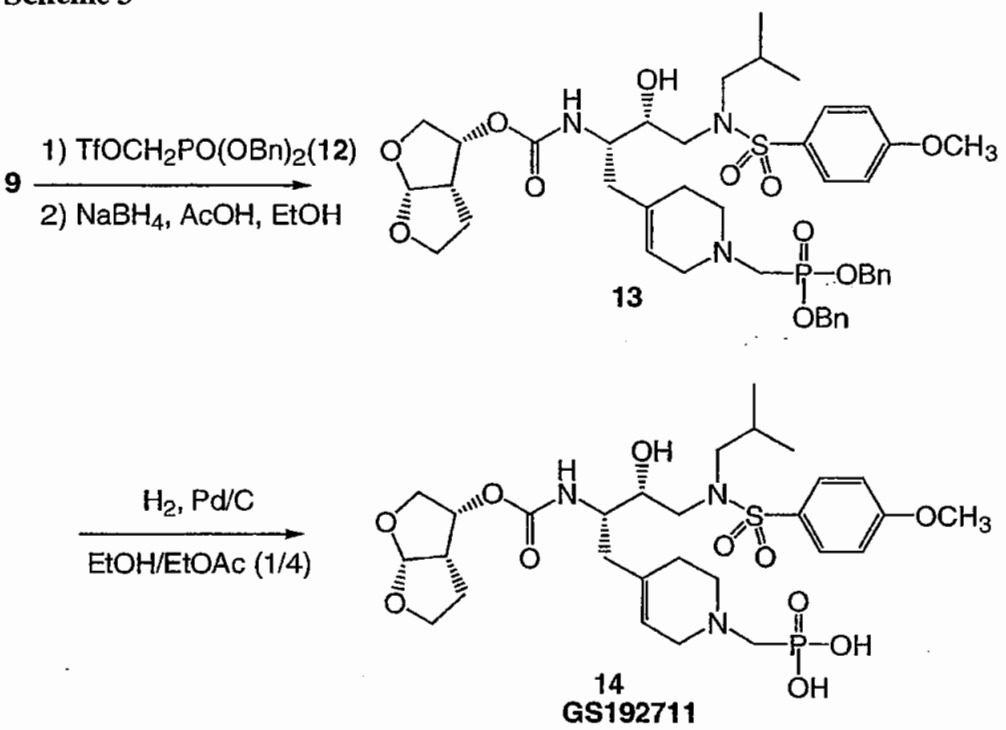


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Example 7

The tetrahydropyridine-diethyl phosphonate 11: A solution of the pyridine **9** (10.4 mg, 0.018 mmol) and the triflate **10** (8.1 mg, 0.027 mmol, in acetone-d_6 (0.75 mL) was stored at room temperature for 9 h and the solution was concentrated under reduced pressure: ^{31}P NMR (acetone-d_3) δ 14.7; MS (ESI) 714 (M^+). The concentrated crude pyridinium salt was dissolved in ethanol (2 mL) and stirred at room temperature as $NaBH_4$ (~10 mg, Aldrich) was added occasionally over 4 h. To the mixture was added a solution of acetic acid (0.6 mL, Aldrich) in ethanol (3 mL) until the pH of the mixture became 3~4. More $NaBH_4$ and acetic acid were added until the reaction was completed. The mixture was carefully concentrated under reduced pressure and the residue was dissolved in saturated NaHCO3 solution (10 mL). The product was extracted using EtOAc (10 mL x 3) and washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to obtain the product **11** (8.5 mg, 64%): ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 2H, J = 8.7 Hz), 7.00 (d, 2H, J = 8.7 Hz), 5.71 (d, 1H, J = 5.1 Hz), 5.41 (br, 1H), 5.15-5.08 (m, 1H), 5.00 (br, 1H), 4.14 (dq, 4H, J = 7.2 Hz), 4.06-3.94 (m, 2H), 3.88 (s, 3H), 3.92-3.80 (m, 2H), 3.75 (dd, 1H, J = 9.6 and 6.6 Hz), 3.79-3.61 (m, 1H), 3.24-2.94 (m, 6H), 2.85 (d, 2H, J = 11.7 Hz), 2.88-2.76 (m, 2H), 2.75-2.63 (m, 1H), 2.38-2.29 (m, 1H), 2.24-2.2.12 (m, 2H), 2.12-1.78 (m, 4H), 1.30 (t, 6H, J = 7.1 Hz), 0.94 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.3 Hz); ^{31}P NMR ($CDCl_3$) δ 24.6; MS (ESI) 740 (M+Na).

Scheme 3



Example 8

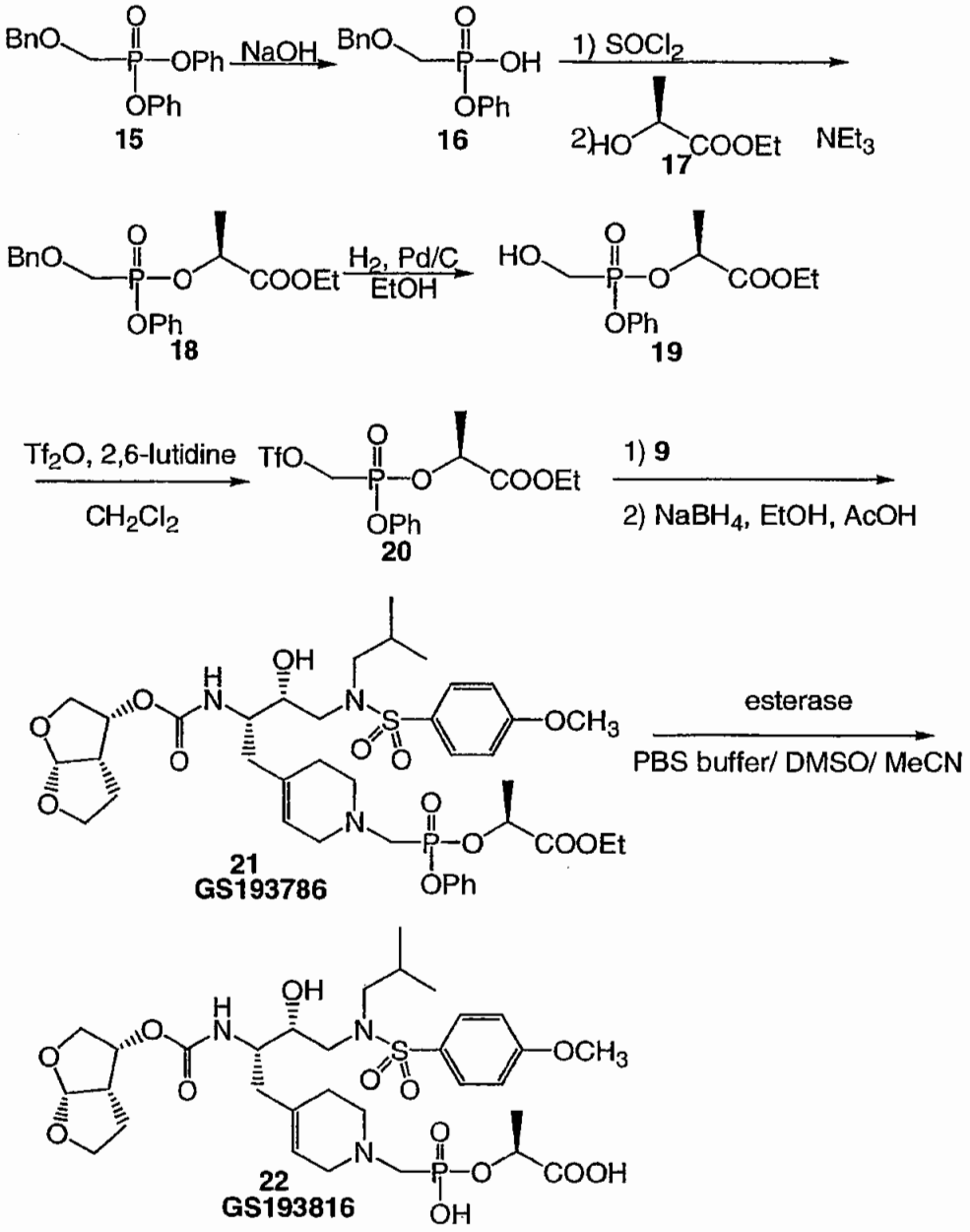
The tetrahydropyridine-dibenzyl phosphonate 13: The compound **13** was obtained by the same procedure as described for compound **11** using the pyridine **9** (10.0 mg, 0.018 mmol) and the triflate **12** (9.4 mg, 0.022 mmol). The product **13** was purified by preparative TLC to afford the dibenzyl phosphonate **13** (8.8 mg, 59%): ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 2H, J = 8.7 Hz), 7.35 (s, 10H), 7.00 (d, 2H, J = 8.7 Hz), 5.65 (d, 1H2H, J = 5.1 Hz), 5.39 (br, 1H), 5.15-4.92 (m, 6H), 4.03-3.77 (m, 6H), 3.77-3.62 (m, 2H), 3.56 (br, 1H), 3.24-2.62 (m, 9H), 2.32 (d, 1H, J = 13.5 Hz), 2.24-1.75 (m, 6H), 0.94 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.3 Hz); ^{31}P NMR ($CDCl_3$) δ 25.5; MS (ESI) 842 (M+H).

Example 9

The phosphonic acid 14: A mixture of the dibenzyl phosphonate **13** (8.8 mg, 0.011 mmol) and 10% Pd/C in EtOAc (2 mL) and EtOH (0.5 mL) was stirred under H_2 atmosphere for 10 h at room temperature. After the mixture was filtered through celite, the filtrate was concentrated to dryness to afford the product **14** (6.7 mg, quantitative): ^{1}H NMR (CD_3OD) δ 7.76 (d, 2H, J = 9.0 Hz), 7.10 (d, 2H, J = 9.0 Hz), 5.68 (d, 1H, J = 5.1 Hz), 5.49 (br, 1H), 5.11 (m, 1H), 3.90 (s, 3H), 4.04-3.38 (m, 10H), 3.22 (d, 2H, J = 12.9 Hz), 3.18-3.00 (m, 2H),

2.89-2.75 (m, 2H), 2.68-2.30 (m, 3H), 2.21-1.80 (m, 4H), 0.92 (d, 3H, J = 6.3 Hz), 0.85 (d, 3H, J = 6.3 Hz); ^{31}P NMR (CD_3OD) δ 6.29; MS (ESI) 662 (M+H).

Scheme 4



Example 10

Diphenyl benzyloxymethylphosphonate 15: To a solution of diphenylphosphite (46.8 g, 200 mmol, Aldrich) in acetonitrile (400 mL) (at ambient temperature) was added potassium carbonate (55.2 g, 400 mmol) followed by the slow addition of benzyl chloromethyl ether (42

mL, 300 mmol, about 60%, Fluka). The mixture was stirred overnight, and was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with water, saturated NaCl, dried (Na_2SO_4), filtered and evaporated. The crude product was chromatographed on silica gel to afford the benzylether (6.8 g, 9.6%) as a colorless liquid.

Example 11

Monoacid 16: To a solution of diphenyl benzyloxymethylphosphonate 15 (6.8 g, 19.1 mmol) in THF (100 mL) at room temperature was added 1N NaOH in water (21 mL, 21 mmol). The solution was stirred 3 h. The THF was evaporated under reduced pressure and water (100 mL) was added. The aqueous solution was cooled to 0°C, neutralized to pH 7 with 3N HCl and washed with EtOAc. The aqueous solution was again cooled to 0°C, acidified with 3N HCl to pH 1, saturated with sodium chloride, and extracted with EtOAc. The organic layer was washed with brine and dried (Na_2SO_4), filtered and evaporated, then co-evaporated with toluene to yield the monoacid (4.0 g, 75%) as a colorless liquid. ^{1}H NMR ($CDCl_3$) δ 7.28-7.09 (m, 10H), 4.61 (s, 2H), 3.81 (d, 2H);. ^{31}P NMR ($CDCl_3$) δ 20.8.

Example 12

Ethyl lactate phosphonate 18: To a solution of monoacid 16 (2.18 g,7.86 mmol) in anhydrous acetonitrile (50 mL) under a nitrogen atmosphere was slowly added thionyl chloride (5.7 mL, 78mmol). The solution was stirred in a 70°C oil bath for three hours, cooled to room temperature and concentrated. The residue was dissolved in anhydrous dichloromethane (50mL), and this solution cooled to 0°C and stirred under a nitrogen atmosphere. To the stirring solution was added ethyl (S)-(-)-lactate (2.66 mL, 23.5 mmol) and triethylamine (4.28 mL, 31.4 mmol). The solution was warmed to room temperature and allowed to stir for one hour. The solution was diluted with ethyl acetate, washed with water, brine, citric acid and brine again, dried ($MgSO_4$), filtered through Celite, concentrated under reduced pressure and chromatographed on silica gel using 30% ethylacetate in hexane. The two diastereomers were pooled together. ^{1}H NMR ($CDCl_3$) δ 7.40-7.16 (m, 20H), 5.18-5.13 (m, 2H), 4.73 (s, 2H), 4.66 (d, 2H), 4.28-4.11 (m, 5H), 4.05 (d, 2H), 3.95 (d, 2H), 1.62 (d, 3H), 1.46 (d, 3H), 1.30-1.18 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 19.6, 17.7.

Example 13

Ethyl lactate phosphonate with free alcohol 19: Ethyl lactate phosphonate 18 was dissolved in EtOH (50mL) and under a nitrogen atmosphere 10% Pd-C (approximately 20 wt %) was added. The nitrogen atmosphere was replaced with hydrogen (1atm) and the suspension stirred for two hours. 10% Pd-C was again added (20 wt %) and the suspension stirred five hours longer. Celite was added, the reaction mixture was filtered through Celite and the filtrate was concentrated to afford 1.61 g (71% from monoacid 16) of the alcohol as a colorless liquid. ^{1}H NMR ($CDCl_3$) δ 7.40-7.16 (m, 10H), 5.16-5.03 (m, 2H), 4.36-4.00 (m, 8H), 1.62 (d, 3H), 1.46 (d, 3H), 1.30-1.22 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 22.3, 20.0.

Example 14

Triflate 20: To a solution of ethyl lactate phosphonate with free alcohol 19 (800 mg, 2.79 mmol) in anhydrous dichloromethane (45 mL) chilled to -40°C under a nitrogen atmosphere was added triflic anhydride (0.516 mL, 3.07 mmol) and 2-6 lutidine (0.390 mL, 3.34 mmol). The solution was stirred for 3 hr, then warmed to -20°C and stirred one hour longer. 0.1 equivalents of triflic anhydride and 2-6 lutidine were then added and stirring was resumed for 90 minutes more. The reaction mixture was diluted with ice-cold dichloromethane, washed with ice-cold water, washed with ice-cold brine and the organic layer was dried ($MgSO_4$) and filtered. The filtrate was concentrated and chromatographed on silica gel using 30% EtOAc in hexane as eluent to afford 602 mg (51%) of the triflate diastereomers as a slightly pink, transparent liquid. ^{1}H NMR ($CDCl_3$) δ 7.45-7.31 (m, 4H), 7.31-7.19 (m, 6H), 5.15-4.75 (m, 6H), 4.32-4.10 (4H), 1.62 (d, 3H), 1.50 (d, 3H), 1.30-1.22 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 10.3, 8.3.

Example 15

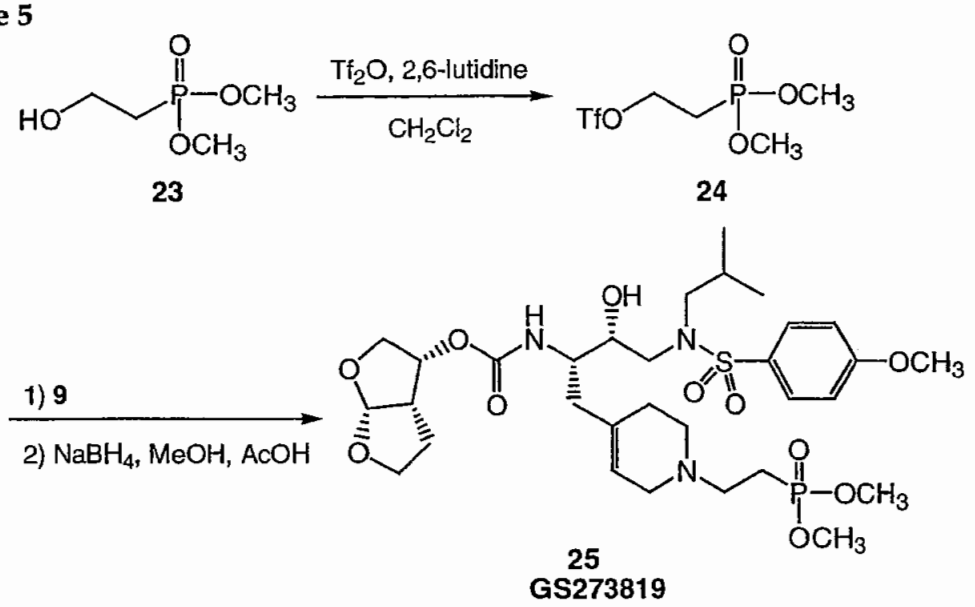
The tetrahydropyridine-prodrug 21: A solution of the pyridine **9** (11.1 mg, 0.020 mmol) and the triflate **20** (11.4 mg, 0.027 mmol) in acetone-d_6 (0.67 mL, Aldrich) was stored at room temperature for 7 h and the solution was concentrated under reduced pressure: ^{31}P NMR (acetone-d_6) δ 11.7, 10.9; MS (ESI) 838 (M+H). The concentrated crude pyridinium salt was dissolved in ethanol (1 mL) and added 2~3 drops of a solution of acetic acid (0.6 mL, Aldrich) in ethanol (3 mL). The solution was stirred at 0°C as $NaBH_4$ (7~8 mg, Aldrich) was

added. More acetic acid solution was added to adjust pH 3~4 of the reaction mixture. Additions of $NaBH_4$ and the acetic acid solution were repeated until the reaction was completed. The mixture was carefully concentrated under reduced pressure and the residue was purified by chromatography on C18 reverse phase column material followed by preparative TLC using C18 reverse phase plate to obtain the prodrug **21** (13.6 mg, 70%) as a 2:3 mixture of two diastereomers: ^{1}H NMR (CD_3CN) δ 7.78 (d, 2H, J = 9.0 Hz), 7.48-7.42 (m, 2H), 7.35-7.27 (m, 3H), 7.10 (d, 2H, J = 9.0 Hz), 5.86 (m, 1H), 5.60 (m, 1H), 5.48 (br, 1H), 5.14-5.03 (m, 2H), 4.29-4.13 (m, 2H), 3.89 (s, 3H), 3.97-3.32 (m, 12H), 3.29 (br, 0.4H), 3.24 (br, 0.6H), 3.02-2.82 (m, 4H), 2.64-2.26 (m, 3H), 2.26-2.08 (m, 1H), 1.94-1.76 (m, 3H), 1.57 (d, 1.8H, J = 6.9 Hz), 1.46 (d, 1.2H, J = 6.9 Hz), 1.28 (d, 1.2H, J = 6.9 Hz), 1.21 (d, 1.8H, J = 7.2 Hz), 0.92-0.88 (m, 6H); ^{31}P NMR (CD_3CN) δ 14.4 (0.4P), 13.7 (0.6P); MS (ESI) 838 (M+H).

Example 16

Metabolite 22: To a solution of the prodrug **21** (10.3 mg, 0.011 mmol) in DMSO (0.1 mL) and acetonitrile (0.2 mL) was added 0.1 M PBS buffer (3 mL) mixed thoroughly to result a suspension. To the suspension was added porcine liver esterase suspension (0.05 mL, EC3.1.1.1, Sigma). After the suspension was stored in 37°C for 1.5 h, the mixture was centrifuged and the supernatant was taken. The product was purified by HPLC and the collected fraction was lyophilized to result the product **22** as trifluoroacetic acid salt (7.9 mg, 86%): ^{1}H NMR (D_2O) δ 7.70 (d, 1H), 7.05 (d, 2H), 5.66 (d, 1H), 5.40 (br, 1H), 5.02 (br, 1H), 4.70 (br, 1H), 3.99-3.89 (m, 2H), 3.81 (s, 3H), 3.83-3.50 (m, 8H), 3.34-2.80 (m, 7H), 2.50-2.18 (m, 3H), 2.03 (m, 1H), 1.92-1.70 (m, 3H), 1.39 (d, 3H), 0.94 (d, 3H), 0.93 (d, 3H); ^{31}P NMR (D_2O) δ 9.0, 8.8; MS (ESI) 734 (M+H).

Scheme 5



Example 17

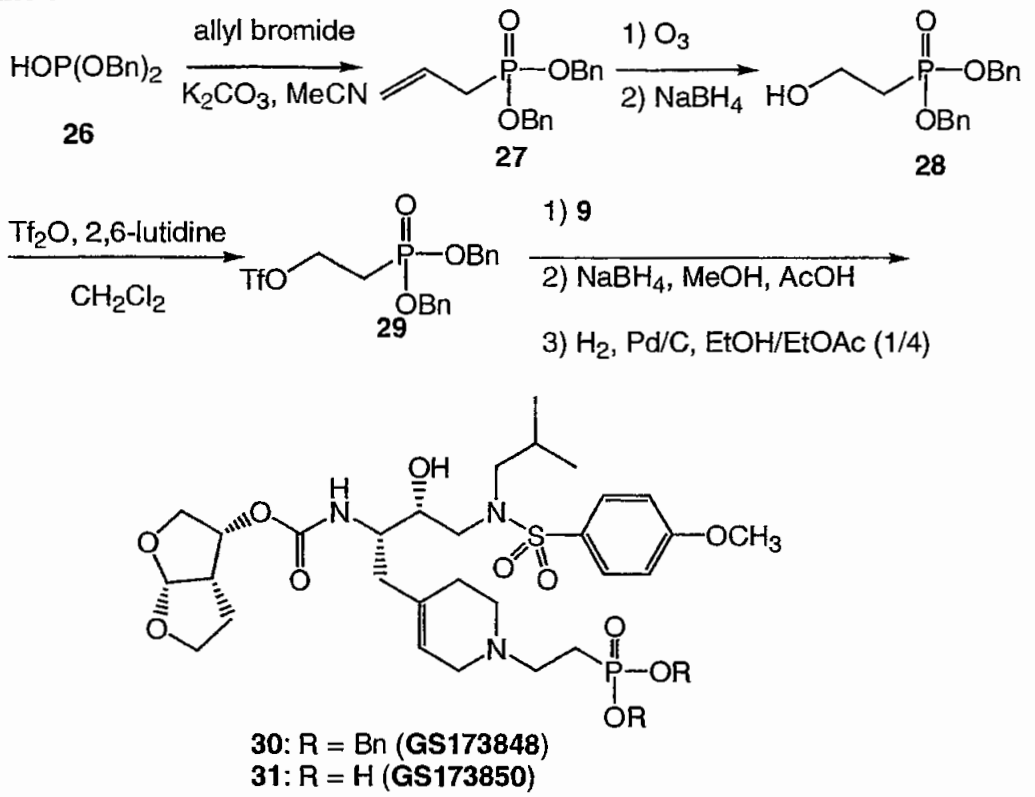
Triflate 24: Triflate **24** was prepared analogously to triflate **20**, except that dimethylhydroxyethylphosphonate **23** (Aldrich) was substituted for ethyl lactate phosphonate with free alcohol **19**.

Example 18

Tetrahydropyridine 25: Tetrahydropyridine **25** was prepared analogously to tetrahydropyridine **30**, except that triflate **24** was substituted for triflate **29**.

^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H), 7.01 (d, 2H), 5.71 (d, 2H), 5.43 (bs, 1H), 5.07-4.87 (m, 1H), 4.16-3.46 (m, 13H), 3.34-3.18 (m, 3H), 3.16-2.80 (m, 5H), 2.52-1.80 (m, 12H), 1.28-1.04 (m, 3H+H_2O peak), 0.98-0.68 (m, 6H).

Scheme 6



Example 19

Dibenzyl phosphonate with double bond 27: To a stirring solution of allyl bromide (4.15 g, 34 mmol, Aldrich) and dibenzylphosphite (6 g, 23 mmol, Aldrich) in acetonitrile (25 mL) was added potassium carbonate (6.3 g, 46 mmol, powder 325 mesh Aldrich) to create a suspension, which was heated to 65°C and stirred for 72 hours. The suspension was cooled to room temperature, diluted with ethyl acetate, filtered, and the filtrate was washed with water, then brine, dried ($MgSO_4$), concentrated and used directly in the next step.

Example 20

Dibenzylhydroxyethylphosphonate 28: Dibenzyl phosphonate with double bond 27 was dissolved in methanol (50mL), chilled to -78°C, stirred, and subjected to ozone by bubbling ozone into the solution for three hours until the solution turned pale blue. The ozone flow was stopped and oxygen bubbling was done for 15 minutes until the solution became colorless. Sodium borohydride (5 g, excess) was added slowly portionwise. After the evolution of gas subsided the solution was allowed to warm to room temperature, concentrated, diluted with ethyl acetate, made acidic with acetic acid and water and

partitioned. The ethyl acetate layer was washed with water, then brine and dried ($MgSO_4$), filtered, concentrated and chromatographed on silica gel eluting with a gradient of eluent from 50% ethyl acetate in hexane to 100% ethyl acetate, affording 2.76 g of the desired product. ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 10H), 5.16-4.95 (m, 4H), 3.94-3.80 (dt, 2H), 2.13-2.01 (dt, 2H); ^{31}P NMR ($CDCl_3$) δ 31.6.

Example 21

Dibenzyl phosphonate 30: A solution of the alcohol **28** (53.3 mg, 0.174 mmol) and 2,6-lutidine (0.025 mL, 0.215 mmol, Aldrich) in CH_2Cl_2 (1 mL) was stirred at –45°C as trifluoromethanesulfonic anhydride (0.029 mL, 0.172 mmol, Aldrich) was added. The solution was stirred for 1 h at –45°C and evaporated under reduced pressure to obtain the crude triflate **29**.

A solution of the crude triflate **29**, 2,6-lutidine (0.025 mL, 0.215 mmol, Aldrich), and the pyridine **9** in acetone-d_6 (1.5 mL, Aldrich) was stored at room temperature for 2 h. The solution was concentrated under reduced pressure to obtain crude pyridinium product:^{31}P NMR (acetone-d_6) δ 25.8; MS (ESI) 852 (M^+).

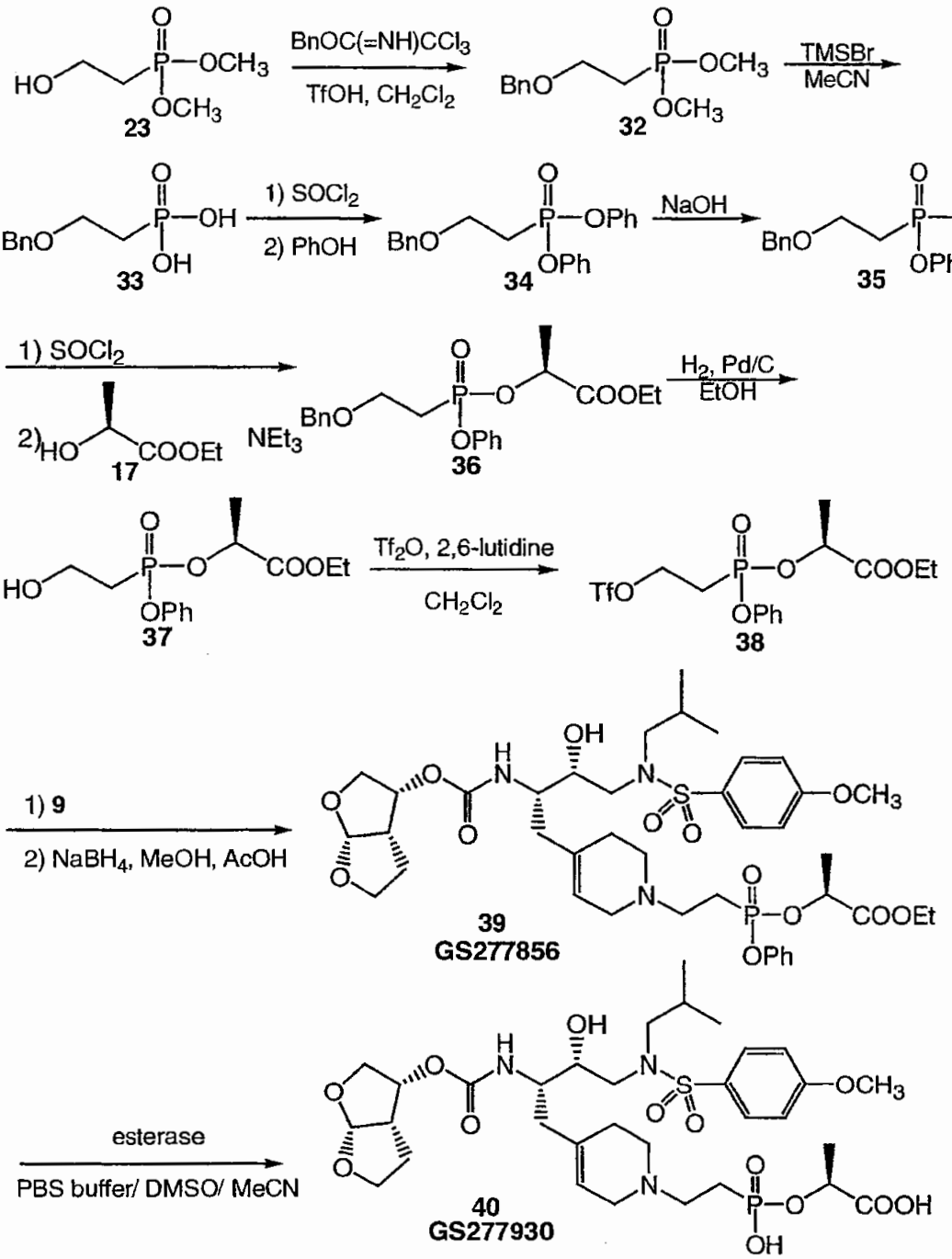
To a solution of the crude pyridinium salt in ethanol (2 mL) was added 7~8 drops of a solution of acetic acid (0.4 mL, Aldrich) in ethanol (2 mL). The solution was stirred at 0°C as $NaBH_4$ (7~8 mg) was added. The solution was maintained to be pH 3-4 by adding the acetic acid solution. More $NaBH_4$ and the acetic acid were added until the reduction was completed. After 4 h, the mixture was concentrated and the remaining residue was dissolved in saturated $NaHCO_3$ (10 mL). The product was extracted with EtOAc (10 mL x 3), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by repeated chromatography on silica gel followed by HPLC purification. Lyophilization of the collected fraction resulted the product **30** (13.5 mg, 26%) as trifluoroacetic acid salt: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, J = 8.7 Hz), 7.36 (br, 10H), 7.00 (d, 2H, J = 8.7 Hz), 5.69 (d, 1H, J = 5.1 Hz), 5.41 (br, 1H), 5.13-4.93 (m, 6H), 4.05-2.5 (m, 19H), 3.88 (s, 3H), 2.5-1.9 (m, 5H), 1.90-1.74 (m, 2H), 0.88 (d, 6H, J = 6.1 Hz); ^{31}P NMR ($CDCl_3$) δ 25.8; MS (ESI) 856 (M+H).

Example 22

Phosphonic acid 31: A mixture of the dibenzyl phosphonate **30** (9.0 mg, 0.009 mmol) and 10% Pd/C (5.2 mg, Aldrich) in EtOAc (2 mL) and ethanol (0.5 mL) was stirred under H_2 atmosphere for 3 h at room temperature. After the mixture was filtered through celite, a drop

of trifluoroacetic acid (Aldrich) was added to the filtrate and the filtrate was concentrated to dryness to afford the product **31** (6.3 mg, 86%): ^{1}H NMR (CD_3OD) δ 7.76 (d, 2H, J = 9.0 Hz), 7.11 (d, 2H, J = 9.0 Hz), 5.69 (d, 1H, J = 5.1 Hz), 5.54 (br, 1H), 5.09 (br, 1H), 4.05-3.84 (m, 4H), 3.89 (s, 3H), 3.84-3.38 (m, 9H), 3.07 (dd, 2H, J = 13.5 and 8.4 Hz), 2.9-2.31 (m, 5H), 2.31-1.83 (m, 6H), 0.92 (d, 3H, J = 6.3 Hz), 0.85 (d, 3H, J = 6.9 Hz); ^{31}P NMR (CD_3OD) δ 21.6; MS (ESI) 676 (M+H).

Scheme 7



Example 23

Benzylether 32: A solution of dimethyl hydroxyethylphosphonate (5.0 g, 32.5 mmol, Across) and benzyl 2,2,2-trichloroacetimidate (97.24 mL, 39.0 mmol, Aldrich) in CH_2Cl_2 (100 mL) at 0°C under a nitrogen atmosphere was treated with trifluoromethanesulfonic acid (0.40 mL). Stirring was performed for three hours at 0°C and the reaction was then allowed to warm to

room temperature while stirring continued. The reaction continued for 15 hours, and the reaction mixture was then diluted with dichloromethane, washed with saturated sodium bicarbonate, washed with brine, dried ($MgSO_4$), concentrated under reduced pressure and chromatographed on silica gel eluting with a gradient of eluent from 60% EtOAc in hexane to 100% EtOAc to afford 4.5 g, (57%) of the benzyl ether as a colorless liquid. ^{31}P NMR ($CDCl_3$) δ 31.5.

Example 24

Diacid 33: A solution of benzylether 32 (4.5 g, 18.4 mmol) was dissolved in anhydrous acetonitrile (100mL), chilled to 0°C under a nitrogen atmosphere and treated with TMS bromide (9.73 mL, 74mmol). The reaction mixture was warmed to room temperature and after 15 hours of stirring was concentrated repeatedly with MeOH/water to afford the diacid, which was used directly in the next step. ^{31}P NMR ($CDCl_3$) δ 31.9.

Example 25

Diphenylphosphonate 34 : Diacid 33 (6.0 g, 27 mmol) was dissolved in toluene and concentrated under reduced pressure three times, dissolved in anhydrous acetonitrile, stirred under a nitrogen atmosphere, and treated with thionyl chloride (20 mL, 270 mmol) by slow addition. The solution was heated to 70°C for two hours, then cooled to room temperature, concentrated and dissolved in anhydrous dichloromethane, chilled to -78°C and treated with phenol (15 g, 162 mmol) and triethylamine (37 mL, 270 mmol). The reaction mixture was warmed to room temperature and stirred for 15 hours, and was then diluted with ice cold dichloromethane, washed with ice cold 1 N. NaOH, washed with ice cold water, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was used directly in the next step. ^1H NMR ($CDCl_3$) δ 7.40-7.16 (d, 15H), 4.55 (s, 2H), 3.98-3.84 (m, 2H), 2.55-2.41 (m, 2H); ^{31}P NMR ($CDCl_3$) δ 22.1.

Example 26

Mono acid 35: Monoacid 35 was prepared using conditions analogous to those used to prepare monoacid 16, except that diphenylphosphonate 34 was substituted for benzylether 15. ^1H NMR ($CDCl_3$) δ 7.38-7.16 (d, 10H), 4.55 (s, 2H), 3.82-3.60 (m, 3H), 2.33-2.21 (m, 2H); ^{31}P NMR ($CDCl_3$) δ 29.0.

Example 27

Ethyl lactate phosphonate 36: Ethyl lactate phosphonate 36 was prepared analogously to ethyl lactate phosphonate 18 except monoacid 35 was substituted for monoacid 16. ^{31}P NMR ($CDCl_3$) δ 27.0, 25.6.

Example 28

Ethyl lactate phosphonate with free alcohol 37: Ethyl lactate phosphonate with free alcohol 37 was prepared analogously to ethyl lactate phosphonate with free alcohol 19 except that ethyl lactate phosphonate 36 was substituted for ethyl lactate phosphonate 18. ^{31}P NMR ($CDCl_3$) δ 28.9, 26.8.

Example 29

Triflate 38: A solution of the alcohol **37** (663 mg, 2.19 mmol) and 2,6-lutidine (0.385 mL, 3.31 mmol, Aldrich) in CH_2Cl_2 (5 mL) was stirred at –45°C as trifluoromethanesulfonic anhydride (0.48 mL, 2.85 mmol, Aldrich) was added. The solution was stirred for 1.5 h at –45°C, diluted with ice-cold water (50 mL), and extracted with EtOAc (30 mL x 2). The combined extracts were washed with ice cold water (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to obtain a crude mixture of two diastereomers (910 mg, 96%, 1:3 ratio): ^1H NMR (acetone-d_6) δ 7.48-7.37 (m, 2H), 7.37-7.18 (m, 3H), 5.2-4.95 (m, 3H), 4.3-4.02 (m, 2H), 3.38-3.0 (m, 1H), 3.0-2.7 (m, 2H), 2.1-1.9 (m, 1H), 1.52 (d, 1H), 1.4 (d, 2H), 1.4-1.1)m, 3H); ^{31}P NMR (acetone-d_6) δ 21.8 (0.75P), 20.5 (0.25P).

Example 30

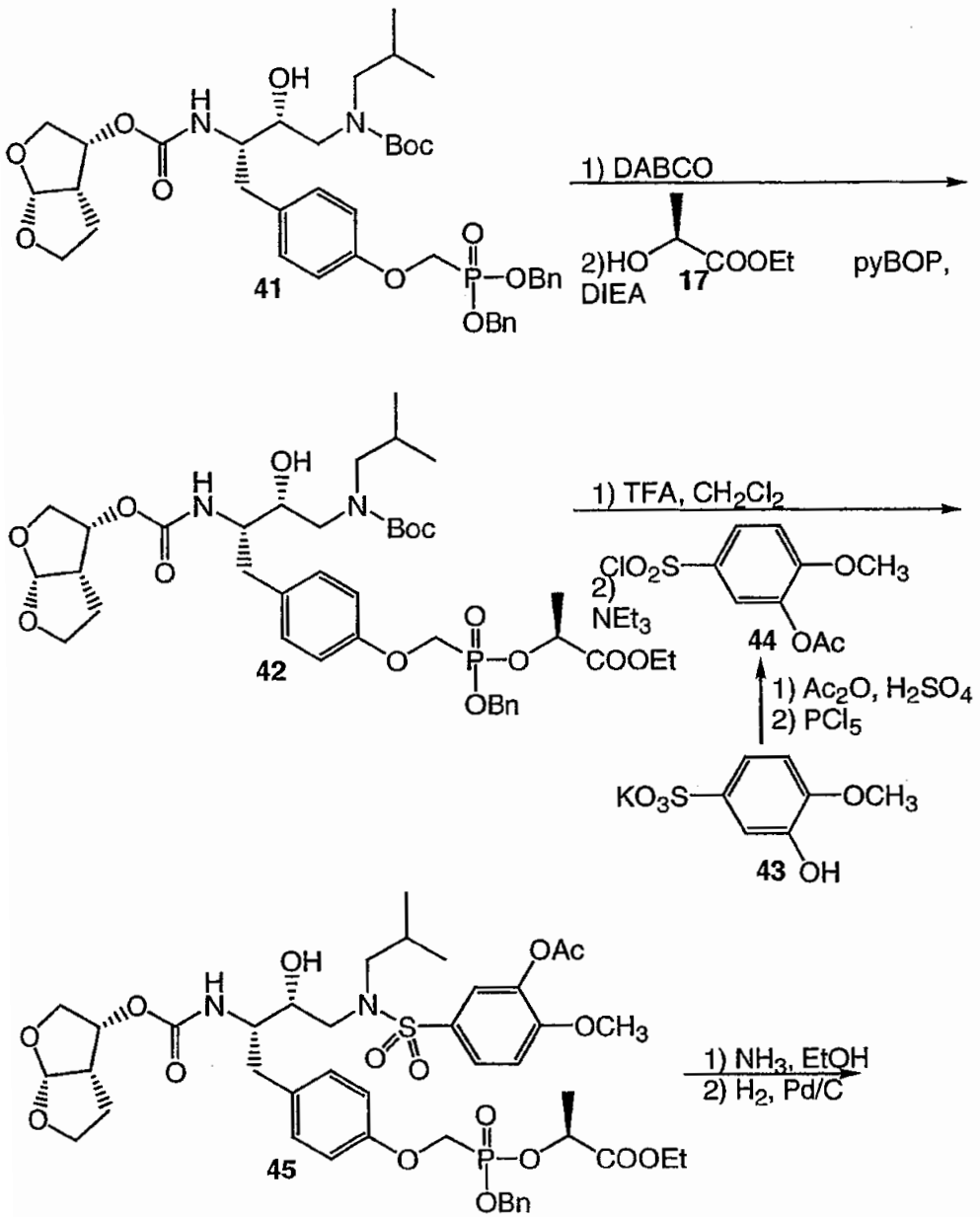
The prodrug 39: A solution of the crude triflate **38** (499 mg, 1.15 mmol) and the pyridine **9** (494 mg, 0.877 mmol) in acetone (5 mL) was stirred at room temperature for 16.5 h. The solution was concentrated under reduced pressure to obtain the crude pyridinium salt.
To a solution of the crude pyridinium salt in ethanol (10 mL) was added 5 drops of a solution of acetic acid (1 mL) in ethanol (5 mL). The solution was stirred at 0°C as $NaBH_4$ (~10 mg, Aldrich) was added. The solution was maintained to be pH 3-4 by adding the acetic acid solution. More $NaBH_4$ and the acetic acid were added until the reduction was completed. After 5.5 h, the mixture was concentrated under reduced pressure and the remaining residue was dissolved in ice-cold saturated $NaHCO_3$ (50 mL). The product was extracted with ice-

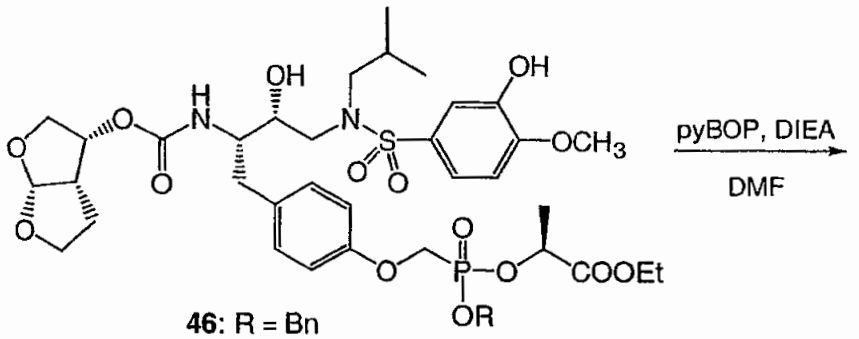
cold EtOAc (30 mL x 2) and the combined extracts were washed with 50% saturated $NaHCO_3$ (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by a chromatography on silica gel followed by a chromatography on C18 reverse phase column material. Lyophilization of the collected fraction resulted the product **39** mixture (376 mg, 50%, ~2.5:1 ratio) as trifluoroacetic acid salt: ^{1}H NMR (CD_3CN+TFA) δ 7.78 (d, 2H, J = 8.7 Hz), 7.52-7.42 (m, 2H); 7.37-7.22 (m 3H), 7.10 (d, 2H, J = 8.7 Hz), 5.78 (d, 1H, J = 9.0 Hz), 5.64 (m, 1H), 5.50 (br, 1H), 5.08 (m, 2H), 4.31-4.12 (m, 2H), 4.04-3.42 (m, 11H), 3.90 (s, 3H), 3.29 (m, 2H), 3.23 -3.16 (m, 1H), 3.08-2.78 (m, 6H), 2.76-2.27 (m, 5H), 2.23-2.11 (m, 1H), 2.08-1.77 (m, 3H),1.58 (d, 0.9H, J = 7.2 Hz),1.45 (d, 2.1H, J = 6.6 Hz), 1.32-1.20 (m, 3H), 0.95 - 0.84 (m, 6H); ^{31}P NMR (CD_3CN+TFA) δ 24.1 and 23.8, 22.2 and 22.1; MS (ESI) 852 (M+H).

Example 31

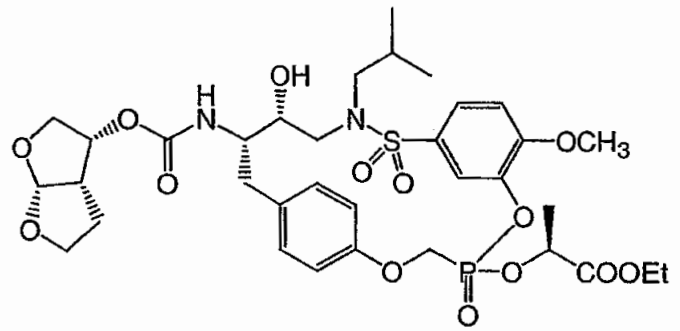
Metabolite 40: To a solution of the prodrug **39** (35.4 mg, 0.037 mmol) in DMSO (0.35 mL) and acetonitrile (0.70 mL) was added 0.1 M PBS buffer (10.5 mL) mixed thoroughly to result a suspension. To the suspension was added porcine liver esterase suspension (0.175 mL, EC3.1.1.1, Sigma). After the suspension was stored in 37°C for 6.5 h, the mixture was filtered through 0.45 um membrane filter and the filtrate was purified by HPLC. The collected fraction was lyophilized to result the product **40** as trifluoroacetic acid salt (28.8 mg, 90%): ^{1}H NMR (D_2O) δ 7.96 (d, 2H, J = 8.7 Hz), 7.32 (d, 2H, J = 8.7 Hz), 5.89 (d, 1H, J = 5.1 Hz), 5.66 (br, 1H), 5.27 (m, 1H), 4.97 (m, 1H), 4.23-4.12 (m, 2H), 4.08 (s, 3H), 4.06-3.10 (m, 14H), 3.03 (dd, 1H, J = 14.1 and 6.6 Hz), 2.78-1.97 (m, 9H), 1.66 (d, 3H, J = 6.9 Hz),1.03 (d, 3H, J = 7.5 Hz),1.01 (d, 3H, J = 6.9 Hz); ^{31}P NMR (CD_3CN+TFA) δ 20.0, 19.8; MS (ESI) 748 (M+H).

Scheme 8


1) DABCO
2)HO
DIEA
17
COOEt
pyBOP,
41
OBn
Boc
1) TFA, CH2Cl2
ClO2S
2)
NEt3
44
OAc
OCH3
42
1) Ac2O, H2SO4
2) PCl5
KO3S
43
OH
45
1) NH3, EtOH
2) H2, Pd/C



46: R = Bn
47: R = H



48A: a minor diastereomer (**GS277932**)
48B: a major diastereomer (**GS277933**)

Example 32

Compound 42: The dibenzyl phosphonate **41** (947 mg, 1.21 mmol) was treated with DABCO (140.9 mg, 1.26mmol, Aldrich) in 4.5 mL toluene to obtain the monoacid (890 mg, 106%). The crude monoacid (890 mg) was dried by evaporation with toluene twice and dissolved in DMF (5.3 mL) with ethyl (*S*)-lactate (0.3 mL, 2.65 mmol, Aldrich) and pyBOP (945 mg, 1.82 mmol, Aldrich) at room temperature. After diisopropylethylamine (0.85 mL, 4.88 mmol, Aldrich) was added, the solution was stirred at room temperature for 4 h and concentrated under reduced pressure to a half volume. The resulting solution was diluted with 5% aqueous HCl (30 mL) and the product was extracted with EtOAc (30 mL x 3). After the combined extracts were dried ($MgSO_4$) and concentrated, the residue was chromatographed on silica gel to afford the compound **42** (686 mg, 72%) as a mixture of two diastereomers (2:3 ratio): ^{1}H NMR ($CDCl_3$) δ 7.46-7.32 (m, 5H), 7.13 (d, 2H, *J* = 8.1 Hz), 6.85 (t, 2H, *J* = 8.1 Hz), 5.65 (m, 1H), 5.35-4.98 (m, 4H), 4.39 (d, 0.8H, *J* = 10.2 H), 4.30-4.14 (m, 3.2H), 3.98 (dd, 1H, *J* = 9.3 and 6.0 Hz), 3.92-3.78 (m, 3H), 3.78-3.55 (m, 3H), 3.16-2.68 (m, 6H), 1.85 (m, 1H), 1.74-1.55 (m, 2H), 1.56 (d, 1.8H, *J* = 7.2 Hz), 1.49 (d, 1.2H), 1.48 (s, 9H), 1.30-1.23 (m, 3H), 0.88 (d, 3H, *J* = 6.3 Hz), 0.87 (d, 3H, *J* = 6.3 Hz); ^{31}P NMR ($CDCl_3$) δ 20.8 (0.4P), 19.5 (0.6P); MS (ESI) 793 (M+H).

Example 33

Compound 45: A solution of compound **42** (101 mg, 0.127 mmol) and trifluoroacetic acid (0.27 mL, 3.5 mmol, Aldrich) in CH_2Cl_2 (0.6 mL) was stirred at 0°C for 3.5 h and concentrated under reduced pressure. The resulting residue was dried in vacuum to result the crude amine as TFA salt.

A solution of the crude amine salt and triethylamine (0.072 mL, 0.52 mmol, Aldrich) in CH_2Cl_2 (1 mL) was stirred at 0°C as the sulfonyl chloride **42** (37 mg, 0.14 mmol) was added. After the solution was stirred at 0°C for 4 h and 0.5 h at room temperature, the reaction mixture was diluted with saturated $NaHCO_3$ (20 mL) and extracted with EtOAc (20 mL x 1; 15 mL x 2). The combined organic fractions were washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by chromatography on silica gel provided the sulfonamide **45** (85 mg, 72%) as a mixture of two diastereomers (~1:2 ratio): ^{1}H NMR ($CDCl_3$) δ 7.45-7.31 (m, 7H), 7.19 (d, 1H, J = 8.4 Hz), 7.12 (d, 2H, J = 7.8 Hz), 6.85 (m, 2H), 5.65 (d, 1H, J = 5.4 Hz), 5.34-5.16 (m, 2H), 5.13-4.97 (m, 2H), 4.97-4.86 (m, 1H), 4.38 (d, 0.7H, J = 10.8 Hz), 4.29-4.12 (m, 3.3H), 3.96 (dd, 1H, J = 9.3 and 6.3 Hz), 3.89 (s, 3H), 3.92-3.76 (m, 3H), 3.76-3.64 (m, 2H), 3.64-3.56 (br, 1H), 3.34-3.13 (m, 1H), 3.11-2.70 (m, 6H), 2.34 (s, 3H), 1.86 (m, 1H, J = 7.0 Hz), 1.75-1.58 (m, 2H), 1.56 (d, 2H, J = 7.2 Hz), 1.49 (d, 1H, J = 7.2 Hz), 1.29-1.22 (m, 3H), 0.94 (d, 3H, J = 6.6 Hz), 0.90 (d, 3H, J = 6.9 Hz); ^{31}P NMR ($CDCl_3$) δ 20.7 (0.3P), 19.5 (0.7P); MS (ESI) 921 (M+H).

Example 34

Compound 46: Compound **45** (257 mg, 0.279 mmol) was stirred in a saturated solution of ammonia in ethanol (5 mL) at 0°C for 15 min and the solution was concentrated under reduced pressure. Purification of the residue by chromatography on silica gel provided compound **46** (2.6 mg, 84%): ^{1}H NMR ($CDCl_3$) δ 7.48-7.34 (m, 4H), 7.22-7.05 (m, 5H), 7.01 (d, 1H, J = 8.1 Hz), 6.87-6.80 (m, 2H), 5.68 (d, 1H, J = 4.8 Hz), 5.32 (dd, 1.3H, J = 8.7 and 1.8 Hz), 5.22 (d, 0.7H, J = 9.0 Hz), 5.11-5.00 (m, 3H), 4.47-4.14 (m, 4H), 4.00 (dd, 1H, J = 9.9 and 6.6 Hz), 3.93 (s, 3H), 3.95-3.63 (m, 5H), 3.07-2.90 (m, 4H), 2.85-2.75 (m, 1H), 2.75-2.63 (m, 2H), 1.88-1.67 (m, 3H), 1.65-1.55 (m, 2H), 1.57 (d, 2H, J = 6.9 Hz), 1.50 (d, 1H, J = 7.2 Hz), 1.31-1.20 (m, 3H), 0.95 (d, 3H, J = 6.6 Hz), 0.88 (d, 3H, J = 6.3 Hz); ^{31}P NMR ($CDCl_3$) δ 20.7 (0.3P), 19.6 (0.7P); MS (ESI) 879 (M+H).

Example 35

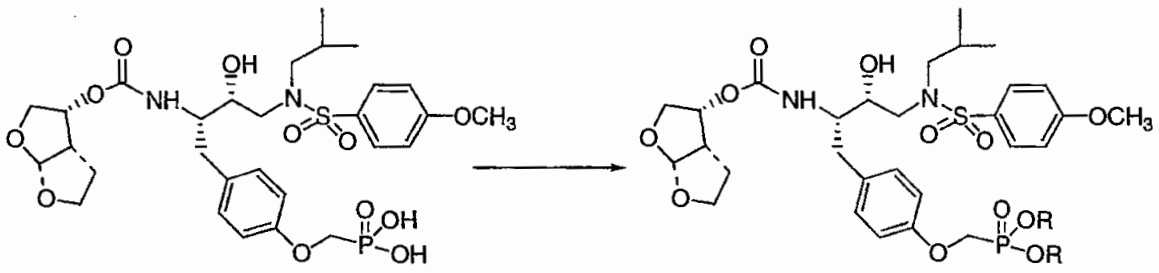
Compound 47: A mixture of compound **46** (176 mg, 0.200 mmol) and 10% Pd/C (9.8 mg, Aldrich) in EtOAc (4 mL) and ethanol (1 mL) was stirred under H_2 atmosphere for 3 h at room temperature. After the mixture was filtered through celite, the filtrate was concentrated to dryness to afford compound **47** (158 mg, 100%) as white powder: ^{1}H NMR ($CDCl_3$) δ 7.30-7.16 (m, 2H), 7.12 (d, 2H, J = 7.5 Hz), 7.01 (d, 1H, J = 7.8 Hz), 6.84 (d, 2H, J = 7.5 Hz), 5.66 (d, 1H, J = 4.5 Hz), 5.13-4.97 (m, 2H), 4.38-4.10 (m, 4H), 3.93 (s, 3H), 4.02-3.66 (m, 6H), 3.13-2.69 (m, 7H), 1.96-1.50 (m, 3H), 1.57 (d, 3H, J = 6.6 Hz), 1.26 (t, 3H, J = 7.2 Hz), 0.93 (d, 3H, J = 6.0 Hz), 0.88 (d, 3H, J = 6.0 Hz); ^{31}P NMR ($CDCl_3$) δ 20.1; MS (ESI) 789 (M+H).

Example 36

Compound 48A and 48B: A solution of pyBOP (191 mg, 0.368 mmol, Aldrich) and diisopropylethylamine (0.1 mL, 0.574 mmol, Aldrich) in DMF (35 mL) was stirred at room temperature as a solution of compound **47** (29 mg, 0.036 mmol) in DMF (5.5 mL) was added over 16 h. After addition, the solution was stirred at room temperature for 3 h and concentrated under reduced pressure. The residue was dissolved in ice-cold water and extracted with EtOAc (20 mL x 1; 10 mL x 2). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel followed by preparative TLC gave two isomers of structure **48** (1.0 mg, 3.6% and 3.6 mg, 13%). Isomer **48A**: ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 1H), 7.12 (br, 1H), 7.01 (d, 2H, J = 8.1 Hz), 6.98 (br, 1H), 6.60 (d, 2H, J = 8.1 Hz), 5.75 (d, 1H, J = 5.1 Hz), 5.37-5.28 (m, 2H), 5.18 (q, 1H, J = 8.7 Hz), 4.71 (dd, 1H, J = 14.1 and 7.5 Hz), 4.29 (m, 3H), 4.15-4.06 (m, 1H), 3.99 (s, 3H), 4.05-3.6 (m, 5H), 3.35 (m, 1H), 3.09 (br, 1H), 2.90-2.78 (m, 3H), 2.2-2.0 (m, 3H), 1.71 (d, 3H, J = 6.6 Hz), 1.34 (t, 3H, J = 6.9 Hz), 1.01 (d, 3H, J = 6.3 Hz), 0.95 (d, 3H, J = 6.3 Hz); ^{31}P NMR ($CDCl_3$) δ 17.8; MS (ESI) 793 (M+Na); isomer **48B**: ^{1}H NMR ($CDCl_3$) δ 7.46 (d, 1H, J = 9.3 Hz), 7.24 (br, 1H), 7.00 (d, 2H, J = 8.7 Hz), 6.91 (d, 1H, J = 8.7 Hz), 6.53 (d, 2H, J = 8.7 Hz), 5.74 (d, 1H, J = 5.1 Hz), 5.44 (m, 1H), 5.35 (d, 1H, J = 9.0 Hz), 5.18 (q, 1H, J = 7.2 Hz), 4.68 (dd, 1H, J = 14.4 and 6.3 Hz), 4.23 (m, 3H), 4.10 (m, 1H), 4.04 (s, 3H), 3.77-4.04 (m, 6H), 3.46 (dd, 1H, J = 12.9 and 11.4 Hz), 3.08 (br, 1H), 2.85 (m, 2H), 2.76 (dd, 1H, J = 12.9 and 4.8 Hz), 1.79-2.11 (m, 3H), 1.75 (d, 3H, J = 6.6 Hz), 1.70 (m, 2H),

1.27 (t, 3H, J = 6.9 Hz), 1.01 (d, 3H, J = 6.6 Hz), 0.93 (d, 3H, J = 6.6 Hz); ^{31}P NMR ($CDCl_3$) δ 15.4; MS (ESI) 793 (M+Na).

Example 1



1

2 R = CH_3
3 R = $CH(CH_3)_2$

Example 1A

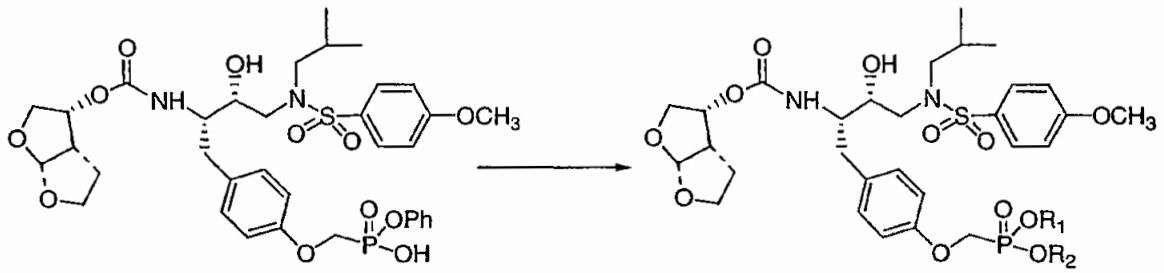
Dimethylphosphonic ester **2** (R = CH_3): To a flask was charged with phosphonic acid **1** (67 mg, 0.1 mmol), methanol (0.1 mL, 2.5 mmol) and 1, 3-dicyclohexylcarbodiimide (83 mg, 0.4 mmol), then pyridine (1 mL) was added under N_2. The resulted mixture was stirred at 60 –70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH_4Cl, brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol/CH_2Cl_2, 1% to 7%) to give **2** (39 mg, 56 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.71(d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.10-4.92 (m, 4H), 4.26 (d, J = 9.9 Hz, 2H), 3.96 -3.65 (m overlapping s, 15H), 3.14-2.76 (m, 7H), 1.81-1.55 (m, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 21.7; MS (ESI) 723 (M+Na).

Example 1B

Diisopropylphosphonic ester **3** (R = CH (CH_3)$_2$) was synthesized in the same manner in 60% yield. ^{1}H NMR ($CDCl_3$) δ 7.71(d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.1 Hz, 1H), 5.08-4.92 (m, 3H), 4.16 (d, J = 10.5 Hz, 2H), 3.98 -3.68 (m overlapping s, 9H), 3.16-2.78 (m, 7H),

1.82-1.56 (m, 3H), 1.37 (t, J = 6.3 Hz, 6H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.3; MS (ESI) 779 (M+Na).

Example 2



4 5

Compound	R_1	R_2
5a	OPh	mix-Hba-Et
5b	OPh	(*S*)-Hba-Et
5c	OPh	(*S*)-Hba-tBu
5d	OPh	(*S*)-Hba-EtMor
5e	OPh	(*R*)-Hba-Et

Example 2A

Monolactate **5a** (R1 = OPh, R2 = Hba-Et): To a flask was charged with monophenyl phosphonate **4** (250 mg, 0.33 mmol), 2-hydroxy-n-butyric acid ethyl ester (145 mg, 1.1 mmol) and 1, 3-dicyclohexylcarbodiimide (226 mg, 1.1 mmol), then pyridine (2.5 mL) was added under N_2. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH_4Cl, brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/CH_2Cl_2, 1:1) to give **5a** (150 mg, 52 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.14 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.65 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.21 (m, 3H), 1.04-0.86 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 17.5 and 15.1; MS (ESI) 885 (M+Na).

Example 2B

Monolactate **5b** (R1 = OPh, R2 = (*S*)-Hba-Et): To a flask was charged with monophenyl phosphonate **4** (600 mg, 0.8 mmol), (*S*)-2-hydroxy-n-butyric acid ethyl ester (317 mg, 2.4 mmol) and 1, 3-dicyclohexylcarbodiimide (495 mg, 2.4 mmol), then pyridine (6 mL) was added under N_2. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH_4Cl, brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/CH_2Cl_2, 1:1) to give **5b** (360 mg, 52 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.65 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.23 (m, 3H), 1.04-0.86 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 17.5 and 15.2; MS (ESI) 885 (M+Na).

Example 2C

Monolactate **5c**(R1 = OPh, R2 = (*S*)-Hba-tBu): To a flask was charged with monophenyl phosphonate **4** (120 mg, 0.16 mmol), tert-butyl (*S*)-2-hydroxybutyrate (77 mg, 0.48 mmol) and 1, 3-dicyclohexylcarbodiimide (99 mg, 0.48 mmol), then pyridine (1 mL) was added under N_2. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH_4Cl, brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/CH_2Cl_2, 1:1) to give **5c** (68 mg, 48 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.14 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.64 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.44 (d, J = 11 Hz, 9H), 1.04-0.86 (m, 9H); ^{31}P NMR ($CDCl_3$) δ 17.5 and15.2; MS (ESI) 913 (M+Na).

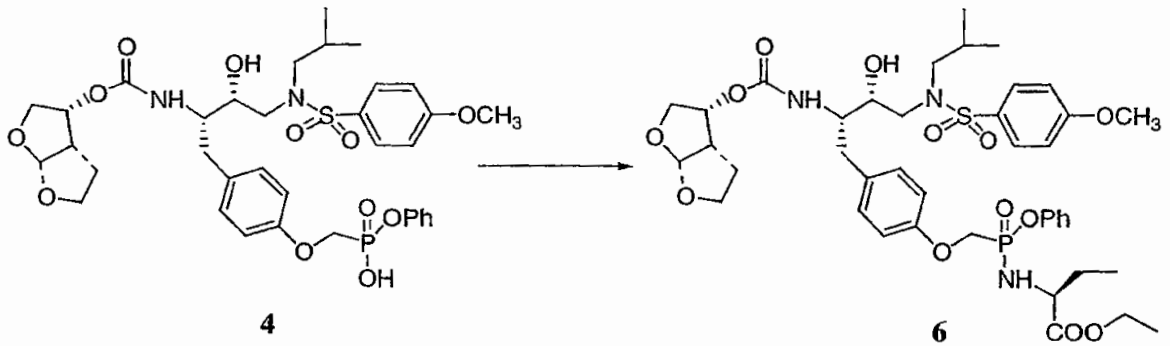
Example 2D

Monolactate **5d** (R1 = OPh, R2 = (*S*)-Lac-EtMor): To a flask was charged with monophenyl phosphonate **4** (188 mg, 0.25 mmol), (*S*)-lactate ethylmorpholine ester (152 mg, 0.75 mmol)

and 1, 3-dicyclohexylcarbodiimide (155 mg, 0.75 mmol), then pyridine (2mL) was added under N_2. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was washed with ethyl acetate and the combined organic phase was washed with NH_4Cl, brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol/CH_2Cl_2, 1:9) to give **5d** (98 mg, 42 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.34-7.20 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.65 (m, 1H), 5.21-4.99 (m, 3H), 4.57-4.20 (m, 4H), 3.97 -3.63 (m overlapping s, 13H), 3.01-2.44 (m, 13H), 1.85-1.50 (m, 6H), 0.92 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.5, 3H); ^{31}P NMR ($CDCl_3$) δ 17.4 and 15.3; MS (ESI) 934(M).

Example 2E

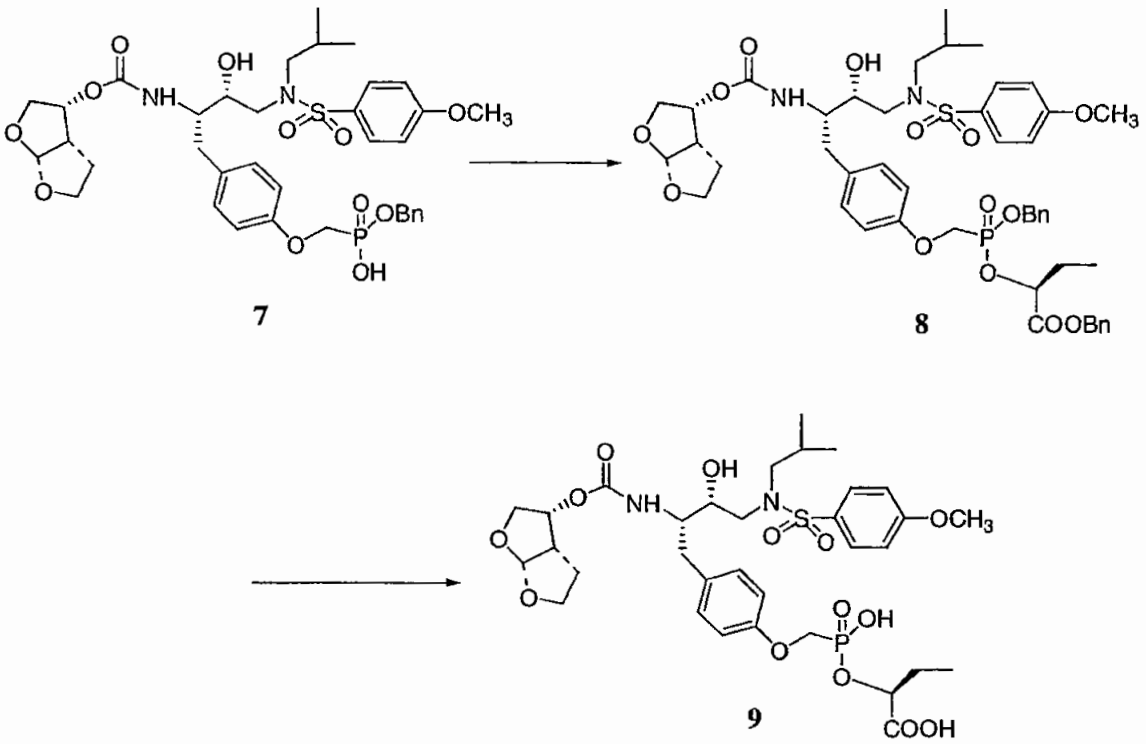
Monolactate **5e** (R1 = OPh, R2 = (*R*)-Hba-Et): To a flask was charged with monophenyl phosphonate **4** (600 mg, 0.8 mmol), (*R*)-2-hydroxy-n-butyric acid ethyl ester (317 mg, 2.4 mmol) and 1, 3-dicyclohexylcarbodiimide (495 mg, 2.4 mmol), then pyridine (6 mL) was added under N_2. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH_4Cl, brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/CH_2Cl_2, 1:1) to give **5e** (345 mg, 50 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.65 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.23 (m, 3H), 1.04-0.86 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 17.5 and15.1; MS (ESI) 885 (M+Na).



4 6

Example 3

Monoamidate **6**: To a flask was charged with monophenyl phosphonate **4** (120 mg, 0.16 mmol), L-alanine butyric acid ethyl ester hydrochloride (160 mg, 0.94 mmol) and 1, 3-dicyclohexylcarbodiimide (132 mg, 0.64 mmol), then pyridine (1 mL) was added under N_2. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH_4Cl, brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol/CH_2Cl_2, 1:9) to give **6** (55 mg, 40 %) as a white solid. ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.37-7.23 (m, 5H), 7.16 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.1Hz, 1H), 5.10-4.92 (m, 3H), 4.28 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.23 (m, 3H), 1.04-0.86 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 20.7 and 19.6; MS (ESI) 884(M+Na).



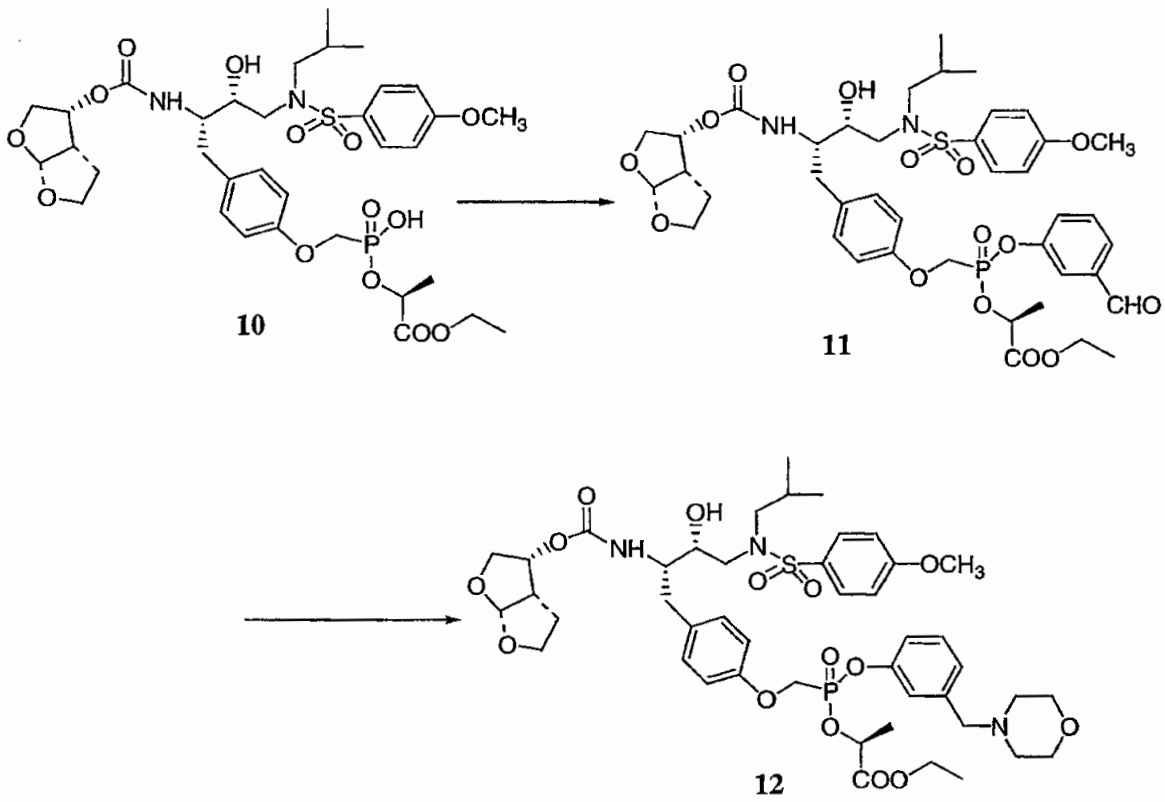
Example 4A

Compound **8**: To a stirred solution of monobenzyl phosphonate **7** (195 mg, 0.26mmol) in 1 mL of DMF at room temperature under N_2 was added benzyl-(s)-lactate (76 mg, 0.39 mmol) and PyBOP (203 mg, 0.39mmol), followed by DIEA (181µL, 1 mmol). After 3 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate/hexane 1:1) to give **8** (120 mg, 50%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.38-7.34 (m, 5H), 7.12 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.81(d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.24-4.92 (m, 7H), 4.28 (m, 2H), 3.96 -3.67 (m overlapping s, 9H), 3.16-2.76 (m, 7H), 1.95-1.62 (m, 5H), 0.99-0.87 (m, 9H); ^{31}P NMR ($CDCl_3$) δ 21.0 and 19.7; MS (ESI) 962 (M+Na).

Example 4B

Compound **9**: A solution of compound **8** (100 mg) was dissolved in EtOH/ EtOAc (9 mL/ 3mL), treated with 10 % Pd/C (10 mg) and was stirred under H_2 atmosphere (balloon) for 1.5 h. The catalyst was removed by filtration through celite. The filtered was evaporated under reduced pressure, the residue was triturated with ether and the solid was collected by filtration to afford the compound **9** (76mg, 94%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.59 (d, J = 5.4 Hz, 1H), 5.03-4.95 (m, 2H), 4.28 (m, 2H), 3.90 -3.65 (m overlapping s,

9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 1.96 (m, 3H), 1.61 (m, 2H), 1.18 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 18.3; MS (ESI) 782 (M+Na).



10 11 12

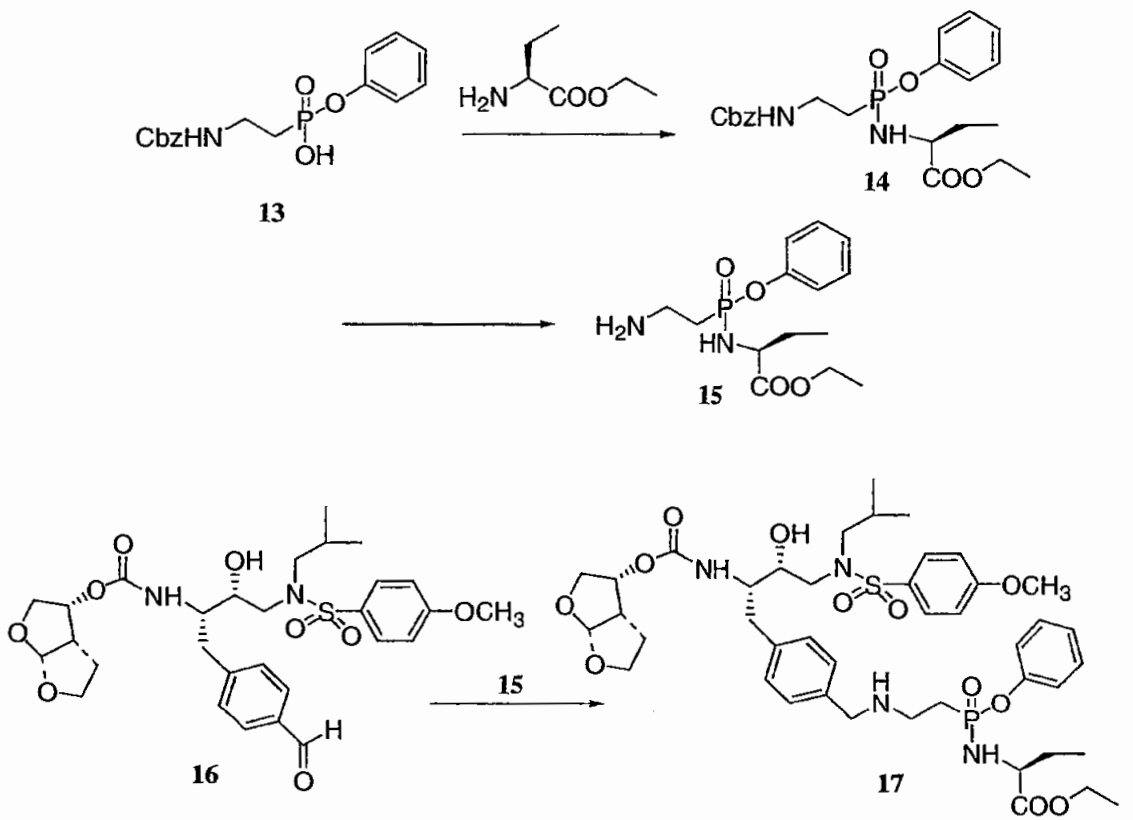
Example 5A

Compound **11**: To a stirred solution of compound **10** (1 g, 1.3mmol) in 6 mL of DMF at room temperature under N_2 was added 3-hydroxybenzaldehyde (292 mg, 2.6 mmol) and PyBOP (1 g, 1.95mmol), followed by DIEA (0.9 mL, 5.2 mmol). After 5 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate/hexane 1:1) to give **11** (800 mg, 70%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 9.98 (s, 1H), 7.79-6.88 (m, 12H), 5.65 (m, 1H), 5.21-4.99 (m, 3H), 4.62-4.16 (m, 4H), 3.99 -3.61 (m overlapping s, 9H), 3.11-2.79 (m, 5H), 1.85-1.53 (m, 6H), 1.25 (m, 3H), 0.90 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 17.9 and 15.9; MS (ESI) 899 (M+ Na).

Example 5B

Compound **12**: To a stirred solution of compound **11** (920 mg, 1.05 mmol) in 10 mL of ethyl acetate at room temperature under N_2 was added morpholine (460 mg, 5.25 mmol) and acedic

acid (0.25 mL, 4.2 mmol), followed by sodium cyanoborohydride (132 mg, 2.1 mmol). After 20h, the solvent was removed under reduced pressure, and the residue was diluted with ethyl acetate and the combined organic phase was washed with NH_4Cl, brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol / CH_2Cl_2, 6%) to give **12** (600 mg, 60%) as a white solid. ^1H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.27 (m, 4H), 7.15 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.7 Hz, 2H), 6.89 (m, 2H), 5.65 (m, 1H), 5.21-5.02 (m, 3H), 4.58-4.38 (m, 2H), 4.21-4.16 (m, 2H), 3.99 -3.63 (m overlapping s, 15H), 3.47 (s, 2H), 3.18-2.77 (m, 7H), 2.41 (s, 4H), 1.85-1.53 (m, 6H), 1.25 (m, 3H), 0.90 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 17.4 and 15.2; MS (ESI) 971 (M+Na).



Example 6A

Compound **14**: To a stirred solution of compound **13** (1 g, 3 mmol) in 30 mL of acetonitrile at room temperature under N_2 was added thionyl chloride (0.67 mL, 9 mmol). The resulted mixture was stirred at 60-70°C for 0.5 h. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 30 mL of DCM, followed by DIEA (1.7 mL, 10 mmol), L-alanine butyric acid ethyl ester hydrochloride (1.7 g, 10 mmol) and TEA (1.7 mL, 12 mmol). After 4h at room temperature, the solvent was removed under

reduced pressure, and the residue was diluted with DCM and washed with brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (Hexane/EtOAc 1:1) to give **14** (670 mg, 50%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.33-7.11 (m, 10H), 5.70 (m, 1H), 5.10 (s, 2H), 4.13-3.53 (m, 5H), 2.20-2.10 (m, 2H), 1.76-1.55 (m, 2H), 1.25-1.19 (m, 3H), 0.85-0.71 (m, 3H); ^{31}P NMR ($CDCl_3$) δ 30.2 and 29.9; MS (ESI) 471 (M+Na).

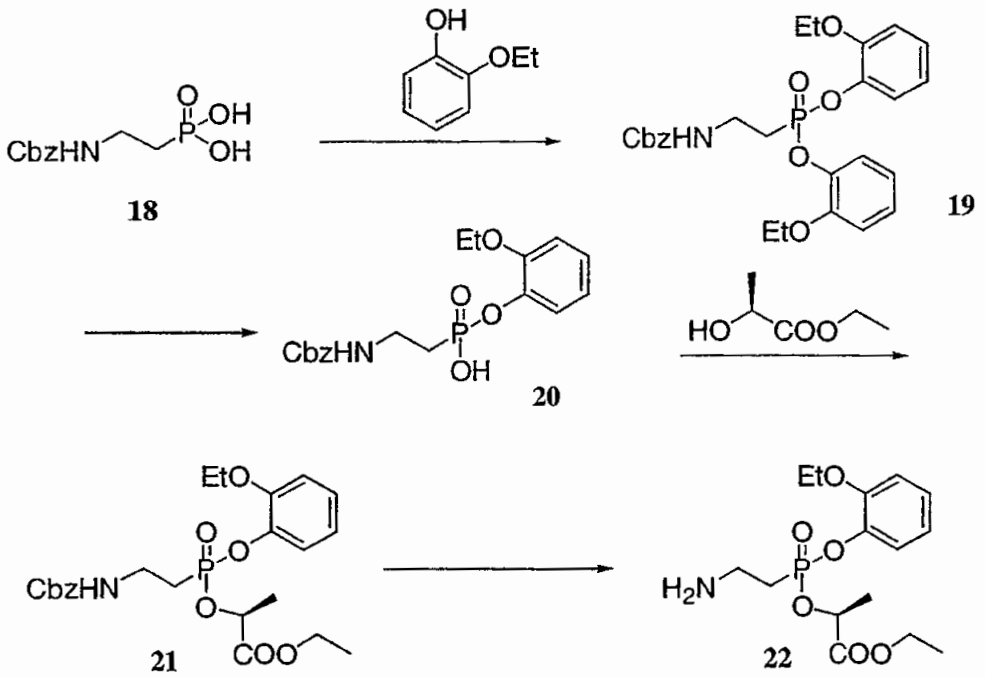
Example 6B

Compound **15**: A solution of compound **14** (450mg) was dissolved in 9 mL of EtOH, then 0.15 mL of acetic acid and 10 % Pd/C (90 mg) was added. The resulted mixture was stirred under H2 atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound **15** (300mg, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.29-7.12 (m, 5H), 4.13-3.53 (m, 5H), 2.20-2.10 (m, 2H), 1.70-1.55 (m, 2H), 1.24-1.19 (m, 3H), 0.84-0.73(m, 3H); ^{31}P NMR ($CDCl_3$) δ 29.1 and 28.5; MS (ESI) 315 (M+1).

Example 6C

Monoamdidate **17**: To a stirred solution of compound **16** (532 mg, 0.9 mmol) in 4 mL of 1,2-dichloroethane was added compound **15** (300 mg, 0.96 mmol) and $MgSO_4$ (50 mg), the resulted mixture was stirred at room temperature under argon for 3h, then acetic acid (1.3 mL, 23 mmol) and sodium cyanoborohydride (1.13 g, 18 mmol) were added. The reaction mixture was stirred at room temperature for 1 h under argon. Then aqueous $NaHCO_3$ (50 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOH / EtOAc, 1/9) to give **17** (600 mg, 60%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 8.7 Hz, 2H), 7.33-7.13 (m, 9H), 7.00 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.11-4.98 (m, 2H), 4.22 -3.68 (m overlapping s, 15H), 3.20-2.75 (m, 9H), 2.21-2.10 (m, 2H), 1.88-1.55(m, 5H), 1.29-1.19 (m, 3H), 0.94-0.70 (m, 9H); ^{31}P NMR ($CDCl_3$) δ 31.8 and 31.0; MS (ESI) 889 (M).

Example 7



Example 7A

Compound **19**: To a stirred solution of compound **18** (3.7 g, 14.3 mmol) in 70 mL of acetonitrile at room temperature under N_2 was added thionyl chloride (6.3 mL, 86 mmol). The resulted mixture was stirred at 60-70°C for 2 h. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 150 mL of DCM, followed by TEA (12 mL, 86 mmol) and 2-ethoxyphenol (7.2 mL, 57.2 mmol). After 20h at room temperature, the solvent was removed under reduced pressure, and the residue was diluted with ethyl acetate and washed with brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (DCM/EtOAc 9:1) to give **19** (4.2 g, 60%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.32-6.83 (m, 13H), 5.22 (m, 1H), 5.12 (s, 2H), 4.12-3.73 (m, 6H), 2.52-2.42 (m, 2H), 1.41-1.37 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 25.4; MS (ESI) 522 (M+Na).

Example 7B

Compound **20**: A solution of compound **19**(3 g, 6 mmol) was dissolved in 70 mL of acetonitrile at 0°C, then 2N NaOH (12 mL, 24 mmol) was added dropwisely. The reaction mixture was stirred at room temperature for 1.5 h. Then the solvent was removed under reduced pressure, and the residue diluted with water and extracted with ethyl acetate. The aqueous layer was acidified with conc. HCl to PH = 1, then extracted with ethyl acetate,

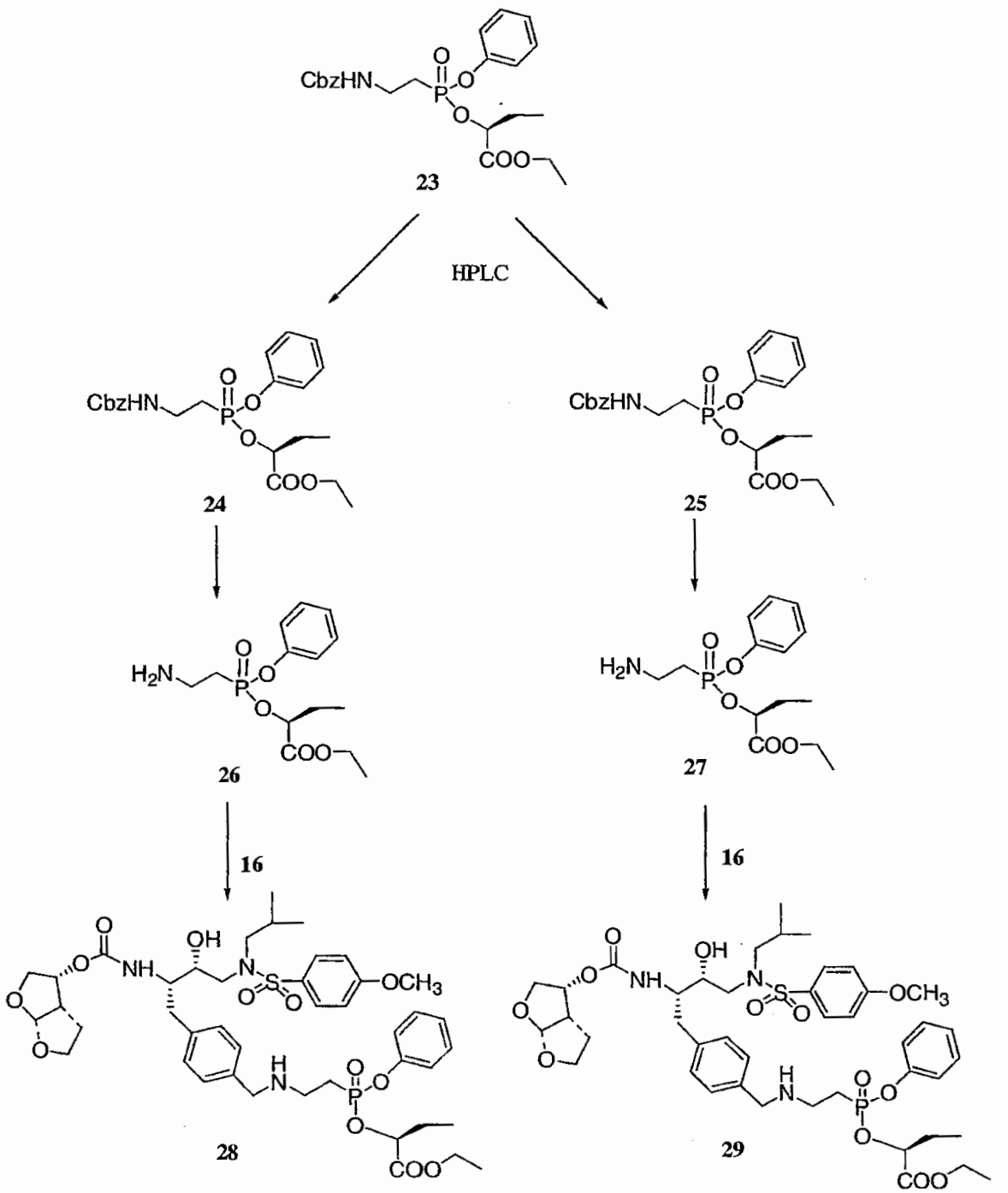
combined the organic layer and dried over Na_2SO_4, filtered and concentrated to give compound **20** (2 g, 88%) as a off-white solid. ^1H NMR ($CDCl_3$) δ 7.33-6.79 (m, 9H), 5.10 (s, 2H), 4.12-3.51 (m, 6H), 2.15-2.05 (m, 2H), 1.47-1.33 (m, 3H); ^{31}P NMR ($CDCl_3$) δ 30.5; MS (ESI) 380 (M+1).

Example 7C

Compound **21**: To a stirred solution of compound **20** (1 g, 2.6 mmol) in 20 mL of acetonitrile at room temperature under N_2 was added thionyl chloride (1.1 mL, 15.6 mmol). The resulted mixture was stirred at 60-70°C for 45 min. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 25 mL of DCM, followed by TEA (1.5 mL, 10.4 mmol) and (S) lactate ethyl ester (0.9 mL, 7.8 mmol). After 20h at room temperature, the solvent was removed under reduced pressure, and the residue was diluted with DCM and washed with brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (DCM / EtOAc 3:1) to give **21** (370 mg, 30%) as a yellow oil. ^1H NMR ($CDCl_3$) δ 7.33- 6.84 (m, 9H), 6.17-6.01 (m, 1H), 5.70 (m, 1H), 5.18-5.01 (m, 3H), 4.25-4.04 (m, 4H), 3.78-3.57 (m, 2H), 2.38-2.27 (m, 2H), 1.5-1.23 (m, 9H); ^{31}P NMR ($CDCl_3$) δ 29.2 and 27.3; MS (ESI) 502 (M+Na).

Example 7D

Compound **22**: A solution of compound **21** (370mg) was dissolved in 8 mL of EtOH, then 0.12 mL of acetic acid and 10 % Pd/C (72 mg) was added. The resulted mixture was stirred under H_2 atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound **22** (320mg, 96%) as a colorless oil. ^1H NMR ($CDCl_3$) 7.27- 6.86 (m, 4H), 5.98 (s, 2H), 5.18-5.02 (m, 1H), 4.25-4.06 (m, 4H), 3.34-3.24 (m, 2H), 2.44-2.30 (m, 2H), 1.62-1.24 (m, 9H); ^{31}P NMR ($CDCl_3$) δ 28.3 and 26.8; MS (ESI) 346 (M+1).



Example 8A

Compound **24**: Compound **23** was purified using a Dynamax SD-200 HPLC system. The mobile phase consisted of acetonitrile: water (65:35, v/v) at a flow rate of 70 mL/ min. The injection volume was 4 mL. The detection was by fluorescence at 245 nm and peak area ratios were used for quantitations. Retention time was 8.2 min for compound **24** as yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.36-7.19 (m, 10H), 5.88 (m, 1H), 5.12 (s, 2H), 4.90-4.86 (m, 1H),

4.26-4.12 (m, 2H), 3.72-3.61(m, 2H), 2.36-2.29 (m, 2H), 1.79-1.74 (m, 2H); 1.27 (t, J = 7.2 Hz, 3H), 0.82 (t, J = 7.2 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 28.3; MS (ESI) 472 (M+Na).

Example 8B

Compound **25** was purified in the same manner and retention time was 7.9 min for compound **25** as yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.34-7.14 (m, 10H), 5.75 (m, 1H), 5.10 (s, 2H), 4.96-4.91 (m, 1H), 4.18-4.12 (m, 2H), 3.66-3.55(m, 2H), 2.29-2.19 (m, 2H), 1.97-1.89 (m, 2H); 1.21 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 26.2; MS (ESI) 472 (M+Na).

Example 8C

Compound **26**: A solution of compound **24** (1 g) was dissolved in 20 mL of EtOH, then 0.3 mL of acetic acid and 10 % Pd/C (200 mg) was added. The resulted mixture was stirred under H2 atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound **26** (830mg, 99 %) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.46-7.19 (m, 5H), 4.92-4.81 (m, 1H), 4.24-4.21 (m, 2H), 3.41-3.28 (m, 2H), 2.54-2.38 (m, 2H), 1.79-1.74 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 0.80 (t, J = 7.2 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 26.9; MS (ESI) 316 (M+1).

Example 8D

Compound **27**: A solution of compound **25** (700g) was dissolved in 14 mL of EtOH, then 0.21 mL of acetic acid and 10 % Pd/C (140 mg) was added. The resulted mixture was stirred under H2 atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound **27** (510mg, 98 %) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.39-7.18 (m, 5H), 4.98-4.85 (m, 1H), 4.25-4.22 (m, 2H), 3.43-3.28 (m, 2H), 2.59-2.41 (m, 2H), 1.99-1.85 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 24.2; MS (ESI) 316 (M+1).

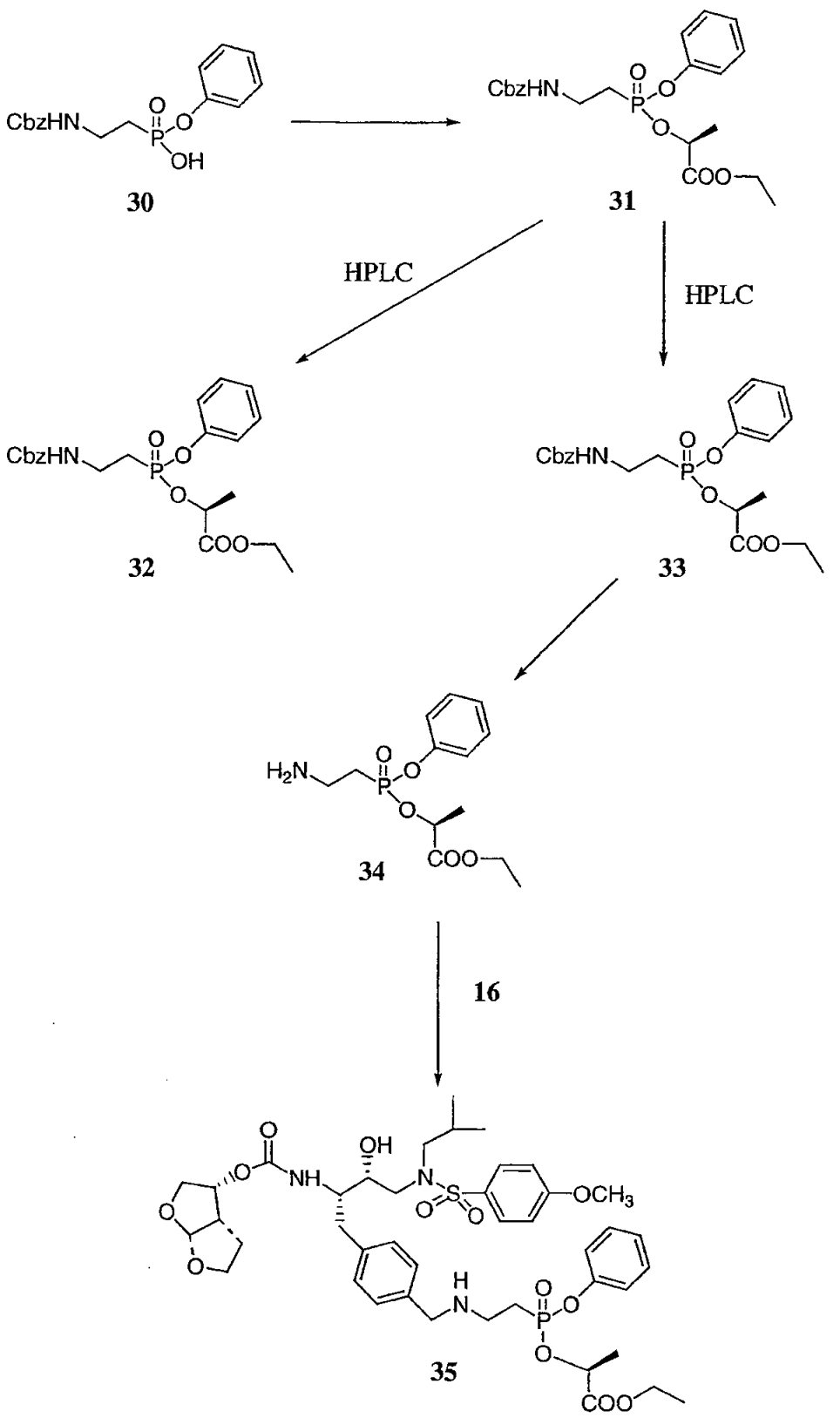
Example 8E

Compound **28**: To a stirred solution of compound **16** (1.18 g, 2 mmol) in 9 mL of 1,2-dichloroethane was added compound **26** (830 mg, 2.2 mmol) and $MgSO_4$ (80 mg), the resulted mixture was stirred at room temperature under argon for 3h, then acetic acid (0.34

mL, 6 mmol) and sodium cyanoborohydride (251mg, 4 mmol) were added. The reaction mixture was stirred at room temperature for 2 h under argon. Then aqueous $NaHCO_3$ (50 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOH/EtOAc, 1/9) to give **28** (880 mg, 50 %) as a white solid. ^1H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.35-7.16 (m, 9H), 6.99 (d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.03-4.85 (m, 3H), 4.24 -3.67 (m overlapping s, 15H), 3.14-2.70 (m, 9H), 2.39-2.28 (m, 2H), 1.85-1.51 (m, 5H), 1.29-1.25 (m, 3H), 0.93-0.78 (m, 9H); ^{31}P NMR ($CDCl_3$) δ 29.2; MS (ESI) 912 (M+Na).

Example 8F

Compound **29**: To a stirred solution of compound **16** (857 g, 1.45 mmol) in 7 mL of 1,2-dichloroethane was added compound **27** (600 mg, 1.6 mmol) and $MgSO_4$ (60 mg), the resulted mixture was stirred at room temperature under argon for 3h, then acetic acid (0.23 mL, 3 mmol) and sodium cyanoborohydride (183mg, 2.9 mmol) were added. The reaction mixture was stirred at room temperature for 2 h under argon. Then aqueous $NaHCO_3$ (50 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOH/EtOAc, 1/9) to give **29** (650 mg, 50 %) as a white solid. ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.35-7.16 (m, 9H), 7.00 (d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.03-4.90 (m, 3H), 4.17 -3.67 (m overlapping s, 15H), 3.16-2.77 (m, 9H), 2.26-2.19 (m, 2H), 1.94-1.53 (m, 5H), 1.26-1.18 (m, 3H), 1.00-0.87 (m, 9H); ^{31}P NMR ($CDCl_3$) δ 27.4; MS (ESI) 912 (M+Na).


CbzHN
OH
30
CbzHN
COO
31
HPLC
HPLC
CbzHN
COO
32
CbzHN
COO
33
H2N
COO
34
16
OH
NH
OCH3
H
N
35
COO

Example 9A

Compound **31**: To a stirred solution of compound **30** (20 g, 60 mmol) in 320 mL of toluene at room temperature under N_2 was added thionyl chloride (17.5 mL, 240 mmol) and a few drops of DMF. The resulted mixture was stirred at 60-70°C for 3 h. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 280 mL of DCM, followed by TEA (50 mL, 360 mmol) and (S) lactate ethyl ester (17 mL, 150 mmol). After 20h at room temperature, the solvent was removed under reduced pressure, and the residue was diluted with DCM and washed with brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (DCM / EtOAc , 1:1) to give **31** (24 g, 92 %) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.33-7.18 (m, 10H), 5.94-6.63 (m, 1H), 5.70 (m, 1H), 5.12-4.95 (m, 3H), 4.24-4.14 (m, 2H), 3.72-3.59(m, 2H), 2.35-2.20 (m, 2H), 1.58-1.19 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 28.2 and 26.2; MS (ESI) 458 (M+Na).

Example 9B

Compound **32**: Compound **31** was purified using a Dynamax SD-200 HPLC system. The mobile phase consisted of acetonitrile: water (60:40, v/v) at a flow rate of 70 mL/ min. The injection volume was 3 mL. The detection was by fluorescence at 245 nm and peak area ratios were used for quantitations. Retention time was 8.1 min for compound **32** as yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.33-7.18 (m, 10H), 5.94-6.63 (m, 1H), 5.70 (m, 1H), 5.12-4.95 (m, 3H), 4.24-4.14 (m, 2H), 3.72-3.59(m, 2H), 2.35-2.20 (m, 2H), 1.58-1.19 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 28.2; MS (ESI) 458 (M+Na).

Example 9C

Compound **33** was purified in the same manner and retention time was 7.9 min for compound **33** as yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.33-7.18 (m, 10H), 5.94-6.63 (m, 1H), 5.70 (m, 1H), 5.12-4.95 (m, 3H), 4.24-4.14 (m, 2H), 3.72-3.59(m, 2H), 2.35-2.20 (m, 2H), 1.58-1.19 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 26.2; MS (ESI) 458 (M+Na).

Example 9D

Compound **34**: A solution of compound **33** (3.2 g) was dissolved in 60 mL of EtOH, then 0.9 mL of acetic acid and 10 % Pd/C (640 mg) was added. The resulted mixture was stirred

under H_2 atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound **34** (2.7 g, 99 %) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.42-7.18 (m, 5H), 6.10 (s, 1H), 5.15-5.02 (m, 1H), 4.24-4.05 (m, 2H), 3.25-3.16 (m, 2H), 2.36-2.21 (m, 2H), 1.61-1.58 (m, 3H), 1.35- 1.18, m, 3H); ^{31}P NMR ($CDCl_3$) δ 26.1; MS (ESI) 302 (M+1).

Example 9E

Compound **35**: To a stirred solution of compound **16** (8.9 g, 15 mmol) in 70 mL of 1,2-dichloroethane was added compound **34** (8.3 g, 23 mmol) and $MgSO_4$ (80 mg), the resulted mixture was stirred at room temperature under argon for 2.5h, then acetic acid (3 mL, 52.5 mmol) and sodium cyanoborohydride (1.9g, 30 mmol) were added. The reaction mixture was stirred at room temperature for 1.5 h under argon. Then aqueous $NaHCO_3$ (100 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOH/EtOAc, 1/9) to give **35** (8.4 g, 64 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 8.7 Hz, 2H), 7.36-7.17(m, 9H), 7.00 (d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.1 Hz, 1H), 5.07-4.97 (m, 3H), 4.19 -3.67 (m overlapping s, 13H), 3.15-2.78 (m, 9H), 2.25-2.19 (m, 2H), 1.91-1.54 (m, 6H), 1.24-1.20 (m, 3H), 0.94-0.87 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 27.4; MS (ESI) 876 (M+1).

Resolution of Compound 35 **Diastereomers**

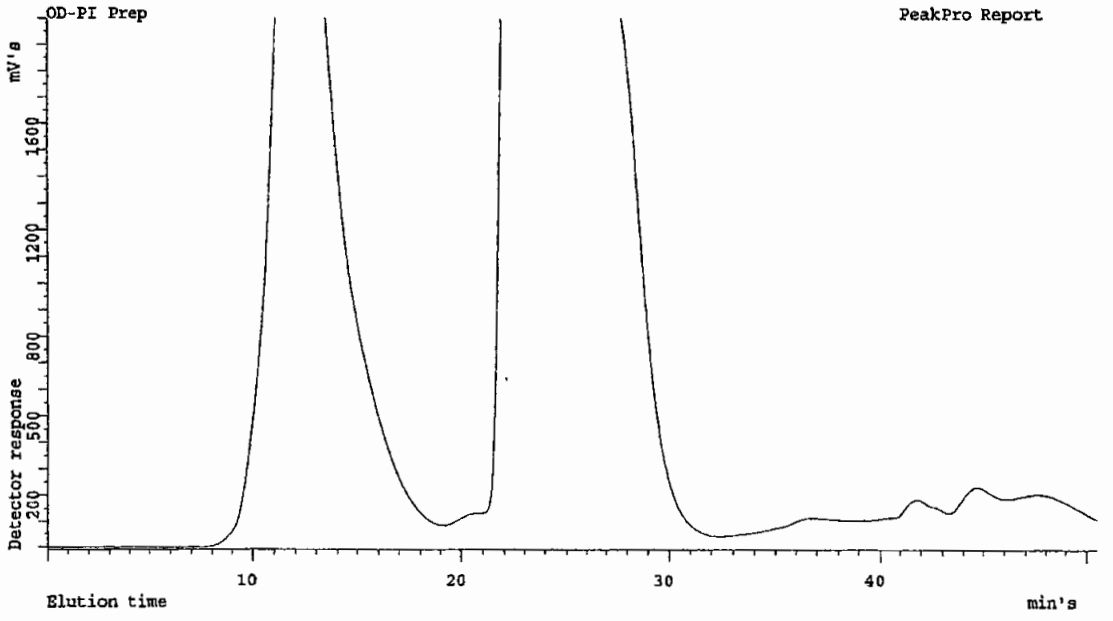
Analysis was performed on an analytical Daicel Chiralcel OD column, conditions described below, with a total of about 3.5 mg compound **35** free base injected onto the column. This lot was about a 3:1 mixture of major to minor diastereomers where the lactate ester carbon is a 3:1 mix of R and S configurations.

Two injections of 3.8 and 3.5 mg each were made using the conditions described below. The isolated major diastereomer fractions were evaporated to dryness on a rotary evaporator under house vacuum. The chromatographic solvents were displaced by two portions of ethyl acetate followed by a single portion of ethyl acetate – trifluoroacetic acid (about 95:5) and a final high vacuum strip to aid in removal of trace solvents. This yielded the major diastereomer trifluoroacetate salt as a gummy solid.

The resolved minor diastereomer was isolated for biological evaluation by an 11 mg injection, performed on an analytical Daicel Chiralcel OD column, using the conditions described in below. The minor diastereomer of 35 **was isolated as the trifluoroacetate salt by the conditions described above.**

Larger scale injections (~ 300 mg **35** per injection) were later performed on a Daicel Chiralcel OD column semi-preparative column with a guard column, conditions described below. A minimal quantity of isopropyl alcohol was added to heptane to dissolve the 3:1 diastereomeric mix of **35** and the resolved diastereomers sample, and the isolated fractions were refrigerated until the eluted mobile phase was stripped.

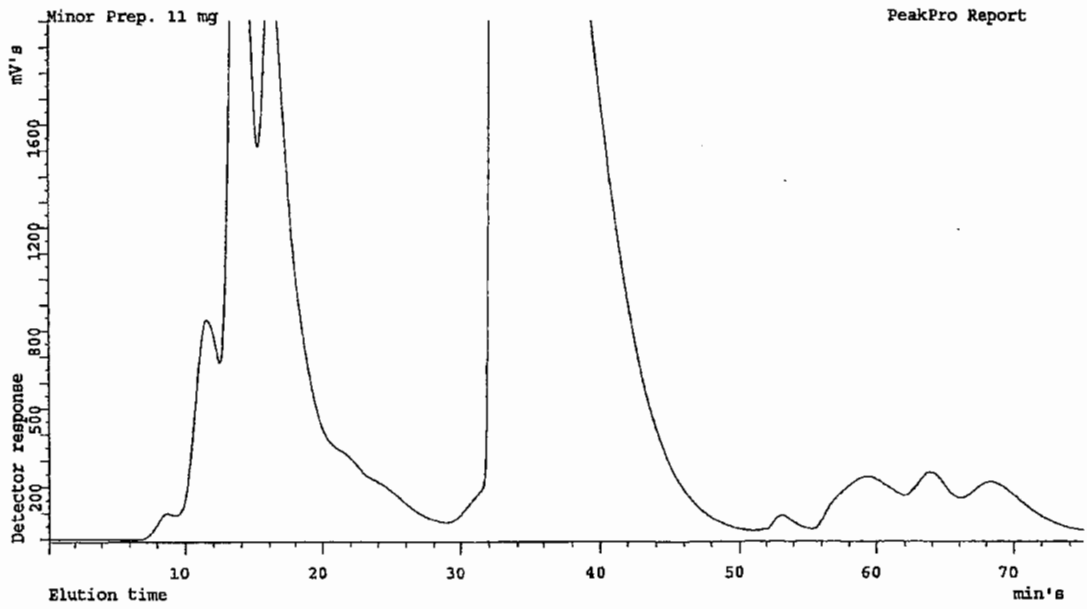
Analytical Column, ~ 4 mg Injection, Heptane – EtOH (20:80) Initial



HPLC CONDITIONS

Column	: Chiralcel OD, 10 µm, 4.6 x 250 mm
Mobile Phase	: Heptane – Ethyl Alcohol (20:80 initial)
	: 100% Ethyl Alcohol (final)
	Note: Final began after first peak eluted
Flow Rate	: 1.0 mL/min
Run Time	: As needed
Detection	: UV at 250 nm
Temperature	: Ambient
Injection	: ~ 4 mg on Column
Sample Prep.	: Dissolved in ~ 1 mL heptane – ethyl alcohol (50:50)
Retention Times	: **35** Minor ~ 14 min
	: **35** Major ~ 25 min

Analytical Column, ~ 6 mg Injection, Heptane – EtOH (65:35) Initial

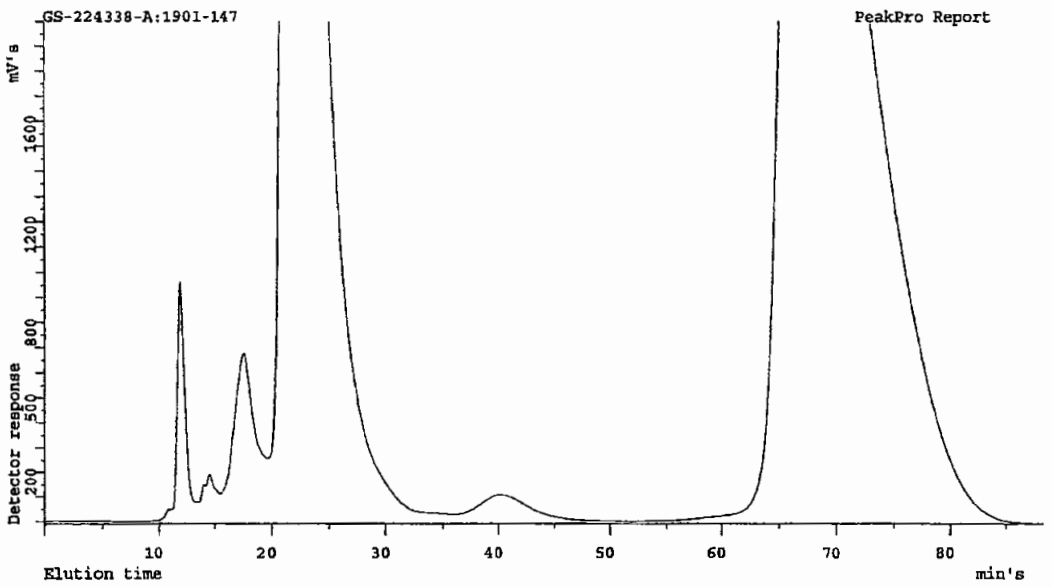


5

HPLC CONDITIONS

Column	: Chiralcel OD, 10 μm, 4.6 x 250 mm
Mobile Phase	: Heptane – Ethyl Alcohol (65:35 initial)
	: Heptane – Ethyl Alcohol (57.5:42.5 intermediate)
	Note: Intermediate began after impurity peaks eluted
	: Heptane – Ethyl Alcohol (20:80 final)
	Note: Final mobile phase began after minor diastereomer eluted
Flow Rate	: 1.0 mL/min
Run Time	: As needed
Detection	: UV at 250 nm
Temperature	: Ambient
Injection	: ~ 4 mg on Column
Sample Prep.	: Dissolved in ~ 1 mL heptane – ethyl alcohol (50:50)
Retention Times	: **35** Minor ~ 14 min
	: **35** Major ~ 40 min

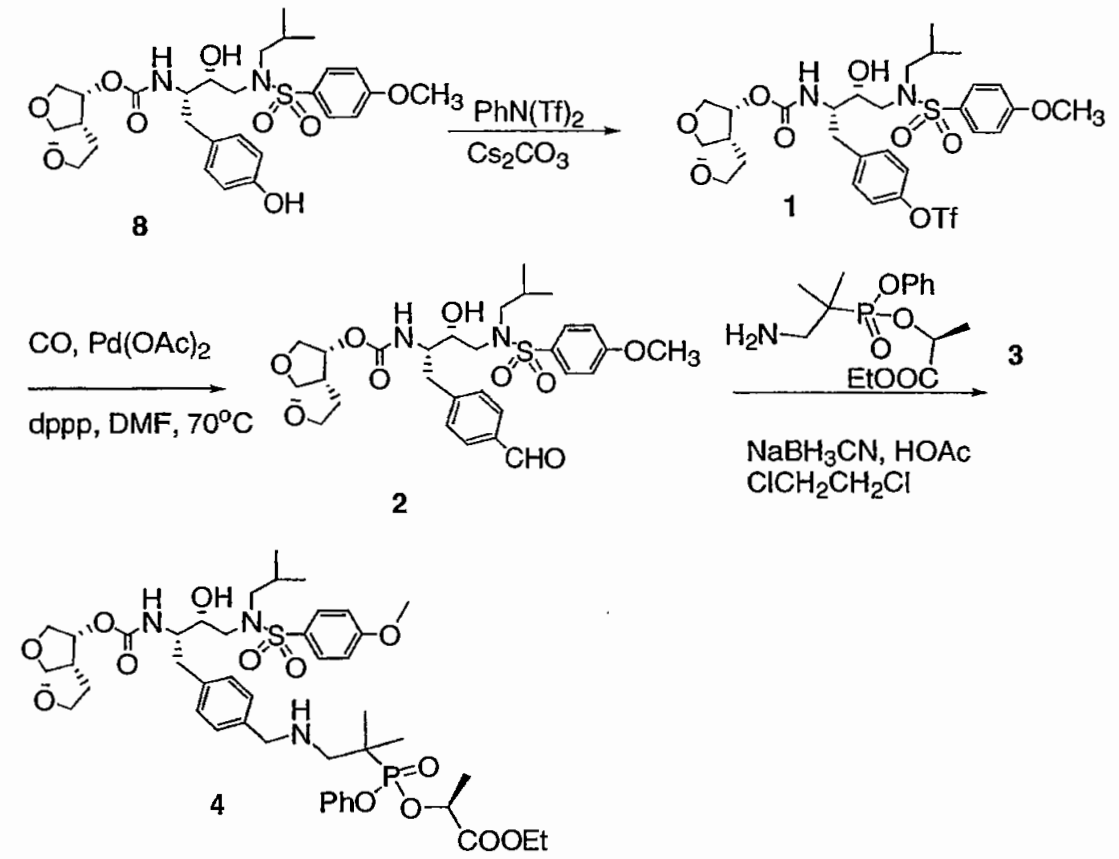
Semi-Preparative Column, ~ 300 mg Injection, Heptane – EtOH (65:35) Initial



5

HPLC CONDITIONS

Columns	: Chiralcel OD, 20 µm, 21 x 50 mm (guard)
	: Chiralcel OD, 20 µm, 21 x 250 mm
Mobile Phase	: Heptane – Ethyl Alcohol (65:35 initial)
	: Heptane – Ethyl Alcohol (50:50 intermediate) Note: Intermediate began after minor diastereomer peak eluted
	: Heptane – Ethyl Alcohol (20:80 final) Note: Final mobile phase began after major diastereomer began to elute
Flow Rate	: 10.0 mL/min
Run Time	: As needed
Detection	: UV at 260 nm
Temperature	: Ambient
Injection	: ~ 300 mg on Column
Sample Prep.	: Dissolved in ~ 3.5 mL hetpane – ethyl alcohol (70:30)
Retention Times	: **35** Minor ~ 14 min
	: **35** Major ~ 40 min


PhN(Tf)2
Cs2CO3
CO, Pd(OAc)2
dppp, DMF, 70°C
NaBH3CN, HOAc
ClCH2CH2Cl
EtOOC
8
1
2
3
4
5
6
7
Mel. NaH,
THF, -10°C
PtO2, 1N HCl,
H2, EtoH
TMS-Br
CH3CN
1. CBZ-Cl
2. SOCl2, 70°C
3. PhOH, DIPEA
1. NaOH, CH3CN
2. BOp-reagent
DIPEA, L-actate
ethyl ester
H2, 10% Pd/C,
TFA (1 eq.)

Example 29

Triflate derivative **1**: A THF-CH_2Cl_2 solution (30mL-10 mL) of **8** (4 g, 6.9 mmol), cesium carbonate (2.7 g, 8 mmol), and N-phenyltrifluoromethane sulfonimide (2.8 g, 8 mmol) was reacted overnight. The reaction mixture was worked up, and concentrated to dryness to give crude triflate derivative **1**.

Aldehyde **2**: Crude triflate **1** (4.5 g, 6.9 mmol) was dissolved in DMF (20 mL), and the solution was degassed (high vacuum for 2 min, Ar purge, repeat 3 times). Pd(OAc)2 (0.12 g, 0.27 mmol), and bis(diphenylphosphino)propane (dppp, 0.22 g, 0.27 mmol) were added, the solution was heated to 70°C. Carbon monoxide was rapidly bubbled through the solution, then under 1 atmosphere of carbon monoxide. To this solution were slowly added TEA (5.4 mL, 38 mmol), and triethylsilane (3 ml), 18 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was worked up, and purified on silica gel column chromatograph to afford aldehyde **2** (2.1 g, 51 %). (Hostetler, et al J. Org. Chem., 1999. 64, 178-185).

Lactate prodrug **4**: Compound 4 is prepared as described above procedure for Example 9E, Compound 35 by the reductive amination between 2 and 3 with $NaBH_3CN$ in 1,2-dichloroethane in the presence of HOAc.

Example 30 Preparation of Compound 3

Diethyl (cyano(dimethyl)methyl) phosphonate **5**: A THF solution (30 mL) of NaH (3.4 g of 60% oil dispersion, 85 mmol) was cooled to –10°C, followed by the addition of diethyl (cyanomethyl)phosphonate (5g, 28.2 mmol) and iodomethane (17 g, 112 mmol). The resulting solution was stirred at –10°C for 2 hr, then 0°C for 1 hr, was worked up, and purified to give dimethyl derivative **5** (5 g, 86 %).

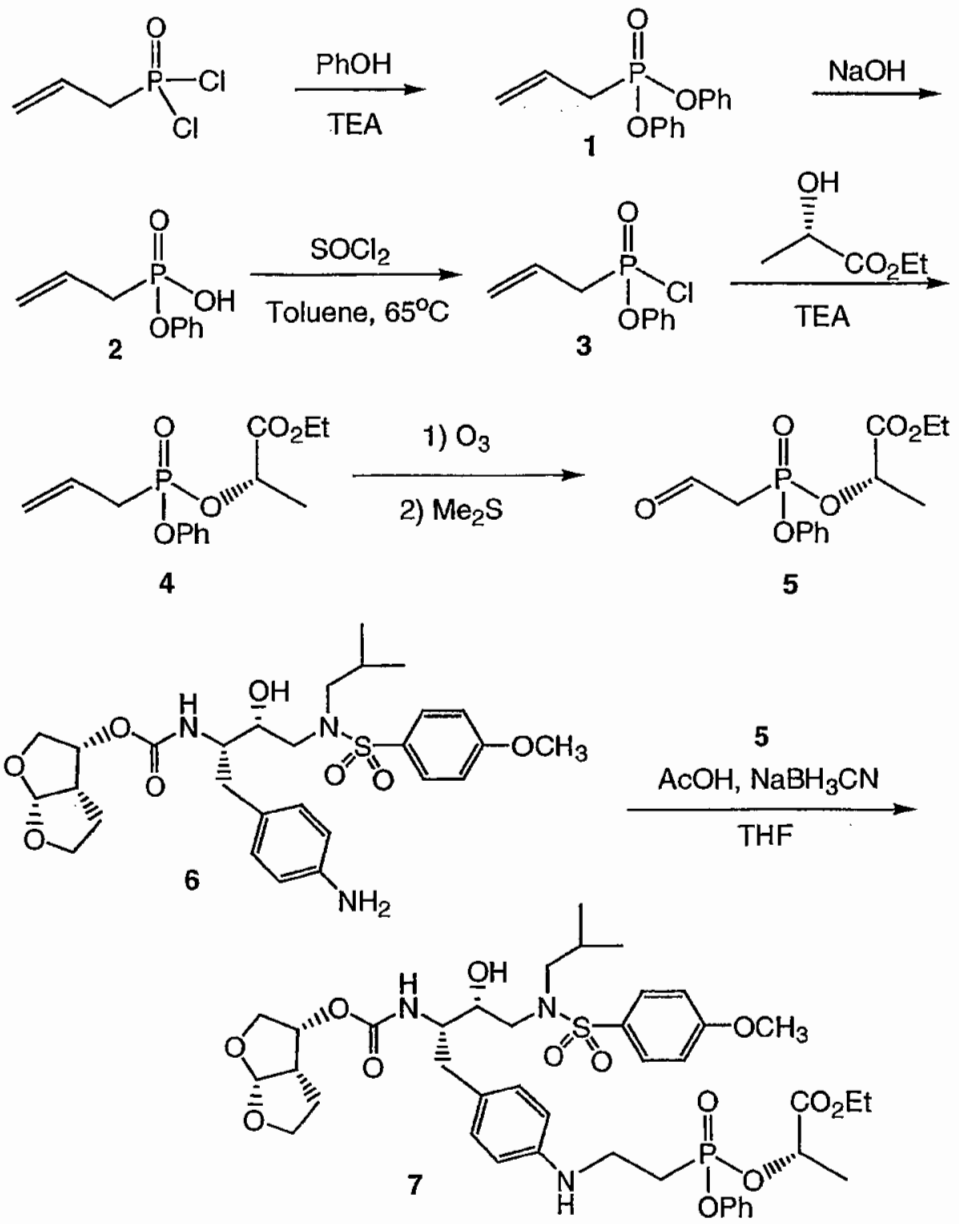
Dietyl (2-amino-1,1-dimethyl-ethyl)phosphonate **6**: Compound **5** was reduced to amine derivative **6** by the described procedure (J. Med. Chem. 1999, 42, 5010-5019).

A solution of ethanol (150 mL) and 1N HCl aqueous solution (22 mL) of 5 (2.2 g, 10.7 mmol) was hydrogenated at 1 atmosphere in the presence of PtO_2 (1.25 g) at room temperature overnight. The catalyst was filtered through a celite pad. The filtrate was concentrated to dryness, to give crude **6** (2.5g, as HCl salt).

2-Amino-1,1-dimethyl-ethyl phosphonic acid **7**: A solution of CH_3CN (30 mL) of crude **6** (2.5 g) was cooled to 0°C, and treated with TMSBr (8 g, 52 mmol) for 5 hr. The reaction mixture was stirred with methanol for 1.5 hr at room temperature, concentrated, recharged with methanol, concentrated to dryness to give crude **7** which was used for next reaction without further purification.

Lactate phenyl (2-amino-1,1-dimethyl-ethyl)phosphonate **3**: Compound **3** is synthesized according to the procedures described in Example 9D, Compound 34 for the preparation of lactate phenyl 2-aminoethyl phosphonate 34. Compound **7** is protected with CBZ, followed by the reaction with thionyl chloride at 70°C. The CBZ protected dichlorodate is reacted phenol in the presence of DIPEA. Removal of one phenol, follow by coupling with ethyl L-lactate leads N-CBZ-2-amino-1,1-dimethyl-ethyl phosphonate derivative. Hydrogenation of N-CBZ derivative at 1 atmosphere in the presence of 10 % Pd/C and 1 eq. of TFA affords compound **3** as TFA salt.

Scheme 1



Example 1

Monophenol Allylphosphonate **2**: To a solution of allylphosphonic dichloride (4 g, 25.4 mmol) and phenol (5.2 g, 55.3 mmol) in CH_2Cl_2 (40 mL) at 0°C was added TEA (8.4 mL, 60 mmol). After stirred at room temperature for 1.5 h, the mixture was diluted with hexane-ethyl acetate and washed with HCl (0.3 N) and water. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (eluted with 2:1 hexane-ethyl acetate) to afford crude product diphenol

allylphosphonate **1** (7.8 g, containing the excessive phenol) as an oil which was used directly without any further purification. The crude material was dissolved in CH_3CN (60 mL), and NaOH (4.4N, 15 mL) was added at 0°C. The resulted mixture was stirred at room temperature for 3 h, then neutralized with acetic acid to pH = 8 and concentrated under reduced pressure to remove most of the acetonitrile. The residue was dissolved in water (50 mL) and washed with CH_2Cl_2 (3X25 mL). The aqueous phase was acidified with concentrated HCl at 0°C and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, evaporated and co-evaporated with toluene under reduced pressure to yield desired monophenol allylphosphonate **2** (4.75 g. 95%) as an oil.

Example 2

Monolactate Allylphosphonate **4**: To a solution of monophenol allylphosphonate **2** (4.75 g, 24 mmol) in toluene (30 mL) was added $SOCl_2$ (5 mL, 68 mmol) and DMF (0.05 mL). After stirred at 65°C for 4 h , the reaction was completed as shown by ^{31}P NMR. The reaction mixture was evaporated and co-evaporated with toluene under reduced pressure to give mono chloride **3** (5.5 g) as an oil. To a solution of chloride **3** in CH_2Cl_2 (25 mL) at 0°C was added ethyl (s)-lactate (3.3 mL, 28.8 mmol), followed by TEA. The mixture was stirred at 0°C for 5 min then at room temperature for 1 h, and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2N), the organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford desired monolactate **4** (5.75 g, 80%) as an oil (2:1 mixture of two isomers): ^1H NMR ($CDCl_3$) δ 7.1-7.4 (m, 5H), 5.9 (m, 1H), 5.3 (m, 2H), 5.0 (m, 1H), 4.2 (m, 2H), 2.9 (m, 2H), 1.6; 1.4 (d, 3H), 1.25 (m, 3H); ^{31}P NMR ($CDCl_3$) δ 25.4, 23.9.

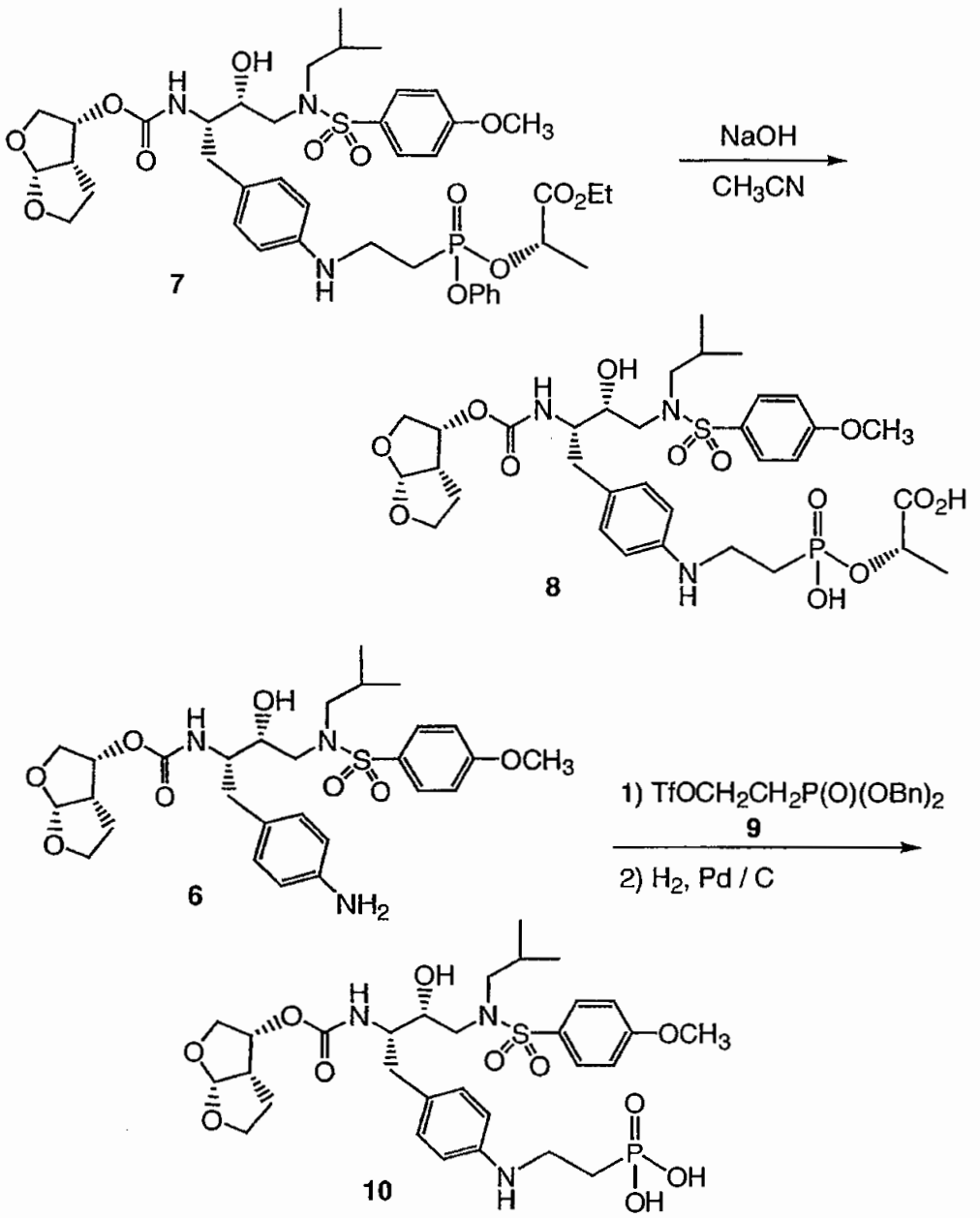
Example 3

Aldehyde **5**: A solution of allylphosphonate **4** (2.5 g, 8.38 mmol) in CH_2Cl_2 (30 mL) was bubbled with ozone air at –78°C until the solution became blue, then bubbled with nitrogen until the blue color disappeared. Methyl sulfide (3 mL) was added at –78°C. The mixture was warmed up to room temperature, stirred for 16 h and concentrated under reduced pressure to give desired aldehyde **5** (3.2 g, as a 1:1 mixture of DMSO): ^1H NMR ($CDCl_3$) δ 9.8 (m, 1H), 7.1-7.4 (m, 5H), 5.0 (m, 1H), 4.2 (m, 2H), 3.4 (m, 2H), 1.6; 1.4 (d, 3H), 1.25 (m, 3H); ^{31}P NMR ($CDCl_3$) δ 17.7, 15.4.

Example 4

Compound **7**: To a solution of aniline **6** (reported before) (1.62 g, 2.81 mmol) in THF (40 mL) was added acetic acid (0.8 mL, 14 mmol), followed by aldehyde **5** (1.3 g, 80%, 3.46 mmol) and $MgSO_4$ (3 g). The mixture was stirred at room temperature for 0.5 h, then $NaBH_3CN$ (0.4 g, 6.37 mmol) was added. After stirred for 1 h, the reaction mixture was filtered. The filtrate was diluted with ethyl acetate and washed with $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give compound **6** (1.1g, 45%) as a 3:2 mixture of two isomers, which were separated by HPLC (mobile phase, 70% CH_3CN/H_2O; flow rate: 70 mL/min; detection: 254 nm; column: 8μ C18, 41X250 mm, Varian). Isomer A (0.39 g): ^1H NMR ($CDCl_3$) δ 7.75 (d, 2H), 7.1-7.4 (m, 5H), 7.0 (m, 4H), 6.6 (d, 2H), 5.65 (d, 1H), 5.05 (m, 2H), 4.9 (d, 1H), 4.3 (brs, 1H), 4.2 (q, 2H), 3.5-4.0 (m, 6H), 3.9 (s, 3H), 2.6-3.2 (m, 9H), 2.3 (m, 2), 1.6-1.9 (m, 5H), 1.25 (t, 3H), 0.9 (2d, 6H); ^{31}P NMR ($CDCl_3$) δ 26.5; MS (ESI): 862 (M+H). Isomer B (0.59 g): ^1H NMR ($CDCl_3$) δ 7.75 (d, 2H), 7.1-7.4 (m, 5H), 7.0 (m, 4H), 6.6 (d, 2H), 5.65 (d, 1H), 5.05 (m, 2H), 4.9 (d, 1H), 4.5 (brs, 1H), 4.2 (q, 2H), 3.5-4.0 (m, 6H), 3.9 (s, 3H), 2.7-3.2 (m, 9H), 2.4 (m, 2), 1.6-1.9 (m, 2H), 1.4 (d, 3H), 1.25 (t, 3H), 0.9 (2d, 6H); ^{31}P NMR ($CDCl_3$) δ 28.4; MS (ESI): 862 (M+H).

Scheme 2



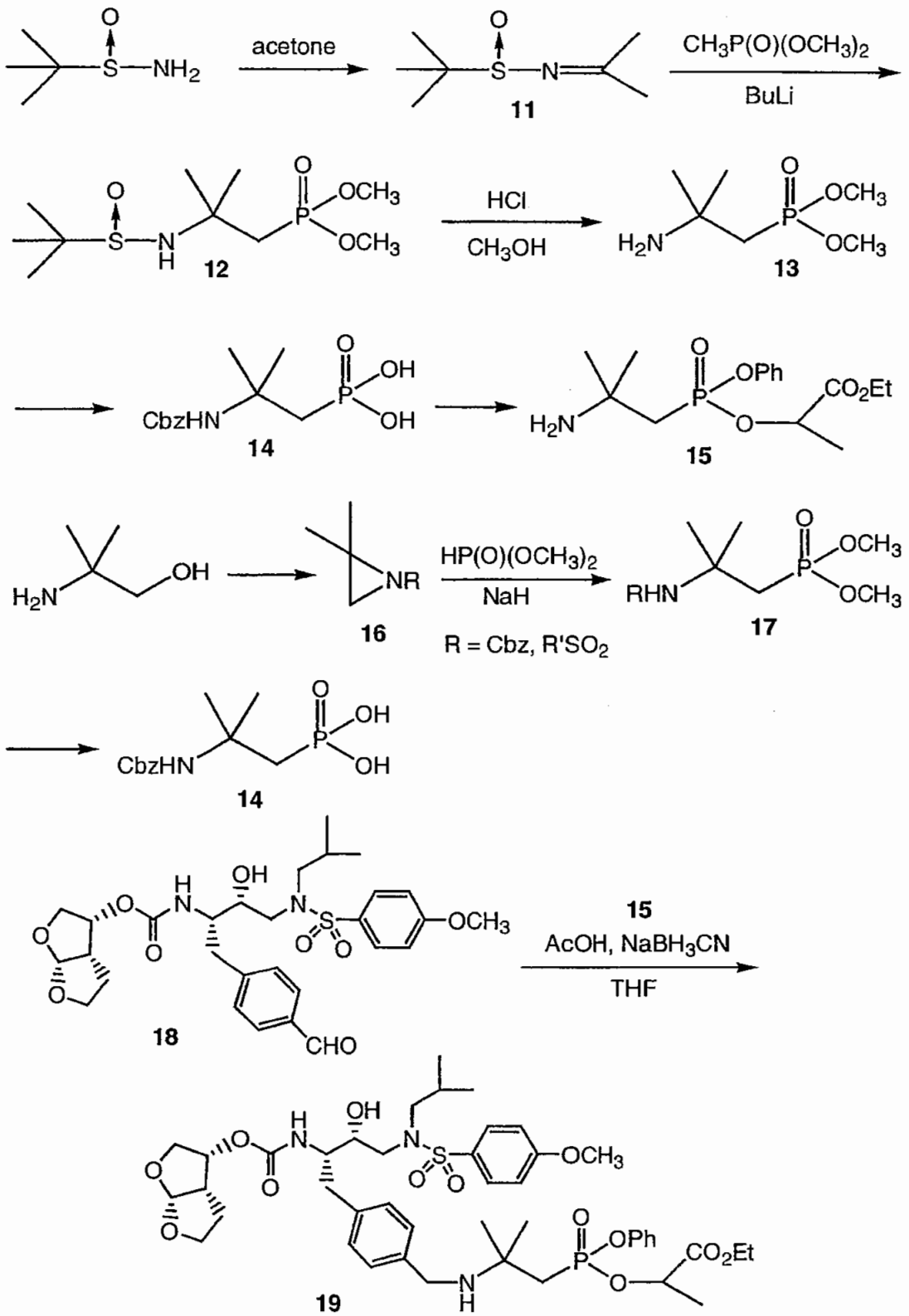
Example 5

Acid **8**: To a solution of compound **7** (25 mg, 0.029 mmol) in acetonitrile (1 mL) at 0°C was added NaOH (1N, 0.125 mL). The mixture was stirred at 0°C for 0.5 h and at room temperature for 1 h. The reaction was quenched with acetic acid and purified by HPLC to give acid **8** (10 mg, 45%). ^{1}H NMR (CD_3OD) δ 7.8 (d, 2H), 7.5 (d, 2H), 7.4 (d, 2H), 7.1 (d, 2H), 5.6 (d, 1H), 4.9 (m, 3H), 3.2-4.0 (m, 6H), 3.9 (s, 3H), 2.6-3.2 (m, 9H), 2.05 (m, 2), 1.4-1.7 (m, 2H), 1.5 (d, 3H), 0.9 (2d, 6H); ^{31}P NMR (CD_3OD) δ 20.6; MS (ESI): 758 (M+H).

Example 6

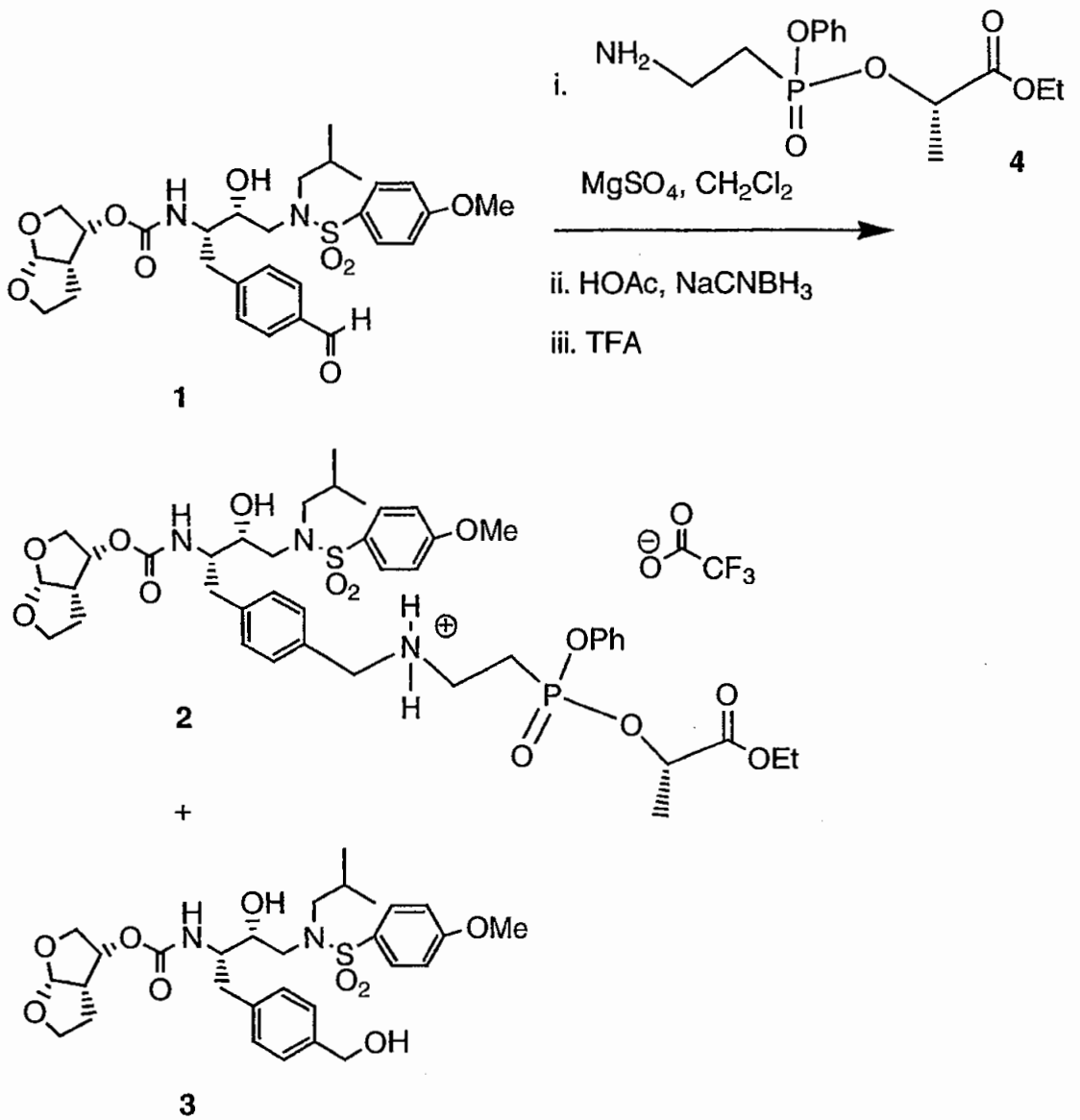
Diacid **10**: To a solution of triflate **9** (94 mg, 0.214 mmol) in CH_2Cl_2 (2 mL) was added a solution of aniline 6 (100 mg, 0.173 mmol) in CH_2Cl_2 (2 mL) at –40°C, followed by 2,6-lutidine (0.026 mL). The mixture was warmed up to room temperature and stirred for 1 h. Cesium carbonate (60 mg) was added and the reaction mixture was stirred for additional 1 h. The mixture was diluted with ethyl acetate, washed with HCl (0.2N), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by HPLC to afford dibenzyl phosphonate (40 mg). To a solution of this dibenzyl phosphonate in ethanol (3 mL) and ethyl acetate (1 mL) was added 10% Pd/C (40 mg). The mixture was stirred under hydrogen atmosphere (balloon) for 4 h. The reaction mixture was diluted with methanol, filtered and concentrated under reduced pressure. The residue was washed with ethyl acetate and dried to give desired product diacid **10** (20 mg). ^{1}H NMR (CD_3OD) δ 7.8 (d, 2H), 7.3 (d, 2H), 7.1 (2d, 4H), 5.6 (d, 1H), 4.9 (m, 2H), 3.4-4.0 (m, 6H), 3.9 (s, 3H), 2.5-3.2 (m, 9H), 2.0 (m, 2), 1.4-1.7 (m, 2H), 0.9 (2d, 6H); ^{31}P NMR (CD_3OD) δ 22.1; MS (ESI): 686 (M+H).

Scheme 3



The synthesis of compound **19** is outlined in Scheme 3. Condensation of 2-methyl-2-propanesulfinamide with acetone give sulfinyl imine **11** (J. Org. Chem. 1999, 64, 12).

Addition of dimethyl methylphosphonate lithium to **11** afford **12**. Acidic methanolysis of **12** provide amine **13**. Protection of amine with Cbz group and removal of methyl groups yield phosphonic acid **14**, which can be converted to desired **15** using methods reported earlier on. An alternative synthesis of compound **14** is also shown in Scheme 3. Commercially available 2-amino-2-methyl-1-propanol is converted to aziridines **16** according to literature methods (J. Org. Chem. 1992, 57, 5813; and Syn. Lett. 1997, 8, 893). Aziridine opening with phosphite give **17** (Tetrahedron Lett. 1980, 21, 1623). Deprotection (and, if necessary, reprotection) of **17** afford **14**. Reductive amination of amine **15** and aldehyde **18** provides compound **19**.

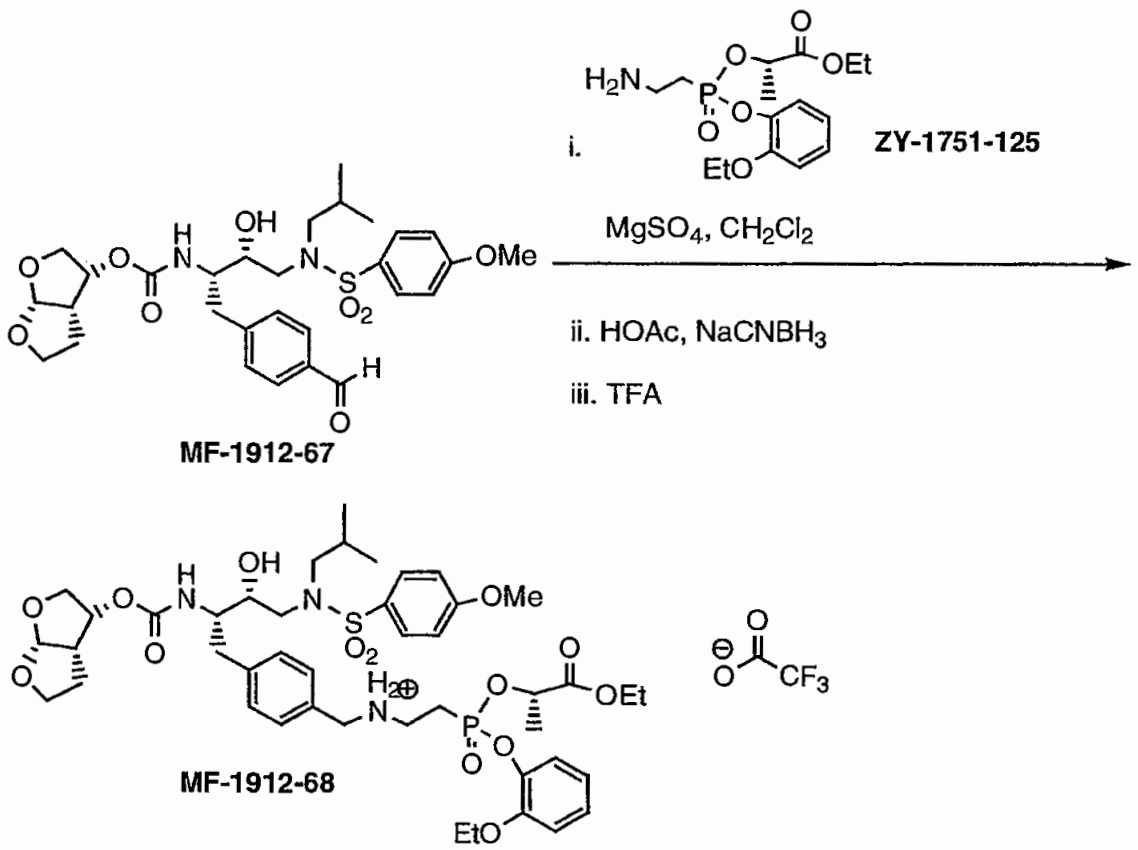


Example 1

2-{[2-(4-{2-(Hexahydro-furo[2,3-b]furan-3-yloxycarbonylamino)-3-hydroxy-4-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-butyl}-benzylamino)-ethyl]-phenoxy-phosphinoyloxy}-propionic acid ethyl ester **2** (Compound 35, previous Example 9E).

A solution of **1** (2.07 g, 3.51 mmol) and **4** (1.33 g, 3.68 mmol of a 4:1 mixture of two diastereomers at the phosphorous center) were dissolved in 14 mL of $(CH_2Cl_2)_2$ to provide a clear solution. Addition of $MgSO_4$ (100 mg) to the solution resulted in a white cloudy mixture. The solution was stirred at ambient temperature for 3 hours when acetic acid (0.80 mL, 14.0 mmol) and sodium cyanoborohydride (441 mg, 7.01 mmol) were added. Following the reaction progress by TLC showed complete consumption of the aldehyde starting materials in 1 hour. The reaction mixture was worked up by addition of 200 mL of saturated aqueous $NaHCO_3$ and 400 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 two more times (2 x 300 mL). The combined organic extracts were dried *in vacuo* and purified by column chromatography (EtOAc- 10% MeOH: EtOAc) to provide the desired product as a foam. The early eluting compound from the column was collected and characterized as alcohol **3** (810 mg, 39%). Addition of TFA (3 x 1 mL) generated the TFA salt which was lyopholized from 50 mL of a 1:1 CH_3CN: H_2O to provide 1.63 g (47%) of the product **2** as a white powder. ^1H NMR (CD_3CN) δ 8.23 (br s, 2H), 7.79 (d, *J*= 8.4 Hz, 2H), 7.45- 7.13 (m, 9H), 7.09 (d, *J*= 8.4 Hz, 2H), 5.86 (d, *J*= 9.0 Hz, 1H), 5.55 (d, *J*= 4.8 Hz, 1H), 5.05-4.96 (m, 1H), 4.96- 4.88 (m, 1H), 4.30-4.15 (m, 4H), 3.89 (s, 3H), 3.86- 3.76 (m, 4H), 3.70- 3.59 (m, 4H), 3.56- 3.40 (m, 2H), 3.34 (d, *J*= 15 Hz, 1H), 3.13 (d, *J*= 13.5 Hz, 1H), 3.06- 2.93 (m, 2H), 2.92- 2.80 (m, 2H), 2.69- 2.43 (m, 3H), 2.03- 1.86 (m, 1H), 1.64- 1.48 (m, 1H), 1.53 and 1.40 (d, *J*= 6.3 Hz, *J*= 6.6 Hz, 3H), 1.45- 1.35 (m, 1H), 1.27 and 1.23 (t, *J*= 6.9 Hz, *J*= 7.2 Hz, 3H), 0.90 (t, *J*= 6.9 Hz, 6H). ^{31}P NMR (CD_3CN) δ 24.47, 22.86. ESI $(M+H)^+$ 876.4.

Example 2

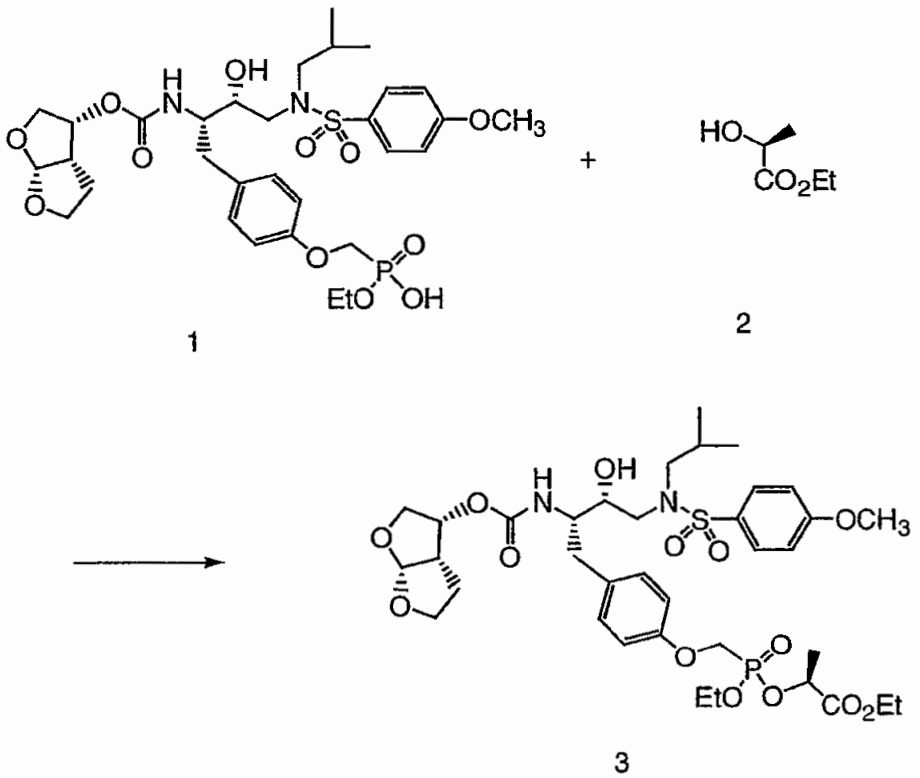


2-{[2-(4-{2-(Hexahydro-furo[2,3-b]furan-3-yloxycarbonylamino)-3-hydroxy-4-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-butyl}-benzylamino)-ethyl]-phenoxy-phosphinoyloxy}-propionic acid ethyl ester (**MF-1912-68**):

A solution of **MF-1912-67** (0.466 g, 0.789 mmol) and **ZY-1751-125** (0.320 g, 0.789 mmol of a 1:1 mixture of two diastereomers at the phosphorous center) were dissolved in 3.1 mL of $(CH_2Cl_2)_2$ to provide a clear solution. Addition of $MgSO_4$ (20 mg) to the solution resulted in a white cloudy mixture. The solution was stirred at ambient temperature for 3 hours when acetic acid (0.181 mL, 3.16 mmol) and sodium cyanoborohydride (99 mg, 1.58 mmol) were added. Following the reaction progress by TLC showed complete consumption of the aldehyde starting materials in 1.5 hour. The reaction mixture was worked up by addition of 50 mL of saturated aqueous $NaHCO_3$ and 200 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 two more times (2 x 200 mL). The combined organic extracts were dried *in vacuo* and purified by column chromatography (EtOAc- 10% MeOH: EtOAc) to provide the desired product as a foam. The early eluting compound from the column was collected and characterized to be MF-1912-48b alcohol (190 mg, 41%). Addition of TFA (3 x 1 mL) generated the TFA salt which was lyopholized from 50 mL of a 1:1 CH_3CN: H_2O to

provide 0.389 g (48%) of the product as a white powder. ^{1}H NMR (CD3CN) δ 8.39 (br s, 2H), 7.79 (d, *J*= 8.7 Hz, 2H), 7.40 (d, *J*= 7.5 Hz, 2H), 7.34 (d, *J*= 8.1 Hz, 2H), 7.26-7.16 (m, 2H), 7.10 (d, *J*= 9 Hz, 3H), 7.01- 6.92 (m, 1H), 5.78 (d, *J*= 9.0 Hz, 1H), 5.55 (d, *J*= 5.1 Hz, 1H), 5.25-5.03 (m, 1H), 4.95- 4.88 (m, 1H), 4.30- 4.17 (m, 4H),4.16- 4.07 (m, 2H), 3.90 (s, 3H), 3.88-3.73 (m, 4H), 3.72- 3.60 (m, 2H), 3.57- 3.38 (m, 2H), 3.32 (br d, *J*= 15.3 Hz, 1H), 3.13 (br d, *J*= 14.7 Hz, 1H), 3.05- 2.92 (m, 2H), 2.92- 2.78 (m, 2H), 2.68- 2.48 (m, 3H), 2.03- 1.90 (m, 1H), 1.62- 1.51 (m, 1H), 1.57 and 1.46 (d, *J*= 6.9 Hz, *J*= 6.9 Hz, 3H), 1.36- 1.50 (m, 1H), 1.43- 1.35 (m, 4H), 1.33- 1.22 (m, 3H), 0.91 (t, *J*= 6.6 Hz, 6H). ^{31}P NMR (CD_3CN) δ 25.27, 23.56. ESI $(M+H)^+$ 920.5.

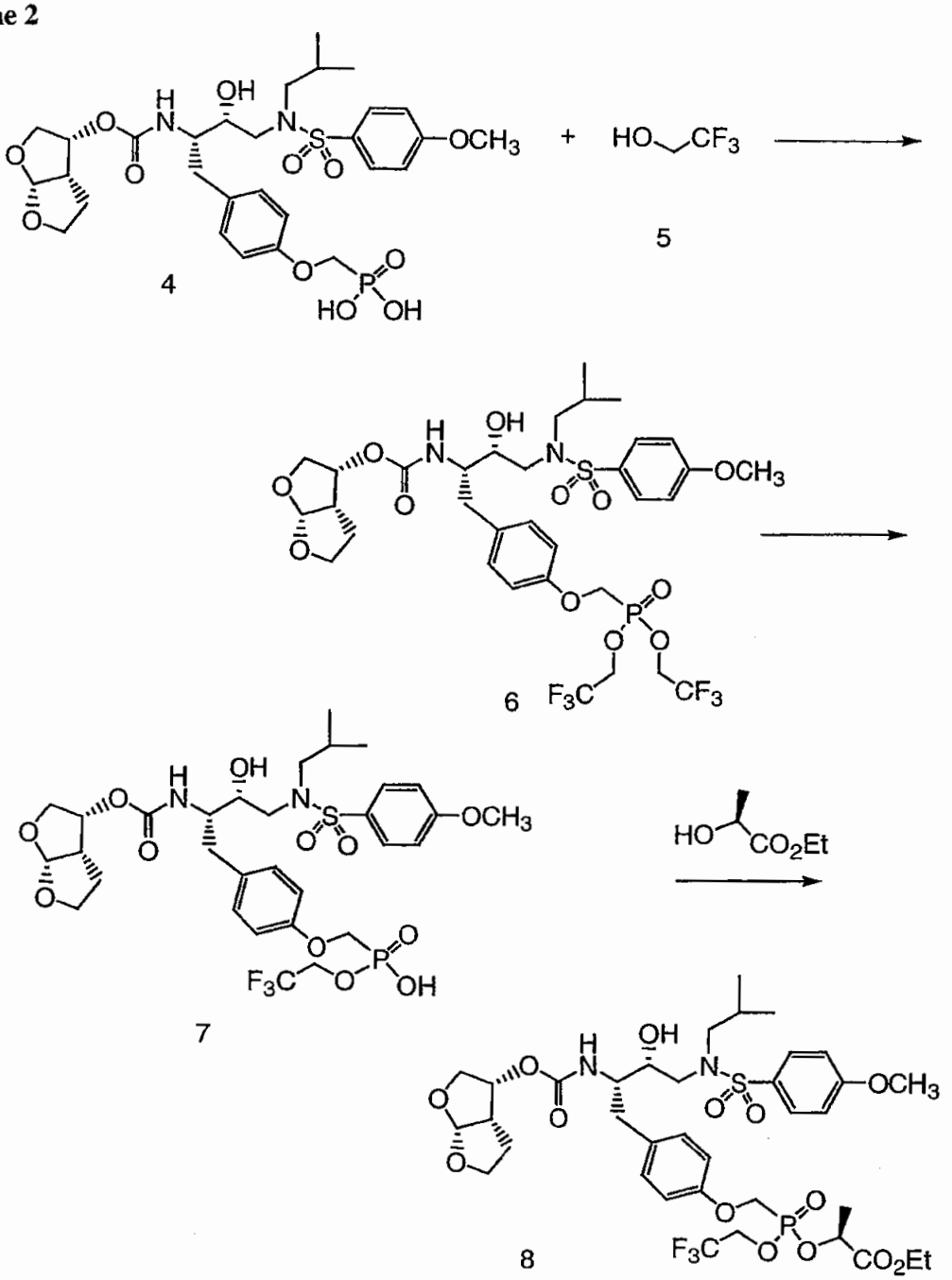
Scheme 1



1 2

3

Scheme 2



Example 1

Mono-Ethyl mono-lactate 3: To a solution of 1 (96mg, 0.137 mmol) and ethyl lactate 2 (0.31 mL, 2.7 mmol) in pyridine (2 mL) was added N, N-dicyclohexylcarbodiimide (170 mg, 0.822 mmol). The solution was stirred for 18h at 70°C. The mixture was cooled to room temperature and diluted with dichloromethane. The solid was removed by filtration and the filtrate was concentrated. The residue was suspended in diethyl ether/dichloromethane and

filtered again. The filtrate was concentrated and mixture was chromatographed on silica gel eluting with EtOAc/hexane to provide compound 3 (43 mg, 40%) as a foam: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H), 7.00 (d, 2H); 7.00 (d, 2H), 6.88 (d, 2H), 5.67 (d, 1H), 4.93-5.07 (m, 2H), 4.15-4.39 (m, 6H), 3.70-3.99 (m, 10H), 2.76-3.13 (m, 7H), 1.55-1.85 (m, 9H), 1.23-1.41 (m, 6H), 0.90 (dd, 6H); ^{31}P NMR ($CDCl_3$) δ 19.1, 20.2; MS (ESI) 823 (M+Na).

Example 2

Bis-2,2,2-trifluoroethyl phosphonate 6: To a solution of 4 (154mg, 0.228 mmol) and 222,-trifluoroethanol 5 (1 mL, 13.7 mmol) in pyridine (3 mL) was added N, N-dicyclohexylcarbodiimide (283 mg, 1.37 mmol). The solution was stirred for 6.5h at 70°C. The mixture was cooled to room temperature and diluted with dichloromethane. The solid was removed by filtration and the filtrate was concentrated. The residue was suspended in dichloromethane and filtered again. The filtrate was concentrated and mixture was chromatographed on silica gel eluting with EtOAc/hexane to provide compound 6 (133 mg, 70%) as a foam: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H), 7.21 (d, 2H); 7.00 (d, 2H), 6.88 (dd, 2H), 5.66 (d, 1H), 4.94-5.10 (m, 3H), 4.39-4.56 (m, 6H), 3.71-4.00 (m, 10H), 2.77-3.18 (m, 7H), 1.67-1.83(m, 2H), 0.91 (dd, 4H); ^{31}P NMR ($CDCl_3$) δ 22.2; MS (ESI) 859 (M+Na).

Example 3

Mono-2,2,2-trifluoroethyl phosphonate 7: To a solution of 6 (930mg, 1.11 mmol) in THF (14 mL) and water (10 mL) was added an aqueous solution of NaOH in water (1N, 2.2 mL). The solution was stirred for 1h at 0°C. An excess amount of Dowex resin (H^+) was added to until pH=1. The mixture was filtered and the filtrate was concentrated under reduced pressure. The concentrated solution was azeotroped with EtOAc/toluene three times and the white powder was dried *in vacuo* provide compound 7 (830 mg, 100%). ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H), 7.11 (d, 2H); 6.99 (d, 2H), 6.85 (d, 2H), 5.63 (d, 1H), 5.26 (m, 1H), 5.02 (m, 1H), 4.40 (m, 1H), 4.14 (m, 4H), 3.60-3.95 (m, 12H), 2.62-3.15 (m, 15H), 1.45-1.84 (m, 3H), 1.29 (m, 4H), 0.89 (d, 6H); ^{31}P NMR ($CDCl_3$) δ 19.9; MS (ESI) 723 (M+Na).

Example 4

Mono-2,2,2-trifluoroethyl mono-lactate 8: To a solution of 7 (754mg, 1 mmol) and N, N-dicyclohexylcarbodiimide (1.237 g, 6 mmol) in pyridine (10 mL) was added ethyl lactate

(2.26 mL, 20 mmol). The solution was stirred for 4.5h at 70°C. The mixture was concentrated and the residue was suspended in diethyl ether (5 mL) and dichloromethane (5 mL) and filtered. The solid was washed a few times with diethyl ether. The combined filtrate was concentrated and the crude product was chromatographed on silica gel, eluting with EtOAc and hexane to provide compound 8 (610 mg, 71%) as a foam. ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H), 7.16 (d, 2H); 6.99 (d, 2H), 6.88 (dd, 2H), 5.66 (d, 1H), 4.95-5.09 (m, 2H), 4.19-4.65 (m, 6H), 3.71-4.00 (m, 9H), 2.76-3.13 (m, 6H), 1.57-1.85 (m, 7H), 1.24-1.34 (m, 4H), 0.91 (dd, 6H); ^{31}P NMR ($CDCl_3$) δ 20.29, 21.58; MS (ESI) 855 (M+1).

Example 1

Boc-protected hydroxylamine **1**: A solution of diethyl hydroxymethyl phosphonate triflate (0.582 g, 1.94 mmol) in dichloromethane (19.4 mL) was treated with triethylamine (0.541 mL, 3.88 mmol). Tert-butyl N-hydroxy-carbamate (0.284 g, 2.13 mmol) was added and the reaction mixture was stirred at room temperature overnight. The mixture was partitioned between dichloromethane and water. The organic phase was washed with saturated NaCl, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (1/1 – ethyl acetate/hexane) affording the BOC-protected hydroxylamine **1** (0.41 g, 75%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1H), 4.21 (d, 2H), 4.18 (q, 4H), 1.47 (s, 9H), 1.36 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 19.3.

Example 2

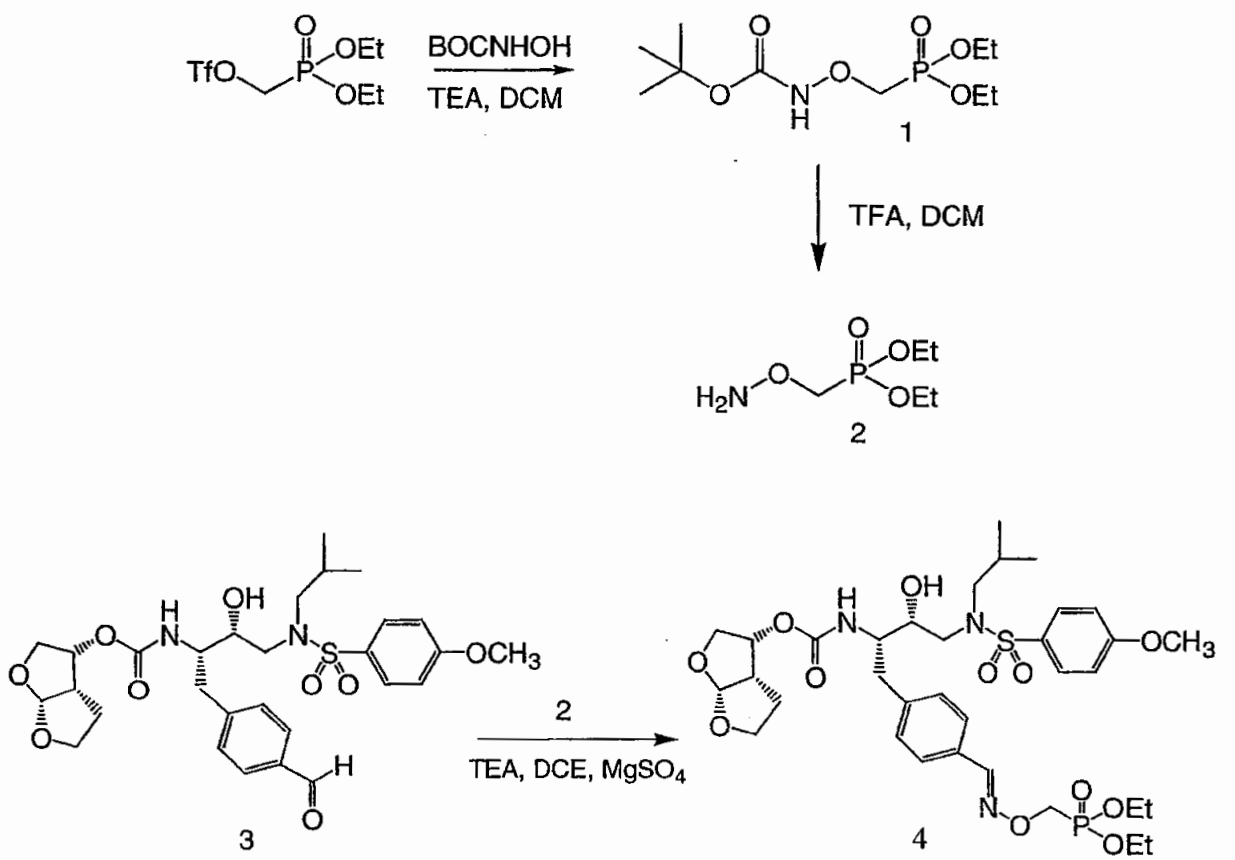
Hydroxylamine **2**: A solution of BOC-protected hydroxylamine **1** (0.305 g, 1.08 mmol) in dichloromethane (2.40 mL) was treated with trifluoroacetic acid (0.829 mL, 10.8 mmol). The reaction was stirred for 1.5 hours at room temperature and then the volatiles were evaporated under reduced pressure with toluene to afford the hydroxylamine **2** (0.318 g, 100%) as the TFA salt which was used directly without any further purification: ^{1}H NMR ($CDCl_3$) δ 10.87 (s, 2H), 4.45 (d, 2H), 4.24 (q, 4H), 1.38 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 16.9; MS (ESI) 184 (M+H).

Example 3

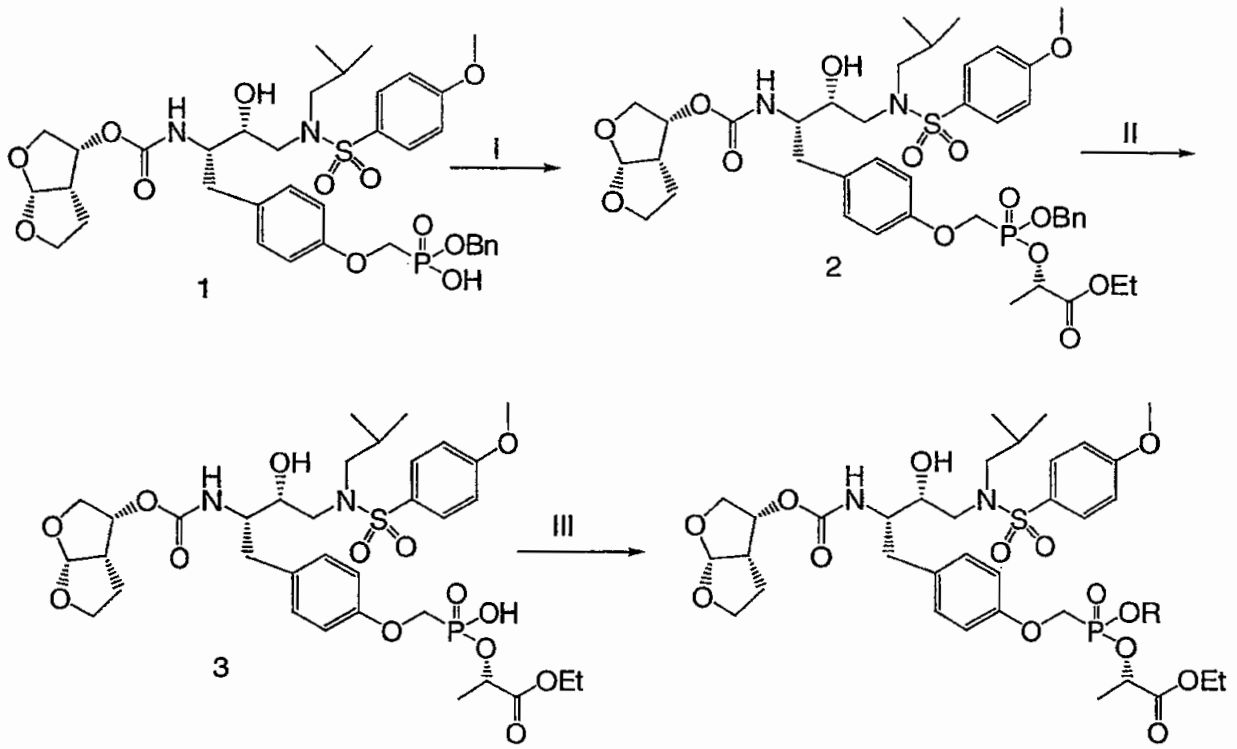
Oxime **4**: To a solution of aldehyde **3** (96 mg, 0.163 mmol) in 1,2-dichloroethane (0.65 mL) was added hydroxylamine **2** (72.5 mg, 0.244 mmol), triethylamine (22.7 μL, 0.163 mmol) and $MgSO_4$ (10 mg). The reaction mixture was stirred at room temperature for 2 hours then

the mixture was partitioned between dichloromethane and water. The organic phase was washed with saturated NaCl, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (90/10 – ethyl acetate/hexane) affording, GS-277771, oxime **4** (0.104 g, 85%) as a solid: ^1H NMR ($CDCl_3$) δ 8.13 (s, 1H), 7.72 (d, 2H), 7.51 (d, 2H), 7.27 (d, 2H), 7.00 (d, 2H), 5.67 (d, 1H), 5.02 (m, 2H), 4.54 (d, 2H), 4.21 (m, 4H), 3.92 (m, 1H), 3.89 (s, 3H), 3.88 (m, 1H), 3.97-3.71 (m, 2H), 3.85-3.70 (m, 2H), 3.16-2.99 (m, 2H), 3.16-2.81 (m, 7H), 1.84 (m, 1H), 1.64-1.48 (m, 2H), 1.37 (t, 6H), 0.94-0.90 (dd, 6H); ^{31}P NMR ($CDCl_3$) δ 20.0; MS (ESI) 756 (M+H).

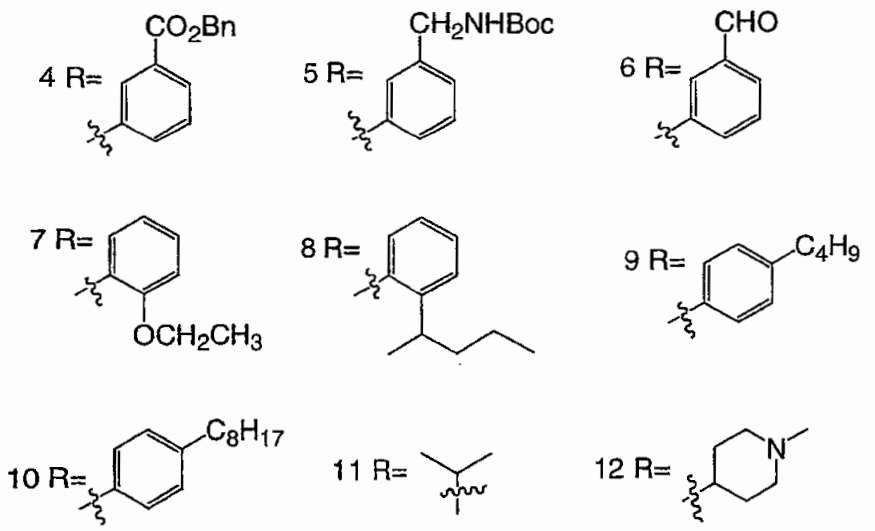
Scheme 1



Scheme 1



I.Ethyl(S)-(-)lactate/Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/ DIPEA/EtOAc; II. H_2/20%Pd-C/EtOAc-EtOH; III. ROH/Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/ DIPEA/EtOAc



Example 1

Compound 1 was prepared according to methods from previous Schemes

Example 2

Compound 2: To a solution of compound 1 (5.50 g, 7.30 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (5.70g, 10.95 mmol), and Ethyl(S)-(-)lactate (1.30 g, 10.95 mmol) in DMF (50 mL) was added Diisopropylethylamine(5.08 mL, 29.2 mmol). The mixture was stirred for 7 hours after which was diluted in EtOAc. The organic phase was washed with H_2O (5X), brine, dried over $MgSO_4$ and *concentrated in vacuo*. The residue was purified by silica gel chromatography (CH_2Cl_2/Isopropanol= 100/4) to give 3.45 g of compound 2.

Example 3

Compound 3: To the mixture of compound 2 (3.45 g) in EtOH/EtOAc (300 mL/100 mL) was added 20% Pd/C(0.700 g). The mixture was hydrogenated for 1 hour. Celite was added and the mixture was stirred for 10 minutes. The mixture was filtered through a pad of celite and washed with ethanol. Concentration gave 2.61 g of compound 3.

Example 4

Compound 4: To a solution of compound 3 (1.00 g, 1.29 mmol) in dry dimethylformamide (5 mL) was added 3-Hydroxy-benzoic acid benzyl ester (0.589 g, 2.58 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.34 g, 2.58 mmol), followed by addition of Diisopropylethylamine (900 µL, 5.16 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2/Isopropanol= 100/3) to provide 67.3 mg of compound 4: ^{1}H NMR ($CDCl_3$) δ 7.91 (2H,d, J=8.9 Hz), 7.75 (2H, m), 7.73-7.3 (13H,m), 7.25 (2H, m), 7.21-6.7(6H, m), 5.87(1H, m), 5.4-4.8(6H, m), 4.78-4.21 (4H, m), 3.98 (3H,s), 2.1-1.75 (8H, m), 1.55 (3H, m), 1.28(3H, m), 0.99(6H, m).

Example 5

Compound 5: To a solution of compound 3 (1.40 g, 1.81 mmol) in dry dimethylformamide (5 mL) was added (4-Hydroxy-benzyl)-carbamic acid tert-butyl ester (0.80 g, 3.62 mmol),

Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.74 g, 3.62 mmol), followed by addition of Diisopropylethylamine (1.17 ml, 7.24 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2/Isopropanol= 100/3.5) to provide 770 mg of compound 5: ^1H NMR ($CDCl_3$) δ 7.8(2H, d, J=8.9Hz), 7.4 (2H, m), 7.3-6.8 (8H, m), 5.75 (1H, m), 5.3-5.1(2H, m), 4.6-4.23 (4H,m), 3.98 (3H, s), 3.7-2.6 (15H, m), 2.2-1.8 (12H, m), 1.72 (3H, s), 1.58(3H, m), 1.25 (3H, m), 0.95 (6H, m).

Example 6

Compound 6: To a solution of compound 3 (1.00 g, 1.29 mmol) in dry dimethylformamide (6 mL) was added 3-Hydroxybenzaldehyde (0.320 g, 2.60 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.35 g, 2.60 mmol), followed by addition of Diisopropylethylamine (901 µL, 5.16 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2/Isopropanol= 100/5) to provide 880 mg of compound 6.

Example 7

Compound 7: To a solution of compound 3 (150 mg, 0.190 mmol) in dry dimethylformamide (1 mL) was added 2-Ethoxy-phenol (48.0 µL, 0.380 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (198 mg, 0.380 mmol), followed by addition of Diisopropylethylamine (132 µL, 0.760 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2/Isopropanol= 100/4) to provide 84.7 mg of compound 7: ^1H NMR ($CDCl_3$) δ 7.73 (2H, d, J=8.9 Hz), 7.15 (2H, m), 7.01-6.9 (8H, m), 5.66 (1H, m), 5.22-5.04 (2H, m), 4.56- 4.2 (6H, m), 4.08 (2H, m), 3.89 (3H, m), 3.85-3.69 (6H, m), 3.17-2.98 (7H, m), 2.80(3H, m) 1.86 (1H, m),1.65(2H, m), , 1.62-1.22 (6H, m), 0.92(6H, m).

Example 8

Compound 8: To a solution of compound 3 (50.0 mg, 0.0650 mmol) in dry dimethylformamide (1 mL) was added 2-(1-methylbutyl) phenol (21.2 mg, 0.130 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (67.1 mg, 0.130 mmol), followed by addition of Diisopropylethylamine (45.0 µL, 0.260 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 8.20 mg of compound 8: ^{1}H NMR ($CDCl_3$) δ 7.73 (2H, d, J=8.9 Hz), 7.25 (2H, m), 7.21-6.89 (8H, m), 5.7(1H, m), 5.29-4.9 (2H, m), 4.56- 4.2 (6H, m), 3.89 (3H, m), 3.85-3.69 (6H, m), 3.17-2.89 (8H, m), 2.85(3H, m), 2.3-1.65(4H, m), 1.55-1.35 (6H, m), 0.92(6H, m).

Example 9

Compound 9: To a solution of compound 3 (50.0 mg, 0.0650 mmol) in dry dimethylformamide (1 mL) was added) 4-N-Butylphenol (19.4 mg, 0.130 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (67.1 mg, 0.130 mmol), followed by addition (45.0 µL, 0.260 mmol) of Diisopropylethylamine. The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 9.61 mg of compound 9: ^{1}H NMR ($CDCl_3$) δ 7.8(2H, d, J=8.9 Hz), 7.4 (2H, m), 7.3-6.8 (8H, m), 5.75 (1H, m), 5.3-4.5 (4H, m), 4.3-3.4.1 (4H, m), 3.9 (3H, m), 3.3-2.59 (11H, m), 2.25 (2H, m), 1.85-1.5 (5H, m), 1.4-1.1(10H, m), 0.95(9H, m).

Example 10

Compound 10: To a solution of compound 3 (50.0 mg, 0.0650 mmol) in dry dimethylformamide (1 mL) was added 4-Octylphenol (26.6 mg, 0.130 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (67.1 mg, 0.130 mmol), followed by addition of Diisopropylethylamine (45.0 µL, 0.260 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 7.70 mg of compound 10: ^{1}H NMR ($CDCl_3$) δ 7.75 (2H, d, J=8.9 Hz), 7.3 (2H, m), 7.2-6.8 (8H, m), 5.70 (1H, m), 5.3-4.9 (4H, m), 4.6- 3.9 (4H, m),

3.89 (3H, m), 3.85-2.59 (12H, m), 2.18-1.75 (10H, m), 1.69-1.50 (8H, m), 1.4-1.27(6H,m), 0.95(9H, m).

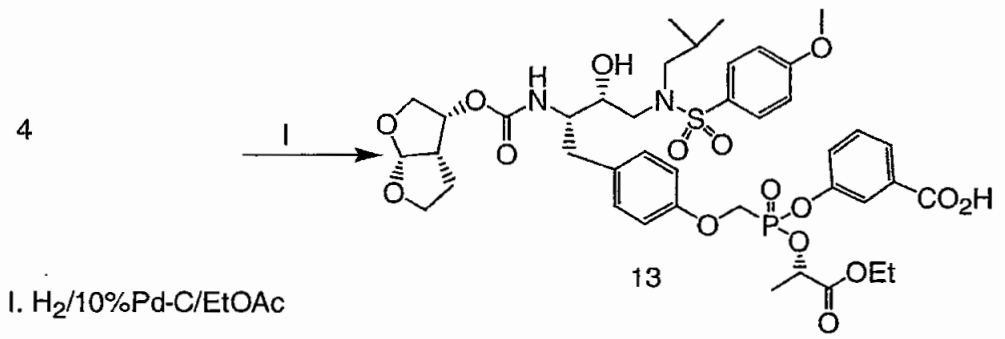
Example 11

Compound 11: To a solution of compound 3 (100 mg, 0.120 mmol) in dry dimethylformamide (1 mL) was added Isopropanol (20.0 µL, 0.240 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (135 mg, 0.240 mmol), followed by addition of Diisopropylethylamine (83.0 µL, 0.480 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2/Isopropanol= 100/4) to provide 12.2 mg of compound 11: ^{1}H NMR ($CDCl_3$) δ 7.71 (2H, d, J=8.9 Hz), 7.15 (2H, m), 7.0 (2H, m), 6.89 (2H, m), 5.65 (1H, m), 5.03-4.86(4H, m), 4.34-4.19 (3H, m), 3.89 (3H, s), 3.88 (1H, m), 3.82 (2H, m), 3.65 (4H, m), 3.2-2.9 (11H, m), 2.80(3H, m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m), 1.30(3H,m), 0.92(6H, m).

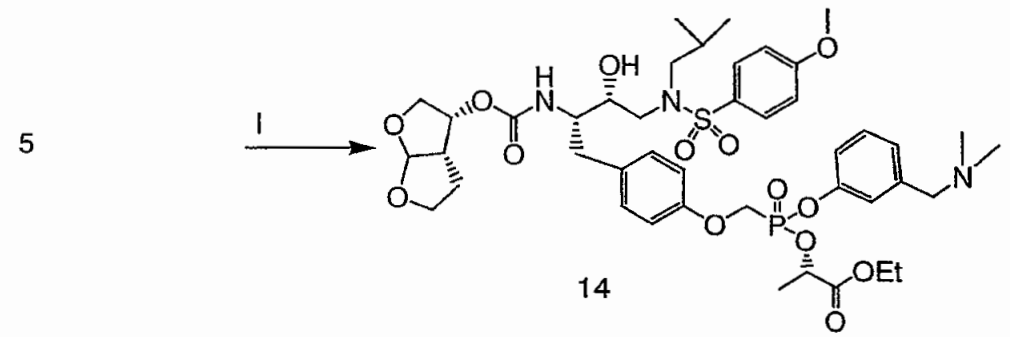
Example 12

Compound 12: To a solution of compound 3 (100 mg, 0.120 mmol) in dry dimethylformamide (1mL) was added 4-Hyrdroxy-1-methylpiperidine (30.0 mg, 0.240 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (135 mg, 0.240 mmol), followed by addition of Diisopropylethylamine (83.0 µL, 0.480 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 50.1 mg of compound 12: ^{1}H NMR ($CDCl_3$) δ 7.73 (2H, d, J=8.9 Hz), 7.18 (2H, m), 7.0 (2H, m), 6.9 (2H, m), 5.67 (1H, m), 5.2-4.9 (4H, m), 4.30-4.11 (4H, m), 3.98 (1H, m), 3.89 (3H, s), 3.87 (1H, m), 3.75 (2H, m), 3.5-3.3 (4H, m), 3.2-2.9 (14H, m), 2.80(3H, m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m), 1.30(3H,m), 0.92(6H, m).

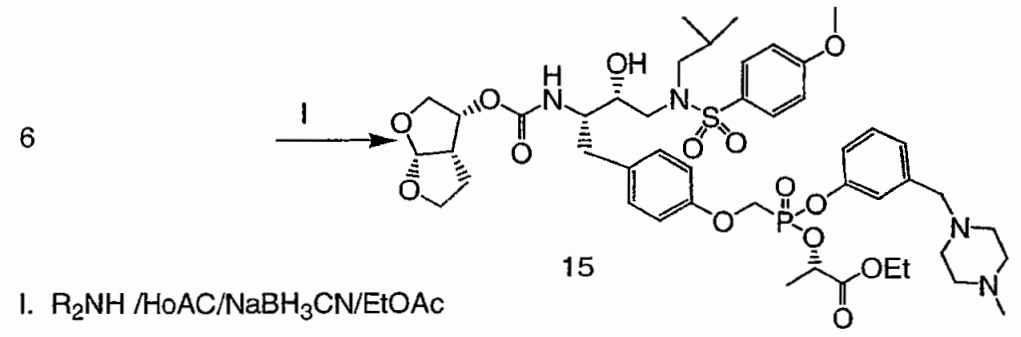
Scheme 2



Scheme 3



Scheme 4



Example 13

Compound 13: To a solution of compound 4 (4.9 g)) in EtOAc (150ml) was added 20% Pd/C (0.90 g),the reaction mixture was hydrogenated for 1 hour. Celite was added and the mixture was stirred for 10 minutes. The mixture was filtered through a pad of celite and washed with ethanol. Concentration gave 4.1 g of compound 13: ^{1}H NMR ($CDCl_3$) δ 7.91 (2H,d, J=8.9 Hz),

7.75 (2H, m), 7.73-7.3 (8H, m), 7.25 (2H, m), 7.21-6.7(6H, m), 5.4-4.8(6H, m), 4.78-4.21 (4H, m), 3.98 (3H,s), 2.1-1.75 (8H, m), 1.55 (3H, m), 1.28(3H, m), 0.99(6H, m).

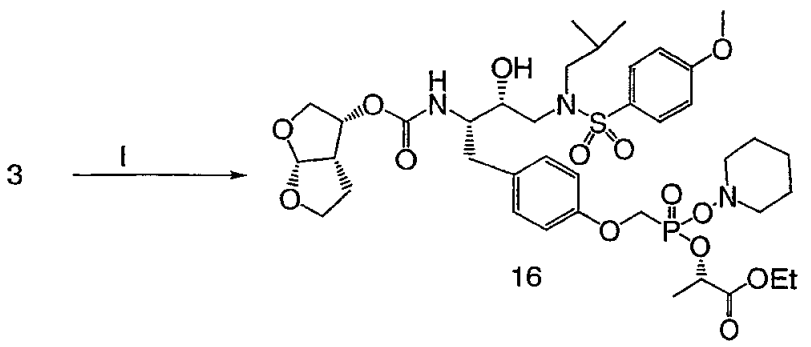
Example 14

Compound 14: To a solution of compound 5 (0.770 g, 0.790 mmol) in dichloromethane (10 mL), under ice-cooling, was added triflouroacetic acid (5 mL), the resulting mixture was stirred at 25°C for two hours. The reaction mixture was concentrated under reduced pressure and the residue was co-evaporated with EtOAc to provide an yellow oil. To a solution of the above oil in (10 mL) of EtOAc, under ice-cooling and stirring was added formaldehyde (210 µL, 2.86 mmol), acetic acid (252 µL, 4.30 mmol), followed by sodium cyanoborohydride (178 mg, 2.86 mmol). The mixture was further stirred at 25°C for 2 hours. The above mixture was concentrated and diluted with EtOAc and washed with H_2O (3X), brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using reversed-phase HPLC to provide 420 mg of compound 14: ^{1}H NMR ($CDCl_3$) δ 7.8(2H, d, J=8.9Hz), 7.4 (2H, m), 7.3-6.8 (8H, m), 5.75 (1H, m), 5.3-5.1(2H, m), 4.6-4.23 (4H,m), 3.98 (3H, s), 3.7-2.6 (15H, m), 2.2-1.8 (8H, m), 1.72 (3H, s), 1.58(3H, m), 1.25 (3H, m), 0.95 (6H, m).

Example 15

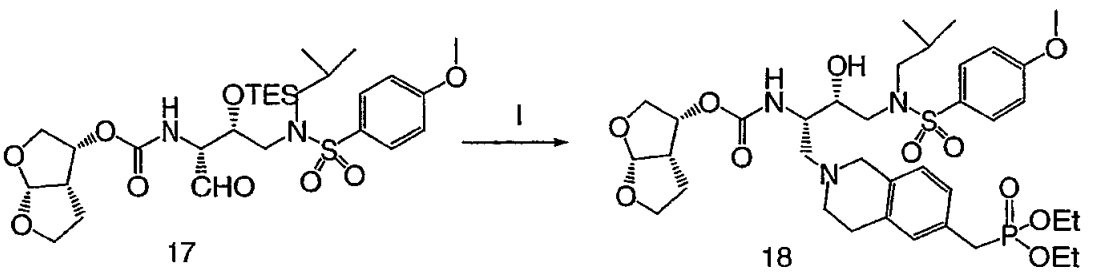
Compound 15: To a solution of compound 6 (100mg, 0.114 mmol) in EtOAc (1 mL) was added 1-Methyl-piperazine (63.2 mg, 0.570 mmol), acetic acid (34.0 µl, 0.570 mmol) followed by Sodium Cyanoborohydride (14.3 mg, 0.228mmol). The mixture was stirred at 25°C for 14 hours. The reaction mixture was concentrated and diluted with EtOAc and washed with H_2O (5X), brine (2x), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using silica gel chromatography (CH_2Cl_2/Isopropanol= 100/6.5) to give 5.22 mg of compound 15: ^{1}H NMR ($CDCl_3$) δ 7.73 (2H, d, J=8.9 Hz), 7.4-7.18(8H, m), 7.1-6.89 (2H, m), 5.67 (1H, m), 5.2-4.9 (4H, m), 4.30-4.11 (4H, m), 3.98 (1H, m), 3.89 (3H, s), 3.87 (1H, m), 3.75 (2H, m), 3.5-3.3 (4H, m), 3.2-2.9 (10H, m), 2.80-2.25 (8H,m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m), 1.30(3H,m), 0.92(6H, m).

Scheme 5



I.Piperidin-1-ol/DCC/Pyridine

Scheme 6



I. a:R_2NH /HOAc/$NaBH_3CN$/EtOAc b: 2%HF/CH_3CN

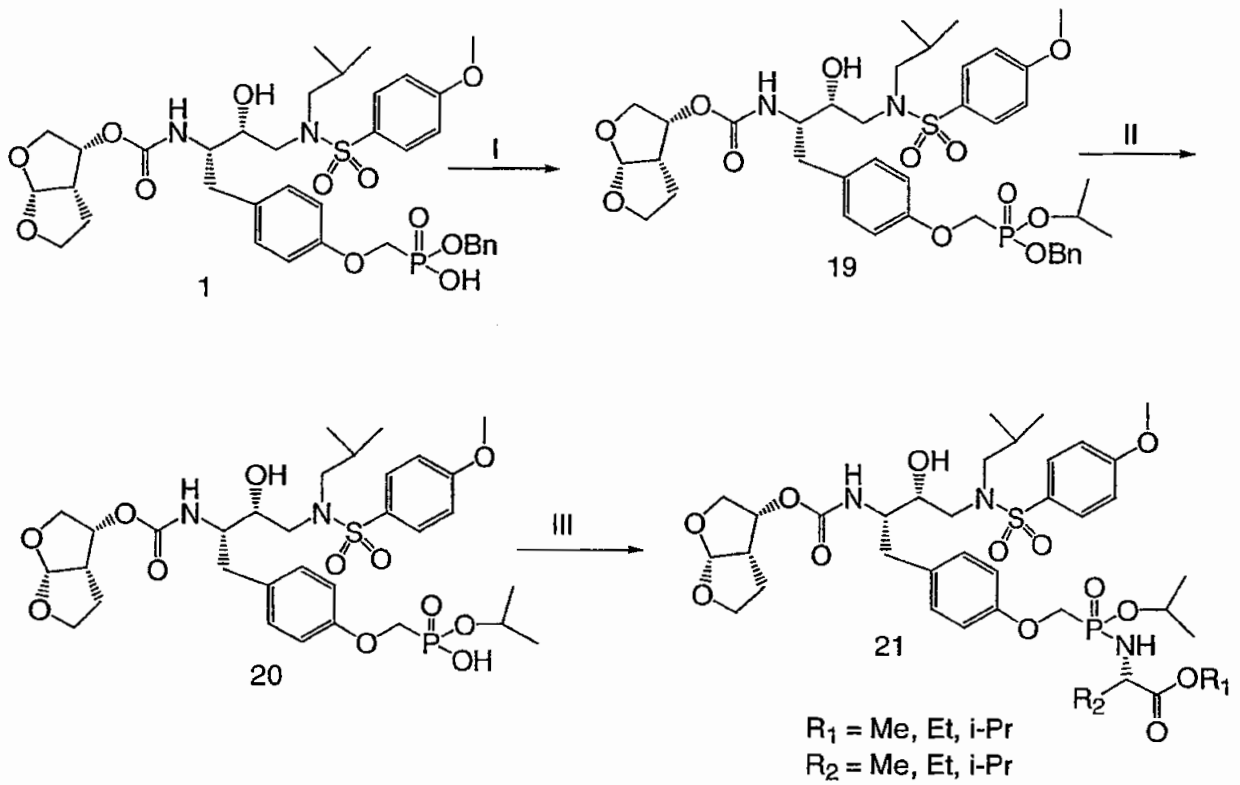
Example 16

Compound 16: To a solution of compound 3 (100mg, 0.120 mmol) in Pyridine (600 μL) was added Piperidin-1-ol (48.5 mg, 0.480 mmol), followed by N,N-Dicyclohexylcarbodiimide (99.0 mg, 0.480 mmol). The mixture was stirred for 6 hours, the solvent was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (CH_2Cl_2/Methanol= 100/5) to provide 17 mg of compound 16: ^1H NMR ($CDCl_3$) δ 7.73 (2H, d, J=8.9 Hz), 7.16 (2H, m), 7.0 (2H, m), 6.9 (2H, m), 5.68 (1H, m), 5.17 (1H, m), 5.04 (1H, m), 4.5-4.2 (4H, m), 3.90 (3H, s), 3.75 (2H, m), 3.5-3.3 (4H, m), 3.2-2.9 (10H, m), 2.80(3H, m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m), 1.5-1.27 (9H,m), 0.92(6H, m).

Example 17

Compound 18: To a solution of compound 17 (148 mg, 0.240 mmol) in 4 mL of Methanol was added (1,2,3,4-Tetrahydro-isoquinolin-6-ylmethyl)-phosphonic acid diethyl ester (70.0 mg, 0.240 mmol), acetic acid (43.0 μL, 0.720 mmol). The reaction mixture was stirred for 3 minutes, followed by addition of Sodium Cyanoborohydride (75.3 mg, 1.20 mmol). The reaction mixture was stirred at 25°C for 14 hours. The reaction mixture was diluted with EtOAc and washed with H_2O (3X), brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using silica gel chromatography (CH_2Cl_2/Isopropanol= 100/5) to give 59 mg of TES protected intermediate. 83 μL of 48% HF solution was added to acetonitrile (4 mL) to prepare the 2% HF solution. The above 2% HF solution was added to TES protected intermediate (47 mg, 0.053 mmol) and the reaction mixture was stirred for 2 hours. The solvent was concentrated and the residue was diluted with EtOAc, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using silica gel chromatography (CH_2Cl_2/Methanol= 100/10) to give 35.2 mg of compound 18: ^{1}H NMR ($CDCl_3$) δ 7.73 (2H, d, J=8.9 Hz), 7.05 (2H, m), 6.89 (2H, m), 6.76 (1H, m), 5.75 (1H, m), 5.67 (1H, m), 5.3 (2H, m), 4.2-3.6 (12 H, m), 3.4-2.4 (11 H, m), 2.1-1.8 (6H, m), 1.4-1.28 (8 H, m), 0.92(6H, m).

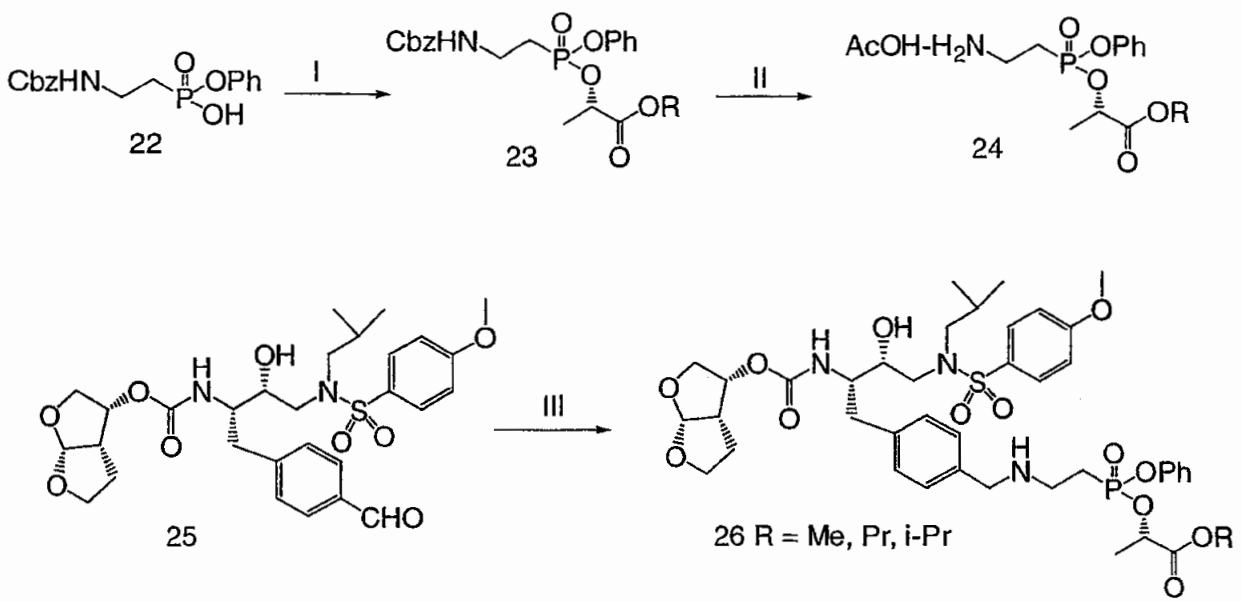
Scheme 7



I. Isopropanol/Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/ DIPEA/DMF;
II. H_2/10%Pd-C/EtOAc-EtOH;
III. RNH_2/Aldrithiol-2/PPh_3/iPr_2NEt/pyridine

Compound 19 is prepared following the procedure for compound 2 by using monoacid 1. Compound 20 is made following a hydrogenation of compound 19. Mono acid 20 reacts with corresponding amino esters in the presence of Aldrithiol-2 and triphenylphosphine to form compound 21.

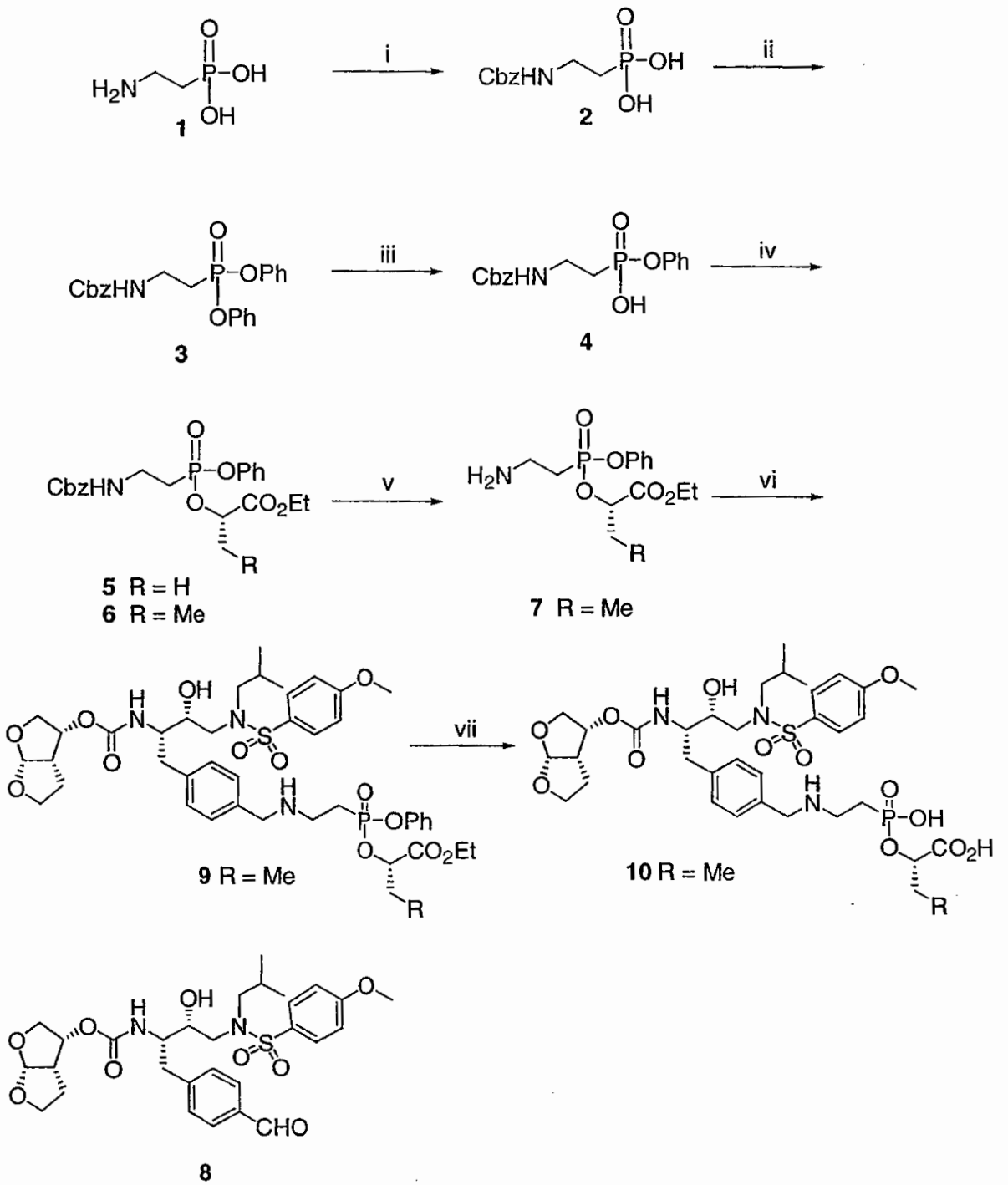
Scheme 8



I. a. $SOCl_2$/60 C; b. Alkyl (s)-lactate/Et_3N; II. H_2/10%Pd-C/EtOAc-HOAc;
III. a. compound 25/$MgSO_4$;b. HOAc/$NaBH_3CN$

Monoacid 22 is treated with thionyl chloride at 60°C to form monochloridate, which reacts with corresponding alkyl (s)lactate to generate monolactate 23. Monolactate 23 is hydrogenated with 10%Pd-C in the presence of acetic acid to form amine 24. Aldehyde 25 reacts with amine 24 in the presence of $MgSO_4$ to form the intermediate imine, which is reduced with sodium cyanoborohydride to afford compound 26.

Scheme 1



Reagents and conditions: i. CbzCl, NaOH, tol/H_2O, 100%; ii. a. $SOCl_2$, DMF, tol, 65°C; b. PhOH, Et_3N, CH_2Cl_2, 71%; iii. aq. NaOH, CH_3CN, 79%; iv. a. $SOCl_2$, DMF, tol, 65°C; b. ethyl lactate, Et_3N, CH_2Cl_2, (**5**) 85%; 2-hydroxy butyric acid ethyl ester, Et_3N, CH_2Cl_2, (**6**) 75%; v. H_2, AcOH, 10% Pd/C, EtOH, 94%; vi. a. **7** + **8**, 1,2-DCE, $MgSO_4$; b. $NaBH_3CN$, AcOH, 50%; vii. pig liver esterase, 20% DMSO/PBS, 40°C, 25%.

Example 1

Compound 2: A 3L, 3-neck flask was equipped with a mechanical stirrer and addition funnel and charged with 2-aminoethyl phosphonic acid (60.0g, 480 mmol). 2N Sodium hydroxide (480 mL, 960 mmol) was added and flask cooled to 0°C. Benzyl chloroformate (102.4 g, 600 mmol) in toluene (160mL) was added dropwise with vigorous stirring. The reaction mixture was stirred at 0°C for 30 minutes, then at room temperature for 4 h. 2N sodium hydroxide (240 mL, 480 mmol) was added, followed by benzyl chloroformate (20.5 g, 120 mmol) and the reaction mixture was vigorously stirred for 12 h. The reaction mixture was washed with diethyl ether (3x). The aqueous layer was acidified to pH 2 with concentrated HCl to give a white precipitate. Ethyl acetate was added to the mixture and concentrated HCl (80 mL, 960 mmol) was added. The aqueous layer was extracted with ethyl acetate and combined organic layer was dried ($MgSO_4$) and concentrated to give a waxy, white solid (124 g, 479 mmol, 100%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.45-7.30 (m, 5 H, Ar), 5.06 (d, J = 14.7 Hz, 2 H, CH_2Ph), 3.44-3.31 (m, 2 H, NCH_2CH_2), 2.03-1.91 (m, 2 H, CH_2CH_2P); ^{31}P NMR (121 MHz, CD_3OD): δ 26.3.

Example 2

Compound 3: To a mixture of compound 2 (50.0 g, 193 mmol) in toluene (1.0 L) was added DMF (1.0 mL) followed by thionyl chloride (56 mL, 768 mmol). The reaction mixture was heated at 65°C for 3-4 h under a stream of argon. The reaction mixture was cooled to room temperature and concentrated. Residual solvent was removed under high vacuum for 1 h. The residue was dissolved in CH_2Cl_2 (1.0 L) and cooled to 0°C. Triethylamine (161 mL, 1158 mmol) was added, followed by phenol (54.5 g, 579 mmol). The reaction mixture was warmed to room temperature overnight, then washed with 1.0N HCl, saturated $NaHCO_3$ solution, brine and dried ($MgSO_4$). Concentrated and purified (silica gel, 1:1 EtOAc/Hex) to give a pale yellow solid (56 g, 136 mmol, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.10 (m, 15 H, Ar), 5.53 (br s, 1 H, N*H*), 5.11 (br s, 2 H, CH_2Ph), 3.72-3.60 (m, 2 H, NCH_2CH_2), 2.49-2.30 (m, 2 H, CH_2CH_2P); ^{31}P NMR (121 MHz, $CDCl_3$): δ 22.9.

Example 3

Compound 4: To a solution of compound **3** (64 g, 155.6 mmol) in acetonitrile (500 mL) at 0°C was added 2.0M sodium hydroxide. The reaction mixture was stirred at 0°C for 30 min, then at room temperature for 2.5 h. The reaction mixture was concentrated to 100 mL and diluted with H_2O (500 mL). The aqueous solution was washed with EtOAc (3 x 300 mL). The aqueous layer was acidified to pH 1 with concentrated HCl, producing a white precipitated. The mixture was extracted with EtOAc (4 x 300 mL) and combined organic layer was washed with brine and dried ($MgSO_4$). Concentration gave a solid, which was recrystallized from hot EtOAc (450 mL) to give a white solid (41.04 g, 122 mmol, 79%). ^1H NMR (300 MHz, CD_3OD): δ 7.45-7.10 (m, 10 H, Ar), 5.09 (s, 2 H, CH_2Ph), 3.53-3.30 (m, 2 H, NCH_2CH_2), 2.25-2.10 (m, 2 H, CH_2CH_2P); ^{31}P NMR (121 MHz, CD_3OD): δ 24.5.

Example 4

Compound 5: To a mixture of compound **4** (28 g, 83 mmol) in toluene (500 mL) was added DMF (1.0 mL), followed by thionyl chloride (36.4 mL, 499 mmol). The mixture was heated at 65°C for 2 h providing a pale yellow solution. The reaction mixture was concentrated and dried for 45 min under high vacuum. The residue was dissolved in anhydrous CH_2Cl_2 (350 mL) and cooled to 0°C. Triethylamine (45.3 mL, 332 mmol) was added slowly, followed by the dropwise addition of ethyl lactate (18.8 mL, 166 mmol). The reaction mixture was stirred at 0°C for 30 min, then warmed to room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl, saturated $NaHCO_3$ solution, brine and dried ($MgSO_4$). Concentration and purification (silica gel, 1:5 to 1:0 EtOAc/Hex) gave a pale yellow oil (30.7 g, 71 mmol, 85%) as a mixture of diastereomers which were separated by HPLC (Dynamax reverse phase C–18 column, 60% acetonitrile/H_2O). More polar diastereomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.10 (m, 10 H, Ar), 5.65 (s, 1 H, N*H*), 5.12 (s, 2 H, CH_2Ph), 5.10-5.00 (m, 1 H, OC*H*C) 4.17 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 3.62 (dt, J_1 = 20.4 Hz, J_2 = 6.0 Hz, 2 H, NCH_2CH_2), 2.25 (dt, J_1 = 18.0 Hz, J_2 = 6.0 Hz, 2 H, CH_2CH_2P), 1.60 (dd, J_1 = J_2= 6.9 Hz, 3 H, CHCH_3), 1.23 (t, J = 6.9 Hz, 3 H, OCH_2CH_3); ^{31}P NMR (121 MHz, $CDCl_3$): δ 26.2. Less polar diastereomer: ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.10 (m, 10 H, Ar), 5.87 (s, 1 H, N*H*), 5.13 (s, 2 H, CH_2Ph), 5.10-5.00 (dq, J_1 = J_2 = 6.9 Hz, 1 H, OC*H*C) 4.22 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 3.68 (dt, J_1 = 21.6 Hz, J_2 = 6.9 Hz, 2 H, NCH_2CH_2), 2.40-2.20 (m, 2 H, CH_2CH_2P), 1.49 (dd, J_1 = 70.2 Hz, J_2 = 6.9 Hz, 3 H, CHCH_3), 1.28 (t, J = 6.9 Hz, 3 H, OCH_2CH_3); ^{31}P NMR (121 MHz, $CDCl_3$): δ 28.3.

Example 5

Compound 6: 2-Hydroxy-butyric acid ethyl ester was prepared as follows: To a solution of L-2-aminobutyric acid (100g, 970 mmol) in 1.0 N H_2SO_4 (2 L) at 0°C was added $NaNO_2$ (111 g, 1610 mmol) in H_2O (400 mL) over 2 h. The reaction mixture was stirred at room temperature for 18h. Reaction mixture was extracted with EtOAc (4x) and combined organic layer was dried ($MgSO_4$) and concentrated to give a yellow solid (41.5 g). This solid was dissolved in absolute ethanol (500 mL) and concentrated HCl (3.27 mL, 39.9 mmol) was added. Reaction mixture was heated to 80°C. After 24 h, concentrated HCl (3 mL) was added and reaction continued for 24 h. Reaction mixture was concentrated and product was distilled to give a colorless oil (31 g, 235 mmol, 59%).

To a mixture of compound **4** (0.22 g, 0.63 mmol) in anhydrous acetonitrile (3.0 mL) was added thionyl chloride (0.184 mL, 2.52 mmol). The mixture was heated at 65°C for 1.5 h providing a pale yellow solution. The reaction mixture was concentrated and dried for 45 min under high vacuum. The residue was dissolved in anhydrous CH_2Cl_2 (3.3 mL) and cooled to 0°C. Triethylamine (0.26 mL, 1.89 mmol) was added slowly, followed by the dropwise addition of 2-hydroxy-butyric acid ethyl ester (0.167 mL, 1.26 mmol). The reaction mixture was stirred at 0°C for 5 min, then warmed to room temperature overnight. The reaction mixture was concentrated, dissolved in EtOAc and washed with 1.0 N HCl, saturated $NaHCO_3$ solution, brine and dried ($MgSO_4$). Concentration and purification (silica gel, 3:2 EtOAc/Hex) gave a pale yellow oil (0.21 g, 0.47 mmol, 75%). For major diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.10 (m, 10 H, Ar), 5.91 (s, 1 H, N*H*)), 5.12 (s, 2 H, CH_2Ph), 4.94-4.83 (m, 1 H, OC*H*C), 4.27-4.12 (m, 2 H, OCH_2CH$_3$), 3.80-3.50 (m, 2 H, NCH_2CH$_2$), 2.39-2.19 (m, 2 H, CH$_2$CH_2P), 1.82-1.71 (m, 2 H, CHCH_2CH$_3$), 1.30-1.195 (m, 3 H, OCH$_2$CH_3), 0.81 (t, J = 7.5 Hz, 3 H, CHCH$_2$CH_3); ^{31}P NMR (120 MHz, $CDCl_3$): δ 28.3. For minor diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.10 (m, 10 H, Ar), 5.74 (s, 1 H, N*H*)), 5.11 (s, 2 H, CH_2Ph), 4.98-4.94 (m, 1 H, OC*H*C), 4.27-4.12 (m, 2 H, OCH_2CH$_3$), 3.80-3.50 (m, 2 H, NCH_2CH$_2$), 2.39-2.19 (m, 2 H, CH$_2$CH_2P), 1.98-1.82 (m, 2 H, CHCH_2CH$_3$), 1.30-1.195 (m, 3 H, OCH$_2$CH_3), 1.00 (t, J = 7.5 Hz, 3 H, CHCH$_2$CH_3); ^{31}P NMR (121 MHz, $CDCl_3$): δ 26.2.

Example 6

Compound 7: A mixture of compound **6**, (0.53 g, 1.18 mmol) acetic acid (0.135 mL, 2.36 mmol) and 10% palladium on activated carbon (0.08 g) in absolute ethanol (12 mL) was stirred under a hydrogen atmosphere (1 atm) for 3 h. Reaction mixture was filtered through Celite, concentrated, and resubjected to identical reaction conditions. After 2 h, Celite was added to the reaction mixture and mixture was stirred for 2 min, then filtered through a pad of Celite and concentrated. Dried under high vacuum to give the diasteromeric acetate salt as a oil (0.42 g, 1.11 mmol, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.10 (m, 5 H, Ar), 5.00-4.80 (m, 1 H, OC*H*C), 4.28-4.10 (m, 2 H, O*CH*$_2$CH$_2$), 3.32-3.14 (m, 2 H, NC*H*$_2$CH$_2$), 2.45-2.22 (m, 2 H, CH$_2$C*H*$_2$P), 1.97 (s, 3 H, Ac), 1.97-1.70 (m, 2 H, CHC*H*$_2$CH$_3$), 1.30-1.18 (m, 3 H, OCH$_2$C*H*$_3$), 1.00 (t, *J* = 7.5 Hz, 1 H, CHCH$_2$C*H*$_3$), 0.80 (t, *J* = 7.5 Hz, 2 H, CHCH$_2$C*H*$_3$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 27.6 (major, 1.85), 26.0 (minor, 1.01).

Example 7

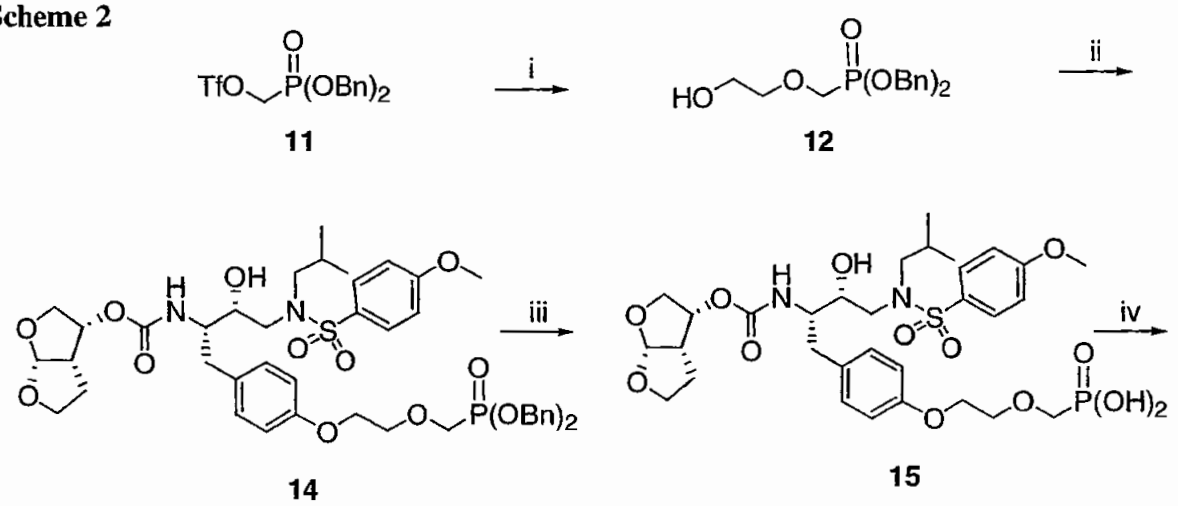
Compound 9: A solution of aldehyde **8** (0.596 g, 1.01 mmol) and compound **7** (0.42 g, 1.11 mmol) were stirred together in 1,2-dichloroethane (4.0 mL) in the presence of $MgSO_4$ for 3 h. Acetic acid (0.231 mL, 4.04 mmol) and sodium cyanoborohydride (0.127 g, 2.02 mmol) were added and reaction mixture was stirred for 50 min at room temperature. Reaction mixture was quenched with saturated $NaHCO_3$ solution, diluted with EtOAc, and vigorously stirred for 5 min. Brine was added and extracted with EtOAc (2x). Combined organic layer was dried ($MgSO_4$) concentrated and purified (silica gel, EtOAc, then 10% EtOH/EtOAc) to give a colorless foam. Acetonitrile (4 mL) and trifluoroacetic acid (0.06 mL) were added and concentrated to a volume of 1 mL. H_2O (10 mL) was added and lyophilized to give the TFA salt as a white powder (0.51 g, 0.508 mmol, 50%). ^{1}H NMR (300 MHz, CD_3CN): δ 7.79 (d, *J* = 8.4 Hz, 2 H, (SO$_2$C(C*H*)$_2$), 7.43-7.20 (m, 9 H, Ar), 7.10 (d, *J* = 8.4 Hz, 2 H, (C*H*)$_2$COCH$_3$), 5.85 (d, *J* = 8.4 Hz, 1 H, N*H*), 5.55 (d, *J* = 4.5 Hz, 1 H, OC*H*O), 5.00-4.75 (m, 2 H, CH$_2$C*H*OC(O), POC*H*C), 4.39-4.05 (m, 2 H, PhC*H*$_2$N, OC*H*$_2$CH$_3$), 3.89 (s, 3 H, OC*H*$_3$), 3.88-3.30 (m, 9H), 3.15-2.84 (m, 5 H), 2.65-2.42 (m, 3 H), 2.10-1.68 (m, 5 H), 1.65-1.15 (m, 5 H), 1.05-0.79 (m, 9 H); ^{31}P NMR (121 MHz, CD_3CN): δ 24.8 (major, 1.85), 23.1 (minor, 1.01).

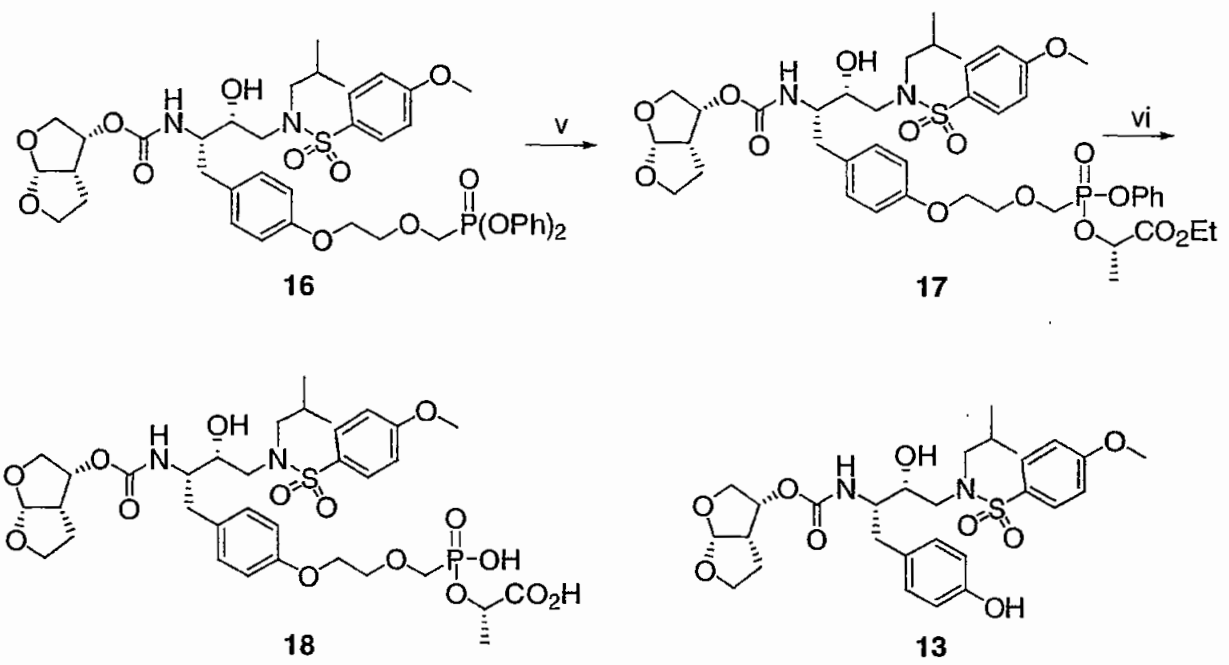
Example 8

Compound 10: Compound **9** (0.041 g, 0.041 mmol) was dissolved in DMSO (1.9 mL) and to this solution was added phosphate buffered saline, pH 7.4 (10 mL) and pig liver esterase

(Sigma, 0.2 mL). Reaction mixture was stirred for 24 h at 40°C. After 24 h, additional esterase (0.2 mL) was added and reaction was continued for 24 h. Reaction mixture was concentrated, resuspended in methanol and filtered. Filtrate was concentrated and purified by reverse phase chromatography to give a white powder after lyophilization (8 mg, 0.010 mmol, 25%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.78 (d, J = 8.9 Hz, 2 H, $(SO_2C(CH)_2)$, 7.43-7.35 (m, 4 H, Ar), 7.11 (d, J = 8.9 Hz, 2 H, $(CH)_2COCH_3$), 5.62 (d, J = 5.2 Hz, 1 H, OC*H*O), 4.96-4.77 (m, 2 H, $CH_2CHOC(O)$, POC*H*C), 4.21 (br s, 2 H, $PhCH_2N$), 3.97-3.70 (m, 6 H), 3.90 (s, 3 H, OCH_3), 3.50-3.30 (m, 3 H), 3.26-3.02 (m, 2 H), 2.94-2.58 (m, 4 H), 2.09-1.78 (m, 5 H), 1.63-1.52 (m, 2 H), 1.05-0.97 (m, 3 H); 0.94 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.7 Hz, 3 H); ^{31}P NMR (121 MHz, CD_3OD): δ 20.8.

Scheme 2





Reagents and conditions: i. ethylene glycol, $Mg(OtBu)_2$, DMF, 48%; ii. a. Tf_2O, 2,6-lutidine, CH_2Cl_2, -78°C; b. **13**, $CsCO_3$, CH_3CN, 0°C to room temperature, 65%; iii. H_2, Pd/C, EtOH, 107%; iv. DCC, PhOH, pyr, 70°C, 31%; v. a. NaOH, CH_3CN, 0°C; b. DCC, ethyl lactate, pyr, 70°C, 52%; vi. CH_3CN, DMSO, PBS, porcine liver esterase, 38°C, 69%.

Example 9

Compound 12: To a solution of compound **11** (4.10 g, 9.66 mmol) and anhydrous ethylene glycol (5.39 mL, 96.6 mmol) in anhydrous DMF (30 mL) at 0°C was added powdered magnesium *tert*-butoxide (2.05 g, 12.02 mmol). The reaction mixture was stirred at 0°C for 1.5 h, then concentrated. The residue was partitioned between EtOAc and H_2O and washed with 1 N HCl, saturated $NaHCO_3$ solution, and brine. Organic layer dried ($MgSO_4$), concentrated and purified (silica gel, 4% MeOH/CH_2Cl_2) to give a colorless oil (1.55 g, 48%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.37 (s, 10 H, Ar), 5.40-5.05 (m, 4 H, CH_2Ph), 3.84 (d, J = 8.1 Hz, 2 H, PCH_2O), 3.70-3.60 (m, 4 H, OCH_2CH_2O, OCH_2CH_2O); ^{31}P NMR (121 MHz, $CDCl_3$): δ 22.7.

Example 10

Compound 14: To a solution of compound **12** (0.75 g, 2.23 mmol) and 2,6-lutidine (0.78 mL, 6.69 mmol) in CH_2Cl_2 (20 mL) at –78°C was added trifluoromethanesulfonic anhydride (0.45

mL, 2.68 mmol). The reaction mixture was stirred at –78°C for 40 min, then diluted with CH_2Cl_2 and washed with 1 N HCl, saturated $NaHCO_3$ and dried ($MgSO_4$). Concentration gave a yellow oil that was dissolved in anhydrous acetonitrile (20 mL). Phenol **13** (1.00 g, 1.73 mmol) was added to the solution, which was cooled to 0°C. Cesium carbonate (0.619 g, 1.90 mmol) was added and reaction mixture was stirred at 0°C for 2 h, then at room temperature for 1.5 h. Additional cesium carbonate (0.200 g, 0.61 mmol) was added and reaction was continued for 1.5 h, then filtered. Concentration of the filtrate and purification (silica gel, 3% MeOH/CH_2Cl_2) gave a yellow gum (1.005 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 8.7 Hz, 2 H, $SO_2C(CH)_2$), 7.34 (s, 10 H, $PhCH_2O$), 7.11 (d, J = 8.1Hz, 2 H, $CH_2C(CH)_2(CH)_2$), 6.98 (d, J = 8.7 Hz, 2 H, $(CH)_2COCH_3$), 6.78 (d, J = 8.7 Hz, 2 H, $(CH)_2COCH_2$), 5.62 (d, J = 5.4 Hz, 1 H, $OCHO$), 5.16-4.97 (m, 6 H), 4.05-3.65 (m, 12 H), 3.86 (s, 3 H, OCH_3), 3.19-2.66 (m, 7 H), 1.95-1.46 (m, 3 H), 0.92 (d, J = 6.6 Hz, 3 H, $CH(CH_3)_2$), 0.88 (d, J = 6.6 Hz, 3 H, $CH(CH_3)_2$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 21.9.

Example 11

Compound 15: A mixture of compound **14** (0.410 g, 0.457 mmol) and 10% palladium on carbon (0.066 g) in ethanol (5.0 mL) was stirred under a hydrogen atmosphere (1 atm) for 16 h. Celite was added and the mixture was stirred for 5 min, then filtered through Celite and concentrated to give a foam (0.350 g, 107%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.76 (d, J = 8.7 Hz, 2 H, $SO_2C(CH)_2$), 7.15 (d, J = 8.4Hz, 2 H, $CH_2C(CH)_2(CH)_2$), 7.08 (d, J = 8.4 Hz, 2 H, $(CH)_2COCH_3$), 6.82 (d, J = 8.4 Hz, 2 H, $(CH)_2COCH_2$), 5.59 (d, J = 5.4 Hz, 1 H, $OCHO$), 5.16-4.97 (masked by CD_3OH, 1 H), 4.09-4.02 (m, 2 H), 3.99-3.82 (m, 10 H), 3.88 (s, 3 H, OCH_3), 3.52-3.32 (m, 1 H), 3.21-2.75 (m, 5 H), 2.55-2.40 (m, 1 H), 2.10-1.95 (m, 1 H), 1.75-1.25 (m, 2 H), 0.93 (d, J = 6.3 Hz, 3 H, $CH(CH_3)_2$), 0.88 (d, J = 6.6 Hz, 3 H, $CH(CH_3)_2$); ^{31}P NMR (121 MHz, CD_3OD): δ 19.5.

Example 12

Compound 16: Compound **15** (0.350 g, 0.488 mmol) was coevaporated with anhydrous pyridine (3 x 10 mL), each time filling with N_2. Residue was dissolved in anhydrous pyridine (2.5 mL) and phenol (0.459 g, 4.88 mmol) was added. This solution was heated to 70°C, then 1,3-dicyclohexylcarbodiimide (0.403 g, 1.93 mmol) was added and reaction mixture was heated at 70°C for 7 h. Reaction mixture was concentrated, coevaporated with toluene and

residue obtained was diluted with EtOAc, precipitating 1,3-dicyclohexylurea. The mixture was filtered and filtrate concentrated and residue obtained was purified (silica gel, 2% MeOH/CH_2Cl_2, then another column 75% EtOAc/Hex) to give a clear oil (0.1324 g, 31%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 8.7 Hz, 2 H, $SO_2C(CH)_2$), 7.41-7.18 (m, 10 H, Ar), 7.14 (d, J = 8.4Hz, 2 H, $CH_2C(CH)_2(CH)_2$), 6.99 (d, J = 9.0 Hz, 2 H, $(CH)_2COCH_3$), 6.83 (d, J = 8.4 Hz, 2 H, $(CH)_2COCH_2$), 5.64 (d, J = 5.1 Hz, 1 H, OC*H*O), 5.16-4.92 (m, 2 H), 4.32-3.62 (m, 12 H), 3.87 (s, 3 H, OCH_3), 3.22-2.73 (m, 7 H), 1.95-1.75 (m, 3 H), 0.93 (d, J = 6.6 Hz, 3 H, $CH(CH_3)_2$), 0.88 (d, J = 6.6 Hz, 3 H, $CH(CH_3)_2$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 14.3.

Example 13

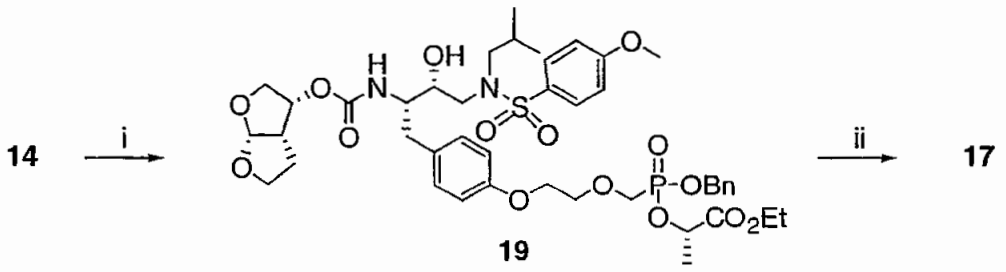
Compound 17: To a solution of compound **16** (0.132 g, 0.152 mmol) in acetonitrile (1.5 mL) at 0°C was added 1.0 M NaOH (0.38 mL, 0.381 mmol). Reaction mixture was stirred for 2 h at 0°C, then Dowex 50 (H+) resin was added until pH = 1. The resin was removed by filtration and the filtrate was concentrated and washed with EtOAc/Hex (1:2, 25 mL), then dried under high vacuum to give a clear film (0.103 g, 85%). This film was coevaporated with anhydrous pyridine (3 x 5 mL), filling with N_2. The residue was dissolved in anhydrous pyridine (1 mL) and ethyl lactate (0.15 mL, 1.30 mmol) was added and reaction mixture was heated at 70°C. After 5 min, 1,3-dicyclohexylcarbodiimide (0.107 g, 0.520 mmol) was added and reaction mixture was stirred at 70°C for 2.5 h. Additional 1,3-dicyclohexylcarbodiimide (0.055 g, 0.270 mmol) was added and reaction continued for another 1.5 h. Reaction mixture was concentrated and coevaporated with toluene and diluted with EtOAc, precipitating 1,3-dicyclohexylurea. The mixture was filtered and filtrate concentrated and residue obtained was purified (silica gel, 80 to 100% EtOAc/Hex) to give a white foam (0.0607 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 8.7 Hz, 2 H, $SO_2C(CH)_2$), 7.39-7.16 (m, 5 H, Ar), 7.13 (d, J = 8.1Hz, 2 H, $CH_2C(CH)_2(CH)_2$), 6.99 (d, J = 9.0 Hz, 2 H, $(CH)_2COCH_3$), 6.82 (d, J = 8.4 Hz, 2 H, $(CH)_2COCH_2$), 5.64 (d, J = 5.1 Hz, 1 H, OC*H*O), 5.16-4.92 (m, 3 H), 4.35-3.65 (m, 14 H), 3.87 (s, 3 H, OCH_3), 3.22-2.73 (m, 7 H), 1.95-1.80 (m, 3 H), 1.59 (d, J = 6.9Hz, 1.5 H, $CCHCH_3$), 1.47 (d, J = 7.2 Hz, 1.5 H, $CCHCH_3$), 1.37-1.18 (m, 3 H), 0.92 (d, J = 6.6 Hz, 3 H, $CH(CH_3)_2$), 0.88 (d, J = 6.6 Hz, 3 H, $CH(CH_3)_2$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 19.2, 17.2.

Example 14

Compound 18: Compound **17** (11.5 mg, 0.013 mmol) was dissolved in DMSO (0.14 mL) and acetonitrile (0.29 mL). PBS (pH 7.4, 1.43 mL) was added slowly with stirring. Porcine liver esterase (Sigma, 0.1 mL) was added and reaction mixture was gently stirred at 38°C. After 24 h, additional porcine liver esterase (0.1 mL) and DMSO (0.14 mL) were added and reaction mixture stirred for 48 h at 38°C. Reaction mixture concentrated and methanol was added to precipitate the enzyme. The mixture was filtered, concentrated and purified by reverse phase chromatography to give a white powder after lyophilization (7.1 mg, 69%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.76 (d, J = 8.7 Hz, 2 H, $SO_2C(CH)_2$), 7.15 (d, J = 8.4 Hz, 2 H, $CH_2C(CH)_2(CH)_2$), 7.08 (d, J = 9.0 Hz, 2 H, $(CH)_2COCH_3$), 6.83 (d, J = 8.7 Hz, 2 H, $(CH)_2COCH_2$), 5.59 (d, J = 5.1 Hz, 1 H, $OCHO$), 5.16-4.90 (masked by CD_3OH, 2 H), 4.19-3.65 (m, 12 H), 3.88 (s, 3 H, OCH_3), 3.50-3.27 (m, 1 H), 3.20-2.78 (m, 5 H), 2.55-2.40 (m, 1 H), 2.05-1.90 (m, 1 H), 1.75-1.30 (m, 2 H), 1.53 (d, J = 6.6 Hz, 3 H, $CCHCH_3$), 0.93 (d, J = 6.6 Hz, 3 H, $CH(CH_3)_2$), 0.88 (d, J = 6.6 Hz, 3 H, $CH(CH_3)_2$); ^{31}P NMR (121 MHz, CD_3OD): δ 16.7.

Alternatively, compound **17** was prepared as described below (Scheme 3).

Scheme 3



Reagents and conditions: i. a. **14**, DABCO, tol, reflux, b. ethyl lactate, PyBOP, DIPEA, DMF, 59%; ii. a. H_2, Pd/C, EtOH; b. PhOH, PyBOP, DIPEA, DMF, 35%.

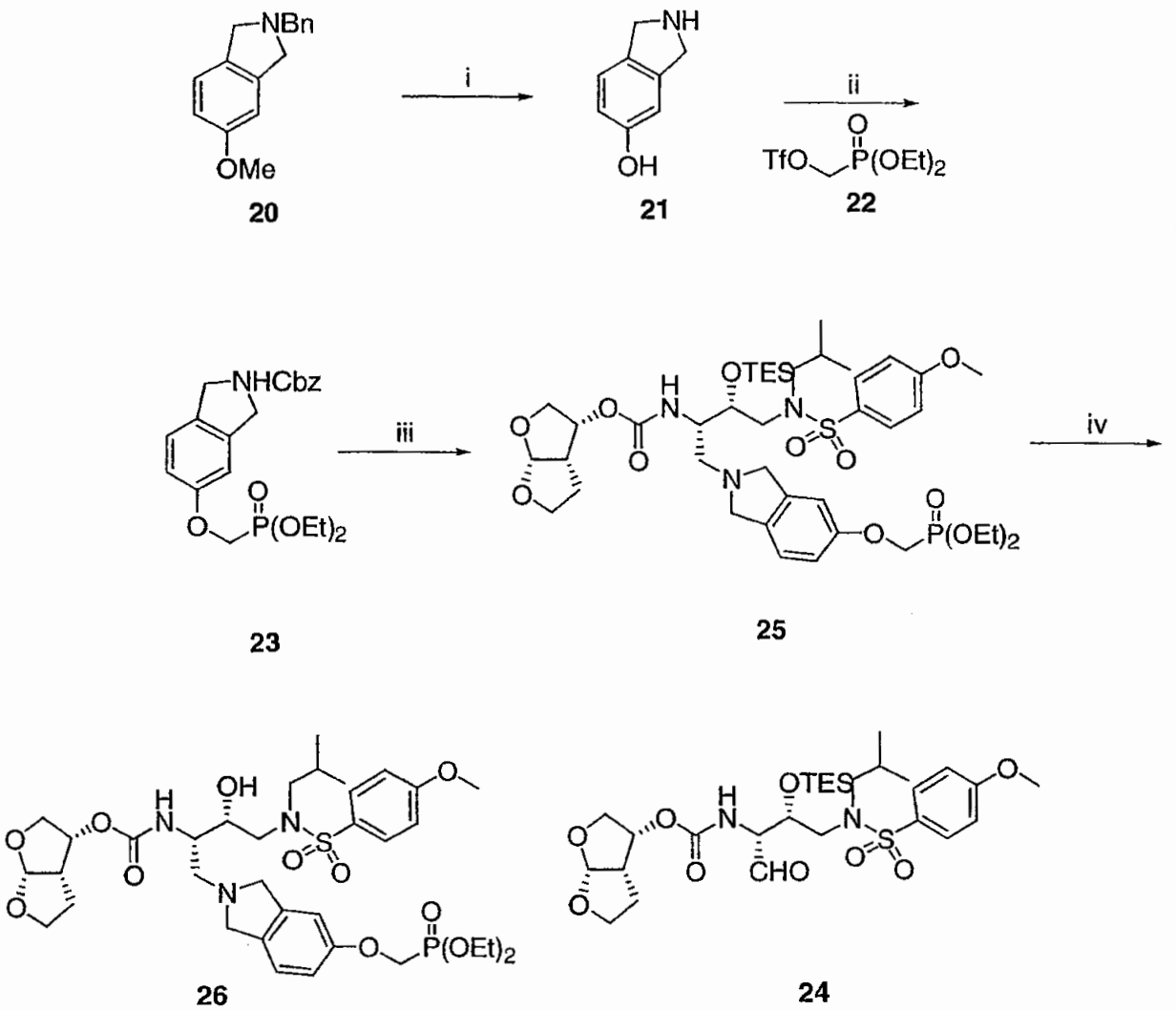
Example 15

Compound 19: To a solution of compound **14** (0.945 g, 1.05 mmol) in anhydrous toluene (10.0 mL) was added 1,4-diazobicyclo[2.2.2] octane (0.130 g, 1.16 mmol) and reaction mixture was refluxed for 2 h. After cooling to room temperature, reaction mixture was diluted with EtOAc and washed with 1.0 N HCl and dried ($MgSO_4$). Concentration gave a white foam (0.785 g, 93%). Residue was dissolved in anhydrous DMF (10.0 mL) and to this solution was added ethyl (S)-lactate (0.23 mL, 2.00 mmol) and diisopropylethylamine (0.70 mL, 4.00 mmol), followed by benzotriazol-1-yloxytripyrroldinophosphonium hexafluorophosphate (1.041 g, 2.00 mmol). Reaction mixture was stirred for 20 h, then concentrated and residue was dissolved in EtOAc and washed with 1.0 N HCl, saturated $NaHCO_3$, brine and dried ($MgSO_4$). Concentration and purification (silica gel, 2 % $MeOH/CH_2Cl_2$) gave an off-white foam (0.520 g, 59%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J = 7.5 Hz, 2 H, $SO_2C(CH)_2$), 7.50-7.27 (m, 4 H, Ar), 7.12 (d, J = 8.1Hz, 2 H, $CH_2C(CH)_2(CH)_2$), 7.00 (d, J = 6.6 Hz, 2 H, $(CH)_2COCH_3$), 6.81 (d, J = 8.4 Hz, 2 H, $(CH)_2COCH_2$), 5.64 (d, J = 5.1 Hz, 1 H, $OCHO$), 5.37-4.90 (m, 5 H), 4.35-3.65 (m, 14 H), 3.88 (s, 3 H, OCH_3), 3.24-2.70 (m, 7 H), 1.90-1.70 (m, 3 H), 1.54 (d, J = 6.9Hz, 1.5 H, $CCHCH_3$), 1.47 (d, J = 6.9 Hz, 1.5 H, $CCHCH_3$), 1.37-1.22 (m, 3 H), 0.93 (d, J = 6.3 Hz, 3 H, $CH(CH_3)_2$), 0.89 (d, J = 6.0 Hz, 3 H, $CH(CH_3)_2$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 22.3, 21.2.

Example 16

Compound 17: A mixture of compound **19** (0.520 g, 0.573 mmol) and 10% palladium on carbon (0.055 g) in ethanol (10 mL) was stirred under a hydrogen atmosphere (1 atm) for 2 h. Celite was added to the reaction mixture and stirred for 5 min, then mixture was filtered through Celite and concentrated to give a white foam (0.4649 g, 99%). Residue was dissolved in anhydrous DMF (5.0 mL) and to this solution was added phenol (0.097 g, 1.03 mmol), diisopropylethylamine (0.36 mL, 2.06 mmol) followed by benzotriazol-1-yloxytripyrroldinophosphonium hexafluorophosphate (0.536 g, 1.03 mmol). Reaction mixture was stirred for 20 h, then concentrated and residue was dissolved in EtOAc and washed with 1 N HCl, H_2O, sat. $NaHCO_3$, brine and dried ($MgSO_4$). Concentration and purification (silica gel, 2 % $MeOH/CH_2Cl_2$) gave a white foam (0.180 g, 35%).

Scheme 4



Reagents and conditions: i. a. 48% HBr, 120°C, 65%; b. H_2, $Pd(OH)_2$, EtOH, 100%;
ii. CbzCl, NaOH, tol/H_2O, 0°C to rt, 43%; b. **22**, $CsCO_3$, CH_3CN, 99%;
iii. a. H_2, Pd/C, AcOH, EtOAc/EtOH, 95%; b. **24**, $NaBH(OAc)_3$, 1,2-DCE, 21%;
iv, 4% HF/CH_3CN, 62%.

Example 17

Compound 21: Compound **20** (11.5 g, 48.1 mmol) in 48% HBr (150 mL) was heated at 120°C for 4 h, then cooled to room temperature and diluted with EtOAc. Mixture was neutralized with saturated $NaHCO_3$ solution and solid $NaHCO_3$ and extracted with EtOAc containing MeOH. Organic layer dried ($MgSO_4$), concentrated, and purified (silica gel, 1:2

EtOAc/Hex with 1% MeOH) to give a brown solid (7.0 g, 65%). The resulting compound (7.0 g, 31.1 mmol) and 10% palladium hydroxide (2.1 g) in EtOH (310 mL) was stirred under a hydrogen atmosphere for 1 d, then filtered through Celite and concentrated to give an off-white solid (4.42 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01 (d, J = 7.8 Hz, 1 H, Ar), 6.64 (s, 1 H, Ar), 6.61 (d, J = 8.1 Hz, 2 H, Ar), 4.07 (s, 2 H, ArCH_2N), 4.05 (s, 2 H, ArCH_2N).

Example 18

Compound 22: To a solution of compound **21** (4.42 g, 32.7 mmol) in 1.0 M NaOH (98 mL, 98.25 mmol) at 0°C was added dropwise benzyl chloroformate (7.00 mL, 49.13 mmol) in toluene (7 mL). After addition was complete, reaction mixture was stirred overnight at room temperature. Reaction mixture was diluted with EtOAc and extracted with EtOAc (3x). Combined organic layer was dried ($MgSO_4$), concentrated and purified (silica gel, 2% MeOH/CH_2Cl_2) to give a white solid (3.786 g, 43%). The resulting compound (0.6546 g, 2.43 mmol) was dissolved in anhydrous acetonitrile (10 mL), and compound **23** (0.782 g, 2.92 mmol) was added, followed by cesium carbonate (1.583 g, 4.86 mmol). Reaction mixture was stirred for 2h at room temperature, then filtered, concentrated, and purified (3% MeOH/CH_2Cl_2) to give a brownish oil (1.01 g, 99%).

Example 19

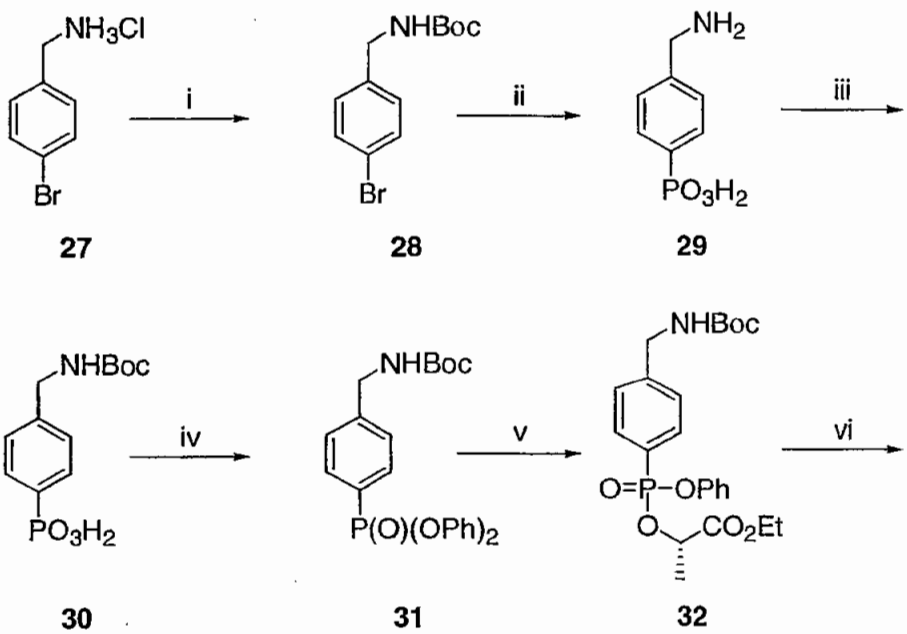
Compound 25: To a solution of compound **22** (0.100 g, 0.238 mmol) in EtOAc/EtOH (2 mL, 1:1) was added acetic acid (14 μL, 0.238 mmol) and 10% palladium on carbon (0.020 g) and the mixture was stirred under a hydrogen atmosphere for 2 h. Celite was added to the reaction mixture and stirred for 5 min, then filtered through Celite. Concentration and drying under high vacuum gave a reddish film (0.0777 g, 95%). The resulting amine (0.0777g, 0.225 mmol) and aldehyde **24** (0.126 g, 0.205 mmol) in 1,2-dichloroethane (1.2 mL) were stirred for 5 min at 0°C, then sodium triacetoxyborohydride (0.0608 g, 0.287 mmol) was added. Reaction mixture was stirred for 1 h at 0°C, then quenched with saturated $NaHCO_3$ solution and brine. Extracted with EtOAc, the organic layer was dried ($MgSO_4$), concentrated and purified (silica gel, 2% MeOH/CH_2Cl_2) to give a brown foam (38.7 mg, 21%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, J = 8.7 Hz, 2 H, Ar), 7.09 (d, J = 8.7 Hz, 1 H, Ar), 7.05-6.72 (m, 4 H, Ar), 5.71 (d, J = 5.1 Hz, 1 H), 5.22-5.07 (m, 2 H), 4.22-4.17 (m, 7 H),

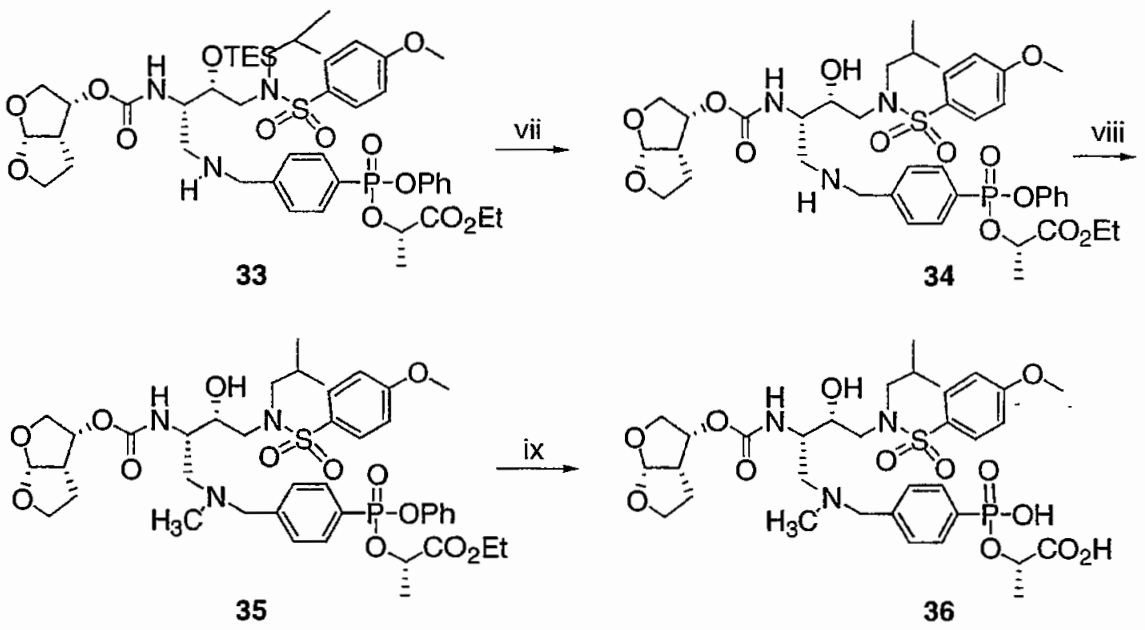
4.16-3.69 (m, 9 H), 3.82 (s, 3 H), 3.25-2.51 (m, 7 H), 2.22-1.70 (m, 3 H), 1.37 (t, J = 6.9 Hz, 6 H), 1.10-0.58 (m, 21 H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 19.5.

Example 20

Compound 26: To a solution of compound **25** (38.7 mg, 0.0438 mmol) in acetonitrile (0.5 mL) at 0°C was added 48% HF (0.02 mL). The reaction mixture was stirred at room temperature for 2 h, then quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. Organic layer was separated, dried ($MgSO_4$), concentrated and purified (silica gel, 3 to 5% MeOH/CH_2Cl_2) to give a red film (21.2 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, J = 8.7 Hz, 2 H, Ar), 7.10 (d, J = 8.7 Hz, 1 H, Ar), 6.97 (d, J = 8.70 Hz, 2 H), 6.90-6.76 (m, 2 H), 5.72 (d, J = 5.1 Hz, 1 H), 5.41 (d, J = 9.0 Hz, 1 H), 5.15 (q, J = 6.6 Hz, 1 H), 4.38-4.17 (m, 7 H), 4.16-3.65 (m, 9 H), 3.87 (s, 3 H), 3.20-2.82 (m, 7 H), 2.75-1.79 (m, 3 H), 1.37 (t, J = 6.9 Hz, 6 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 19.3.

Scheme 5





Reagents and conditions: i. Boc_2O, NaOH, H_2O, 96%;
ii. a. $HP(OEt)_2$, Et_3N, $(PPh_3)_4Pd$, 90°C, b. TMSBr, CH_3CN, 65%;
iii. Boc_2O, NaOH, THF/H_2O, 89%; iv. PhOH, DCC, pyr, 70°C, 71%;
v. a. NaOH, CH_3CN, 94%; b. Et lactate, DCC, pyr, 70°C, 80%; vi. a. TFA, CH_2Cl_2;
b. **24**, AcOH, $NaBH_3CN$, EtOH, 33%; vii. 4% HF/CH_3CN, 88%;
viii. HCHO, AcOH, $NaBH_3CN$, EtOH, 67%;
ix. CH_3CN, DMSO, PBS, porcine liver esterase, 38°C, 21%.

Example 21

Compound 28: To a mixture of 4-bromobenzylamine hydrochloride (15.23 g, 68.4 mmol) in H_2O (300 mL) was added sodium hydroxide (8.21 g, 205.2 mmol), followed by di-*tert*-butyl dicarbonate (16.45g, 75.3 mmol). Reaction mixture was vigorously stirred for 18 h, then diluted with EtOAc (500 mL). Organic layer separated and aqueous layer extracted with EtOAc (200 mL). Combined organic layer was dried ($MgSO_4$), concentrated and dried under high vacuum to give a white solid (18.7 g, 96%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, J = 8.4 Hz, 2 H), 7.12 (d, J = 8.3 Hz, 2 H), 4.82 (s, 1 H, N*H*), 4.22 (d, J = 6.1 Hz, 2 H), 1.41 (s, 9 H).

Example 22

Compound 29: Compound **28** (5.00 g, 17.47 mmol) was coevaporated with toluene. Diethyl phosphite (11.3 mL, 87.36 mmol) was added and mixture was coevaporated with toluene

(2x). Triethylamine (24.0 mL, 174.7 mmol) was added and mixture was purged with argon for 10 min, then tetrakis(triphenylphosphine) palladium(0) (4.00 g, 3.49 mmol) was added. Reaction mixture was refluxed for 18 h, cooled, concentrated and diluted with EtOAc. Washed with 0.5 N HCl, 0.5 M NaOH, H_2O, brine and dried ($MgSO_4$). Concentrated and purification (silica gel, 70% EtOAc/Hex) gave an impure reaction product as a yellow oil (6.0 g). This material (6.0 g) was dissolved in anhydrous acetonitrile (30 mL) and cooled to 0°C. Bromotrimethylsilane (11.5 mL, 87.4 mmol) was added and reaction mixture was warmed to room temperature over 15 h. Reaction mixture was concentrated, dissolved in MeOH (50 mL) and stirred for 1.5 h. H_2O (1 mL) was added and mixture stirred for 2 h. Concentrated to dryness and dried under high vacuum, then triturated with Et_2O containing 2% MeOH to give a white solid (3.06 g, 65 %). ^{1}H NMR (300 MHz, D_2O): δ 7.67 (dd, J = 12.9, 7.6 Hz, 2 H), 7.45-7.35 (m, 2 H), 4.10 (s, 2 H); ^{31}P NMR (121 MHz, D_2O): δ 12.1.

Example 23

Compound 30: Compound **29** (4.78 g, 17.84 mmol) was dissolved in H_2O (95 mL) containing sodium hydroxide (3.57 g, 89.20 mmol). Di-*tert*-butyl dicarbonate (7.63 g, 34.94 mmol) was added, followed by THF (25 mL). The clear reaction mixture was stirred overnight at room temperature then concentrated to ~100 mL. Washed with EtOAc and acidified to pH 1 with 1 N HCl and extracted with EtOAc (7x). Combined organic layer was dried ($MgSO_4$), concentrated and dried under high vacuum. Trituration with Et_2O gave a white powder (4.56 g, 89%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.85-7.71 (m, 2 H), 7.39-7.30 (m, 2 H), 4.26 (s, 2 H), 1.46 (s, 9 H); ^{31}P NMR (121 MHz, CD_3OD): δ 16.3.

Example 24

Compound 31: Compound **30** (2.96 g, 10.32 mmol) was coevaporated with anhydrous pyridine (3 x 10 mL). To this residue was added phenol (9.71 g, 103.2 mmol) and mixture was coevaporated with anhydrous pyridine (2 x 10 mL). Pyridine (50 mL) was added and solution heated to 70°C. After 5 min, 1,3-dicyclohexylcarbodiimide (8.51 g, 41.26 mmol) was added and resulting mixture was stirred for 8 h at 70°C. Reaction mixture was cooled and concentrated and coevaporated with toluene. Residue obtained was diluted with EtOAc and the resulting precipitate was removed by filtration. The filtrate was concentrated and purified (silica gel, 20 to 40% EtOAc/Hex, another column 30 to 40% EtOAc/Hex) to give a

white solid (3.20 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 13.8, 8.2 Hz, 2 H), 7.41-7.10 (m, 14 H), 5.17 (br s, 1 H, N*H*), 4.35 (d, *J* = 5.2 Hz, 2 H), 1.46 (s, 9 H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 11.8.

Example 25

Compound 32: To a solution of compound **31** (3.73 g, 8.49 mmol) in acetonitrile (85 mL) at 0°C was added 1 M NaOH (21.2 mL, 21.21 mmol). Reaction mixture was stirred at 0°C for 30 min, then warmed to room temperature over 4 h. Reaction mixture cooled to 0°C and Dowex (H+) residue was added to pH 2. Mixture was filtered, concentrated and residue obtained was triturated with EtOAc/Hex (1:2) to give a white powder (2.889 g, 94%). This compound (2.00 g, 5.50 mmol) was coevaporated with anhydrous pyridine (3 x 10 mL). The residue was dissolved in anhydrous pyridine (30 mL) and ethyl (S)-lactate (6.24 mL, 55 mmol) and reaction mixture was heated to 70°C. After 5 min, 1,3-dicyclocarbodiiimide (4.54 g, 22.0 mmol) was added. Reaction mixture was stirred at 70°C for 5 h, then cooled and concentrated. Residue was dissolved in EtOAc and precipitate was removed by filtration. The filtrate was concentrated and purified (25 to 35% EtOAc/Hex, another column 40% EtOAc/Hex) to give a colorless oil (2.02 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96-7.85 (m, 2 H), 7.42-7.35 (m, 2 H), 7.35-7.08 (m, 4 H), 5.16-5.00 (m, 1 H), 4.93 (s, 1 H, N*H*), 4.37 (d, *J* = 5.5 Hz, 1 H), 4.21 (q, *J* = 7.3 Hz, 1 H), 4.11 (dq, *J* = 5.7, 2.2 Hz, 1 H), 1.62-1.47 (m, 3 H), 1.47 (s, 9 H), 1.27 (t, *J* = 7.3 Hz, 1.5 H), 1.17 (t, *J* = 7.3 Hz, 1.5 H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 16.1, 15.0.

Example 26

Compound 33: Compound **32** (2.02 g, 4.36 mmol) was dissolved in CH_2Cl_2 (41 mL) and cooled to 0°C. To this solution was added trifluoroacetic acid (3.5 mL) and reaction mixture was stirred at 0°C for 1 h, then at room temperature for 3 h. Reaction mixture was concentrated, coevaporated with EtOAc and diluted with H_2O (400 mL). Mixture was neutralized with Amberlite IRA-67 weakly basic resin, then filtered and concentrated. Coevaporation with MeOH and dried under high vacuum to give the TFA amine salt as a semi-solid (1.48 g, 94%). To a solution of the amine (1.48 g, 4.07 mmol) in absolute ethanol (20 mL) at 0°C was added aldehyde **24** (1.39 g, 2.26 mmol), followed by acetic acid (0.14 mL, 2.49 mmol). After stirring for 5 min, sodium cyanoborohydride (0.284 g, 4.52 mmol)

was added and reaction mixture stirred for 30 min at 0°C. Reaction was quenched with saturated $NaHCO_3$ solution and diluted with EtOAc and H_2O. Aqueous layer was extracted with EtOAc (3x) and combined organic layer was dried ($MgSO_4$), concentrated and purified (silica gel, 2 to 4% MeOH/CH_2Cl_2) to give white foam (0.727 g, 33%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.98-7.86 (m, 2 H), 7.71 (d, J = 8.6 Hz, 2 H), 7.49 (br s, 2 H), 7.38-7.05 (m, 5 H), 6.98 (d, J = 8.8 Hz, 2 H), 5.72 (d, J = 5.1 Hz, 1 H), 5.28-5.00 (m, 2 H), 4.30-3.72 (m, 12 H), 3.42-3.58 (m, 1 H), 3.20-2.68 (m, 7 H), 2.25-1.42 (m, 6 H), 1.26 (t, J = 7.2 Hz, 1.5 H), 1.17 (t, J = 7.2 Hz, 1.5 H), 1.08-0.50 (m, 21 H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 16.1, 15.1.

Example 27

Compound 34: To a solution of compound **33** (0.727 g, 0.756 mmol) in acetonitrile (7.6 mL) at 0°C was added 48% hydrofluoric acid (0.152 mL) and reaction mixture was stirred for 40 min at 0°C, then diluted with EtOAc and H_2O. Saturated $NaHCO_3$ was added and aqueous layer was extracted with EtOAc (2x). Combined organic layer was dried ($MgSO_4$), concentrated and purified (silica gel, 4 to 5% MeOH/CH_2Cl_2) to give a colorless foam (0.5655 g, 88%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.95-7.82 (m, 2 H), 7.67 (d, J = 8.1 Hz, 2 H), 7.41 (br s, 2 H), 7.38-7.05 (m, 5 H), 6.95 (d, J = 7.2 Hz, 2 H), 5.76 (d, J = 7.9 Hz, 1 H), 5.67 (d, J = 5.0 Hz, 1 H), 5.32-4.98 (m, 2 H), 4.25-3.75 (m, 13 H), 3.25-2.70 (m, 7 H), 2.15-1.76 (m, 3 H), 1.53-1.41 (m, 3 H), 1.25-1.08 (m, 3 H), 0.87 (d, J = 4.2 Hz, 6 H); ^{31}P NMR (121 MHz, $CDCl_3$): δ 16.1, 15.0.

Example 28

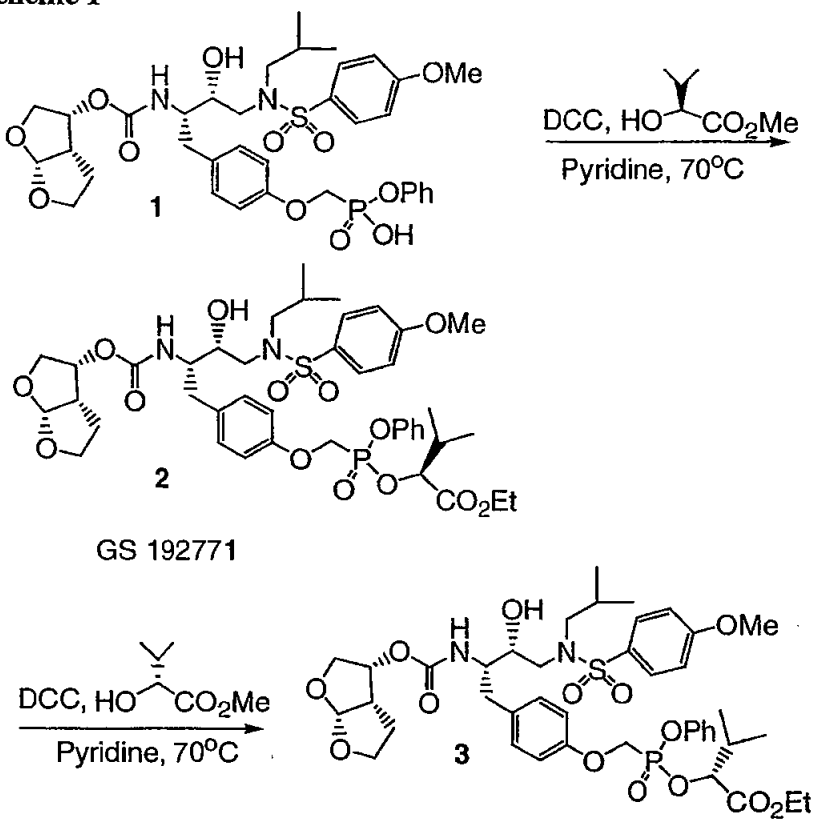
Compound 35: To a solution of compound **33** (0.560 g, 0.660 mmol) in absolute ethanol (13 mL) at 0°C was added 37% formaldehyde (0.54 mL, 6.60 mmol), followed by acetic acid (0.378 mL, 6.60 mmol). The reaction mixture was stirred at 0°C for 5 min, then sodium cyanoborohydride (0.415 g, 6.60 mmol) was added. Reaction mixture was warmed to room temperature over 2 h, then quenched with saturated $NaHCO_3$ solution. EtOAc was added and mixture was washed with brine. Aqueous layer was extracted with EtOAc (2x) and combined organic layer was dried ($MgSO_4$), concentrated and purified (silica gel, 3% MeOH/CH_2Cl_2) to give a white foam (0.384 g, 67%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.95-7.82 (m, 2 H), 7.71 (d, J = 8.4 Hz, 2 H), 7.38 (br s, 2 H), 7.34-7.10 (m, 5 H), 6.98 (d, J = 8.8 Hz, 2 H), 5.72 (d, J = 5.0 Hz, 1 H), 5.50 (br s, 1 H), 5.19-5.01 (m, 2 H), 4.29-3.75 (m, 10 H),

3.85 (s, 3 H), 3.35-2.70 (m, 7 H), 2.23 (s, 3 H), 2.17-1.79 (m, 3 H), 1.54 (d, J = 6.9 Hz, 1.5 H), 1.48 (d, J = 6.8 Hz, 1.5 H), 1.25 (t, J = 7.2 Hz, 1.5 H), 1.16 (t, J = 7.2 Hz, 1.5 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 3 H). ^{31}P NMR (121 MHz, $CDCl_3$): δ 16.0, 14.8.

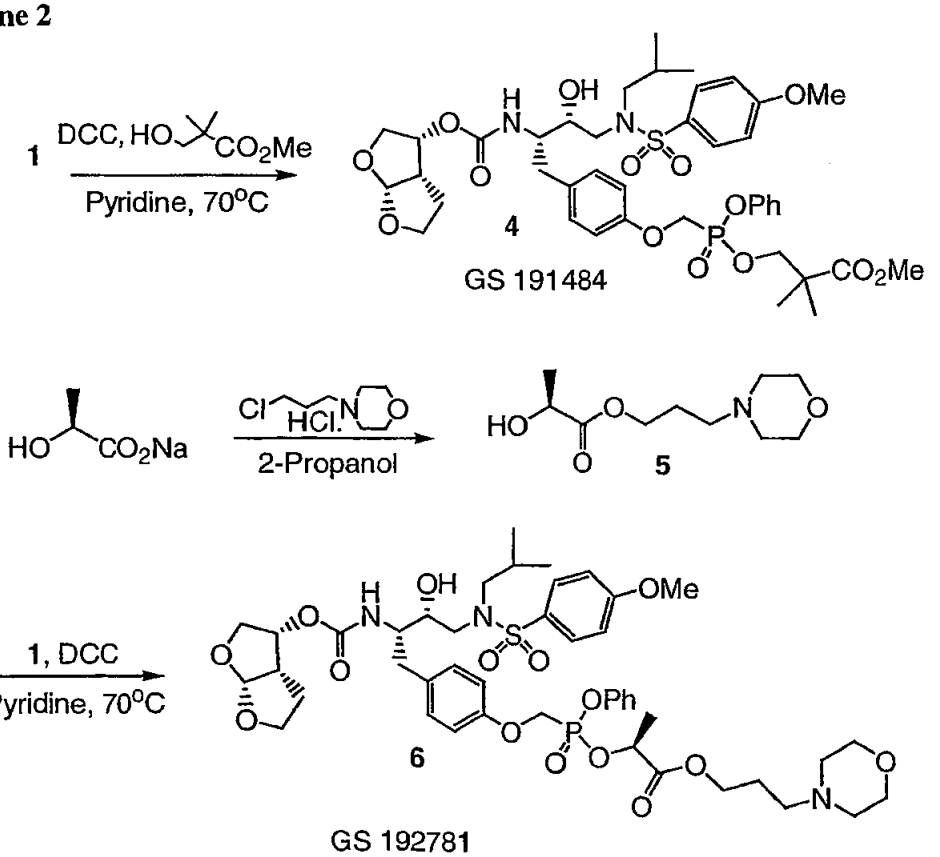
Example 29

Compound 36: To a solution of compound **35** (44 mg, 0.045 mmol) in acetonitrile (1.0 mL) and DMSO (0.5 mL) was added phosphate buffered saline (pH 7.4, 5.0 mL) to give a cloudy white suspension. Porcine liver esterase (200 µL) was added and reaction mixture was stirred for 48 h at 38°C. Additional esterase (600 µL) was added and reaction was continued for 4 d. Reaction mixture was concentrated, diluted with MeOH and the resulting precipitate removed by filtration. Filtrate was concentrated and purified by reverse phase HPLC to give a white powder after lyophilization (7.2 mg, 21%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.95 (br s, 2 H), 7.76 (d, J = 8.4 Hz, 2 H), 7.64 (br s, 2 H), 7.13 (d, J = 8.7 Hz, 2 H), 5.68 (d, J = 5.1 Hz, 1 H), 5.14 (br s, 1 H), 4.77 (br s, 1 H), 4.35-3.59 (m, 8 H), 3.89 (s, 3 H), 3.45-2.62 (m, 10 H), 2.36-1.86 (m, 3 H), 1.44 (d, J = 6.3 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{31}P NMR (121 MHz, CD_3OD): δ 13.8.

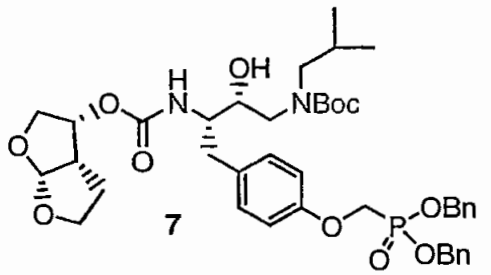
Scheme 1



Scheme 2

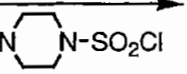


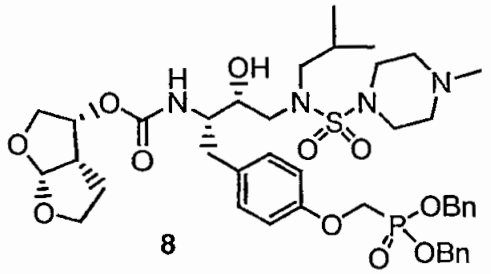
Scheme 3



7

(1) TFA, CH_2Cl_2

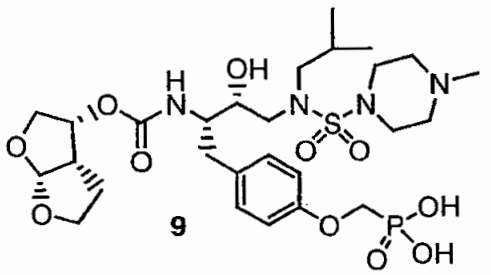
(2) TEA, 



8

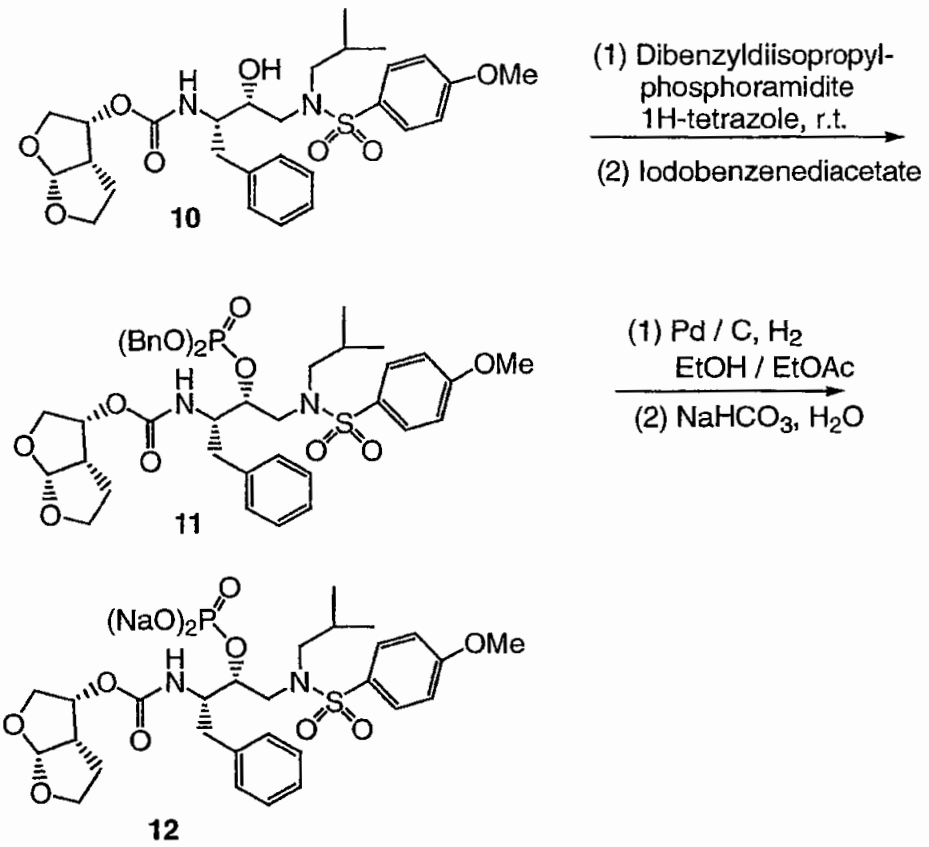
Pd / C, H_2, r.t.

EtOAc, 2-propanol

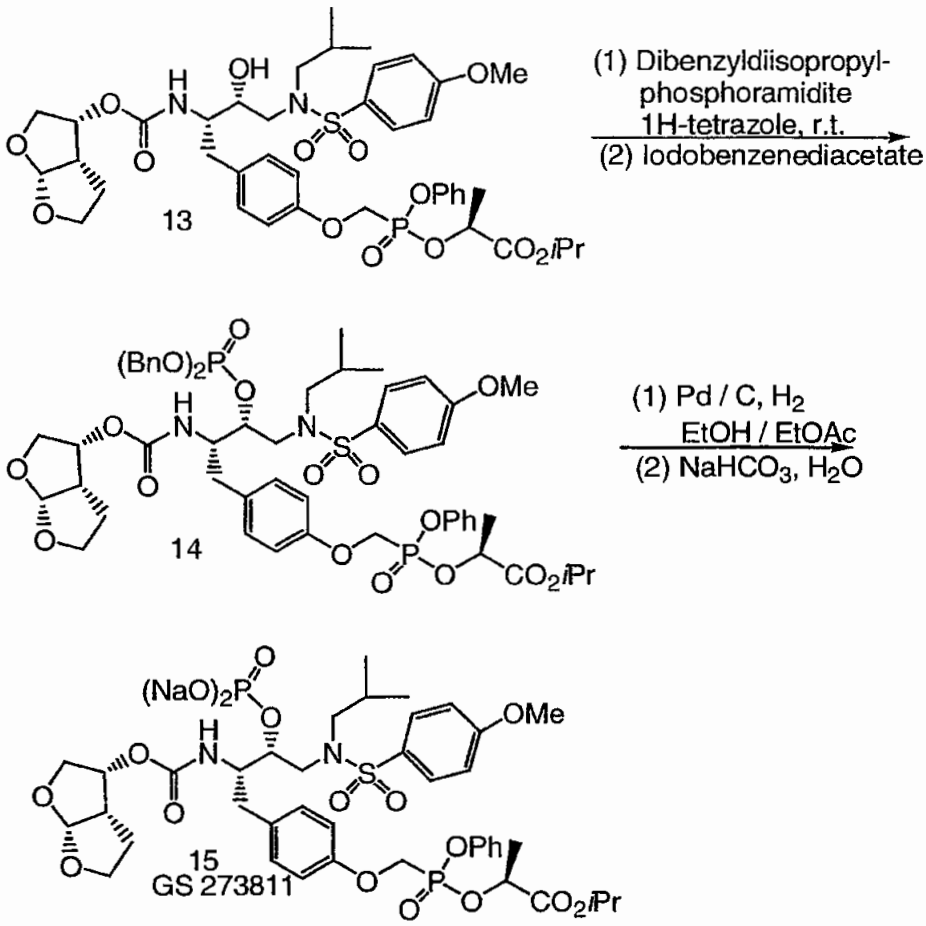


9

Scheme 4


OH
OMe
(1) Dibenzyldiisopropyl-
phosphoramidite
1H-tetrazole, r.t.
(2) Iodobenzenediacetate
10
(BnO)2P
OMe
(1) Pd / C, H2
EtOH / EtOAc
(2) NaHCO3, H2O
11
(NaO)2P
OMe
12

Scheme 5



Example 1

Monophospholactate 2: A solution of 1 (0.11 g, 0.15 mmol) and α-hydroxyisovaleric acid ethyl-(S)-ester (71 mg, 0.49 mmol) in pyridine (2 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (0.10 g, 0.49 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H_2O, saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (35 mg, 28%, GS 192771, 1/1 diastereomeric mixture) as a white solid: ^1H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.36-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.94-6.84 (dd, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.00-4.85 (m, 3H), 4.55 (dd, 1H), 4.41 (dd, 1H), 4.22-4.07 (m, 2H), 3.96-3.68 (m, 9H), 3.12-2.74 (m, 7H), 2.29 (m, 1H), 1.85-1.57

(m, 3H), 1.24 (m, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.9 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 17.7, 15.1.

Example 2

Monophospholactate 3: A solution of 1 (0.11 g, 0.15 mmol) and α-hydroxyisovaleric acid ethyl-(R)-ester (71 mg, 0.49 mmol) in pyridine (2 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (0.10 g, 0.49 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H_2O, saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (35 mg, 28%, GS 192772, 1/1 diastereomeric mixture) as a white solid: ^1H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.35-7.13 (m, 7H), 6.98 (d, J = 8.7 Hz, 2H), 6.93-6.83 (dd, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.04-4.85 (m, 3H), 4.54 (dd, 1H), 4.39 (dd, 1H), 4.21-4.06 (m, 2H), 3.97-3.67 (m, 9H), 3.12-2.75 (m, 7H), 2.27 (m, 1H), 1.83-1.57 (m, 3H), 1.26 (m, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.9 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 17.7, 15.1.

Example 3

Monophospholactate 4: A solution of 1 (0.10 g, 0.13 mmol) and methyl-2,2-dimethyl-3-hydroxypropionate (56 μL, 0.44 mmol) in pyridine (1 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (91 mg, 0.44 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H_2O, saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the monophospholactate (72 mg, 62%, GS 191484) as a white solid: ^1H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.34 (m, 2H), 7.25-7.14 (m, 5H), 7.00 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.05 (m, 2H), 4.38 (d, J = 9.6 Hz, 2H),

4.32-4.20 (m, 2H), 4.00 (m, 2H), 3.87-3.63 (m, 12H), 3.12-2.78 (m, 7H), 1.85-1.67 (m, 3H), 1.20 (m, 6H), 0.91 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 16.0.

Example 4

Lactate 5: To a suspension of lactic acid sodium salt (5 g, 44.6 mmol) in 2-propanol (60 mL) was added 4-(3-chloropropyl)morpholine hydrochloride (8.30 g, 44.6 mmol). The reaction mixture was heated to reflux for 18 h and cooled to room temperature. The solid was filtered and the filtrate was recrystallized from EtOAc / hexane to give the lactate (1.2 g, 12%).

Example 5

Monophospholactate 6: A solution of 1 (0.10 g, 0.13 mmol) and lactate 5 (0.10 g, 0.48 mmol) in pyridine (2 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (0.10 g, 0.49 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and H_2O. The EtOAc layer was washed with saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the monophospholactate (30 mg, 24%, GS 192781, 1/1 diastereomeric mixture) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.38-7.15 (m, 7H), 7.00 (d, J = 8.7 Hz, 2H), 6.91 (m, 2H), 5.65 (d, J = 3.3 Hz, 1H), 5.18-4.98 (m, 3H), 4.54 (dd, 1H), 4.42 (dd, 1H), 4.2 (m, 2H), 4.00-3.67 (m, 16H), 3.13-2.77 (m, 7H), 2.4 (m, 5H), 1.85-1.5 (m, 5H), 1.25 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.4, 15.4.

Example 6

Sulfonamide 8: A solution of dibenzylphosphonate 7 (0.1 g, 0.13 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (1 mL) and cooled to 0°C. Triethylamine (72 µL, 0.52 mmol) was added followed by the treatment of 4-methylpiperazinylsulfonyl chloride (25 mg, 0.13 mmol). The solution was stirred for 1 h at

0°C and the product was partitioned between CH_2Cl_2 and H_2O. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH_2Cl_2) to give the sulfonamide 8 (32 mg, 30%, GS 273835) as a white solid: ^{1}HNMR ($CDCl_3$) δ 7.35 (m, 10H), 7.11 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.2-4.91 (m, 4H), 4.2 (d, J = 10.2 Hz, 2H), 4.0-3.69 (m, 6H), 3.4-3.19 (m, 5H), 3.07-2.75 (m, 5H), 2.45 (m, 4H), 2.3 (s, 3H), 1.89-1.44 (m, 7H), 0.93 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 20.3.

Example 7

Phosphonic Acid 9: To a solution of 8 (20 mg, 0.02 mmol) in EtOAc (2 mL) and 2-propanol (0.2 mL) was added 10% Pd/C (5 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (10 mg, 64%) as a white solid.

Example 8

Dibenzylphosphonate 11: A solution of 10 (85 mg, 0.15 mmol) and 1*H*-tetrazole (14 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) was treated with Dibenzyldiisopropylphosphoramidite (60 µL, 0.20 mmol) and stirred at room temperature overnight. The product was partitioned between CH_2Cl_2 and H_2O, dried with Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography to give the intermediate dibenzylphosphite (85 mg, 0.11 mmol) which was dissolved in CH_3CN (2 mL) and treated with iodobenzenediacetate (51 mg, 0.16 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated. The residue was partitioned between EtOAc and $NaHCO_3$. The organic layer was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate (45 mg, 52%) as a white solid.

Example 9

Disodium Salt of Phosphonic Acid 12: To a solution of 11 (25 mg, 0.03 mmol) in EtOAc (2 mL) was added 10% Pd/C (10 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of

celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid which was dissolved in H_2O (1mL) and treated with $NaHCO_3$ (2.53 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 1 h and lyophilized overnight to give the disodium salt of phosphonic acid (19.77 mg, 95%, GS 273777) as a white solid: ^{1}H NMR (CD_3OD) δ 7.81 (d, J = 9.0 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.27-7.09 (m, 5H), 5.57 (d, J = 5.1 Hz, 1H), 5.07 (m, 1H), 4.87-4.40 (m, 3H), 3.93-3.62 (m, 6H), 3.45-2.6 (m, 6H), 2.0 (m, 2H), 1.55 (m, 1H), 0.95-0.84 (m, 6H).

Example 10

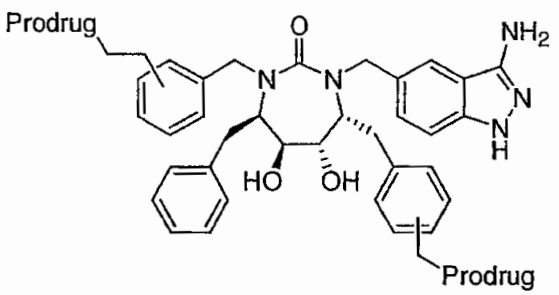
Dibenzylphosphonate 14: A solution of 13 (0.80 g, 0.93 mmol) and 1*H*-tetrazole (98 mg, 1.39 mmol) in CH_2Cl_2 (15 mL) was treated with dibenzyldiisopropylphosphoramidite (0.43 mL, 1.39 mmol) and stirred at room temperature overnight. The product was partitioned between CH_2Cl_2 and H_2O, dried with Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography to give the intermediate dibenzylphosphite (0.68 g, 67%). To a solution of the dibenzylphosphite (0.39 g, 0.35 mmol) in CH_3CN (5 mL) was added iodobenzenediacetate (0.17 g, 0.53 mmol). The reaction mixture was stirred at room temperature for 2 h and concentrated. The residue was partitioned between EtOAc and $NaHCO_3$. The organic layer was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate (0.35 g, 88%) as a white solid.

Example 11

Disodium Salt of Phosphonic Acid 15: To a solution of 14 (0.39 g, 0.35 mmol) in EtOAc (30 mL) was added 10% Pd/C (0.10 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid, which was dissolved in H_2O (3 mL) and treated with $NaHCO_3$ (58 mg, 0.70 mmol). The reaction mixture was stirred at room temperature for 1 h and lyophilized overnight to give the disodium salt of phosphonic acid (0.31 g, 90%, GS 273811) as a white solid: ^{1}H NMR (CD_3OD) δ 7.81 (d, J = 9.0 Hz, 2H), 7.43-7.2 (m, 7H), 7.13 (d, J = 9.0 Hz, 2H), 6.9 (m, 2H), 5.55 (d, J = 4.8 Hz, 1H), 5.07 (m, 2H), 4.87(m, 1H), 4.64-4.4 (m, 4H), 3.93-3.62 (m, 9H), 3.33-2.63 (m, 5H), 2.11 (m, 1H), 1.6-1.42 (m, 4H), 1.38-1.25 (m, 7H), 0.95 (d, J = 6.3 Hz, 3H), 0.84 (d, J = 6.3 Hz, 3H).

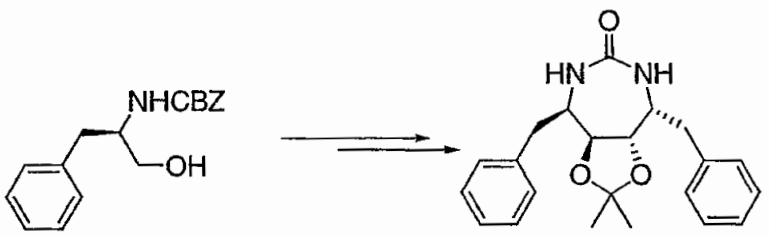
Examples For The Preparation Of Cyclic Carbonyl-Like Phosphonate Protease Inhibitors (CCPPI)

Phosphonamidate Prodrugs



Scheme 1-2	Scaffold Synthesis
Scheme 3-10	P2′-Benzyl ether phosphonates
Scheme 11-13	P2′-Alkyl ether phosphonates
Scheme 14-17	P2′-Benzyl Amide phosphonates
Scheme 18-25	P1-Phosphonates
Scheme 50	Reagents

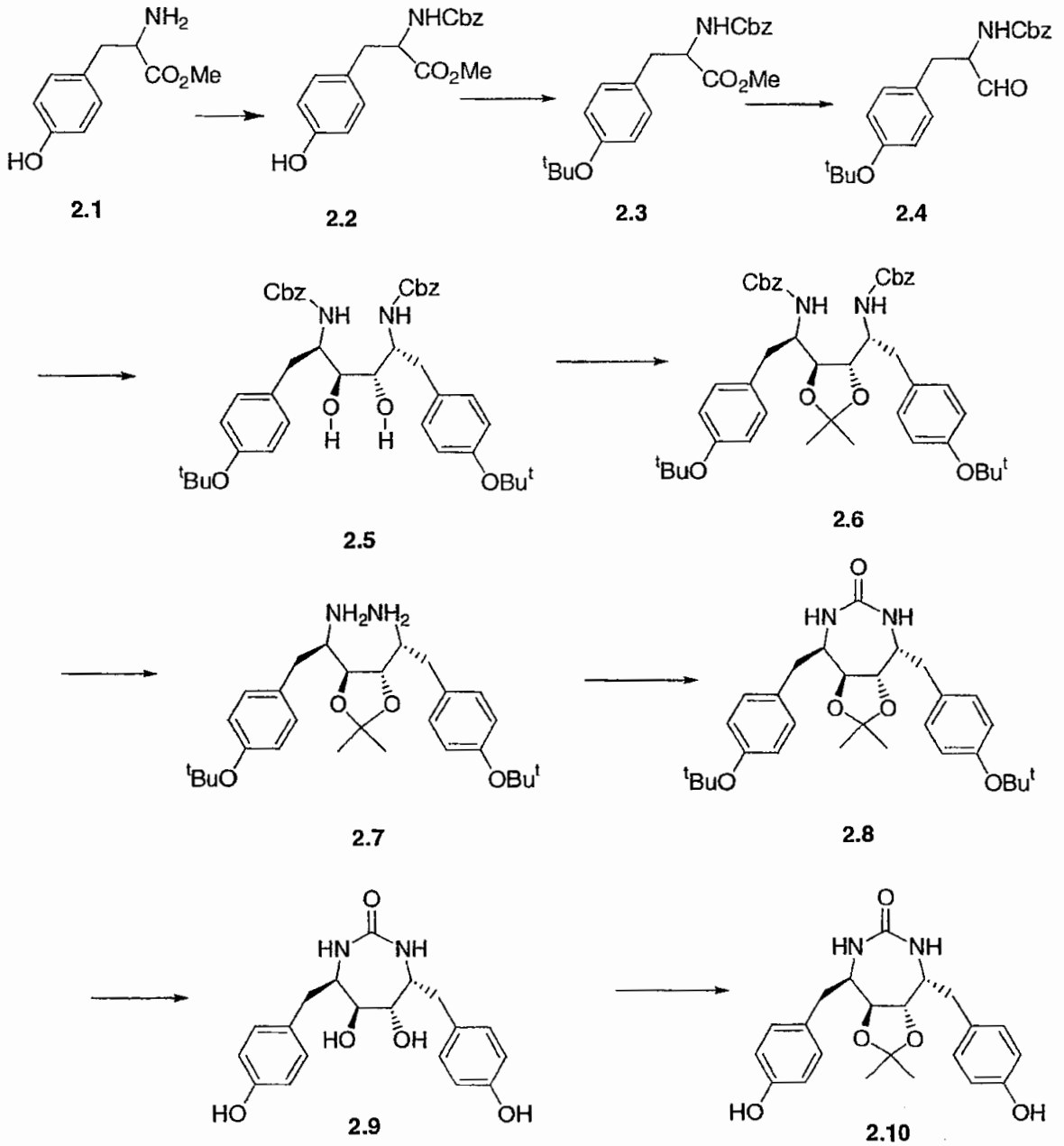
Scheme 1



1 **1.1**

The conversion of **1** to **1.1** is described in J. Org Chem 1996, 61, p444-450

Scheme 2



2-Benzyloxycarbonylamino-3-(4-tert-butoxy-phenyl)-propionic acid methyl ester (2.3)

H-D-Tyr-O-me hydrochloride **2.1** (25 g, 107.7 mmol) is dissolved in methylene chloride (150 mL) and aqueous sodium bicarbonate (22 g in 150 mL water), and then cooled to 0°C. To this resulting solution benzyl chloroformate (20 g, 118 mmol) is slowly added. After complete addition, the resulting solution is warmed to room temperature ,and is then stirred for 2 h. The organic phase is separated, dried over Na_2SO_4, and concentrated under reduced pressure, to give the crude carbamate **2.2** (35g). The crude CBZ-Tyr-OMe product is

dissolved in methylene chloride (300 mL) containing concentrated H_2SO_4. Isobutene is bubbled though the solution for 6 h. The reaction is then cooled to 0°C, and neutralized with saturated $NaHCO_3$ aqueous solution. The organic phase is separated, dried, concentrated under reduced pressure, and purified by silica gel column chromatography to afford the tert-butyl ether **2.3** (25.7 g, 62 %).

[2-(4-tert-Butoxy-phenyl)-1-formyl-ethyl]-carbamic acid benzyl ester (2.4) (Reference J. O. C. 1997, 62, 3884).

To a stirred –78°C methylene chloride solution (60 mL) of **2.3,** DIBAL (82 mL of 1.5 M in toluene, 123 mmol) was added over 15 min. The resultant solution was stirred at –78°C for 30 min. Subsequently, a solution of EtOH/36 % HCl (9/1; 15 mL) is added slowly. The solution is added to a vigorously stirred aqueous HCl solution (600 mL, 1N) at 0°C. The layers are then separated, and the aqueous phase is extracted with cold methylene chloride. The combined organic phases are washed with cold 1N HCl aqueous solution, water, dried over Na_2SO_4, and then concentrated under reduced pressure to give the crude aldehyde **2.4** (20 g, 91 %).

[4-Benzyloxycarbonylamino-1-(4-tert-butoxy-benzyl)-5-(4-tert-butoxy-phenyl)-2,3-dihydroxy-pentyl]-carbamic acid benzyl ester (2.5)

To a slurry of $VCl_3(THF)_3$ in methylene chloride (150 mL) at room temperature is added Zinc powder (2.9 g, 44 mmol), and the resulting solution is then stirred at room temperature for 1 hour. A solution of aldehyde **2.4** (20 g, 56 mmol) in methylene chloride (100 mL) is then added over 10 min. The resulting solution is then stirred at room temperature overnight, poured into an ice-cold H_2SO_4 aqueous solution (8 mL in 200 mL), and stirred at 0°C for 30 min. The methylene chloride solution is separated, washed with 1N HCl until the washing solution is light blue. The organic solution is then concentrated under reduced pressure (solids are formed during concentration), and diluted with hexane. The precipitate is collected and washed thoroughly with a hexane/methylene chloride mixture to give the diol product **2.5**. The filtrate is concentrated under reduced pressure and subjected to silica gel chomatography to afford a further 1.5 g of **2.5**. (Total = 13 g, 65 %).

[1-{5-[1-Benzyloxycarbonylamino-2-(4-tert-butoxy-phenyl)-ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-2-(4-tert-butoxy-phenyl)-ethyl]-carbamic acid benzyl ester (2.6)

Diol **2.5** (5 g, 7 mmol) is dissolved in acetone (120 mL), 2,2-dimethoxypropane (20 mL), and pyridinium p-toluenesulfonate (120 mg, 0.5 mmol). The resulting solution is refluxed for 30 min., and then concentrated under reduced pressure to almost dryness. The resulting mixture is partitioned between methylene chloride and saturated $NaHCO_3$ aqueous solution, dried, concentrated under reduced pressure, and purified by silica gel column chomatography to afford isopropylidene protected diol **2.6** (4.8 g, 92 %).

4,8-Bis-(4-tert-butoxy-benzyl)-2,2-dimethyl-hexahydro-1,3-dioxa-5,7-diaza-azulen-6-one(2.8)

The diol **2.6** is dissolved in EtOAc/EtOH (10 mL/2 mL) in the presence of 10 % Pd/C and hydrogenated at atmospheric pressure to afford the diamino compound **2.7**. To a solution of crude **2.7** in 1,1,2,2-tetrachloroethane is added 1,1-carboxydiimidazole (1.05 g, 6.5 mmol) at room temperature. The mixture is stirred for 10 min, and the resulting solution is then added dropwise to a refluxing 1,1',2,2'-tetrachloroethane solution (150 mL). After 30 min., the reaction mixture is cooled to room temperature, and washed with 5 % citric acid aqueous solution, dried over Na_2SO4, concentrated under reduced pressure, and purified by silica gel column chomatography to afford the cyclourea derivative **2.8** (1.92 g, 60 % over 2 steps).

5,6-Dihydroxy-4,7-bis-(4-hydroxy-benzyl)-[1,3]diazepan-2-one (2.9)

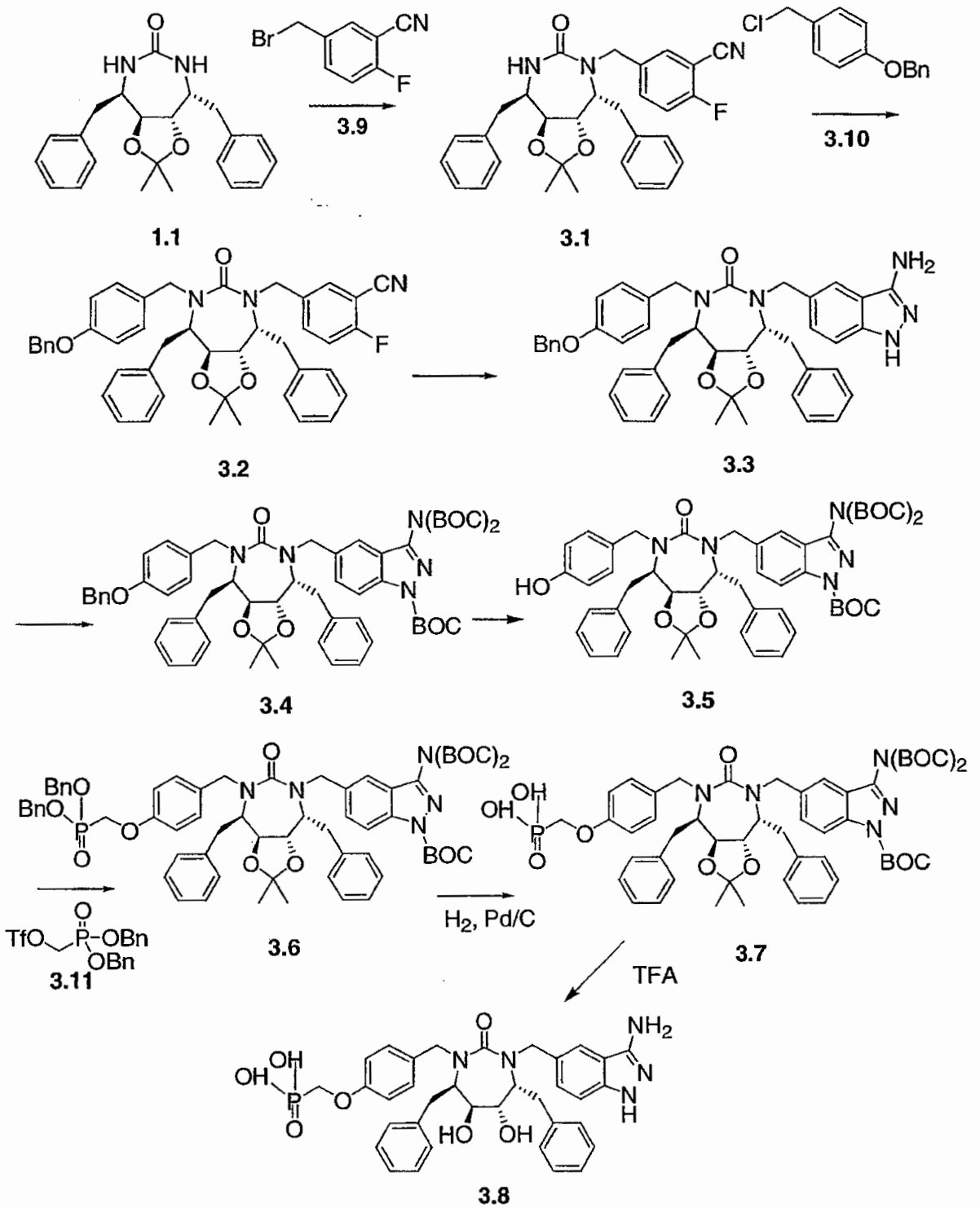
Cyclic Urea **2.8** (0.4 g, 0.78 mmol) was dissolved in dichloromethane (3 mL) and treated with TFA (1 mL). The mixture was stirred at room temperature for 2 h upon which time a white solid precipitated. 2 drops of water and methanol (2 mL) were added and the homogeneous solution was stirred for 1 h and concentrated under reduced pressure. The crude solid, **2.9**, was dried overnight and then used without further purification.

4,8-Bis-(4-hydroxy-benzyl)-2,2-dimethyl-hexahydro-1,3-dioxa-5,7-diaza-azulen-6-one (2.10)

Diol **2.9** (1.8 g, 5.03 mmol) was dissolved in DMF (6 mL) and 2,2-dimethoxypropane (12 mL). P-TsOH (95 mg) was added and the mixture stirred at 65°C for 3 h. A vacuum was applied to remove water and then the mixture was stirred at 65°C for a further 1 h. The excess dimethoxypropane was then distilled and the remaining DMF solution was then

allowed to cool. The solution of acetonide **2.10** can then used without further purification in future reactions.

Scheme 3



3-Cyano-4-fluorobenzyl urea 3.1 : A solution of urea **1.1** (1.6 g, 4.3 mmol) in THF was treated with sodium hydride (0.5 g of 60 % oil dispersion, 13 mmol). The mixture was stirred at room temperature for 30 min and then treated with 3-cyano-4-fluorobenzyl bromide **3.9** (1.0 g, 4.8 mmol). The resultant solution was stirred at room temperature for 3 h, concentrated under reduced pressure, and then partitioned between CH_2Cl_2 and saturated brine solution containing 1 % citric acid. The organic phase was separated , dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 15-25% ethyl acetate in hexanes to yield urea **3.1** (1.5 g, 69 %) as a white form.

Benzyl ether 3.2 : A solution of **3.1** (0.56 g, 1.1 mmol) in DMF (5 mL) was treated with sodium hydride (90 mg of 60 % oil dispersion, 2.2 mmol) and the resultant mixture stirred at room temperature for 30 min. 4-Benzyloxy benzyl chloride **3.10** (0.31 g, 1.3 mmol) was added and the resultant solution stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure and then partitioned between CH_2Cl_2 and saturated brine solution. The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel eluting with 1-10% ethyl acetate in hexanes to yield compound **3.2** (0.52 g, 67 %) as white form.

Indazole 3.3: Benzyl ether **3.2** (0.51 g, 0.73 mmol) was dissolved in n-butanol (10 mL) and treated with hydrazine hydrate (1 g, 20 mmol). The mixture was refluxed for 4 h and then allowed to cool to room temperature. The mixture was concentrated under reduced pressure and the residue was then partitioned between CH_2Cl_2 and 10 % citric acid solution. The organic phase was separated, concentrated under reduced pressure, and then purified by silica gel column eluting with 5% methanol in CH_2Cl_2 to afford indazole **3.3** (0.42 g, 82 %) as white solid.

Boc-indazole 3.4 : A solution of indazole **3.3** (0.4 g, 0.59 mmol) in CH_2Cl_2 (10 mL) was treated with diisopropylethylamine (0.19 g, 1.5 mmol), DMAP (0.18 g, 1.4 mmol), and di-tert-butyl dicarbonate (0.4 g, 2 mmol). The mixture was stirred at room temperature for 3 h and then partitioned between CH_2Cl_2 and 5 % citric acid solution. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The

residue was purified by silica gel eluting with 2% methanol in CH_2Cl_2 to afford **3.4** (0.42 g, 71 %).

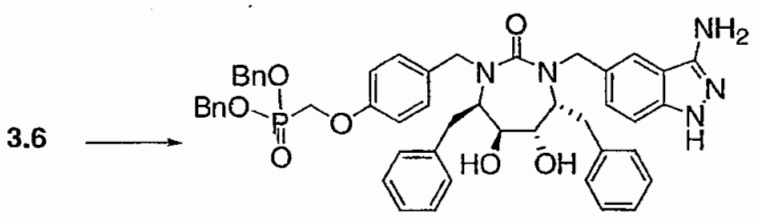
Phenol 3.5 : A solution of **3.4** (300 mg, 0.3 mmol) in ethyl acetate (10 mL) and methanol (10 mL) was treated with 10 % Pd/C (40 mg) and stirred under a hydrogen atmosphere (balloon) for 16 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to yield **3.5** as a white powder. This was used without further purification.

Dibenzyl ester 3.6 : A solution of **3.5** (0.1 mmol) in THF (5 mL) was treated with dibenzyl triflate **3.11** (90 mg, 0.2 mmol), and cesium carbonate (0.19 g, 0.3 mmol). The mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and saturated brine. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 20-40% ethyl acetate in hexanes to afford **3.6** (70 mg, 59 %). ^{1}H NMR ($CDCl_3$): δ 8,07 (d, 1H), 7.20-7.43 (m, 16H), 7.02-7.15 (m, 8 H), 6.80 (d, 2H), 5.07-5.18 (m, 4H), 5.03 (d, 1H), 4.90 (d, 1H), 4.20 (d, 2H), 3.74-3.78 (m, 4H), 3.20 (d, 1H), 3.05 (d, 1H) 2.80-2.97 (m, 4H), 1.79 (s, 9H), 1.40 (s, 18H), 1.26 (s, 6H); ^{31}P NMR ($CDCl_3$): 20.5 ppm.

Phosphonic acid 3.7: A solution of dibenzylphosphonate **3.6** (30 mg) in EtOAc (10 mL) was treated with 10% Pd/C (10 mg) and the mixture was stirred under a hydrogen atmosphere (balloon) for 3 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to afford phosphonic acid **3.7**. This was used without further purification.

Phosphonic acid 3.8: The crude phosphonic acid **3.7** was dissolved in CH_2Cl_2 (2 mL) and treated with trifluoroacetic acid (0.4 mL). The resultant mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure and then purified by preparative HPLC (35 % CH_3CN/65 % H_2O) to afford the phosphonic acid **3.8** (9.4 mg, 55 %). ^{1}H NMR (CD_3OD): δ 7.71 (s, 1H), 7.60 (d, 1H), 6.95-7.40 (m, 15H), 4.65 (d, 2H), 4.17 (d, 2H), 3.50-3.70 (m, 3H), 3.42 (d, 1H), 2.03-3.14 (m, 6H); ^{31}P NMR ($CDCl_3$): 17.30

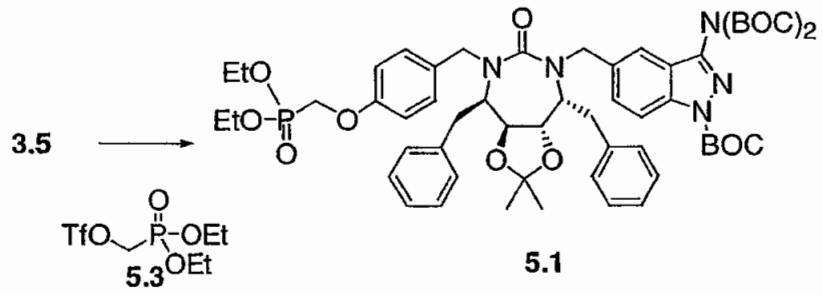
Scheme 4



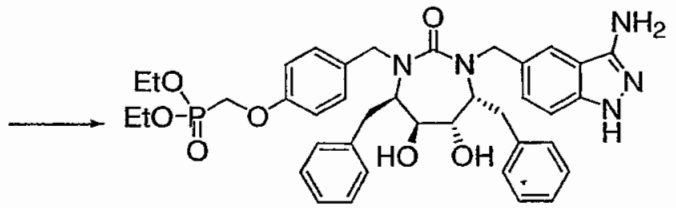
4.1

Dibenzylphosphonate 4.1: A solution of **3.6** (30 mg, 25 μmol) in CH_2Cl_2 (2 mL) was treated with TFA (0.4 mL) and the resultant mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel eluting with 50% ethyl acetate in hexanes to afford **4.1** (5 mg, 24%). ^{1}H NMR ($CDCl_3$): δ 6.96-7.32 (m, 25H), 6.95 (d, 2H), 5.07-5.18 (m, 4H), 4.86 (d, 1H), 4.7 5 (d, 1H), 4.18 (d, 2H), 3.40-3.62 (m, 4H), 3.25 (d, 1H), 2.80-3.15 (m, 6H); ^{31}P NMR ($CDCl_3$) 20.5 ppm; MS : 852 (M + H), 874 (M + Na).

Scheme 5



5.1



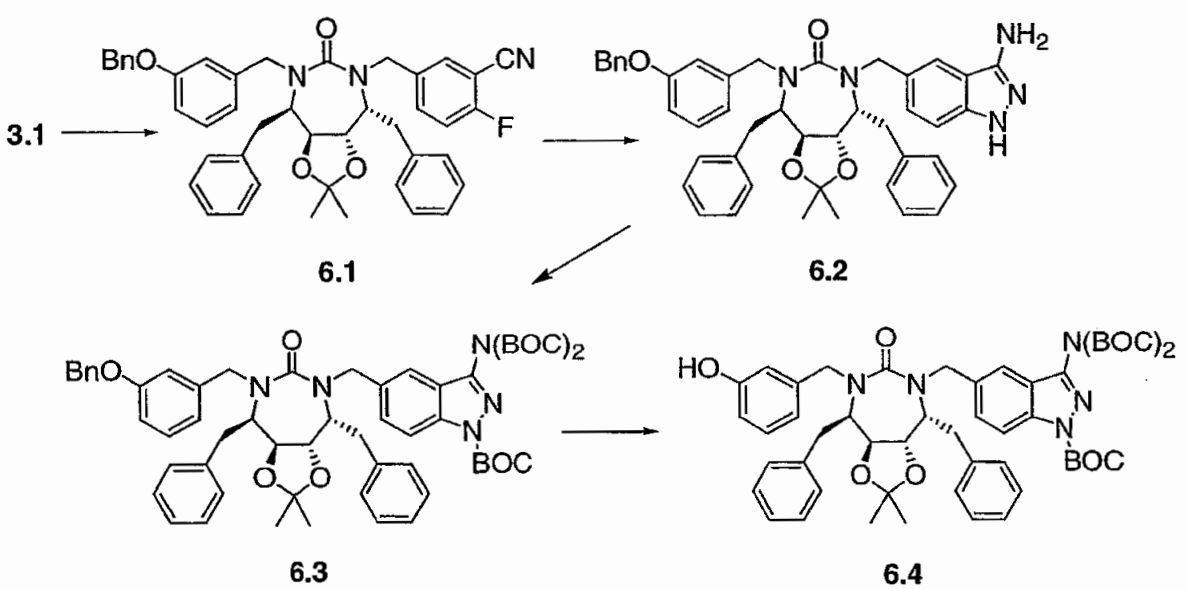
5.2

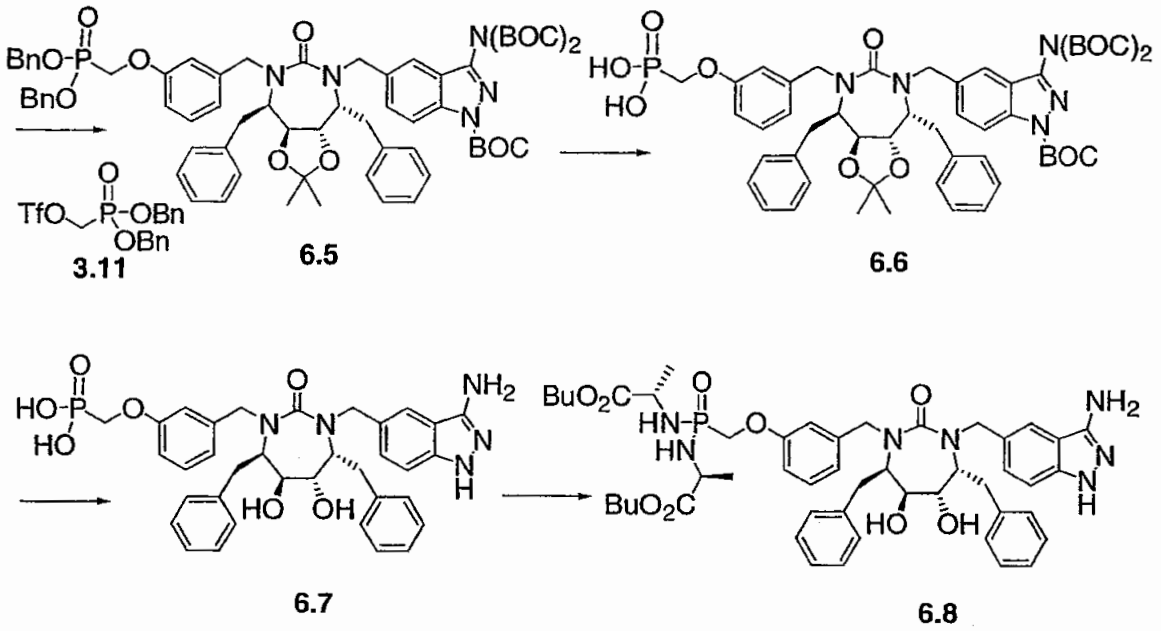
Diethylphosphonate 5.1: A solution of phenol **3.5** (48 mg, 52 μmol) in THF (5 mL) was treated with triflate **5.3** (50 mg, 165 μmol), and cesium carbonate (22 mg, 0.2 mmol). The

resultant mixture was stirred at room temperature for 5 h and then concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and saturated brine. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 7% methanol in CH_2Cl_2 to afford **5.1** (28 mg, 50 %). ^{1}H NMR ($CDCl_3$): δ 8,06 (d, 1H), 7.30-7.43 (m, 7H), 7.02-7.30 (m, 7 H), 6.88 (d, 2H), 5.03 (d, 1H), 4.90 (d, 1H), 4.10-4.25 (m, 6H), 3.64-3.80 (m, 4H), 3.20 (d, 1H), 3.05 (d, 1H) 2.80-2.97 (m, 4H), 1.79 (s, 9H), 1.20-1.50 (m, 30H); ^{31}P NMR ($CDCl_3$): 18.5 ppm; MS :1068 (M + H), 1090 (M + Na).

Diethylphosphonate 5.2: A solution of **5.1** (28 mg, 26 μmol) in CH_2Cl_2 (2 mL) was treated with TFA (0.4 mL) and the resultant mixture was stirred at room temperature for 4 hrs. The mixture was concentrated under reduced pressure and the residue was purified by silica gel to afford **5.2** (11 mg, 55 %). ^{1}H NMR ($CDCl_3$ + 10 % CD_3OD): δ 6.96-7.35 (m, 15H), 6.82 (d, 2H), 4.86(d, 1H), 4.75 (d, 1H), 4.10-4.23 (M, 6H), 3.40-3.62 (m, 4H), 2.80-3.20 (m), 1.31 (t, 6 H); ^{31}P NMR ($CDCl_3$ + 10 % CD_3OD): 19.80 ppm; MS : 728 (M + H).

Scheme 6





3-Benzyloxybenzyl urea 6.1 : The urea **3.1** (0.87 g, 1.7 mmol) was dissolved in DMF and treated with sodium hydride (60% dispersion, 239 mg, 6.0 mmol) followed by m-benzyloxybenzylbromide **6.9** (0.60 g, 2.15 mmol). The mixture was stirred for 5 h and then diluted with ethyl acetate. The solution was washed with water, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 25% ethyl acetate in hexanes to afford urea **6.1** (0.9 g, 75%).

Indazole 6.2: The urea **6.1** (41 mg, 59 μmol) was dissolved in n-butanol (1.5 mL) and treated with hydrazine hydrate (100 μL, 100 mmol). The mixture was refluxed for 2 h and then allowed to cool. The mixture was diluted with ethyl acetate, washed with 10% citric acid solution, brine, saturated $NaHCO_3$, and finally brine again. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure to give the crude product **6.2** (35 mg, 83%). (Chem. Biol. 1998, 5, 597-608).

Boc-indazole 6.3 : The indazole **6.2** (1.04 g, 1.47 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with di-t-butyl dicarbonate (1.28 g, 5.9 mmol), DMAP (0.18 g, 1.9 mmol) and DIPEA (1.02 ml, 9.9 mmol). The mixture was stirred for 3 h and then diluted with ethyl acetate. The solution was washed with 5% citric acid solution, $NaHCO_3$, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 50% ethyl acetate in hexanes to give **6.3** (0.71 g, 49%).

Phenol 6.4 : Compound **6.3** (20 mg, 0.021 mmol) was dissolved in MeOH (1 mL) and EtOAc (1 mL) and treated with 10% Pd/ C catalyst (5 mg). The mixture was stirred under a hydrogen atmosphere (balloon) until completion. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure to afford compound **6.4** (19 mg, 100%).

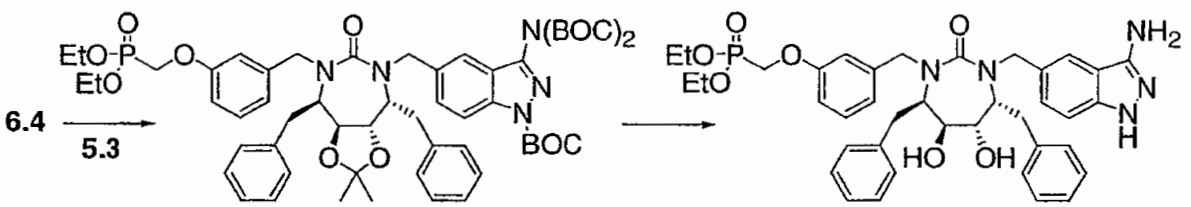
Dibenzyl phosphonate 6.5: A solution of compound **6.4** (0.34 g, 0.37 mmol) in acetonitrile (5 mL) was treated with Cs_2CO_3 (0.36 g, 1.1 mmol) and triflate **3.11** (0.18 mL, 0.52 mmol). The reaction mixture was stirred for 1 h. The reaction mixture was filtered and the filtrate was then concentrated under reduced pressure. The residue was re-dissolved in EtOAc, washed with water, saturated $NaHCO_3$, and finally brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with hexane: EtOAc (1:1) to afford compound **6.5** (0.32 g, 73%).

Phosphonic acid 6.6: Compound **6.5** (208 mg, 0.174 mmol) was treated in the same manner as benzyl phosphonate **3.6** in the preparation of phosphonate diacid **3.7**, except MeOH was used as the solvent, to afford compound **6.6** (166 mg, 94%).

Phosphonic acid 6.7: Compound **6.6** (89 mg, 0.088 mmol) was treated according to the conditions described in Scheme 3 for the conversion of **3.7** into **3.8**. The residue was purified by preparative HPLC eluting with a gradient of 90% methanol in 100 mM TEA bicarbonate buffer and 100% TEA bicarbonate buffer to afford phosphonic acid **6.7** (16 mg, 27%)

Bisamidate 6.8 : Triphenylphosphine (112 mg, 0.43 mmol) and aldrithiol-2 (95 mg, 0.43 mmol) were mixed in dry pyridine (0.5 mL). In an adjacent flask the diacid **6.7** (48 mg, 0.71 mmol) was suspended in dry pyridine (0.5 mL) and treated with DIPEA (0.075 mL 0.43 mmol) and L-AlaButyl ester hydrochloride (78 mg, 0.43 mmol) and finally the triphenylphosphine, aldrithiol-2 mixture. The reaction mixture was stirred under nitrogen for 24 h then concentrated under reduced pressure. The residue was purified by preparative HPLC eluting with a gradient of 5% to 95% acetonitrile in water. The product obtained was then further purified by silica gel eluting with CH_2Cl_2 : MeOH (9:1) to give compound **6.8** (9 mg, 14%).

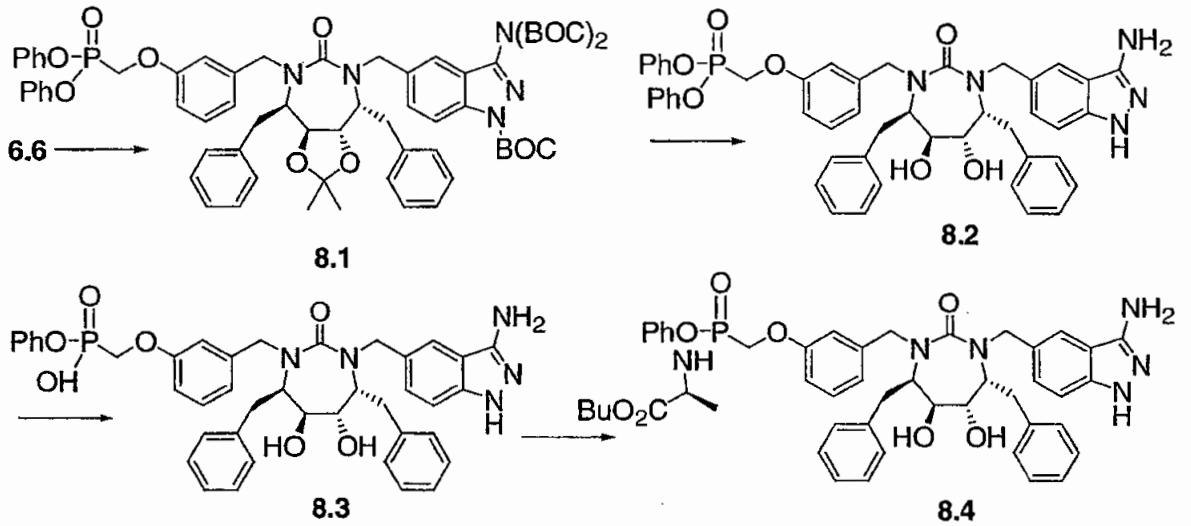
Scheme 7



Diethyl phosphonate 7.1 : Compound **6.4** (164 mg, 0.179 mmol) was treated according to the procedure used to generate compound **6.5** except triflate **5.3** was used in place of triflate **3.11** to afford compound **7.1** (142 mg, 74%).

Diethylphosphonate 7.2 : Compound **7.1** (57 mg, 0.053 mmol) was treated according to the conditions used to form **6.7** from **6.6**. The residue formed was purified by silica gel eluting with CH_2Cl_2 : MeOH (9:1) to afford compound **7.2** (13 mg, 33%).

Scheme 8



Diphenylphosphonate 8.1: A solution of **6.6** (0.67g, 0.66 mmol) in pyridine (10 mL) was treated with phenol (0.62 g, 6.6 mmol) and DCC (0.82 mg, 3.9 mmol). The resultant mixture was stirred at room temperature for 5 min and then the solution was heated at 70°C for 3 h. The mixture was allowed to cool to room temperature and then diluted with EtOAc and water

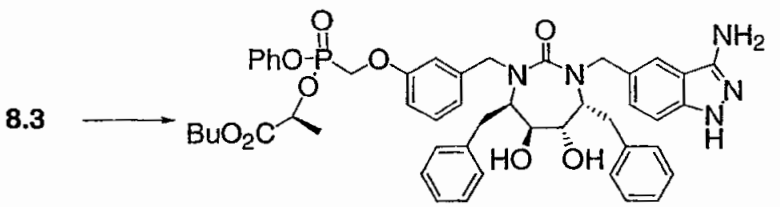
(2 mL). The resultant mixture was stirred at room temperature for 30 min and then concentrated under reduced pressure. The residue was triturated with CH_2Cl_2, and the white solid that formed was removed by filtration. The filtrate was concentrated under reduced pressure and the resultant residue was purified by silica gel eluting with 30% ethyl acetate in hexanes to yield **8.1** (0.5 g, 65 %). ^{1}H NMR ($CDCl_3$): δ 8,08 (d, 1H), 7.41 (d, 1H), 7.05-7.35 (m, 22H), 6.85 (d, 2H), 6.70 (s, 1H). 5.19 (d, 1H), 5.10 (d, 1H), 4.70 (d, 2H), 3.70-3.90 (m, 4H), 3.20 (d, 1H), 3.11 (d, 1H), 2.80-2.97 (m, 4H), 1.79 (s, 9H), 1.40 (s, 18H), 1.30 (s, 6H); ^{31}P NMR ($CDCl_3$): 12.43 ppm

Diphenylphosphonate 8.2 : A solution of **8.1** (0.5 g, 0.42 mmol) in CH_2Cl_2 (4 mL) was treated with TFA (1 mL) and the resultant mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and azeotroped twice with CH_3CN. The residue was purified by silica gel eluting with 5% methanol in CH_2Cl_2 to afford diphenylphosphonate **8.2** (0.25 g, 71 %). ^{1}H NMR ($CDCl_3$): δ 7.03-7.40 (m, 21H), 6.81-6.90 (m, 3H), 4.96 (d, 1H), 4.90 (d, 1H) 4.60-4.70 (m, 2H), 3.43-3.57 (m, 4H), 3.20 (d, 1H), 2.80-2.97 (m, 5H); ^{31}P NMR ($CDCl_3$): 12.13 ppm; MS : 824 (M + H).

Monophenol 8.3 : The monophenol **8.3** (124 mg, 68 %) was prepared from the diphenol **8.2** by treating with 1N NaOH in acetonitrile at 0°C.

Monoamidate 8.4 : To a pyridine solution (0.5 mL) of **8.3** (40 mg, 53 μmol), n-butyl amidate HCl salt (116 mg, 640 μmol), and DIPEA (83 mg, 640 μmol) was added a pyridine solution (0.5 mL) of triphenyl phosphine (140 mg, 640 μmol), and aldrithiol-2 (120 mg, 640 μmol). The resulting solution was stirred at 65°C overnight, worked up, and purified by preparative TLC twice to give **8.4** (1.8 mg). δ 4.96 (d, 1H), 4.90 (d, 1H) 4.30-4.6 (m, 2H), 3.9-4.2 (m, 2H), 3.6-3.70 (m, 4H), 3.2-3.3 (d, 1H), 2.80-3.1 (m, 4H); MS: 875 (M + H) & 897 (M + Na)

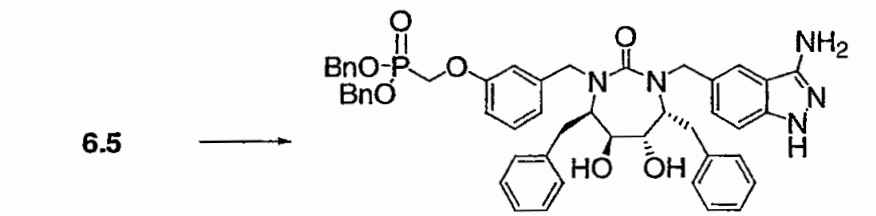
Scheme 9



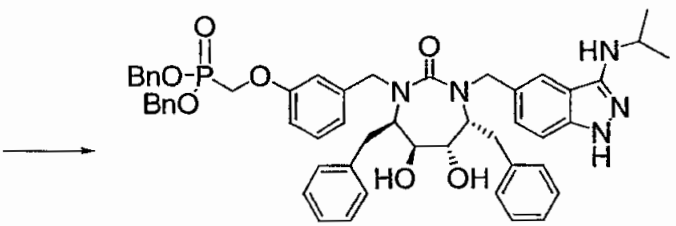
9.1

Monolactate **9.1**: The monolactate **9.1** is prepared from **8.3** using the conditions described above for the preparation of the monoamidate **8.4** except n-butyl lactate was used in place of n-butyl amidate HCl salt.

Scheme 10



10.1

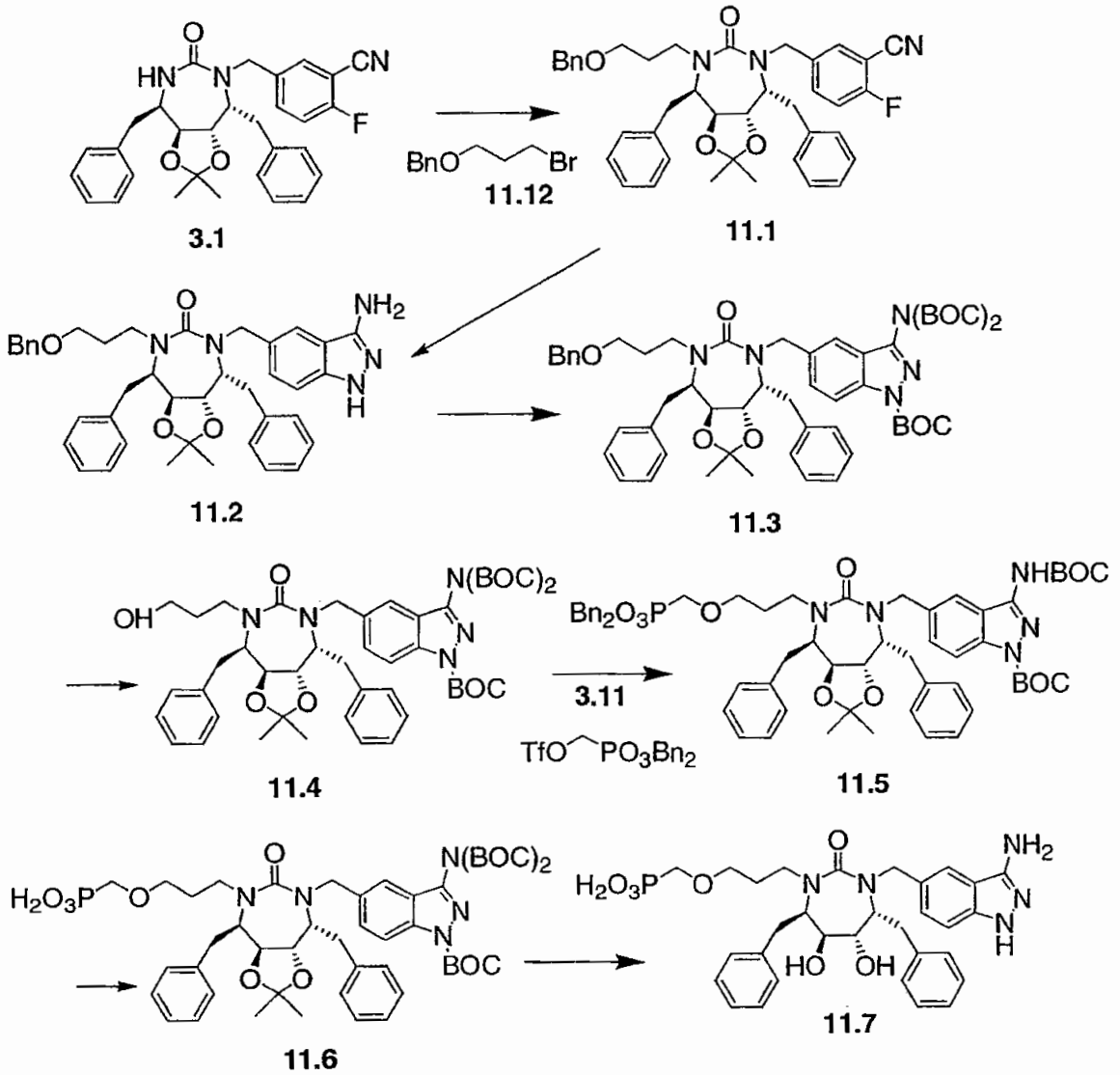


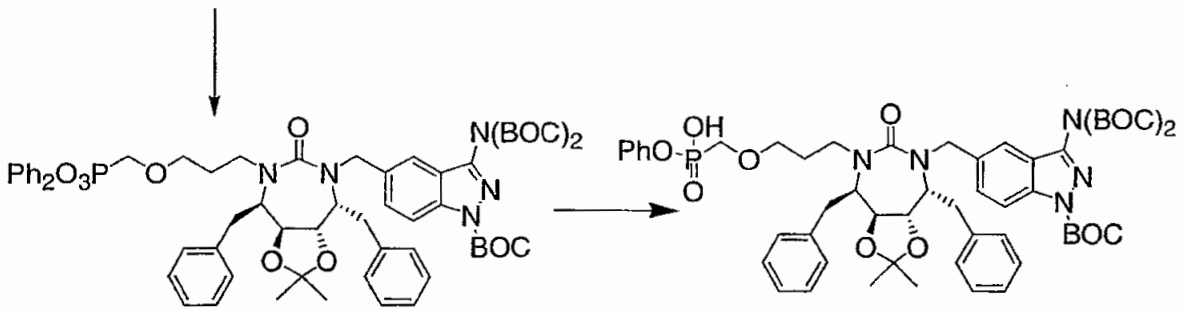
10.2

Dibenzylphosphonate 10.1: Compound **6.5** (16 mg, 0.014 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C. TFA (1 mL) was added and the reaction mixture was stirred for 0.5 h. The mixture was then allowed to warm to room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and azeotroped with toluene. The residue was purified by silica gel eluting with CH_2Cl_2 : MeOH (9:1) to afford compound **10.1** (4 mg, 32%).

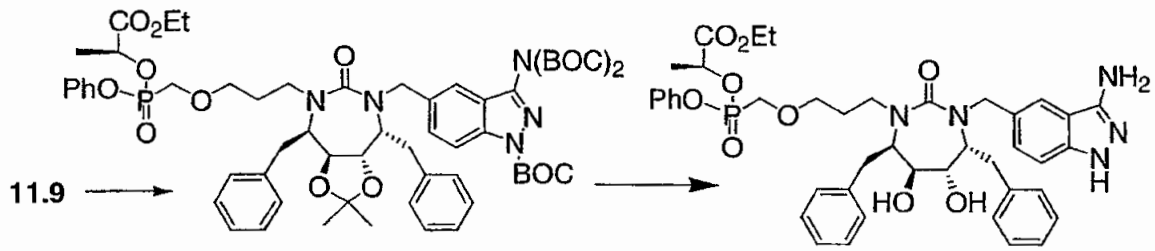
Isopropylamino indazole 10.2 : Compound **10.1** (30 mg, 0.35 mmol) was treated with acetone according to the method of Henke et al. (J. Med Chem. 40 17 (1997) 2706-2725) to yield **10.2** as a crude residue. The residue was purified by silica gel eluting with CH_2Cl_2 : MeOH (93:7) to afford compound **10.2** (3.4 mg, 10%).

Scheme 11

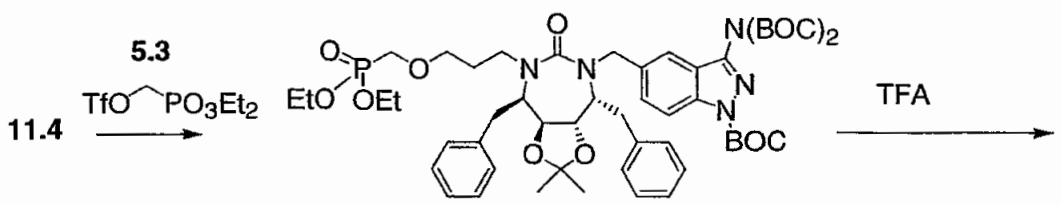




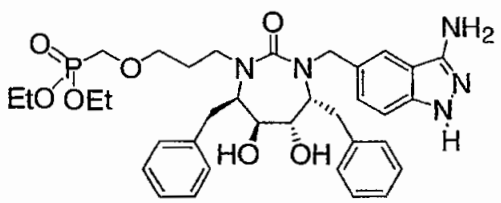
11.8 11.9



11.10 11.11



11.12



11.13

Benzyl ether 11.1: A DMF solution (5 mL) of **3.1** (0.98 g, 1.96 mmol) was treated with NaH (0.24 g of 60 % oil dispersion, 6 mmol) for 30 min, followed by the addition of sodium iodide (0.3 g, 2 mmol), and benzoxypropyl bromide (0.55 g, 2.4 mmol). After the reaction for 3 h at room temperature, the reaction mixture was partitioned between methylene chloride and saturated NaCl, dried, and purified to give **11.1** (0.62 g, 49 %).

Aminoindazole 11.2: A n-butanol solution (10 mL) of **11.1** (0.6 g, 0.92 mmol) and hydrazine hydrate (0.93 g, 15.5 mmol) was heated at reflux for 4 h. The reaction mixture was concentrated under reduced pressure to give crude **11.2** (~0.6 g).

Tri-BOC-Aminoindazole 11.3: A methylene chloride solution (10 mL) of crude **11.2**, DIPEA (0.36 g, 2.8 mmol), $(BOC)_2O$ (0.73 g, 3.3 mmol), and DMAP (0.34 g, 2.8 mmol) was stirred for 5 h at room temperature, partitioned between methylene chloride and 5 % citric acid solution, dried, purified by silica gel column chomatography to give **11.3** (0.51 g, 58 %, 2 steps).

3-Hydroxypropyl cyclic urea 11.4: An ethyl acetate/ethanol solution (30 mL/5 mL) of **11.3** (0.5 g, 0.52 mmol) was hydrogenated at 1 atm in the presence of 10 % Pd/C (0.2 g) for 4 h. The catalyst was removed by filtration. The filtrate was then concentrated under reduced pressure to afford crude **11.4** (0.44 g, 98 %).

Dibenzyl phosphonate 11.5: A THF solution (3 mL) of **11.4** (0.5 g, 0.57 mmol) and triflate dibenzyl phosphonate **3.11** (0.37 g, 0.86 mmol) was cooled to –3°C, followed by addition of n-BuLi (0.7 mL of 2.5 M hexane solution, 1.7 mmol). After 2 h reaction, the reaction mixture was partitioned between methylene chloride and saturated NaCl solution, concentrated under reduced pressure. The residue was redissolved in methylene chloride (10 mL), and reacted with $(BOC)_2O$ (0.15 g, 0.7 mmol) in the presence of DMAP (0.18 g, 0.57 mmol), DIPEA (0.18 g, 1.38 mmol) for 2 h at room temperature. The reaction mixture was worked up, and purified by silica gel chromatography to give **11.5** (0.25 g, 43 %).

Phosphonic diacid 11.7: An ethyl acetate solution (2 mL) of **11.5A** (11 mg, 10.5 μmol) was hydrogenated at 1 atm in the presence of 10% Pd/C (10 mg) for 6 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give crude **11.6**. The crude **11.6** was redissolved in methylene chloride (1 mL) and treated with TFA (0.2 mL) for 4 h at room temperature. The reaction mixture was concentrated under reduced pressure and purified by HPLC to give **11.7** (2 mg, 30%).
NMR (CD_3OD): δ 7.1-7.3 (m, 11H), 7.0-7.1 (d, 2H), 4.95 (d, 1H), 3.95-4.1 (d, 1H), 2.9 -3.3 (m, 4H), 2.3-2.45 (m, 1H), 1.6-1.8 (m, 2H). P NMR (CD_3OD):15.5 ppm. MS: 624 (M + 1).

Diphenyl phosphonate 11.8: A pyridine solution (1 mL) of **11.6** (0.23 g, 0.23 mmol), phenol (0.27 g, 2.8 mmol), and DCC (0.3 g, 1.4 mmol) was stirred for 5 min. at room temperature, then reacted at 70°C for 3 h. The reaction mixture was cooled to room

temperature, concentrated under reduced pressure, and purified by silica gel column chromatograph to afford **11.8** (0.11g, 41 %).

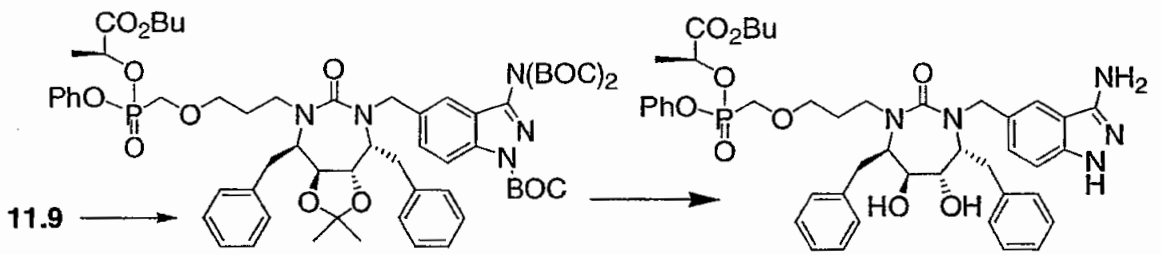
Monophenyl phosphonate 11.9: An acetonitrile solution (2 mL) of **11.8** (0.12 g, 0.107 mmol) at 0°C was treated with 1N sodium hydroxide aqueous solution (0.2 mL) for 1.5 h., then acidified with Dowex (50wx8-200, 120 mg). The Dowex was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was triturated with 10 % EtOAc/90 % hexane twice to afford **11.9** (90 mg, 76 %) as a white solid .

Mono-ethyl lactate phosphonate 11.10: A pyridine solution (0.3 mL) of **11.9** (33 mg, 30 μmol), ethyl lactate (41 mg, 340 μmol), and DCC (31 mg, 146 μmol) was stirred at room temperature for 5 min, then reacted at 70°C for 1.5 h. The reaction mixture was concentrated under reduced pressure, partitioned between methylene chloride and saturated NaCl solution, and purified by silica gel chromatography to give **11.10** (18 mg, 50 %).

Ethyl lactate phosphonate 11.11: A methylene chloride solution (0.8 mL) of **11.10** (18 mg, 15.8 μmol) was treated with TFA (0.2 mL) for 4 h, and then concentrated under reduced pressure. The residue was purified by preparative TLC to give **11.11** (6 mg, 50 %). NMR ($CDCl_3$ + ~10 %CD_3OD): δ 7.0-7.3 (m, 16 H), 6.8-7.0 (m, 2H), 4.9-5.0 (m, 1H), 4.75 (d, 1H), 4.1-4.2 (m, 2H). 3.5-4.0 (m, 10H), 2.18-2.3. (m, 1H), 1.6-1.7 (m, 1), 1.47 & 1.41 (2d, 3H), 1.22 (t, 3H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 19.72 & 17.86 ppm.

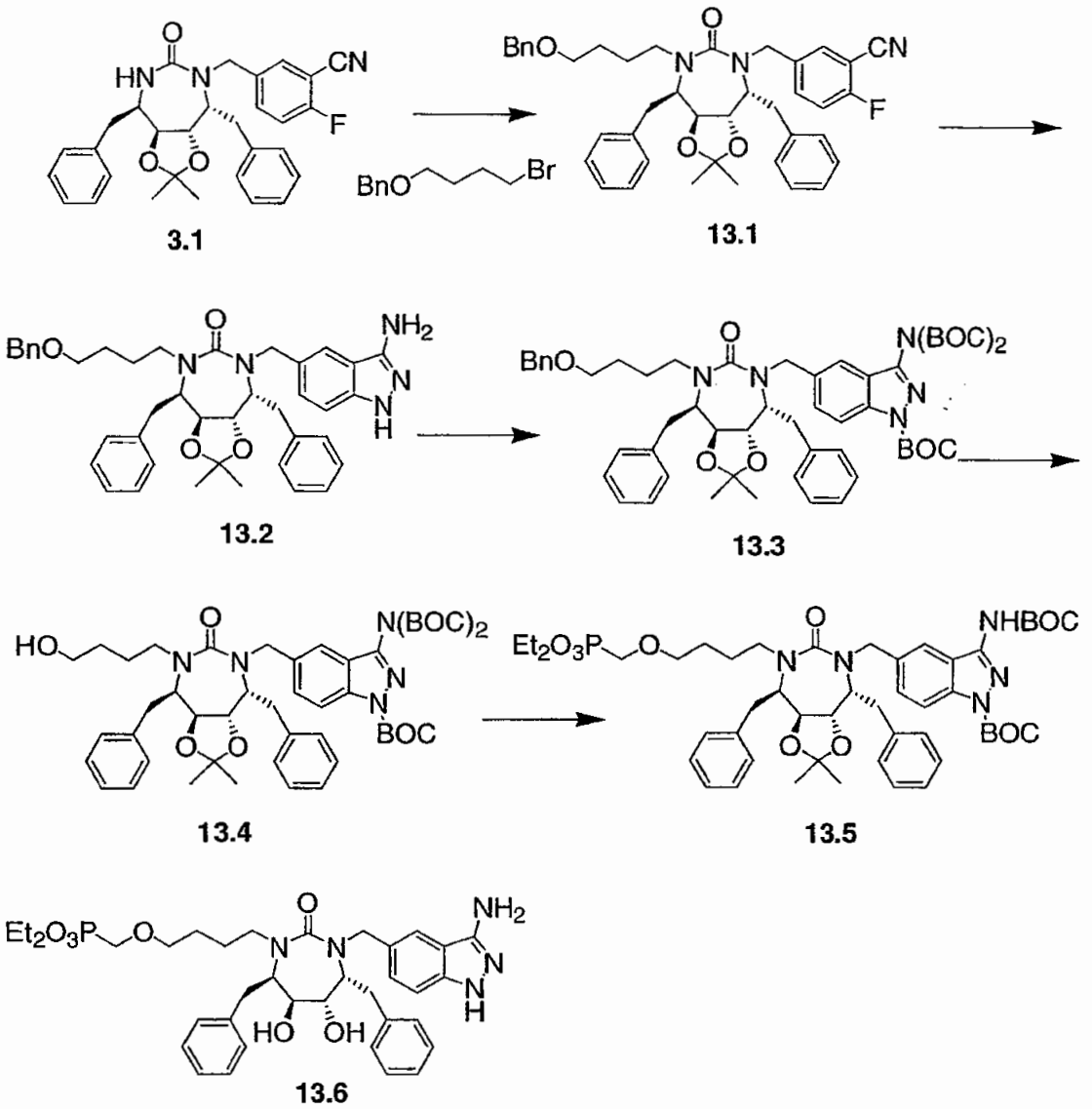
Diethyl phosphonate 11.13: Compound **11.13** (6 mg) was prepared as described above in Scheme 5 from **11.4** (30 mg, 34 μmol) and triflate phosphonate **5.3** (52 mg, 172 μmol), followed by TFA treatment. NMR ($CDCl_3$ + ~10 %CD_3OD): δ 7.1-7.32 (m, 11 H), 6.9-7.0 (d, 2H), 4.75 (d, 1H), 4.1-4.2 (2q, 4H), 3.84-3.9 (m, 1H), 3.4-3.8 (m, 8H), 2.7-3.1 (m, 4H), 2.1-2.5 (m, 1H), 1.5-1.7 (m, 2H), 1.25-1.35 (2t, 6H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 21.63 ppm. MS: 680 (M + 1).

Scheme 12



Butyl lactate phosphonate 12.2: A pyridine solution (0.3 mL) of **11.9** (27 mg, 22 μmol), butyl lactate (31 mg, 265 μmol), and DCC (28 mg, 132 μmol) was stirred at room temperature for 5 min, then reacted at 70°C for 1.5 h. The reaction mixture was concentrated under reduced pressure, partitioned between methylene chloride and saturated NaCl solution, and purified by preparative TLC to give **12.1** (12 mg). A methylene chloride solution (0.8 mL) of **12.1** (12 mg) was treated with TFA (0.2 mL) for 4 h, concentrate. The residue was purified by preparative TLC to give **12.2** (3 mg, 16 %). NMR ($CDCl_3$ + ~10 %CD_3OD): δ 6.8-7.4 (m, 18H), 6.4-6.6 (m), 4.9-5.05 (m, 1H), 4.75 (d, 1H), 4.1-4.2 (m, 2H). 3.5-4.0 (m, 10H), 3.1-3.25 (m, 2H), 2.2-2.35 (m, 1H), 1.8-1.9 (m, 1H), 1.4 & 1.8 (m, 7H), 1.22 (t, 3H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 19.69 & 17.86 ppm.

Scheme 13



Benzyl ether 13.1: A DMF solution (5 mL) of **3.1** (1 g, 2 mmol) was treated with NaH (0.24 g of 60% oil dispersion, 6 mmol) for 30 min, followed by the addition of sodium iodide (0.3 g, 2 mmol),and benzoxybutyl bromide (0.58 g, 2.4 mmol). After the reaction for 5 h at room temperature, the reaction mixture was partitioned between methylene chloride and saturated NaCl, dried, and purified to give **13.1** (0.58 g, 44 %).

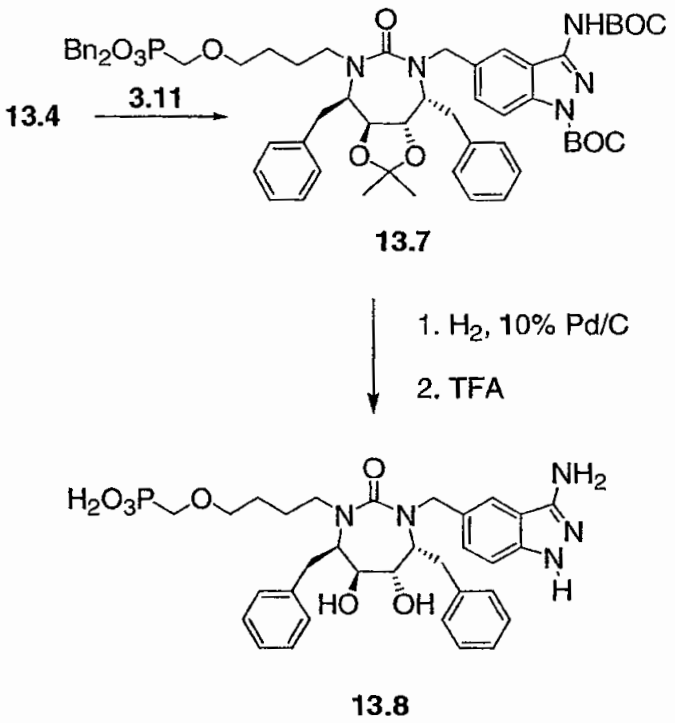
Aminoindazole 13.2: A n-butanol solution (10 mL) of **11.1** (0.58 g, 0.87 mmol) and hydrazine hydrate (0.88 g, 17.5 mmol) was heated at reflux for 4 h. The reaction mixture was concentrated under reduced pressure to give crude **13.2** (0.56 g).

Tri-BOC-aminoindazole 13.3: A methylene chloride solution (10 mL) of **13.2** (0.55 g, 0.82 mmol), DIPEA (0.42 g, 3.2 mmol), $(BOC)_2O$ (0.71 g, 3.2 mmol), and DMAP (0.3 g, 2.4 mmol) was stirred for 4 h at room temperature, partitioned between methylene chloride and 5% citric acid solution, dried, purified by silica gel chromatography to give **13.3** (0.56 g, 71 %, 2 steps).

3-Hydroxybutyl cyclic urea 13.4: An ethyl acetate/methanol solution (30 mL/5 mL) of **11.3** (0.55 g, 0.56 mmol) was hydrogenated at 1 atm in the presence of 10% Pd/C (0.2 g) for 3 h. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure to afford crude **13.4** (0.5 g, 98 %).

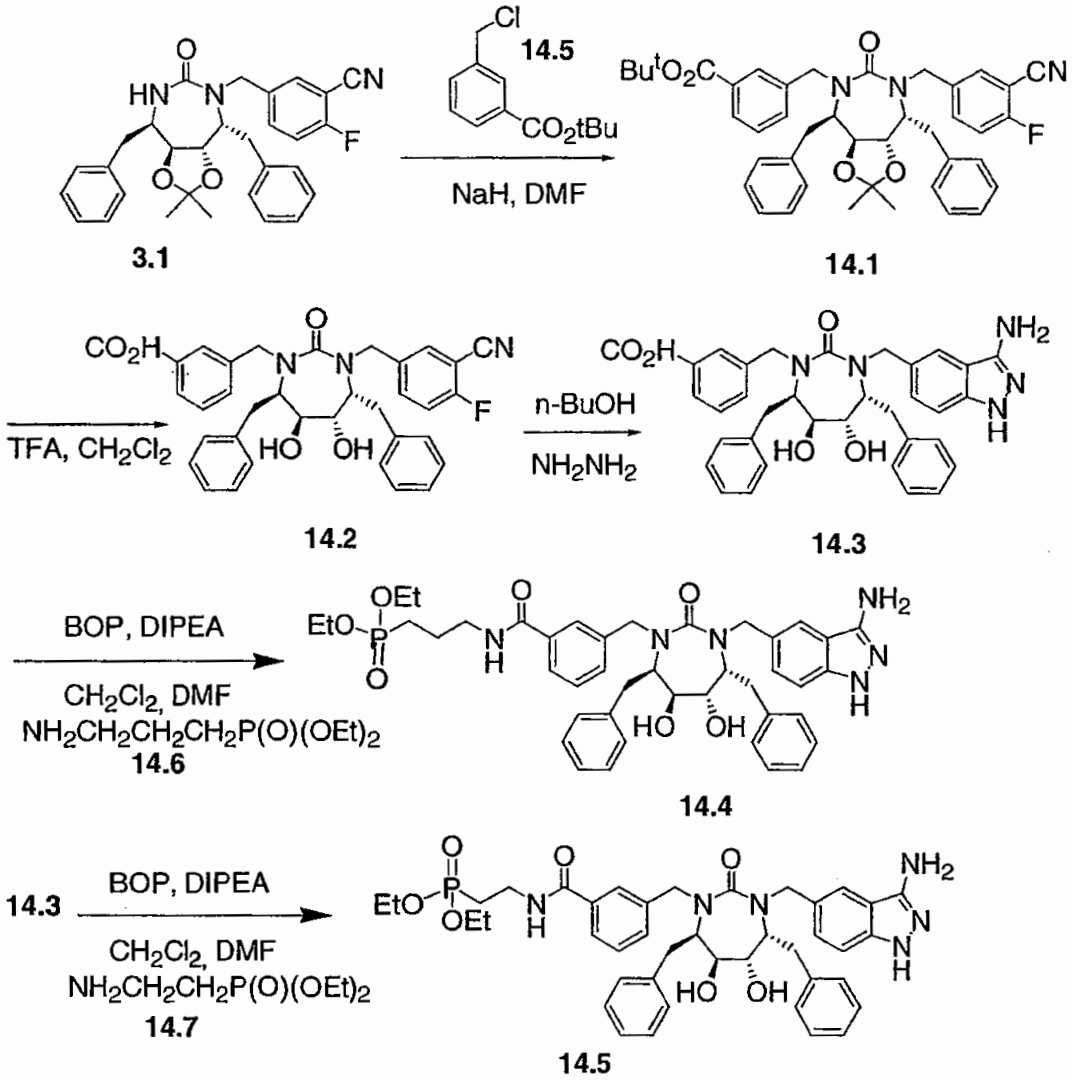
Diethyl phosphonate 13.6: A THF solution (1 mL) of **13.4** (5 mg, 56 μmol) and triflate diethyl phosphonate **5.3** (30 mg, 100 μmol) was cooled to –3°C, followed by addition of n-BuLi (80 μl of 2.5 M hexane solution, 200 μmol). After 2 h reaction, the reaction mixture was partitioned between methylene chloride and saturated NaCl solution, concentrated under reduced pressure to give crude **13.5**. The residue was dissolved in methylene chloride (0.8 mL) and treated with TFA (0.2 mL) for 4 h. concentrated under reduced pressure, and purified by HPLC to give **13.6** (8 mg, 21%). NMR ($CDCl_3$): δ 7.1-7.4 (m, 11H), 7.0-7.1 (m, 2H) 4.81 (d, 1H), 4.1-4.25 (m, 4H). 3.85-3.95 (m, 1H), 3.4-3.8 (m, 7H), 3.3-3.4 (m, 1H), 2.8 - 3.25 (m, 5H), 2.0-2.15 (m, 1H), 1.3-1.85 (m, 10H). P NMR ($CDCl_3$): 21.45 ppm.

Scheme 13a



Phosphonic diacid 13.8: Compound **13.8** (4.5 mg) was prepared from **13.4** as described above for the preparation of **11.7** from **11.4** (Scheme 11). NMR (CD_3OD): δ 7.41 (s, 1H), 7.1-7.4 (m, 10H), 6.9-7.0 (m, 2H) 4.75 (d, 1H), 3.8-4.0 (m, 1H). 3.4-3.8 (m, 8H), 2.8 -3.25 (m, 5H), 2.1-2.25 (m, 1H), 1.6-1.85 (m, 4H). MS: 638 (M + 1).

Scheme 14



t-Butyl ester 14.1: A DMF solution (3 mL) of **3.1** (0.5 g, 1 mmol) was treated with NaH (80 mg of 60% oil dispersion, 2 mmol) for 10 min, followed by the addition of **14.5** (0.25 g, 1.1 mmol). After the reaction for 1 h at room temperature, the reaction mixture was partitioned between methylene chloride and saturated NaCl, dried, and purified to give **14.1** (0.4 g, 59%).

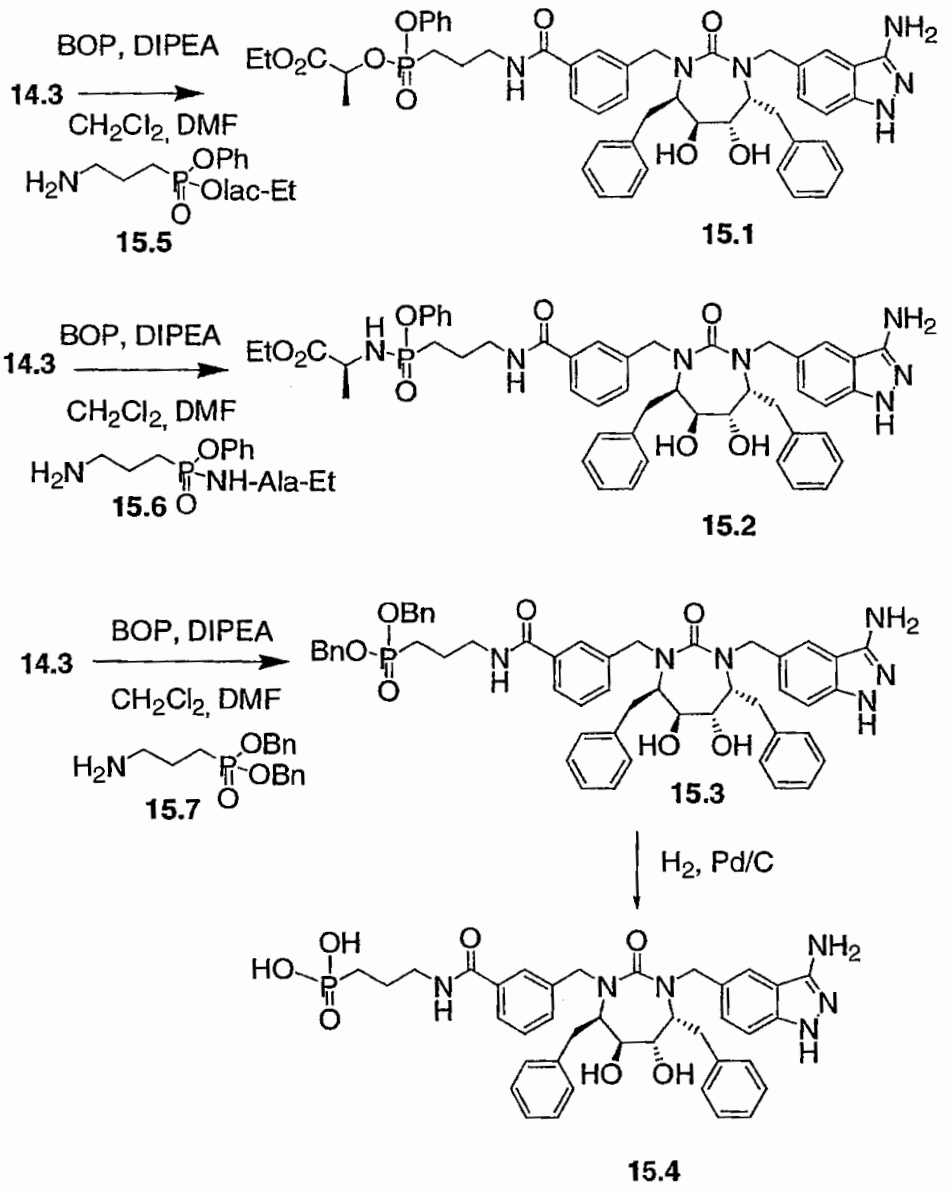
Aminoindazole derivative 14.3: A methylene chloride solution (5 mL) of **14.1** (0.4 g, 0.58 mmol) was treated with TFA (1 mL) at room temperature for 1.5 h, and then concentrated under reduced pressure to give crude **14.2**. The crude **14.2** was dissolved in n-BuOH (5 mL) and reacted with hydrazine hydrate (0.58 g, 11.6 mmol) at reflux for 5 h. The reaction

mixture was concentrated under reduced pressure and purified by silica gel chromatography to give the desired product **14.3** (0.37 g, quantitative yield).

Diethylphosphonate ester 14.4: A methylene chloride solution (3 mL) of **14.3** (23 mg, 38 μmol) was reacted with aminopropyl-diethylphosphonate **14.6** (58 mg, 190 μmol), DIPEA (50 mg, 380 μmol), and ByBOP (21 mg, 48 μmol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was triturated with methylene chloride/hexane. The solid was purified by preparative TLC to give **14.4** (9 mg, 34 %). NMR ($CDCl_3$ + ~10 %CD_3O): δ 7.87 (t, 1H), 7.61 (b, 1H), 7.51 (s, 1H), 7.14-7.2 (m, 10 H), 6.93-7.0 (m, 4H), 4.79 (d, 2H), 3.99-4.04 (m, 4H), 3.38-3.65 (m, 6H), 2.60-3.2 (m, 6 H), 1.70-1.87 (m, 4H), 1.25 (t, 6H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 32.7 ppm.

Diethylphosphonate ester 14.5: A methylene chloride solution (2 mL) of **14.3** (13 mg, 21 μmol) was reacted with aminoethyl-diethylphosphonate oxalate **14.7** (23mg, 85 μmol), DIPEA (22 mg, 170 μmol), and ByBOP (12 mg, 25 μmol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was triturated with methylene chloride/hexane. The solid was purified by preparative TLC to give 14.5 (5mg, 30%). Ms: 783 (M + 1). NMR ($CDCl_3$ + ~10 %CD_3O): δ 7.88 (b, 1H), 7.58 (b, 1H), 7.49 (s, 1H), 7.14-7.2 (m, 10 H), 6.90-7.0 (m, 4H), 4.75 (d, 2H), 3.90-4.04 (m, 4H), 2.50-3.3 (m, 6 H), 1.97-2.08 (m, 2H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 30.12 ppm.

Scheme 15



Monophenol-ethyl lactate phosphonate prodrug 15.1: A methylene chloride/DMF solution (2 mL/0.5 mL) of **14.3** (30 mg, 49 μmol) was reacted with aminopropyl-phenol-ethyl lactate phosphonate **15.5** (100 mg, 233 μmol), DIPEA (64 mg, 495 μmol), and BOP reagent (45 mg, 100 μmol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was triturated with methylene chloride/hexane. The solid was purified by silica gel chromatography to give **15.1** (28 mg, 64 %). NMR ($CDCl_3$ + ~10 %CD_3O): δ 7.83 (b, 1H), 7.59 (b, 1H), 7.51 (s, 1H), 7.14-7.2 (m, 11 H), 6.90-7.0 (m, 4H), 4.75-4.87 (d +

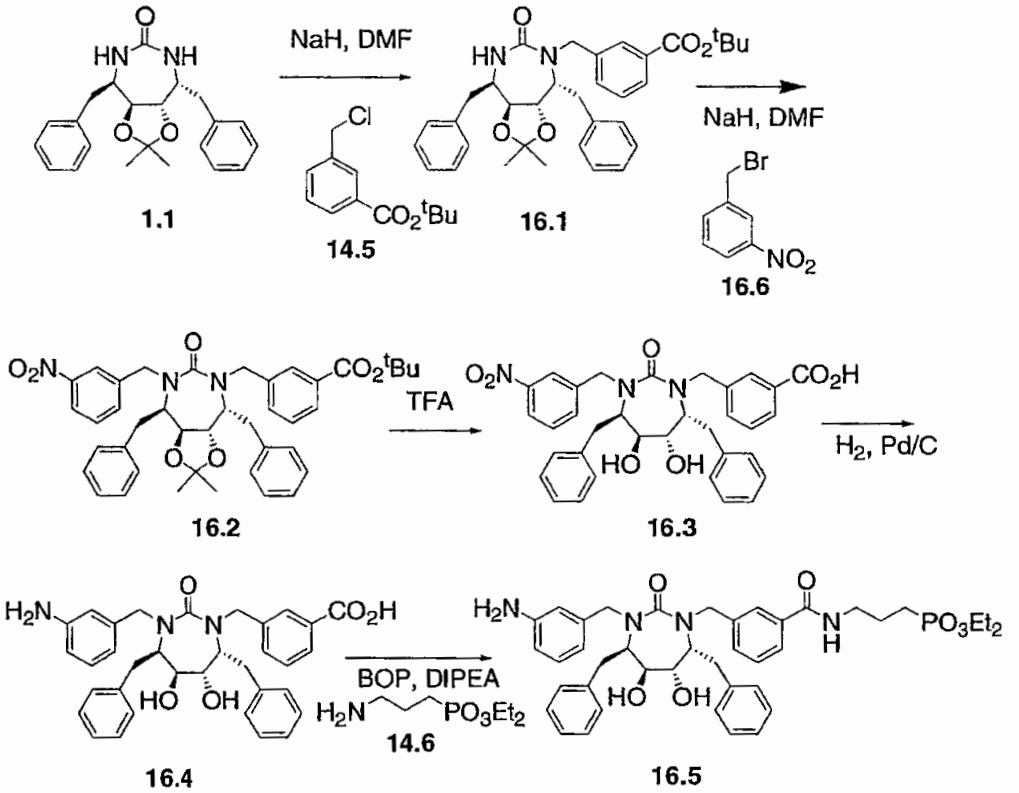
q, 3H), 4.10 (q, 2H), 3.3-3.61 (m, 6H), 2.60-3.2 (m, 6H), 1.92-2.12 (m, 4H), 1.30 (d, 3H), 1.18 (t, 3H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 30.71 ppm. MS: 903 (M + 1).

Phenol-ethyl alanine phosphonate prodrug 15.2: A methylene chloride/DMF solution (2 mL/0.5 mL) of **14.3** (30 mg, 49 μmol) was reacted with aminopropyl-phenol-ethyl alanine phosphonate **15.6** (80 mg TFA salt, 186 μmol), DIPEA (64 mg, 500 μmol), and BOP reagent (45 mg, 100 μmol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was triturated with methylene chloride/hexane. The solid was purified by preparative TLC to give **15.2** (12 mg, 27 %). NMR ($CDCl_3$ + ~10 %CD_3O): δ 7.91 (b, 1H), 7.61 (b, 1H), 7.52 (s, 1H), 7.14-7.2 (m, 11 H), 6.90-7.0 (m, 4H), 4.75 (d, 2H), 3.82-4.1 (2q, 3H), 3.4-3.65 (m, 6H), 2.60-3.15 (m, 6H), 1.8-2.0 (m, 4H), 1.3 (d, 3H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 32.98 & 33.38 ppm. MS: 902 (M + 1).

Dibenzyl phosphonate 15.3: A methylene chloride/DMF solution (2 mL/0.5 mL) of **14.3** (30 mg, 49 μmol) was reacted with aminopropyl dibenzyl phosphonate **15.7** (86 mg TFA salt, 200 μmol), DIPEA (64 mg, 500 μmol), and BOP reagent (45 mg, 100 μmol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was triturated with methylene chloride/hexane. The solid was purified by preparative TLC to give **15.3** (20 mg, 44%). NMR ($CDCl_3$ + ~5%CD_3O): δ 7.50-7.58 (m, 2H), 7.14-7.3 (m, 21 H), 6.90-7.0 (m, 4H), 4.7-5.1 (m, 6H), 3.6-3.8 (m, 4H), 3.3-3.55 (m, 2H), 2.60-3.15 (m, 6H), 1.8-2.0 (m, 4H). P NMR ($CDCl_3$ + ~5 %CD_3OD): 33.7 ppm. MS: 907 (M + 1).

Phosphonic diacid 15.4: An ethanol solution (5 mL) of **15.3** (17 mg, 18.7 μmol) was hydrogenated at 1 atm in the presence of 10 % Pd/C for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give the desired product **15.4** (12 mg, 85%). NMR (CD_3O + 20%$CDCl_3$): δ 7.88 (b, 1H), 7.59 (b, 1H), 7.6 (s, 1H), 7.1-7.25 (m, 10 H), 6.90-7.1 (m, 4H), 4.8 (d, 2H + water peak), 3.6-3.8 (m, 4H), 3.4-3.5 (m, 2H), 1.85-2.0 (m, 4H).

Scheme 16



Monobenzyl derivative 16.1: A DMF solution (4 mL) of **1.1** (0.8 g, 2.2 mmol) was treated with NaH (0.18 g of 60% oil dispersion, 4.4 mmol) for 10 min at room temperature followed by the addition of 14.5 (0.5 g, 2.2 mmol). The resulting solution was reacted at room temperature for 2 h, worked up, and then purified to afford **16.1** (0.48 g, 40%).

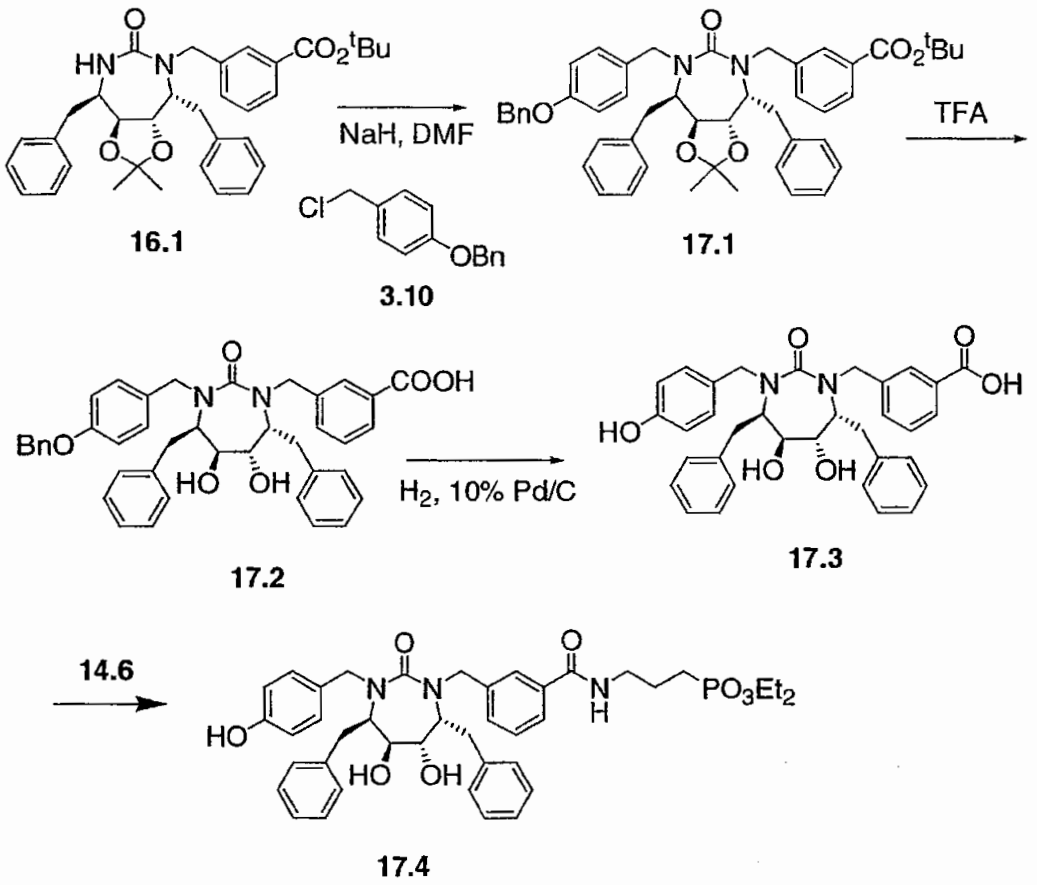
3-Nitrobenzyl cyclic urea derivative 16.2: A DMF solution (0.5 mL) of **16.1** (65 mg, 117 µmol) was treated with NaH (15 mg of 60% oil dispersion, 375 µmol) for 10 min at room temperature, followed by the addition of 3-nitrobenzyl bromide (33 mg, 152 µmol). The resulting solution was reacted at room temperature for 1 h, worked up, and purified by preparative TLC to afford **16.2** (66 mg, 82%).

Diol 16.3: A methylene chloride solution (2 mL) of **16.2** (46 mg, 61 µmol) was treated with TFA (0.4 mL) for 2 h at room temperature, and then concentrated under reduced pressure to afford **16.3**. This material was used without further purification.

3-Aminobenzyl cyclic urea 16.4: An ethyl acetate/ethanol (5 mL/1 mL) solution of **16.3** (crude) was hydrogenated at 1 atm in the presence of 10% Pd/C for 2 h. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure, and purified by preparative TLC to afford **16.4** (26 mg, 70%, 2 steps).

Diethyl phosphonate 16.5: A methylene chloride/DMF solution (2 mL/0.5 mL) of **16.4** (24 mg, 42 μmol) was reacted with aminopropyl-diethylphosphonate ester TFA salt **14.6** (39 mg, 127 μmol), DIPEA (27 mg, 210 μmol), and BOP reagent (28 mg, 63 μmol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was purified by preparative TLC to give **16.5** (20.7 mg, 63 %). NMR ($CDCl_3$ + ~10 %CD_3O): δ 7.62 (b, 1H), 7.51 (s, 1H), 7.0-7.35 (m, 12 H), 6.95 (d, 2H), 6.85 (d, 2H), 4.6-4.71 (2d, 2H), 3.95-4.1 (m, 4H). 3.3-3.55 (m, 3H), 2.60-2.8 (m, 2H), 2.95-.3. 15 (m, 4 H), 1.85-2.0 (m, 4H), 1.25 (t, 6H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 32.65 ppm.

Scheme 17

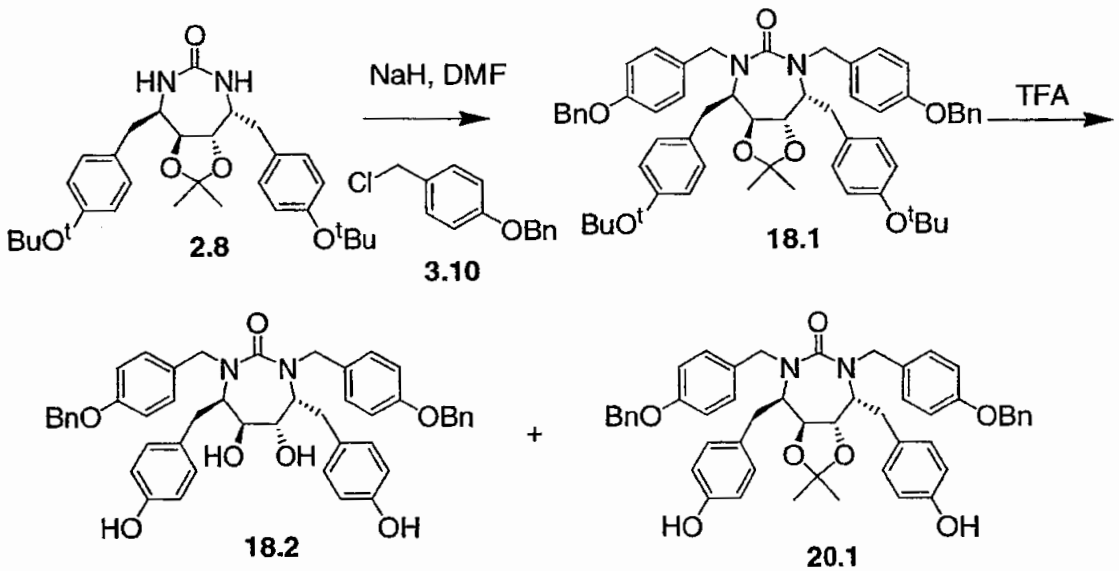


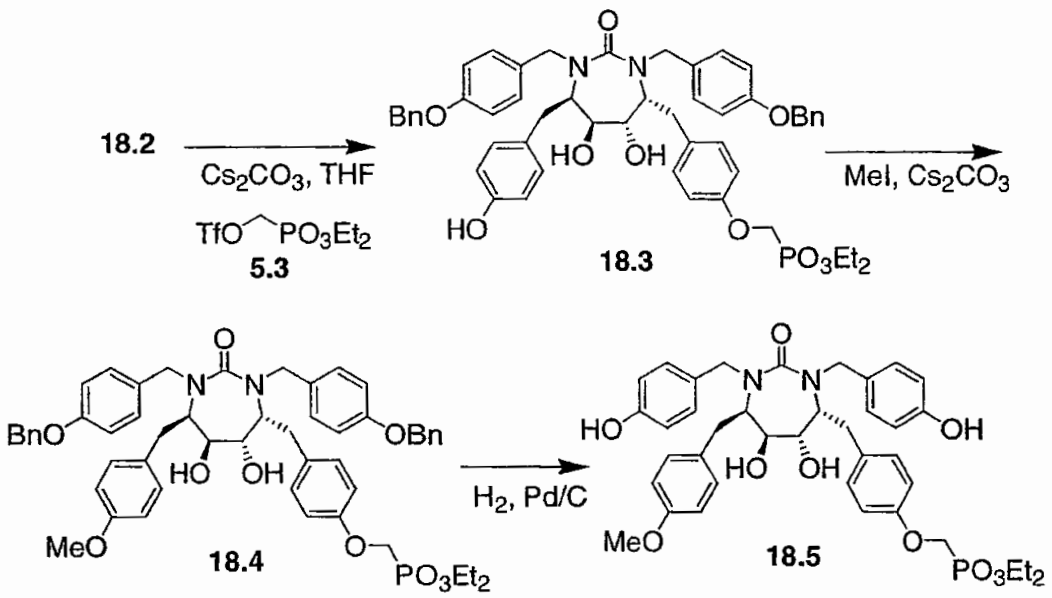
p-Benzoxybenzyl cyclic urea derivative 17.1: A DMF solution (0.5 mL) of **16.1** (65 mg, 117 μmol) was treated with NaH (15 mg of 60% oil dispersion, 375 μmol) for 10 min at room temperature, followed by the addition of 4-benzoxy benzyl chloride **3.10** (35 mg, μmol). The resulting solution was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure, purified by preparative TLC to generate **17.1** (62 mg, 70%).

Diethyl phosphonate 17.3: A methylene chloride solution (2 mL) of **17.1** (46 mg, 61 μmol) was treated with TFA (0.4 mL) for 2 h at room temperature, and then concentrated under reduced pressure to give crude **17.2**. An ethyl acetate/ethanol solution (3 mL/2 mL) of the crude **17.2** was then hydrogenated at 1 atm in the presence of 10% Pd/C (10 mg) for 5 h at room temperature. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure to afford **17.3** (crude).

Diethyl phosphonate cyclic urea 17.4: A methylene chloride/DMF solution (2 mL/0.5 mL) of **17.3** (25 mg, 42 μmol) was reacted with aminopropyl-diethylphosphonate ester TFA salt **14.6** (40 mg, 127 μmol), DIPEA (27 mg, 210 μmol), and BOP reagent (28 mg, 63 μmol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was purified by preparative TLC to give **17.4** (14.6 mg, 44 %). NMR ($CDCl_3$ + ~10 %CD_3O): δ 7.82 (t), 7.62 (d, 1H), 7.51 (s, 1H), 7.05-7.35 (m, 10 H), 6.8-6.95 (2d, 4H), 6.85 (d, 2H), 4.8 (d, 1H), 4.65 (d, 1H), 3.95-4.1 (m, 4H). 3.4-3.75 (m, 6H), 2.60-3.2 (m), 1.85-2.0 (m, 4H), 1.25 (t, 6H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 32.72 ppm.

Scheme 18





Dibenzyl derivative 18.1: A DMF solution (3 mL) of compound **2.8** (0.4 g, 0.78 mmol) was reacted with 60%NaH (0.13 g, 1.96 mmol), 4-benzoxy benzylchloride **3.10** (0.46 g, 1.96 mmol) and sodium iodide (60 mg, 0.39 mmol) at room temperature for 4 h. The reaction mixture was partitioned between methylene chloride and saturated $NaHCO_3$ solution. The organic phase was isolated, dried over Na_2SO_4, concentrated under reduced pressure, and purified by silica gel chromatography to give the desired product **18.1** (0.57 g, 81%).

Diol derivative 18.2 and diphenol derivative 20.1: A methylene chloride solution (4 mL) of **18.1** (0.57 g, 0.63 mmol) was treated with TFA (1 mL) at room temperature for 20 min, concentrated under reduced pressure, and purified by silica gel chromatography to give diol derivative **18.2** (133 mg, 28 %) and diphenol derivative **20.1** (288 mg. 57.6%).

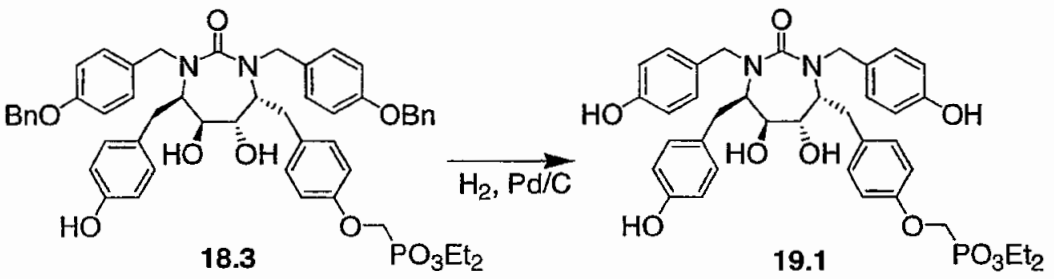
Monophosphonate derivative 18.3: A THF solution (10 mL) of **18.2** (130 mg, 0.17 mmol) was stirred with cesium carbonate (70 mg, 0.21 mmol) and diethylphosphonate triflate **5.3** (52 mg, , 0.17 mmol) at room temperature for 4 h.. The reaction mixture was concentrated under reduced pressure and purified to give **18.3** (64 mg, 41 %), and recovered **18.2** (25 mg, 19%).

Methoxy derivative 18.4: A THF solution (2 mL) of **18.3** (28 mg, 25 μmol) was treated with cesium carbonate (25 mg, 76 μmol) and iodomethane (10 eq. Excess) at room

temperature for 5 h. The reaction mixture was concentrated under reduced pressure and partitioned between methylene chloride and saturated $NaHCO_3$. The organic phase was separated, concentrated under reduced pressure and the residue purified by preparative TLC to afford **18.4** (22 mg, 78%).

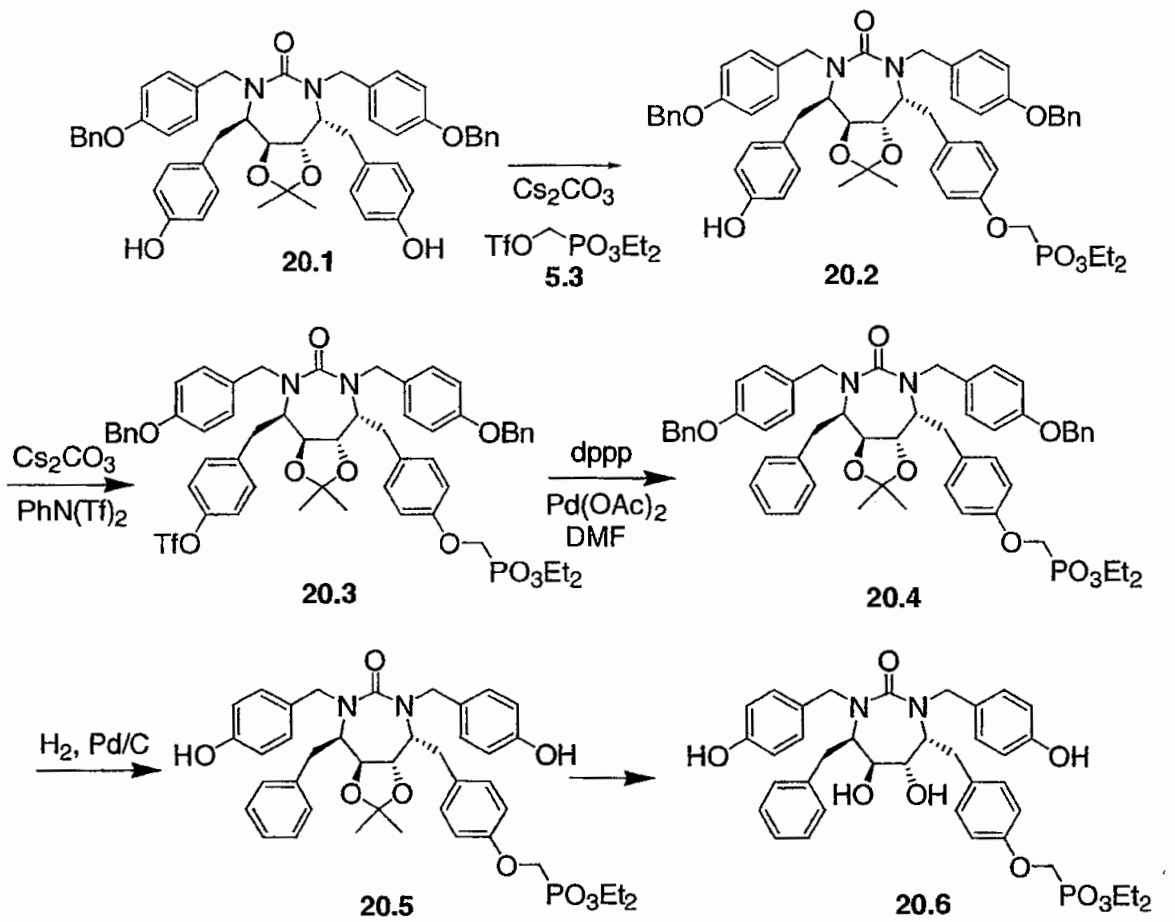
Diethylphosphonate 18.5 : An ethyl acetate/ethanol (2 mL/2 mL) solution of **18.4** (22 mg, 24 μmol) was hydrogenated at 1 atm in the presence of 10% Pd/C for 3 h. The catalyst was removed by filtration, the filtrate was concentrated under reduced pressure to give the desired product **18.5** (18 mg, quantitative). NMR ($CDCl_3$ + ~10 %CD_3O): δ 6.7-7.0 (m, 12 H), 6.62-6.69 (m, 4H), 4.65 (d, 1H), 4.50 (d, 1H), 4.18-4.3 (m, 6H). 3.75 (s, 3H), 3.3-3.4 (m, 4H), 2.8-3.0 (m, 6H), 1.30 (t, 6H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 20.16 ppm.

Scheme 19



Diethyl phosphonate 19.1: An ethyl acetate/ethanol (2 mL/1 mL) solution of **18.3** (14 mg, 15.5 μmol) was hydrogenated at 1 atm in the presence of 10% Pd/C (5 mg) for 3 h. The catalyst was then removed by filtration, and the filtrate was concentrated under reduced pressure to give the desired product **19.1** (10 mg, 90%). NMR ($CDCl_3$ + ~15 %CD_3O): δ 6.6-7.0 (m, 16 H), 4.5-4.65 (2d, 2H), 4.1-4.3 (m, 6H). 2.7-3.0 (m, 6H), 1.29 (t, 6H). P NMR ($CDCl_3$ + ~15 %CD_3OD): 20.12 ppm.

Scheme 20



Monophosphonate 20.2: A THF solution (8 mL) of **20.1** (280 mg, 0.36 mmol) was stirred with cesium carbonate (140 mg, 0.43 mmol) and diethylphosphonate triflate **5.3** (110 mg, 0.36 mmol) at room temperature for 4 h.. The reaction mixture was concentrated under reduced pressure and purified to give **20.2** (130mg, 39%), and recovered **20.1** (76 mg, 27%).

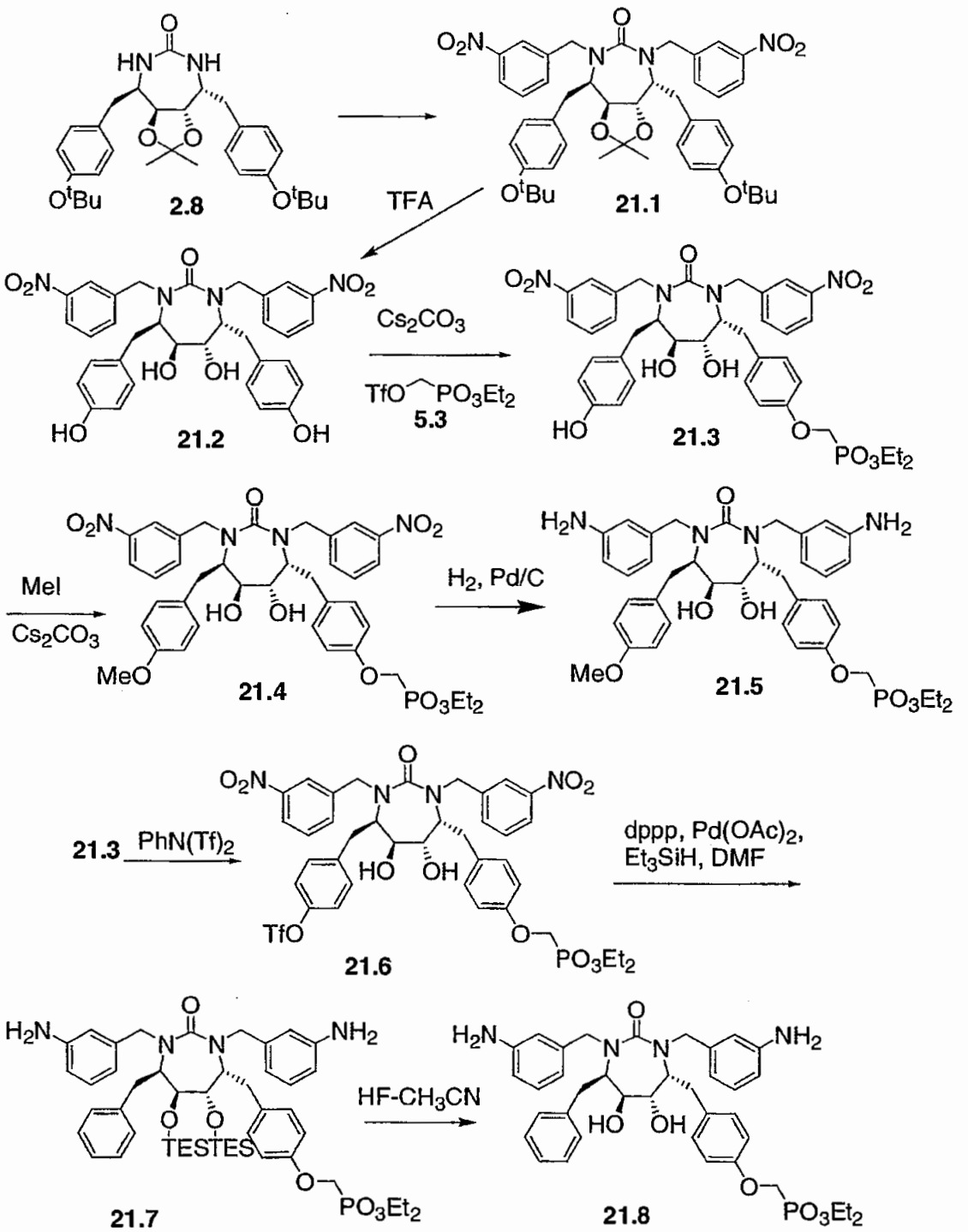
Triflate derivative 20.3: A THF solution (6 mL) of **20.2** (130 mg, 0.13 mmol) was stirred with cesium carbonate (67 mg, 0.21 mmol) and N-phenyltrifluoromethane-sulfonimide (60mg, 0.17 mmol) at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and purified to give **20.3** (125 mg, 84%).

Benzyl ether 20.4: To a DMF solution (2 mL) of $Pd(OAc)_2$ (60 mg, 267 μmol), and dppp (105 mg. 254 μmol) was added **20.3** (120 mg, 111 μmol) under nitrogen, followed by the addition of triethylsilane (0.3 mL). The resulting solution was stirred at room temperature for

4 h, then concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **20.4** (94 mg, 92%).

Diethyl phosphonate 20.6: An ethyl acetate/ethanol (2 mL/2 mL) solution of **20.4** (28 mg, 30 μmol) was hydrogenated at 1 atm in the presence of 10% Pd/C (5 mg) for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give the desired product **20.5**. The crude product **20. 5** was redissolved in methylene chloride (2 mL) and treated with TFA (0.4 mL) and a drop of water. After 1 h stirring at room temperature, the reaction mixture was concentrated under reduced pressure, and purified by preparative TLC plate to give **20.6** (18 mg, 85 %, 2 steps). δ 6.6-7.3 (m, 17 H), 4.65 (d, 1H), 4.58 (d, 1H), 4.18-4.3 (m, 6H), 3.3-3.5 (m, 4H), 2.8-3.1 (m), 1.34 (t, 6H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 20.16 ppm. MS: 705 (M + 1).

Scheme 21



Bis-(3-nitrobenzyl) derivative 21.1: A DMF solution (2 mL) of compound **2.8** (0.3 g, 0.59 mmol) was reacted with 60%NaH (0.07 g, 1.76 mmol), 3-nitrobenzyl bromide (0.38 g, 1.76 mmol) and sodium iodide (60 mg, 0.39 mmol) at room temperature for 3 h. The reaction

mixture was partitioned between methylene chloride and saturated $NaHCO_3$ solution. The organic phase was isolated, dried over Na_2SO_4, concentrated under reduced pressure, and purified by silica gel chromatography to give the desired product **21.1** (0.37 g, 82%).

Diphenol derivative 21.2: A methylene chloride solution (4 mL) of **21.1** (0.37 g, 0.47 mmol) was treated with TFA (1 mL) at room temperature for 3 h, and then concentrated under reduced pressure, and azeotroped with CH_3CN twice to give diphenol derivative **21.2** (0.3 g, quantitative).

Monophosphonate derivative 21.3: A THF solution (8 mL) of **18.2** (0.28g, 0.44 mmol) was stirred with cesium carbonate (0.17 g, 0.53 mmol) and diethylphosphonate triflate **5.3** (0.14 g, 0.44 mmol) at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and purified to give **21.3** (120 mg, 35%), and recovered **21.2** (150 mg, 53%).

Methoxy derivative 21.4: A THF solution (2 mL) of **21.3** (9 mg, 11 μmol) was treated with cesium carbonate (15 mg, 46 μmol) and iodomethane (10 eq. Excess) at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure and partitioned between methylene chloride and saturated $NaHCO_3$. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC to afford **21.4** (9 mg)

Diethylphosphonate 21.5: A ethyl acetate/ethanol (2 mL/0.5 mL) solution of **21.4** (9 mg, 11 μmol) was hydrogenated at 1 atm in the presence of 10% Pd/C for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give the desired product 21.5 (4.3 mg, 49%, 2 steps). NMR ($CDCl_3$ + ~10 %CD_3O): δ 7.0-7.10 (m, 6 H), 6.8-6.95 (m, 4H), 6.5-6.6 (m, 4H), 6.4-6.45 (m, 2H), 4.72 (d, 2H), 4.18-4.3 (m, 6H). 3.72 (s, 3H), 3.4-3.5 (m, 4H), 2.8-3.0 (m, 6H), 1.34 (t, 6H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 19.93 ppm.

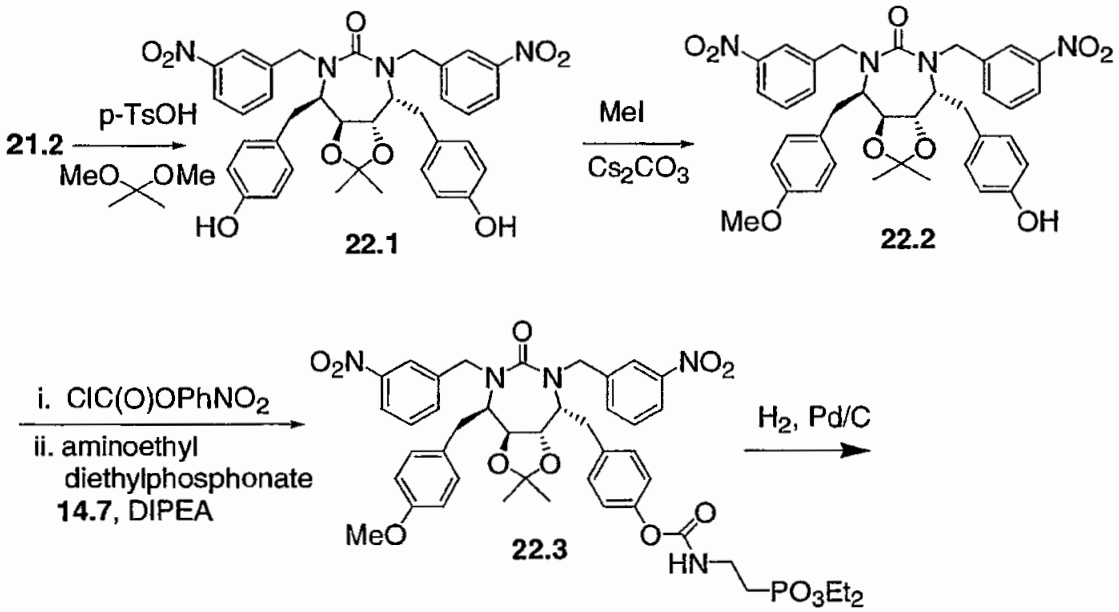
Triflate 21.6: A THF solution (6 mL) of **21.3** (0.1g, 0.14 mmol), cesium carbonate (0.07 g, 0.21 mmol), and N-phenyltrifluoromethane-sulfonimide (60mg, 0.17 mmol) was stirred at

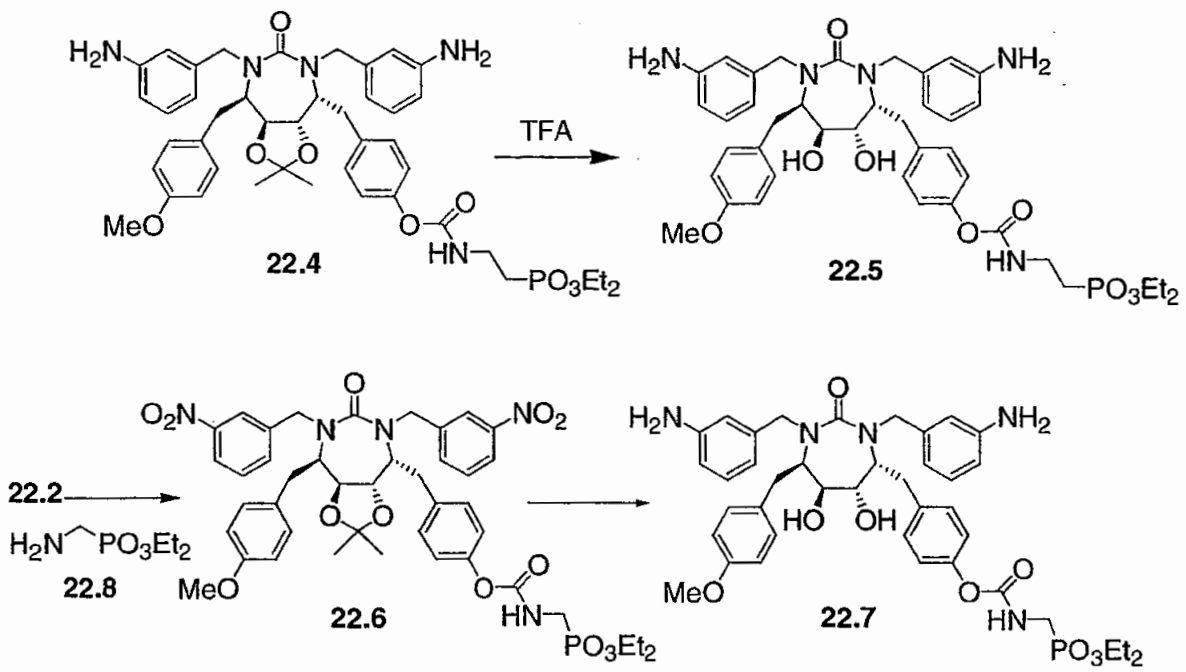
room temperature for 4 h, and then concentrated under reduced pressure, and worked up. The residue was purified by silica gel chromatography to give **21.6** (116 mg, 90%).

Diamine 21.7: A DMF solution (2 mL) of **21.6** (116 mg, 127 μmol), dppp (60 mg, 145 μmol), and $Pd(OAc)_2$ (30 mg, 134 μmol) was stirred under nitrogen, followed by addition of triethylsilane (0.3 mL), and reacted for 4 h at room temperature. The reaction mixture was worked up and purified to give **21.7** (50 mg).

Diethyl phosphonate 21.8: An acetonitrile solution (1 mL) of crude **21.7** (50 mg) was treated with 48% HF (0.1 mL) for 4 h. The reaction mixture was concentrated under reduced pressure, and purified to give **21.8** (10 mg, 11% (2 steps). NMR ($CDCl_3$ + ~10%CD_3O): δ 7.05-7.30 (m, 9 H), 6.8-6.95 (d, 2H), 6.4-6.6 (m, 6H), 4.72 (d, 2H), 4.18-4.3 (m, 6H). 3.4-3.5 (m, 4H), 2.8-3.0 (m, 6H), 1.34 (t, 6H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 19.83 ppm.

Scheme 22





Acetonide 22.1: An acetone/2,2-diemethoxypropane solution (15 mL/5 mL) of compound **21.2** (240 mg, 0.38 mmol) and pyridinium toluenesulfonate (10 mg) was heated at reflux for 30 min. After cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between methylene chloride and saturated $NaHCO_3$ aqueous solution, dried, concentrated under reduced pressure and purified to afford **22.1** (225 mg, 88%).

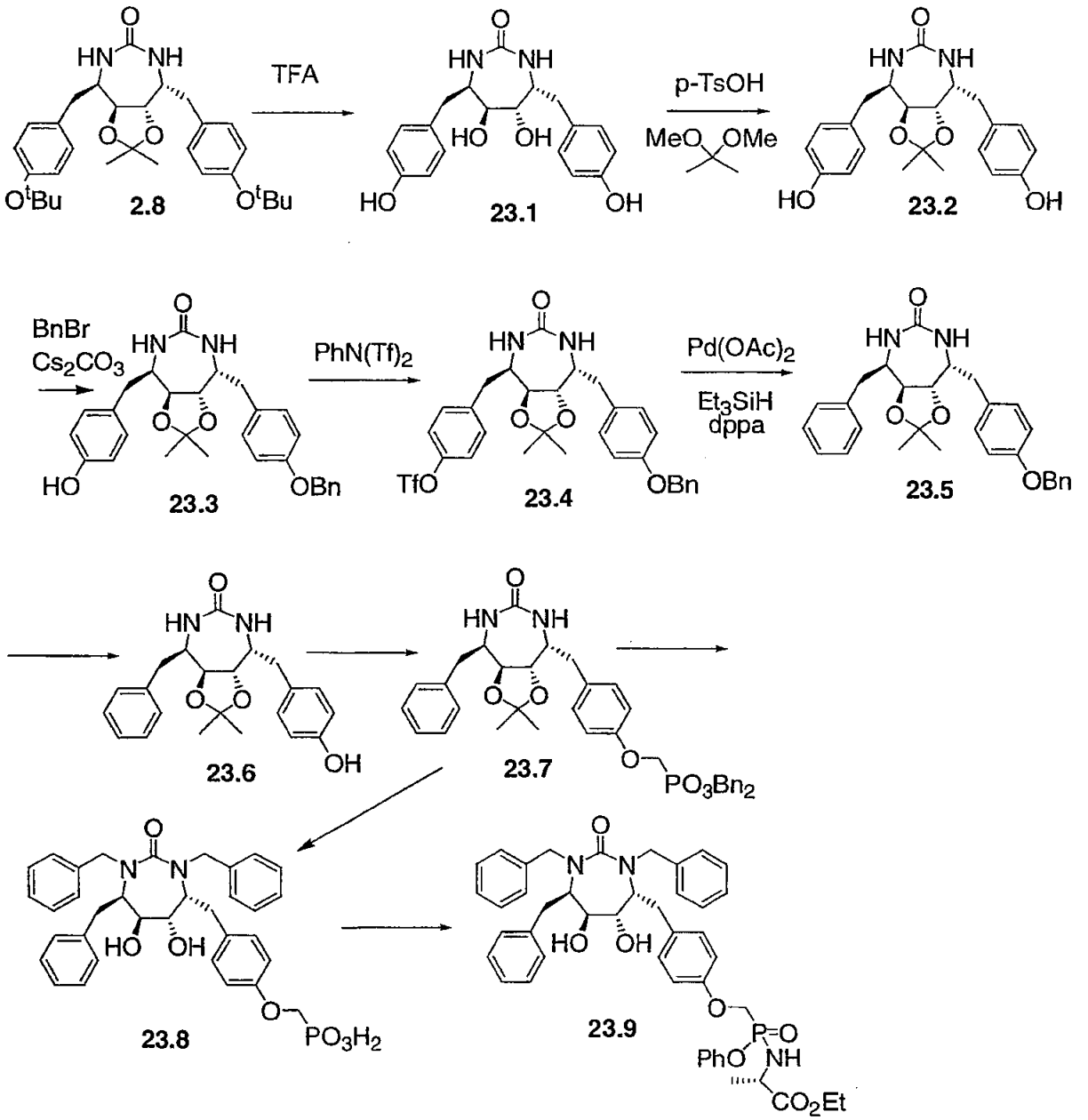
Monomethoxy derivative 22.2: A THF solution (10 mL) of **22.1** (225 mg, 0.33 mmol) was treated with cesium carbonate (160 mg, 0.5 mmol) and iodomethane (52 mg. 0.37 mmol) at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and purified by preparative silica gel column chomatography to afford **22.2** (66 mg, 29%) and recovered starting material **22.1** (25 mg, 11%).

Diethyl phosphonate 22.3: A methylene chloride solution (2 mL) of **22.2** (22 mg, 32 μmol), DIPEA (9 mg, 66 μmol), and p-nitrophenyl chloroformate (8 mg, 40 μmol) was stirred at room temperature for 30 min. The resulting reaction mixture was reacted with DIPEA (10 mg, 77 μmol), and aminoethyl diethylphosphonate **14.7** (12 mg. 45 μmol) at room temperature overnight. The reaction mixture was washed with 5% citric acid solution, saturated $NaHCO_3$, dried, and purified by preparative TLC to afford **22.3** (12 mg, 43%).

Bis(3-aminobenzyl)-diethylphosphonate ester 22.5: An ethyl acetate/t-BuOH (4 mL/2 mL) solution of **22.3** (12 mg, 13 μmol) was hydrogenated at 1 atm in the presence of 10% Pd/C 95 mg) at room temperature for 5 h. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure, and purified by preparative TLC to give **22.4** (8 mg, 72%). A methylene chloride solution (0.5 mL) of **22.4** (8 mg) was treated with TFA (0.1 mL) at room temperature for 1 h., concentrated under reduced pressure, and then azeotroped with CH_3CN twice to afford **22.5** (8.1 mg, 81%). NMR ($CDCl_3$ + ~10 %CD_3OD): δ 7.2 (d, 1H), 6.95-7.15 (m, 6H), 6.75-6.9 (m, 5 H), 4.66 (d, 1H), 4.46 (d, 1H), 4.06-4.15 (m, 4H). 3.75 (s, 3H), 3.6-3.7 (m, 4H), 2.6-3.1 (m, 6H), 2.0-2.1 (m, 2H), 1.30 (t, 6H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 29.53 ppm. MS: 790 (M + 1).

Bis(3-aminobenzyl) diethylphosphonate ester 22.7: Compound **22.7** was prepared from **22.2** (22 mg, 32 μmol) and aminomethyl diethylphosphonate **22.8** as shown above for the preparation of **22.5** from **22.2.** NMR ($CDCl_3$ + ~10 %CD_3OD): δ 7.24 (d, 1H), 6.8-7.12 (m, 11H), 4.66 (d, 1H), 4.45 (d, 1H), 4.06-4.15 (m, 4H). 3.75 (s, 3H), 2.6-3.1 (m, 6H), 1.30 (t, 6H). P NMR ($CDCl_3$ + ~10 %CD_3OD): 22.75 ppm. MS: 776 (M + 1).

Scheme 23



Diol 23.1: To a solution of compound **2.8** (2.98 g, 5.84 mmol) in methylene chloride (14 mL) was added TFA (6 mL). The resulted mixture was stirred at room temperature for 2 h. Methanol (5 mL) and additional TFA (5 mL) were added. The reaction mixture was stirred for additional 4 h and then concentrated under reduced pressure. The residue was washed with hexane/ethyl acetate (1:1) and dried to afford compound **23.1** (1.8 g, 86%) as an off-white solid.

Benzyl ether 23.3: To a solution of compound **23.1** (1.8 g, 5.03 mmol) in DMF (6 mL) and 2,2-dimethoxyl propane (12 mL) was added p-toluenesulfonic acid monohydrate (0.095 g, 0.5 mmol). The resultant mixture was stirred at 65°C for 3 h. The excess 2,2-dimethoxyl propane was slowly distilled. The reaction mixture was cooled to room temperature and charged with THF (50 mL), benzyl bromide (0.8 mL, 6.73 mmol) and cesium carbonate (2.0 g, 6.13 mmol). The resulted mixture was stirred at 65°C for 16 h. The reaction was quenched with acetic acid aqueous solution (4%, 100 mL) at 0°C, and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford desired mono protected compound **23.3** (1.21 g, 49%).

Benzyl ether 23.5: To a solution of compound **23.3** (0.65 g, 1.33 mmol) and N-phenyltrifluoromethanesulfonimide (0.715 g, 2 mmol) in THF (12 mL) was added cesium carbonate (0.65 g, 2 mmol). The mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a pad of silica gel and concentrated under reduced pressure. The residue was purified on silica gel chromatography to give triflate **23.4** (0.85 g). To a solution of 1,3-bis(diphenylphosphino)propane (0.275g, 0.66 mmol) in DMF (10 mL) was added palladium(II) acetate (0.15 g, 0.66 mmol) under argon. This mixture was stirred for 2 min. and then added to triflate **23.4**. After stirring for 2 min., triethylsilane was added and the resulted mixture was stirred for 1.5 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to afford compound **23.5** (0.56 g, 89%).

Phenol 23.6: A solution of **23.5** (0.28 g, 0.593 mmol) in ethyl acetate (5 mL) and isopropyl alcohol (5 mL) was treated with 10% Pd/C (0.05g) and stirred under a hydrogen atmosphere (balloon) for 16 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to yield **23.6** (0.22 g, 97%) as a white solid.

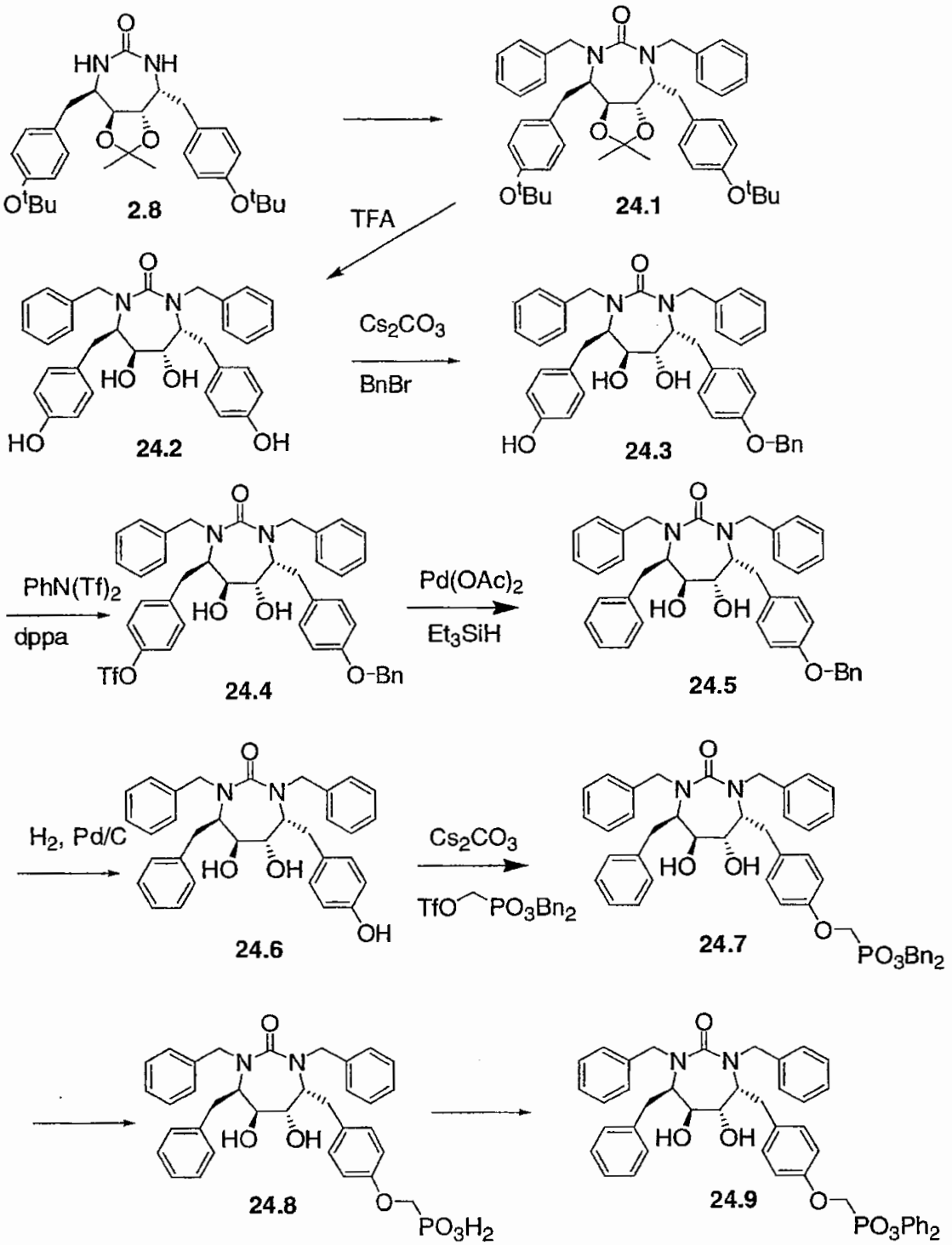
Dibenzyl phosphonate 23.7: To a solution of compound **23.6** (0.215 g, 0.563 mmol) in THF (10 mL) was added dibenzyl triflate **3.11** (0.315 g, 0.74 mmol) and cesium carbonate (0.325g, 1 mmol). The mixture was stirred at room temperature for 2 h, then diluted with ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate, filtered and

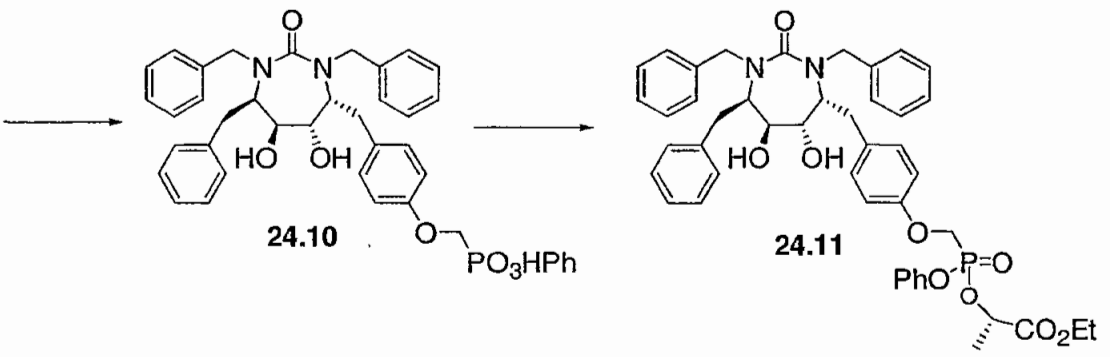
concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford compound **23.7** (0.31 g, 84%).

Diphenyl ester 23.8: A solution of compound **23.7** (0.3 g, 0.457 mmol) and benzyl bromide (0.165 mL, 1.39 mmol) in THF (10 mL) was treated with potassium *tert*-butoxide (1M/THF, 1.2 mL) for 0.5 h. The mixture was diluted with ethyl acetate and washed with HCl (0.2N). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and treated with 10% Pd/C (0.05 g) under hydrogen atmosphere (balloon) for 16 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was treated with TFA (1 mL) in methanol (5 mL) for 1 h, and then concentrated under reduced pressure. The residue was dissolved in pyridine (1 mL) and mixed with phenol (0.45 g, 4.8 mmol) and 1,3-dicyclohexylcarbodiimide (0.38 g, 1.85 mmol). The mixture was stirred at 70°C for 2 h, and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2N). The organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel to afford compound **23.8** (0.085 g, 24%).

Mono amidate 23.9: To a solution of **23.8** (0.085g, 0.11 mmol) in acetonitrile (1 mL) was added sodium hydroxide (1N, 0.25 mL) at 0°C. After stirred at 0°C for 1 h, the mixture was acidified with Dowex resin to pH = 3, and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in pyridine (0.5 mL) and mixed with L-alanine ethyl ester hydrochloride (0.062 g, 0.4 mmol) and 1,3-dicyclohexyl-carbodiimide (0.125 g, 0.6 mmol). The mixture was stirred at 60°C for 0.5 h, and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2N). The organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was purified by HPLC (C-18, 65% acetonitrile / water) to afford compound **23.9** (0.02 g, 23%). ^{1}H NMR (CDCl3): δ 1.2 (m, 3H), 1.4 (m, 3H), 1.8 (brs, 2H), 2.8-3.1 (m, 6H), 3.5-3.7 (m, 4H), 3.78 (m, 1H), 4.0-4.18 (m, 2H), 4.2-4.4 (m, 3H), 4.9 (m, 2H), 6.8-7.4 (m, 24H). 31P NMR (CDCl3): d 20.9, 19.8. MS: 792 (M+1).

Scheme 24


HN
NH
O
O
O
O
O^{t}Bu
O^{t}Bu
2.8
O^{t}Bu
O^{t}Bu
24.1
TFA
HO
OH
HO
OH
24.2
Cs_2CO_3
BnBr
HO
OH
HO
O-Bn
24.3
$PhN(Tf)_2$
dppa
TfO
HO
OH
O-Bn
24.4
$Pd(OAc)_2$
Et_3SiH
HO
OH
O-Bn
24.5
H_2, Pd/C
HO
OH
OH
24.6
Cs_2CO_3
TfO
PO_3Bn_2
HO
OH
O
PO_3Bn_2
24.7
HO
OH
O
PO_3H_2
24.8
HO
OH
O
PO_3Ph_2
24.9



Di-tert butyl ether 24.1: To a solution of compound **2.8** (0.51 g, 1 mmol) and benzyl bromide (0.43g, 2.5 mmol) in THF (6 mL) was added potassium *tert*-butoxide (1M/THF, 2.5 mL). The mixture was stirred at room temperature for 0.5 h, then diluted with ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford compound **24.1** (0.62 g, 90%).

Diol 24.2: To a solution of compound **24.1** (0.62 g, 0.9 mmol) in methylene chloride (4 mL) was added TFA (1 mL) and water (0.1 mL). The mixture was stirred for 2 h, and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford compound **24.2** (0.443g, 92%).

Benzyl ether 24.3: Compound **24.3** was prepared in 46% yield according to the procedure described in Scheme 23 for the preparation of **23.3**.

Triflate 24.4: Compound **24.4** was prepared in 95% yield according to the procedure described in Scheme 23 for the preparation of **23.4**.

Benzyl ether 24.5: Compound **24.5** was prepared in 93% yield according to the procedure described in Scheme 23 for the preparation of **23.5**.

Phenol 24.6: Compound **24.6** was prepared in 96% yield according to the procedure described in Scheme 23 for the preparation of **23.6** from **23.5**.

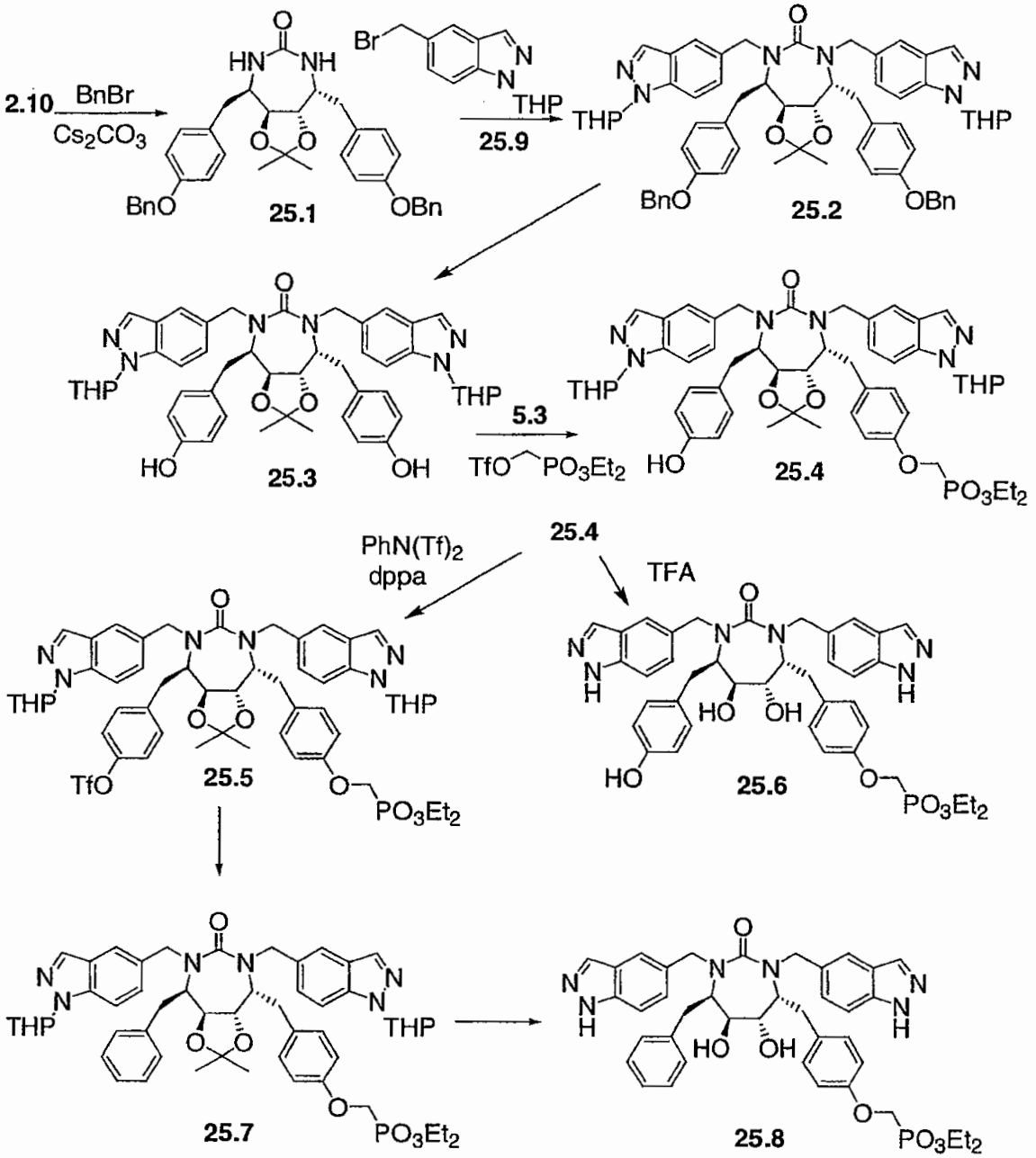
Dibenzyl phosphonate 24.7: Compound **24.7** was prepared in 82% yield according to the procedure described in Scheme 23 for the preparation of **23.7**.

Diacid 24.8: A solution of **24.7** (0.16 g, 0.207 mmol) in ethyl acetate (4 mL) and isopropyl alcohol (4 mL) was treated with 10% Pd/C (0.05g) and stirred under a hydrogen atmosphere (balloon) for 4 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to yield **24.8** (0.125 g, 98%) as a white solid.

Diphenyl ester 24.9: To a solution of compound **24.8** (0.12 g, 0.195 mmol) in pyridine (1 mL) was added phenol (0.19 g, 2 mmol) and 1,3-dicyclohexylcarbodiimide (0.206 g, 1 mmol). The mixture was stirred at 70°C for 2 h, and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2N). The organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel to afford compound **24.9** (0.038 g, 25%).

Mono lactate 24.11: Compound **24.9** was converted, via compound **24.10**, into compound **24.11** in 36% yield according to the procedure described in Scheme 23 for the preparation of **23.9** except utilizing the ethyl lactate ester in place of L-alanine ethyl ester . ^{1}H NMR (CDCl3): δ 1.05 (t, J = 8 Hz, 1.5H), 1.1 (t, J = 8 Hz, 1.5H), 1.45 (d, J = 8 Hz, 1.5H), 1.55 (d, J = 8 Hz, 1.5H), 2.6 (brs, 2H), 2.9-3.1 (m, 6H), 3.5-3.65 (m, 4H), 4.15-4.25 (m, 2H), 4.4-4.62 (m, 2H), 4.9 (m, 2H), 5.2 (m, 1H), 6.9-7.4 (m, 24H). 31P NMR (CDCl3): d 17.6, 15.5. MS: 793 (M+1).

Scheme 25



Dibenzyl ether 25.1: The protection reaction of compound **2.10** with benzyl bromide was carried out in the same manner as described in Scheme 23 to afford compound **25.1**.

Bis indazole 25.2: The alkylation of compound **25.1** with bromide **25.9** was carried out in the same manner as described in Scheme 23 to afford compound **25.2** in 96% yield.

Diol 25.3: A solution of **25.2** (0.18 g, 0.178 mmol) in ethyl acetate (5 mL)) and isopropyl alcohol (5 mL) was treated with 20% Pd(OH)2/C (0.09g) and stirred under a hydrogen atmosphere (balloon) for 24 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to afford **25.3** in quantitative yield.

Diethyl phosphonate 25.4: To a solution of compound **25.3** (0.124 g, 0.15 mmol) in acetonitrile (8 mL) and DMF (1 mL) was added potassium tert-butoxide (0.15 mL, 1M/THF). The mixture was stirred for 10 min. to form a clear solution. Diethyl triflate **5.3** (0.045 g, 0.15 mmol) was added to the reaction mixture. After stirred for 0.5 h, the reaction mixture was diluted with ethyl acetate and washed with HCl (0.1N). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford compound **25.4** (0.039 g, 55% (based on recovered starting material: 0.064 g, 52%).

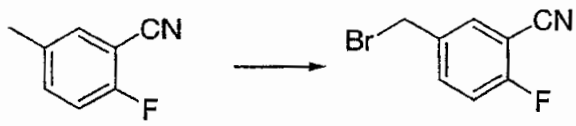
Bisindazole 25.6: A mixture of compound **25.4** (0.027 g), ethanol (1.5 mL), TFA (0.6 mL) and water (0.5 mL) was stirred at 60°C for 18 h. The mixture was concentrated under reduced pressure, and the residue was purified by HPLC to afford compound **25.6** as a TFA salt (0.014 g, 51%). ^{1}H NMR (CD3OD): δ 1.4 (t, J = 8 Hz, 6H), 2.9 (M, 4H), 3.2 (m, 2H), 3.58 (brs, 2H), 3.65 (m, 2H), 4.25 (m, 4H), 4.42 (d, J = 10 Hz, 2H), 4.85 (m, 2H), 6.75 (d, J = 9 Hz, 2H), 6.9 (m, 4H), 7.0 (d, J = 9 Hz, 2H), 7.4-7.6 (m, 6H), 8.1 (brs, 2H). 31P NMR (CD3OD): δ 20.8. MS: 769 (M+1).

Diethyl phosphonate 25.7: Compound **25.4** was converted into compound **25.7** in 76% yield according to the procedures described in Scheme 23 for the conversion of **23.3** into **23.5**.

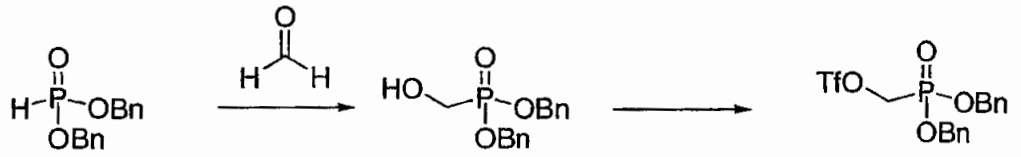
Bis indazole 25.8: Compound **25.7** (0.029 g) was treated in the same manner as compound **25.4** in the preparation of **25.6** to afford compound **25.8** as a TFA salt (0.0175 g, 59%). ^{1}H NMR (CD3OD): δ 1.4 (t, J = 8 Hz, 6H), 3.0 (M, 4H), 3.15 (d, J = 14 Hz, 1H), 3.25 (d, J = 14 Hz, 1H), 3.58 (brs, 2H), 3.65 (m, 2H), 4.25 (m, 4H), 4.42 (d, J = 10 Hz, 2H), 4.85 (m, 2H), 6.9 (d, J = 9 Hz, 2H), 7.0 (d, J = 9 Hz, 2H), 7.1 (d, J = 7 Hz, 2H), 7.2-7.6 (m, 9H), 8.1 (brs, 2H). ^{31}P NMR (CD3OD): δ 20.8. MS: 753 (M+1).

Preparation of Alkylating and Phosphonate Reagents

Scheme 50



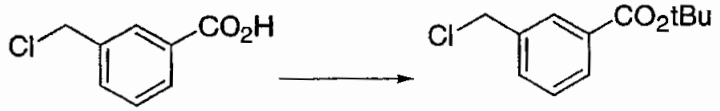
50.1 3.9



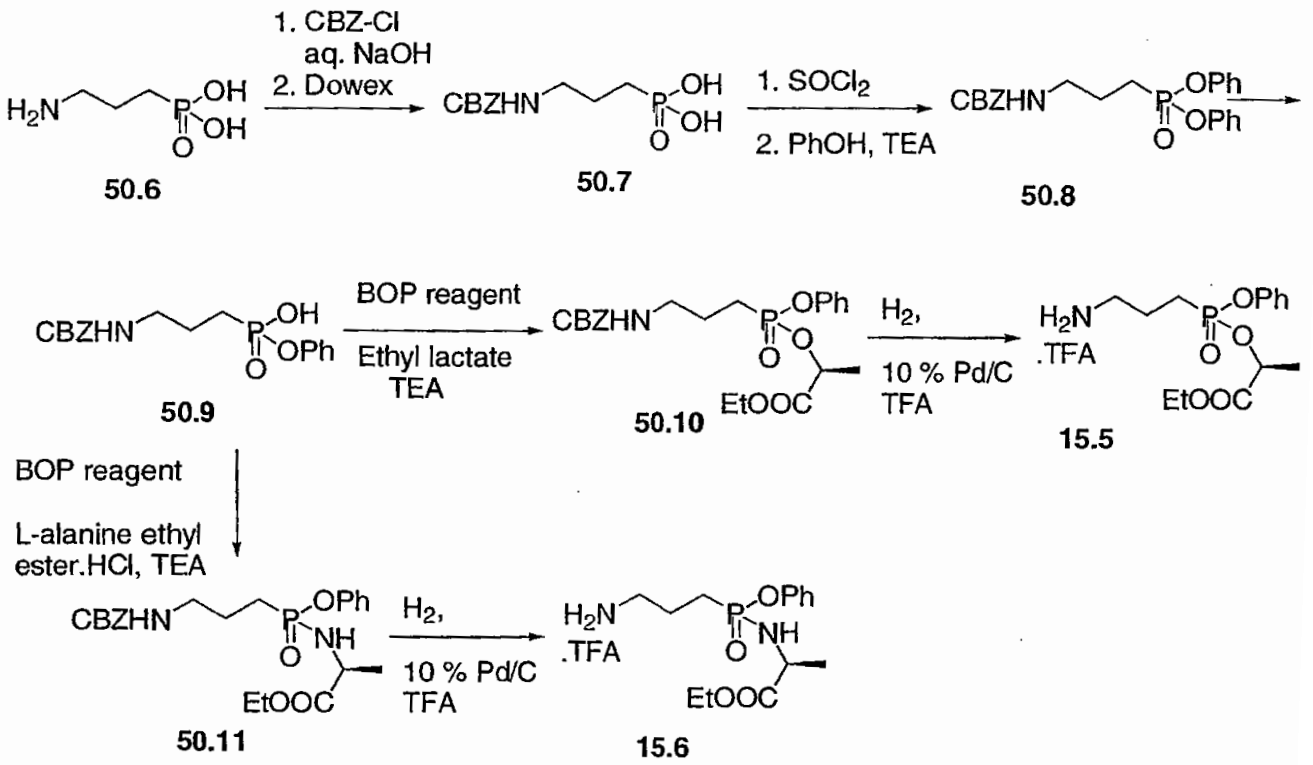
50.2 50.3 3.11



50.4 6.9



50.5 14.5



3-cyano-4-fluoro-benzylbromide 3.9: The commercially available 2—fluoro-4-methylbenzonitrile **50.1** (10 g, 74 mmol) was dissolved in carbon tetrachloride (50 mL) and then treated with NBS (16 g, 90 mmol) followed by AIBN (0.6 g, 3.7 mmol). The mixture was stirred at 85°C for 30 min and then allowed to cool to room temperature. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by silica gel eluting with 5-20% ethyl acetate in hexanes to give **3.9** (8.8 g, 56%).

4-benzyloxy benzyl chloride 3.10 is purchased from Aldrich

Dibenzyl triflate 3.11: To a solution of dibenzyl phosphite **50.2** (100 g, 381 mmol) and formaldehyde (37% in water, 65 mL, 860 mmol) in THF (200 mL) was added TEA (5 mL, 36 mmol). The resulted mixture was stirred for 1 h, and then concentrated under reduced pressure. The residue was dissolved in methylene chloride and hexane (1:1, 300 mL), dried over sodium sulfate, filtered through a pad of silica gel (600 g) and eluted with ethyl acetate and hexane (1:1). The filtrate was concentrated under reduced pressure. The residue **50.3** (95 g) was dissolved in methylene chloride (800 mL), cooled to –78°C and then charged with pyridine (53 mL, 650 mmol). To this cooled solution was slowly added trifluoromethanesulfonic anhydride (120 g, 423 mmol). The resulted reaction mixture was

stirred and gradually warmed up to –15°C over 1.5 h period of time. The reaction mixture was cooled down to about – 50°C, diluted with hexane-ethyl acetate (2:1, 500 mL) and quenched with aqueous phosphoric acid (1M, 100 mL) at –10°C to 0°C. The mixture diluted with hexane-ethyl acetate (2:1, 1000 mL). The organic phase was washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford dibenzyl triflate **3.11** (66 g, 41%) as a colorless oil.

Diethyl triflate 5.3 is prepared as described in Tet Lett. 1986, 27, p1477-1480

3-Benzyloxybenzylbromide 6.9: To a solution of triphenyl phosphine (15.7 g, 60 mmol) in THF (150 mL) was added a solution of carbon tetrabromide (20 g, 60 mmol) in THF (50 mL). A precipitation was formed and stirred for 10 min. A solution of 3-benzyloxybenzyl alcohol **50.4** (10 g, 46.7 mmol) was added. After stirred for 1.5 h, the reaction mixture was filtered and concentrated under reduced pressure. The majority of triphenyl phosphine oxide was removed by precipitation from ethyl acetate-hexane. The crude product was purified by chromatography on silica gel and precipitation from hexane to give the desired product 3-Benzyloxybenzylbromide **6.9** (10 g, 77%) as a white solid.

t-Butyl-3-chloromethyl benzoate 14.5: A benzene solution (15 ml) of 3-chloromethylbenzoic acid **50.5** (1 g, 5.8 mmol) was heated at reflux, followed by the slow addition of N,N-dimethylforamide-di-t-butylacetal (5 m). The resulting solution was refluxed for 4 h, concentrated under reduced pressure and purified by silica gel column to afford **14.5** (0.8 g, 60 %).

Aminopropyl-diethylphosphonate 14.6 is purchased from Acros

Aminoethyl-diethylphosphonate oxalate 14.7 is purchased from Acros

Aminopropyl-phenol-ethyl lactate phosphonate 15.5

N-CBZ-aminopropyl diphenylphosphonate 50.8: An aqueous sodium hydroxide solution (50 mL of 1 N solution, 50 mmol) of 3-aminopropyl phosphonic acid **50.6** (3 g, 1.5 mmol)

was reacted with CBZ-Cl (4.1 g, 24 mmol) at room temperature overnight. The reaction mixture was washed with methylene chloride, acidified with Dowex 50wx8-200. The resin was filtered off. The filtrate was concentrated to dryness. The crude N-CBZ-aminopropyl phosphonic acid **50.7** (5.8 mmol) was suspended in CH_3CN (40 mL), and reacted with thionyl chloride (5.2 g, 44 mmol) at reflux for 4 hr, concentrated, and azeotroped with CH_3CN twice. The reaction mixture was redissolved in methylene chloride (20 mL), followed by the addition of phenol (3.2 g, 23 mmol), was cooled to 0°C. To this 0°C cold solution was added TEA (2.3 g, 23 mmol), and stirred at room temperature overnight. The reaction mixture was concentrated and purified on silica gel column chromatograph to afford **50.8** (1.5 g, 62 %).

Monophenol derivative 50.9: A CH_3CN solution (5 mL) of **50.8** (0.8 g, 1.88 mmol) was cooled to 0°C , and treated with 1N NaOH aqueous solution (4 mL, 4 mmol) for 2 h. The reaction was diluted with water, extracted with ethyl acetate, acidified with Dowex 50wx8-200. The aqueous solution was concentrated to dryness to afford **50.9** (0.56 g, 86%).

Monolactate derivative 50.10: A DMF solution (1 mL) of crude **50.9** (0.17 g, 0.48 mmol), BOP reagent (0.43 g, 0.97 mmol), ethyl lactate (0.12 g, 1 mmol), and DIPEA (0.31 g, 2.4 mmol) was reacted for 4 hr at room temperature. The reaction mixture was partitioned between methylene chloride and 5 % citric acid aqueous solution. The organic solution was separated, concentrated, and purified on preparative TLC to give **50.10** (0.14 g, 66%).

3-Aminopropyl lactate phosphonate 15.5: An ethyl acetate/ethanol solution (10 mL/2 mL) of **50.10** (0.14 g, 0.31 mmol) was hydrogenated at 1 atm in the presence of 10% Pd/C (40 mg) for 3 hr. The catalyst was filtered off. The filtrate was concentrated to dryness to afford **15.5** (0.14 g, quantitative). NMR ($CDCl_3$): δ 8.0-8.2 (b, 3H), 7.1-7.4 (m, 5H), 4.9-5.0 (m, 1H), 4.15-4.3 (m, 2H), 3.1-3.35 (m, 2H), 2.1-2.4 (m, 4H), 1.4 (d, 3H), 1.3 (t, 3H).

Aminopropyl-phenol-ethyl alanine phosphonate 15.6: Compound **15.6** (80 mg) was prepared from the reaction of **50.9** (160 mg, 0.45 mmol) and L-alanine ethyl ester hydrochloride salt (0.11g, 0.68 mmol) in the presence of DIPEA and BOP reagent to give **50.11**, followed by the hydrogenation in the presence of 10% Pd/C and TFA to yield **15.6**. NMR ($CDCl_3$ + ~10 % CD_3OD): δ 8.0-8.2 (b), 7.25-7.35 (t, 2H), 7.1-7.2 (m, 3H), 4.0-4.15

(m, 2H), 3.8-4.0 (m, 1H), 3.0-3.1 (m, 2H), 1.15-1.25 (m, 6H). P NMR ($CDCl_3$ + ~10 % CD_3OD): 32.1 & 32.4 ppm.

Aminopropyl dibenzyl phosphonate 15.7 :

N-BOC-3-aminopropyl phosphonic acid 50.13: A THF-1N aqueous solution (16 mL-16 mL) of 3-aminopropyl phosphonic acid **50.12** (1 g, 7.2 mmol) was reacted with $(BOC)_2O$ (1.7 g, 7.9 mmol) overnight at room temperature. The reaction mixture was concentrated, and partitioned between methylene chloride and water. The aqueous solution was acidified with Dowex 50wx8-200. The resin was filtered off. The filtrate was concentrated to give **50.13** (2.2 g, 92 %).

N-BOC-3-aminopropyl dibenzyl phosphonate 50.14: A CH_3CN solution (10 mL) of **50.13** (0.15 g, 0.63 mmol), cesium carbonate (0.61 g, 1.88 mmol), and benzyl bromide (0.24 g, 1.57 mmol) was heated at reflux overnight. The reaction mixture was cooled to room temperature, and diluted with methylene chloride. The white solid was filtered off, washed thoroughly with methylene chloride. The organic phase was concentrated, and purified on preparative TLC to give **50.14** (0.18 g, 70%). MS: 442 (M + Na).

Aminopropyl dibenzyl phosphonate 15.7: A methylene chloride solution (1.6 mL) of **50.14** (0.18 g) was treated with TFA (0.4 mL) for 1 hr. The reaction mixture was concentrated to dryness, and azeotroped with CH_3CN twice to afford **15.7** (0.2 g, as TFA salt). NMR ($CDCl_3$): δ 8.6 (b, 2H), 7.9 (b, 2H), 7.2-7.4 (m, 10H), 4.71-5.0 (2 abq, 4H), 3.0 (b, 2H), 1.8-2 (m, 4H). 31P NMR ($CDCl_3$): 32.0 ppm. F NMR ($CDCl_3$): -76.5 ppm.

Aminomethyl diethylphosphonate 22.8 is purchased from Acros

Bromomethyl, tetrahydropyran indazole 25.9 is prepared according to J. Org. Chem. 1997, 62, p5627

Activity of the CCPPI Compounds

The enzyme inhibitory potency (Ki), antiviral activity (EC50), and cytotoxicity (CC50) of the tested compounds were measured and demonstrated.

Biological assays used for the characterization of PI prodrugs

HIV-1 Protease Enzyme Assay (*Ki*)

The assay is based on the fluorimetric detection of synthetic hexapeptide substrate cleavage by HIV-1 protease in a defined reaction buffer as initially described by M.V.Toth and G.R.Marshall, Int. J. Peptide Protein Res. 36, 544 (1990)

Substrate: (2-aminobenzoyl)Thr-Ile-Nle-(p-nitro)Phe-Gln-Arg

Substrate supplied by Bachem California, Inc. (Torrance, CA; Cat. no. H-2992)

Enzyme: recombinant HIV-1 protease expressed in E.Coli

Enzyme supplied by Bachem California, Inc. (Torrance, CA; Cat. no. H-9040)

Reaction buffer: 100 mM ammonium acetate, pH 5.3
1 M sodium chloride
1 mM ethylendiaminetetraacetic acid
1 mM dithiothreitol
10% dimethylsulfoxide

Assay protocol for the determination of inhibition constant Ki:

1. Prepare series of solutions containing identical amount of the enzyme (1 to 2.5 nM) and a tested inhibitor at different concentrations in the reaction buffer
2. Transfer the solutions (190 uL each) into a white 96-well plate
3. Preincubate for 15 min at 37°C
4. Solubilize the substrate in 100% dimethylsulfoxide at a concentration of 800 μM. Start the reaction by adding 10 μL of 800 μM substrate into each well (final substrate concentration of 40 μM)
5. Measure the real-time reaction kinetics at 37°C by using Gemini 96-well plate fluorimeter (Molecular Devices, Sunnyvale, CA) at λ(Ex) = 330 nm and λ(Em) = 420 nm
6. Determine initial velocities of the reactions with different inhibitor concentrations and calculate Ki (in picomolar concentration units) value by using EnzFitter program

(Biosoft, Cambridge, U.K.) according to an algorithm for tight-binding competitive inhibition described by Ermolieff J., Lin X., and Tang J., Biochemistry 36, 12364 (1997)

Anti-HIV-1 Cell Culture Assay (EC_{50})

The assay is based on quantification of the HIV-1-associated cytopathic effect by a colorimetric detection of the viability of virus-infected cells in the presence or absence of tested inhibitors. The HIV-1-induced cell death is determined using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) which is converted only by intact cells into a product with specific absorption characteristics as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR, J. Natl. Cancer Inst. 81, 577 (1989).

Assay protocol for determination of EC_{50}:

1. Maintain MT2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.
2. Infect the cells with the wild-type HIV-1 strain IIIB (Advanced Biotechnologies, Columbia, MD) for 3 hours at 37°C using the virus inoculum corresponding to a multiplicity of infection equal to 0.01.
3. Prepare a set of solutions containing various concentrations of the tested inhibitor by making 5-fold serial dilutions in 96-well plate (100 µL/well). Distribute the infected cells into the 96-well plate (20,000 cells in 100 µL/well). Include samples with untreated infected and untreated mock-infected control cells.
4. Incubate the cells for 5 days at 37°C.
5. Prepare XTT solution (6 mL per assay plate) at a concentration of 2mg/mL in a phosphate-buffered saline pH 7.4. Heat the solution in water-bath for 5 min at 55°C. Add 50 µL of N-methylphenazonium methasulfate (5 µg/mL) per 6 mL of XTT solution.
6. Remove 100 µL media from each well on the assay plate.
7. Add 100 µL of the XTT substrate solution per well and incubate at 37°C for 45 to 60 min in a CO_2 incubator.
8. Add 20 µL of 2% Triton X-100 per well to inactivate the virus.
9. Read the absorbance at 450 nm with subtracting off the background absorbance at 650 nm.

10. Plot the percentage absorbance relative to untreated control and estimate the EC_{50} value as drug concentration resulting in a 50% protection of the infected cells.

Cytotoxicity Cell Culture Assay (CC_{50}):

The assay is based on the evaluation of cytotoxic effect of tested compounds using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR, J. Natl. Cancer Inst. 81, 577 (1989).

Assay protocol for determination of CC_{50}:

1. Maintain MT-2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.
2. Prepare a set of solutions containing various concentrations of the tested inhibitor by making 5-fold serial dilutions in 96-well plate (100 µL /well). Distribute cells into the 96-well plate (20,000 cells in 100 µL/well). Include samples with untreated cells as a control.
3. Incubate the cells for 5 days at 37°C.
4. Prepare XTT solution (6 mL per assay plate) in dark at a concentration of 2mg/mL in a phosphate-buffered saline pH 7.4. Heat the solution in a water-bath at 55°C for 5 min. Add 50 µL of N-methylphenazonium methasulfate (5 µg/mL) per 6 mL of XTT solution.
5. Remove 100 µL media from each well on the assay plate and add 100 µL of the XTT substrate solution per well. Incubate at 37°C for 45 to 60 min in a CO_2 incubator.
6. Add 20 µL of 2% Triton X-100 per well to stop the metabolic conversion of XTT.
7. Read the absorbance at 450 nm with subtracting off the background at 650 nm.
8. Plot the percentage absorbance relative to untreated control and estimate the CC50 value as drug concentration resulting in a 50% inhibition of the cell growth. Consider the absorbance being directly proportional to the cell growth.

Resistance Evaluation *(I50V and I84V/L90M fold change)*

The assay is based on the determination of a difference in the susceptibility to a particular HIV protease inhibitor between the wild-type HIV-1 strain and a mutant HIV-1 strain

containing specific drug resistance-associated mutation(s) in the viral protease gene. The absolute susceptibility of each virus (EC_{50}) to a particular tested compound is measured by using the XTT-based cytopathic assay as described above. The degree of resistance to a tested compound is calculated as fold difference in EC_{50} between the wild type and a specific mutant virus. This represents a standard approach for HIV drug resistance evaluation as documented in various publications (e.g. Maguire et al., Antimicrob. Agents Chemother. 46: 731, 2002; Gong et al., Antimicrob. Agents Chemother. 44: 2319, 2000; Vandamme and De Clercq, in Antiviral Therapy (Ed. E. De Clercq), pp. 243, ASM Press, Washington, DC, 2001).

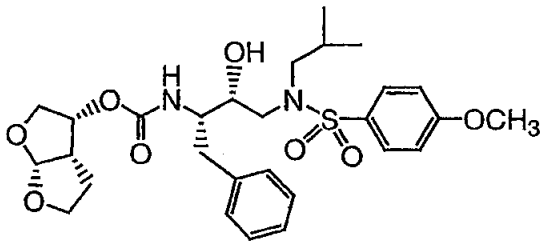
HIV-1 strains used for the resistance evaluation:

Two strains of mutant viruses containing I50V mutation in the protease gene have been used in the resistance assays: one with M46I/I47V/I50V mutations (designated I50V #1) and the other with L10I/M46I/I50V (designated I50V #2) mutations in the viral protease gene. A third virus with I84V/L90M mutations was also employed in the resistance assays. Mutants I50V #1 and I84V/L90M were constructed by a homologous recombination between three overlapping DNA fragments: 1. linearized plasmid containing wild-type HIV-1 proviral DNA (strain HXB2D) with the protease and reverse transcriptase genes deleted, 2. DNA fragment generated by PCR amplification containing reverse transcriptase gene from HXB2D strain (wild-type), 3. DNA fragment of mutated viral protease gene that has been generated by PCR amplification. An approach similar to that described by Shi and Mellors in Antimicrob. Agents Chemother. 41: 2781-85, 1997 was used for the construction of mutant viruses from the generated DNA fragments. Mixture of DNA fragments was delivered into Sup-T1 cells by using a standard electroporation technique. The cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum and antibiotics until the recombinant virus emerged (usually 10 to 15 days following the electroporation). Cell culture supernatant containing the recombinant virus was harvested and stored in aliquots. After verification of protease gene sequence and determination of the infectious virus titer, the viral stock was used for drug resistance studies. Mutant I50V #2 is an amprenavir-resistant HIV-1 strain selected *in vitro* from the wild-type IIIB strain in the presence of increasing concentration of amprenavir over a period of > 9 months using an approach similar to that described by Partaledis et al., J. Virol. 69: 5228-5235, 1995. Virus capable of growing in the presence of 5

μM amprenavir was harvested from the supernatant of infected cells and used for resistance assays following the titration and protease gene sequencing.

Example 37: Activity of the Tested Compounds

The enzyme inhibitory potency (Ki), antiviral activity (EC50), and cytotoxicity (CC50) of the tested compounds are summarized in Table 1.



94-003

Table 1: Enzyme inhibition activity (Ki), antiviral cell culture activity (EC50), and cytotoxicity (CC50) of the tested compounds.

Substitution of (P1)phenyl	Compound	Phosphonate substitution	HIV-1 protease inhibition Ki [pM]	Anti-HIV-1 Cell Culture Activity EC50 [nM]	Cytotoxicity CC50 [μM]
none	Amprenavir	none	45.6 ± 18.2	16 ± 2.2	
none	94-003	none	1.46 ± 0.58	1.4 ± 0.3	
phosphonyl	27	diacid	11.8 ± 6.0	> 100,000	> 100
	28	diethyl	1.2 ± 0.8	5.0 ± 2.8	70
phosphonyl methoxy	11	diacid	2.1 ± 0.2	4,800 ± 1,800	> 100
	13	diethyl	2.6 ± 1.5	3.0 ± 0	50
	14	dibenzyl	12.7 ± 1.9	2.3 ± 0.4	35
	16c	bis(Ala-ethylester)	15.4 ± 0.85	105 ± 43	60
	16d	bis(Ala-butylester)	18.75 ± 3.04	6.0 ± 1.4	
	16e	bis(ABA-ethylester)	8.8 ± 1.7	12.5 ± 3.5	
	16f	bis(ABA-butylester)	3.5 ± 1.4	4.8 ± 1.8	
	16a	bis(Gly-ethylester)	29 ± 8.2	330 ± 230	
	16b	bis(Gly-butylester)	4.9 ± 1.8	17.5 ± 10.5	
	16g	bis(Leu-ethylester)	29 ± 9	6.8 ± 0.4	
	16h	bis(Leu-butylester)	31.7 ± 19.3	120 ± 42	
	16i	bis(Phe-ethylester)		17 ± 12	
	16j	bis(Phe-butylester)		35 ± 7	
	15	bis(POC)	36	825 ± 106	
	11	Monoethyl, monoacid	0.45 ± 0.15	700 ± 0	

Cross-Resistance Profile Assay

The assay is based on the determination of a difference in the susceptibility to a particular HIV protease inhibitor between the wild-type HIV-1 strain and a recombinant HIV-1 strain expressing specific drug resistance-associated mutation(s) in the viral protease gene. The absolute susceptibility of each virus to a particular tested compound is measured by using the XTT-based cytopathic assay as described in Example B. The degree of resistance to a tested compound is calculated as fold difference in EC50 between the wild type and a specific mutant virus.

Recombinant HIV-1 strains with resistance mutations in the protease gene:

One mutant virus (82T/84V) was obtained from NIH AIDS Research and Reference Reagent Program (Rockville, MD). Majority of the mutant HIV-1 strains were constructed by a homologous recombination between three overlapping DNA fragments: 1. linearized plasmid containing wild-type HIV-1 proviral DNA (strain HXB2D) with the protease and reverse transcriptase genes deleted, 2. DNA fragment generated by PCR amplification containing reverse transcriptase gene from HXB2D strain (wild-type), 3. DNA fragment generated by RT-PCR amplification from patients plasma samples containing viral protease gene with specific mutations selected during antiretroviral therapy with various protease inhibitors. Additional mutant HIV-1 strains were constructed by a modified procedure relying on a homologous recombination of only two overlapping DNA fragments: 1. linearized plasmid containing wild-type HIV-1 proviral DNA (strain HXB2D) with only the protease gene deleted, and 2. DNA fragment generated by RT-PCR amplification from patients plasma samples containing viral protease gene with specific mutations. In both cases, mixture of DNA fragments was delivered into Sup-T1 cells by using a standard electroporation technique. The cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum and antibiotics until the recombinant virus emerged (usually 10 to 15 days following the electroporation). Cell culture supernatant containing the recombinant virus was harvested and stored in aliquots. After determination of the virus titer the virus stock was used for drug resistance studies.

Example 39: Cross-Resistance Profile of the Tested Compounds

Cross-resistance profile of currently used HIV-1 protease inhibitors was compared with that of the newly invented compounds (Table 2).

Table 2. Cross-resistance profile of HIV-1 protease inhibitors

Compound	EC 50 [nM] WT HIV -1	Fold Change in EC_{50} Relative to WT HIV-1											Total No. of Resistant Viruses [b]
		8K[a] 46I **90M**	46I **84A**	10I **48V** 54V **82A**	46I 47V **50V**	10R 46I **82T** **84V**	**30N** 50S **82I** 88D	54V 71V **82S**	10F 46I 71V **82T** **90M**	10I **48V** 71V **82A** **90M**	**48V** 54V 71V **82S**	10I **84V** 71V **73S** **90M**	
Amprenavir	20	1.25	**14**	2	**38**	4	0.8	4	**13**	2.5	2	**10**	4
Nelfinavir	14	**13**	**11**	**11.5**	2	3	**43**	**12**	**33**	**27**	**12**	**65**	9
Indinavir	15	4	**10**	**15**	nd	**7**	1	**10**	**13**	**28**	**23**	**43**	8
Ritonavir	15	**34**	**18**	**20**	**13**	**47**	2	**20**	**32**	**22**	**>50**	**42**	10
Saquinavir	4	1	2.5	**11**	1	2.5	1	3	2.5	**12**	**45**	**40**	4
Lopinavir	8	nd	**9**	nd	**19**	**11**	nd	nd	**7.5**	4.5	**60**	**11**	6
Tipranavir	80	nd	1	0.4	0.5	**5**	0.5	3.5	3	0.3	2	**nd**	**1**
94-003	0.5	nd	**8**	0.5	**29**	nd	0.4	3.5	nd	nd	nd	**8**	3
GS 16503	**16**	1.2	1	0.4	3.3	1	0.6	0.9	1	0.4	0.5	2	0
GS 16571	22	1.8	1	0.3	0.8	0.6	0.7	0.6	0.8	0.2	0.2	0.9	0
GS 16587	15	1.5	1	0.5	2	1	1	0.9	1	0.4	0.4	1	0

[a] Resistance-associated mutations present in the viral protease. The highlighted changes represent primary resistance mutations.

[b] Resistance is considered as a 5-fold and higher change in the EC50 value of the mutant virus relative to the wild-type virus.

Example Section N

Plasma and PBMC Exposure Following Intravenous and Oral Administration of Prodrug to Beagle Dogs

The pharmacokinetics of a phosphonate prodrug GS77366 (P1-monoLac-iPr), its active metabolite (metabolite X, or GS77568), and GS8373 were studied in dogs following intravenous and oral administration of the prodrug.

Dose Administration and Sample Collection. The in-life phase of this study was conducted in accordance with the USDA Animal Welfare Act and the Public Health Service Policy on Humane Care and Use of Laboratory Animals, and followed the standards for animal husbandry and care found in the Guide for the Care and Use of Laboratory Animals, 7th Edition, Revised 1996. All animal housing and study procedures involving live animals were carried out at a facility which had been accredited by the Association for Assessment and Accreditation of Laboratory Animal Care - International (AAALAC).

Each animal in a group of 4 female beagle dogs was given a bolus dose of GS77366 (P1-monoLac-iPr) intravenously at 1 mg/kg in a formulation containing 40% PEG 300, 20% propylene glycol and 40% of 5% dextrose. Another group of 4 female beagle dogs was dosed with GS77366 via oral gavage at 20 mg/kg in a formulation containing 60% Vitamin-E TPGS, 30% PEG 400 and 10% propylene glycol.

Blood samples were collected pre-dose, and at 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr and 24 hr post-dose. Plasma (0.5 to 1 mL) was prepared from each sample and kept at -70°C until analysis. Blood samples (8 mL) were also collected from each dog at 2, 8 and 24 hr post dose in Becton-Dickinson CPT vacutainer tubes. PBMCs were isolated from the blood by centrifugation for 15 minutes at 1500 to 1800 G. After centrifugation, the fraction containing PBMCs was transferred to a 15 mL conical centrifuge tube and the PBMCs were washed twice with phosphate buffered saline (PBS) without Ca^{2+} and Mg^{2+}. The final wash of the cell pellet was kept at -70°C until analysis.

Measurement of the prodrug, metabolite X and GS8373 in plasma and PBMCs. For plasma sample analysis, the samples were processed by a solid phase extraction (SPE) procedure outlined below. Speedisk C18 solid phase extraction cartridges (1 mL, 20 mg, 10 µM, from

J.T. Baker) were conditioned with 200 µL of methanol followed by 200 µL of water. An aliquot of 200 µL of plasma sample was applied to each cartridge, followed by two washing steps each with 200 µL of deionized water. The compounds were eluted from the cartridges with a two-step process each with 125 µL of methanol. Each well was added 50 µL of water and mixed. An aliquot of 25 µL of the mixture was injected onto a ThermoFinnigan TSQ Quantum LC/MS/MS system.

The column used in liquid chromatography was HyPURITY® C18 (50 x 2.1 mm, 3.5 um) from Thermo-Hypersil. Mobile phase A contained 10% acetonitrile in 10 mM ammonium formate, pH 3.0. Mobile phase B contained 90% acetonitrile in 10 mM ammonium formate, pH 4.6. The chromatography was carried out at a flow rate of 250 µL/min under an isocratic condition of 40% mobile phase A and 60% mobile phase B. Selected reaction monitoring (SRM) were used to measure GS77366, GS8373 and Metabolite X with the positive ionization mode on the electrospray probe. The limit of quantitation (LOQ) was 1 nM for GS77366, GS8373 and GS77568 (Metabolite X) in plasma.

For PBMC sample analysis, phosphate buffered saline (PBS) was added to each PBMC pellet to bring the total sample volume to 500 µL in each sample. An aliquot of 150 µL from each PBMC sample was mixed with an equal volume of methanol, followed by the addition of 700 µL of 1% formic acid in water. The resulting mixture was applied to a Speedisk C18 solid phase extraction cartridge (1 mL, 20 mg, 10 um, from J.T. Baker) which had been conditioned as described above. The compounds were eluted with methanol after washing the cartridge 3 times with 10% methanol. The solvent was evaporated under a stream of N_2, and the sample was reconstituted in 150 µL of 30% methanol. An aliquot of 75 µL of the solution was injected for LC/MS/MS analysis. The limit of quantitation was 0.1 ng/mL in the PBMC suspension.

Pharmacokinetic Calculations. The pharmacokinetic parameters were calculated using WinNonlin. Noncompartmental analysis was used for all pharmacokinetic calculation. The intracellular concentrations in PBMCs were calculated from the measured concentrations in PBMC suspension on the basis of a reported volume of 0.2 picoliter/cell (B.L. Robins, R.V. Srinivas, C.Kim, N.Bischofberger, and A.Fridland, (1998) Antimicrob. Agents Chemother. 42, 612).

Plasma and PBMC Concentration-time Profiles.

The concentration-time profiles of GS77366, GS77568 and GS8373 in plasma and PBMCs following intravenous dosing of GS77366 were compared at 1 mg/kg in dogs. The data demonstrate that the prodrug can effectively deliver the active components (metabolite X and GS8373) into cells that are primarily responsible for HIV replication, and that the active components in these cells had much longer half-life than in plasma.

The pharmacokinetic properties of GS77568 in PBMCs following oral administration of GS77366 in dogs are compared with that of nelfinavir and amprenavir, two marketed HIV protease inhibitors (Table 3). These data show that the active component (GS77568) from the phosphonate prodrug had sustained levels in PBMCs compared to nelfinavir and amprenavir.

Table 3. Comparison of GS77568 with nelfinavir and amprenavir in PBMCs following oral administration in beagle dogs.

Compound	Dose	$t_{1/2}$ (hr)	$AUC_{(2\text{-}24\ hr)}$
Nelfinavir	17.5 mg/kg	3.0 hr	33,000 nM·hr
Amprenavir	20 mg/kg	1.7 hr	102,000 nM·hr
GS77568	20 mg/kg of GS77366	> 20 hr	42,200 nM·hr

Example Section O

Intracellular Metabolism/In Vitro Stability

1. Uptake and Persistence in MT2 cells, quiescent and stimulated PBMC

The protease inhibitor (PI) phosphonate prodrugs undergo rapid cell uptake and metabolism to produce acid metabolites including the parent phosphonic acid. Due to the presence of charges, the acid metabolites are significantly more persistent in the cells than non-charged PI's. In order to estimate the relative intracellular levels of the different PI prodrugs, three compounds representative of three classes of phosphonate PI prodrugs – bisamidate phosphonate, monoamidate phenoxy phosphonate and monolactate phenoxy phosphonate (Figure 1) were incubated at 10 μM for 1 hr with MT-2 cells, stimulated and quiescent peripheral blood mononuclear cells (PBMC) (pulse phase). After incubation, the cells were washed, resuspended in the cell culture media and incubated for 24 hr (chase phase). At specific time points, the cells were washed, lysed and the lysates were analyzed by HPLC with UV detection. Typically, the cell lysates were centrifuged and 100 uL of the supernatant were mixed with 200 μL of 7.5 uM amprenavir (Internal Standard) in 80% acetonitrile/20% water and injected into an HPLC system (70 μL).

HPLC Conditions:

Analytical Column: Prodigy ODS-3, 75 x 4.6, 3u + C18 guard at 40°C

Gradient:

Mobile Phase A: 20 mM ammonium acetate in 10% ACN/90% H_2O

Mobile Phase B: 20 mM ammonium acetate in 70% ACN/30% H_2O

30-100%B in 4 min, 100%B for 2 min, 30%B for 2 min at 2.5 mL/min.

Run Time: 8 min

UV Detection at 245 nm

Concentrations of Intracellular metabolites were calculated based on cell volume 0.2 μL/mLn cells for PBMC and 0.338 μL / mLn (0.676 uL / mL) for MT-2 cells.

Chemical Structures of Selected Protease Inhibitor Phosphonate Prodrugs and Intracellular Metabolites:

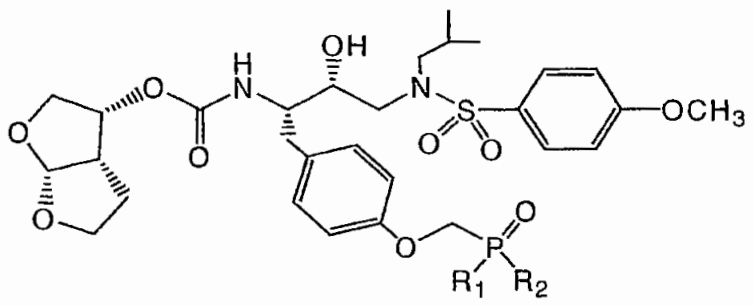


Table 4:

GS No.	R1	R2	EC_{50} (nM)
8373	OH	OH	4,800±1,800
16503	$HNCH(CH_3)COOBu$	$HNCH(CH_3)COOBu$	6.0±1.4
16571	OPh	$HNCH(CH_3)COOEt$	15±5
17394	OPh	$OCH(CH_3)COOEt$	20±7
16576	OPh	$HNCH(CH_2CH_3)COOEt$	12.6±4.8
Met X	OH	$HNCH(CH_3)COOH$	>10,000
Met LX	OH	$OCH(CH_3)COOEt$	1750±354

A significant uptake and conversion of all 3 compounds in all cell types was observed (Table 4). The uptake in the quiescent PBMC was 2-3-fold greater than in the stimulated cells. GS-16503 and GS-16571 were metabolized to Metabolite X and GS-8373. GS-17394 metabolized to the Metabolite LX. Apparent intracellular half-lives were similar for all metabolites in all cell types (7-12 hr). A persistence of Total Acid Metabolites of Protease Inhibitor Prodrugs in Stimulated (A), Quiescent PBMC (B) and MT-2 Cells (C) (1 hr, 10 uM Pulse, 24 hr Chase) was observed.

2. Uptake and Persistence in Stimulated and Quiescent T-cells

Since HIV mainly targets T-lymphocytes, it is important to establish the uptake, metabolism and persistence of the metabolites in the human T-cells. In order to estimate the relative intracellular levels of the different PI prodrugs, GS-16503, 16571 and 17394 were incubated at 10 μM for 1 hr with quiescent and stimulated T-cells (pulse phase). The prodrugs were compared with a non-prodrug PI, nelfinavir. After incubation, the cells were washed, resuspended in the cell culture media and incubated for 4 hr (chase phase). At specific time

points, the cells were washed, lysed and the lysates were analyzed by HPLC with UV detection. The sample preparation and analysis were similar to the ones described for MT-2 cells, quiescent and stimulated PBMC.

Table 5 demonstrate the levels of total acid metabolites and corresponding prodrugs in T-cells following pulse/chase and continuous incubation. There was significant cell uptake/metabolism in T-lymphocytes. There was no apparent difference in uptake between stimulated and quiescent T-lymphocytes. There was significantly higher uptake of phosphonate PI's than nelfinavir. GS17394 demonstrates higher intracellular levels than GS16571 and GS16503. The degree of conversion to acid metabolites varied between different prodrugs. GS-17394 demonstrated the highest degree of conversion, followed by GS-16503 and GS-16571. The metabolites, generally, were an equal mixture of the mono-phosphonic acid metabolite and GS-8373 except for GS-17394, where Metabolite LX was stable, with no GS-8373 formed.

Table 5. Intracellular Levels of Metabolites and Intact Prodrug Following Continuous and 1 hr Pulse/4 hr Chase Incubation (10 μM/0.7 mLn cells/1 mL) of 10 μM PI Prodrugs and Nelfinavir with Quiescent and Stimulated T-cell

		Continuous Incubation				1 hr Pulse /4 hr Chase			
		Quiescent T-cells		Stimulated T-cells		Quiescent T-cells		Stimulated T-cells	
Compound	Time (h)	Acid Met (μM)	Prodrug (μM)	Acid Met (μM)	Prodrug (μM)	Acid Met (μM)	Prodrug (μM)	Acid Met (μM)	Prodrug (μM)
16503	0	1180	42	2278	0	2989	40	1323	139
	2	3170	88	1083	116	1867	4	1137	31
	4	5262	0	3198	31	1054	119	1008	0
16571	0	388	1392	187	1417	1042	181	858	218
	2	947	841	1895	807	1170	82	1006	35
	4	3518	464	6147	474	1176	37	616	25
17394	0	948	1155	186	1194	4480	14	2818	10
	2	7231	413	3748	471	2898	33	1083	51
	4	10153	167	3867	228	1548	39	943	104
Nelfinavir	0		101		86		886		1239
	2		856		846		725		770
	4		992		1526		171		544

3. PBMC Uptake and Metabolism of Selected PI Prodrugs Following 1-hr Incubation in MT-2 Cells at 10, 5 and 1 μM.

To were similar to the determine if the cell uptake/metabolism is concentration dependent, selected PI's were incubated with the 1 mL of MT-2 cell suspension (2.74 mLn cells/mL) for 1 hr at 37°C at 3 different concentrations: 10, 5 and 1 μM. Following incubation, cells were washed twice with the cell culture medium, lysed and assayed using HPLC with UV detection. The sample preparation and analysis ones described for MT-2 cells, quiescent and stimulated PBMC. Intracellular concentrations were calculated based on cell count, a published single cell volume of 0.338 pl for MT-2 cells, and concentrations of analytes in cell lysates. Data are shown in Table 6.

Uptake of all three selected PI's in MT-2 cells appears to be concentration-independent in the 1-10 μM range. Metabolism (conversion to acid metabolites) appeared to be concentration-dependent for GS-16503 and GS-16577 (3-fold increase at 1 μM vs. 10 μM) but independent for GS-17394 (monolactate). Conversion from a respective metabolite X to GS-8373 was concentration-independent for both GS-16503 and GS-16577 (no conversion was observed for metabolite LX of GS-17394).

Table 6. Uptake and Metabolism of Selected PI Prodrugs Following 1-hr Incubation in MT-2 Cells at 10, 5 and 1 μM.

Compound	Extracellular Concentration, μM	Cell-Assosiated Prodrug and Metabolites Concentration, μM				% Conversion to acid metabolites
		Metabolite X	GS8373	Prodrug	Total	
GS-17394	10	1358	0	635	1993	68
	5	916	0	449	1365	67
	1	196	0	63	260	76
GS-16576	10	478	238	2519	3235	22
	5	250	148	621	1043	40
	1	65	36	61	168	64
GS-16503	10	120	86	1506	1712	12
	5	58	60	579	697	17
	1	12	18	74	104	29

* For GS16576, Metabolite X is mono-aminobutyric acid

4. PBMC Uptake and Metabolism of Selected PI Prodrugs Following 1-hr Incubation in Human Whole Blood at 10 μM.

In order to estimate the relative intracellular levels of the different PI prodrugs under conditions simulating the in vivo environment, compounds representative of three classes of phosphonate PI prodrugs – bisamidate phosphonate (GS-16503), monoamidate phenoxy phosphonate (GS-16571) and monolactate phenoxy phosphonate(GS-17394) were incubated at 10 μM for 1 hr with intact human whole blood at 37°C. After incubation, PBMC were isolated, then lysed and the lysates were analyzed by HPLC with UV detection. The results of analysis are shown in Table 7. There was significant cell uptake/metabolism following incubation in whole blood. There was no apparent difference in uptake between GS-16503 and GS-16571. GS-17394 demonstrated significantly higher intracellular levels than GS-16571 and GS-16503.

The degree of conversion to acid metabolites varies between different prodrugs after 1 hr incubation. GS-17394 demonstrated the highest degree of conversion, followed by GS-16503 and GS-16571 (Table 7). The metabolites, generally, were an equimolar mixture of the mono-phosphonic acid metabolite and GS-8373 (parent acid) except for GS-17394, where Metabolite LX was stable with no GS-8373 formed.

Table 7. PBMC Uptake and Metabolism of Selected PI Prodrugs Following 1-hr Incubation in Human Whole Blood at 10 μM (Mean ± SD, N=3).

GS#	Intracellular Prodrug and Metabolites Concentration, μM			Major Intracellular Metabolites
	Acid Metabolite	Prodrug, μM	Total, μM	
16503	279 ± 47	61 ± 40	340 ± 35	X , GS-8373
16571	319 ± 112	137 ± 62	432 ± 208	X, GS-8373
17394	629 ± 303	69 ± 85	698 ± 301	LX

* PBMC Intracellular Volume = 0.2 µL/mln

5. Distribution of PI Prodrugs in PBMC

In order to compare distribution and persistence of PI phosphonate prodrugs with those of non-prodrug PI's, GS-16503, GS-17394 and nelfinavir, were incubated at 10 µM for 1 hr with PBMC (pulse phase). After incubation, the cells were washed, resuspended in the cell culture media and incubated for 20 more hr (chase phase). At specific time points, the cells were washed and lysed. The cell cytosol was separated from membranes by centrifugation at 9000 xg. Both cytosol and membranes were extracted with acetonitrile and analyzed by HPLC with UV detection.

Table 8 shows the levels of total acid metabolites and corresponding prodrugs in the cytosol and membranes before and after the 22 hr chase. Both prodrugs exhibited complete conversion to the acid metabolites (GS-8373 and X for GS-16503 and LX for GS-17394, respectively). The levels of the acid metabolites of the PI phosphonate prodrugs in the cytosol fraction were 2-3-fold greater than those in the membrane fraction after the 1 hr pulse and 10-fold greater after the 22 hr chase. Nelfinavir was present only in the membrane fractions. The uptake of GS-17394 was about 3-fold greater than that of GS-16503 and 30-fold greater than nelfinavir. The metabolites were an equimolar mixture of metabolite X and GS-8373 (parent acid) for GS-16503 and only metabolite LX for GS-17394.

Table 8. Uptake and Cell Distribution of Metabolites and Intact Prodrugs Following Continuous and 1 hr Pulse/22 hr Chase Incubation of 10 μM PI Prodrugs and Nelfinavir with Quiescent PBMC.

GS#	Cell Type	Fraction	Cell-Associated PI, pmol/mln cells			
			1 hr Pulse/ 0 hr Chase		1 hr Pulse/ 22 hr Chase	
			Acid Metabolites	Prodrug	Acid Metabolites	Prodrug
GS-16503	PBMC	Membrane	228	0	9	0
GS-16503	PBMC	Cytosol	390	0	130	0
GS-17394	PBMC	Membrane	335	0	26	0
GS-17394	PBMC	Cytosol	894	0	249	0
Nelfinavir	PBMC	Membrane		42		25
Nelfinavir	PBMC	Cytosol		0		0

Uptake and cell distribution of metabolites and intact prodrugs following 1 hr pulse/22 hr chase incubation of 10 μM PI prodrugs and Nelfinavir with quiescent PBMC were measured.

6. PBMC Extract/Dog Plasma/Human Serum Stability of Selected PI Prodrugs

The *in vitro* metabolism and stability of the PI phosphonate prodrugs were determined in PBMC extract, dog plasma and human serum (Table 9). Biological samples listed below (120 μL) were transferred into an 8-tube strip placed in the aluminum 37°C heating block/holder and incubated at 37°C for 5 min. Aliquots (2.5 μL) of solution containing 1 mM of test compounds in DMSO, were transferred to a clean 8-tube strip, placed in the aluminum 37°C heating block/holder. 60 μL aliquots of 80% acetonitrile/20% water containing 7.5 μM of amprenavir as an internal standard for HPLC analysis were placed into five 8-tube strips and kept on ice/refrigerated prior to use. An enzymatic reaction was started by adding 120 μL aliquots of a biological sample to the strip with the test compounds using a multichannel pipet. The strip was immediately vortex-mixed and the reaction mixture (20 μL) was sampled and transferred to the Internal Standard/ACN strip. The sample was considered the time-zero sample (actual time was 1-2 min). Then, at specific time points, the

reaction mixture (20 µL) was sampled and transferred to the corresponding IS/ACN strip. Typical sampling times were 6, 20, 60 and 120 min. When all time points were sampled, an 80 µL aliquot of water was added to each tube and strips were centrifuged for 30 min at 3000xG. The supernatants were analyzed with HPLC under the following conditions:

Column: Inertsil ODS-3, 75 x 4.6 mm, 3 µm at 40°C.
Mobile Phase A: 20 mM ammonium acetate in 10%ACN/90%water
Mobile Phase B 20 mM ammonium acetate in 70%ACN/30%water
Gradient: 20% B to 100% B in 4 min, 2 min 100% B, 2 min 20% B
Flow Rate: 2 mL/min
Detection: UV at 243 nm
Run Time: 8 min

The biological samples evaluated were as follows:

PBMC cell extract was prepared from fresh cells using a modified published procedure (A. Pompon, I. Lefebvre, J-L. Imbach, S. Kahn, and D. Farquhar, Antiviral Chemistry & Chemotherapy, 5, 91 - 98 (1994)). Briefly, the extract was prepared as following: The cells were separated from their culture medium by centrifugation (1000 g, 15 min, ambient temperature). The residue (about 100 µL, 3.5 x 10^8 cells) was resuspended in 4 mL of a buffer (0.010 M HEPES, pH 7.4, 50 mM potassium chloride, 5 mM magnesium chloride and 5 mM dl-dithiothreitol) and sonicated. The lysate was centrifuged (9000 g, 10 min, 4°C) to remove membranes. The upper layer (0.5 mg protein/mL) was stored at –70°C. The reaction mixture contained the cell extract at about 0.5 mg protein/mL.

Human serum (pooled normal human serum from George King Biomedical Systems, Inc.). Protein concentration in the reaction mixture was about 60 mg protein/mL.

Dog Plasma (pooled normal dog plasma (EDTA) from Pel Freez, Inc.). Protein concentration in the reaction mixture was about 60 mg protein/mL.

Table 9: PBMC Extract/Dog Plasma/Human Serum Stability of Selected PI Prodrugs

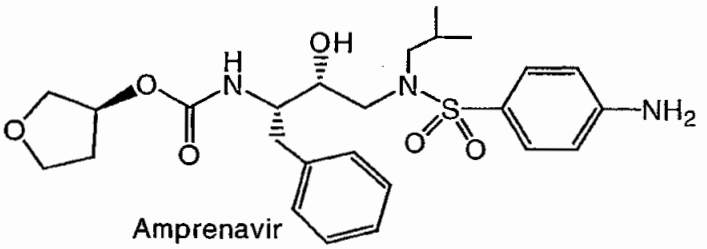
GS#	PBMC Extract[1] $T_{1/2}$, min	Dog Plasma $T_{1/2}$, min	Human Serum $T_{1/2}$, min	HIV EC_{50} (nM)
16503	2	368	>>400	6.0 ± 1.4
16571	49	126	110	15 ± 5
17394	15	144	49	20 ± 7

5

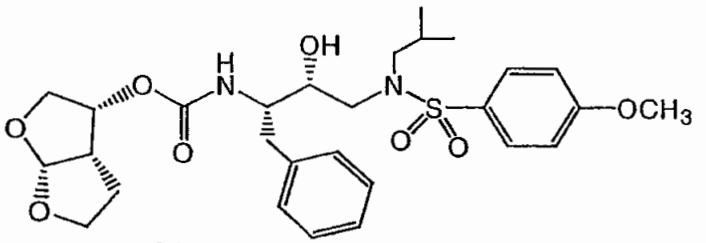
Example Section P

Table 10: Enzymatic and Cellular data

Formula II ALPPI activity



Amprenavir



94-003

Ki [pM]	
≤ 10	+++
> 10 to ≤ 100	++
> 100 to ≤ 1,000	+
> 1,000	-

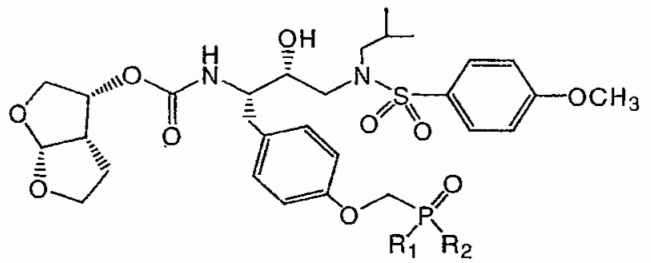
EC_{50} [nM]	
≤ 50	+++
> 50 to ≤ 500	++
> 500 to ≤ 5,000	+
> 5,000	-

I50V and I84V/L90M fold change	
> 30	+++
> 10 to ≤ 30	++
> 3 to ≤ 10	+
≤ 3	-

CC_{50} [µM]	
≤ 5	++
> 5 to ≤ 50	+
> 50	-

Compound	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I50V (#2) fold change	I84V/L90M fold change	CC_{50} (μM)
Saquinavir	++	+++	_	_	+++	
Nelfinavir	+	+++	_	+	+++	
Indinavir	+	+++	_	+	+++	
Ritonavir	++	+++	++	++	+++	
Lopinavir	++	+++	++	+++	++	
Amprenavir	+	+++	+++	+++	++	_
Atazanavir	++	+++	_	_	+++	
Tipranavir	++	++	_	_	+	
94-003	+++	+++	+++	+++	++	+
TMC114	+++	+++	++	++	_	

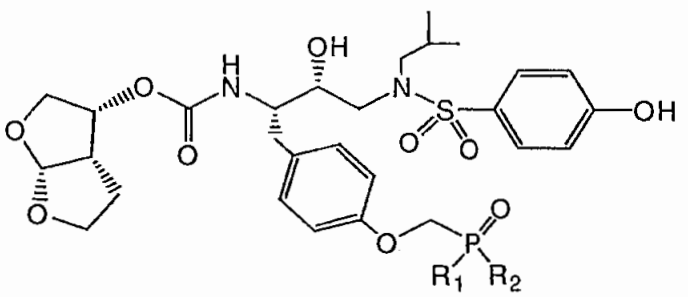
P1-Phosphonic acid and esters



R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} (μM)
OH	OH	+++	+	–	–	–
OMe	OMe	++	+++			
OEt	OEt	+++	+++	–	–	+
OCH_2CF_3	OCH_2CF_3	++	–			
OiPr	OiPr	++	+++	–	–	
OPh	OPh		+++			
OMe	OPh	++	+++			
OEt	OPh	+++	+++			
OBn	OBn	++	+++	–	–	+
OEt	OBn	++	+++			++
OPoc	OPoc		+			
OH	OEt		++			
OH	OPh	+++	–			
OH	OBn		+	–	–	

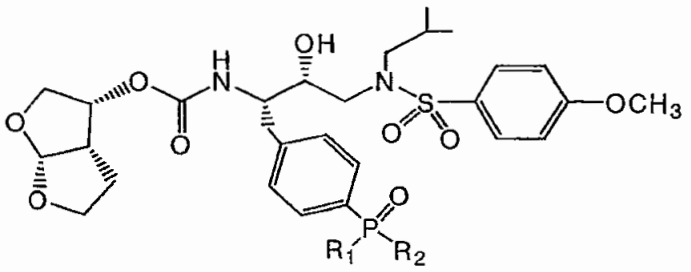
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P1-Phosphonic acid and esters



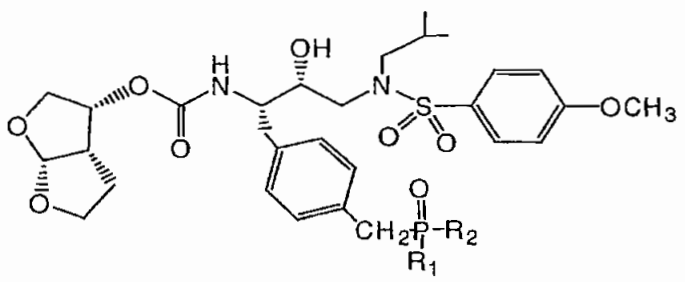
R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} (μM)
OH	OH	+++	+			
Et	Et	+++	+++			

P1-Direct phosphonic acid and esters



R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} μM
OH	OH	++	–			
OEt	OEt	+++	+++	+	–	

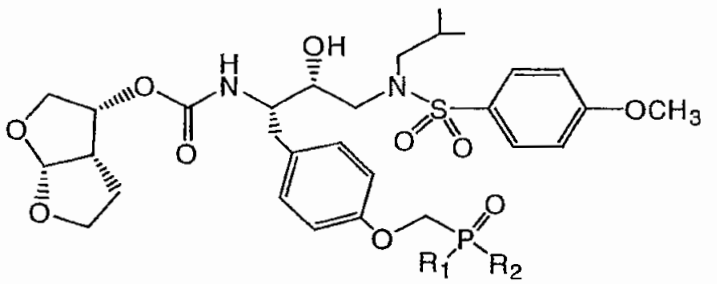
P1-CH_2-phosphonic acid and esters



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R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
OE	OE	+++	+++	+	+	

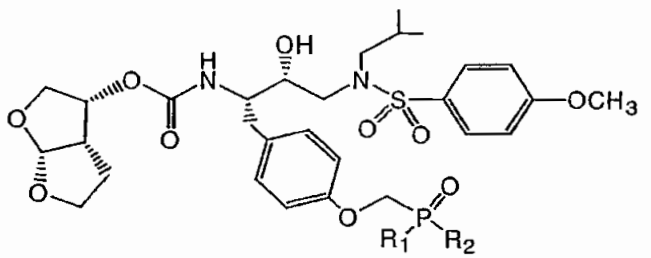
P1-P-Bisamidates



R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} μM
NHEt	NHEt	+++	++	–	–	
Gly-Et	Gly-Et	++	++			
Gly-Bu	Gly-Bu	+++	+++			
Ala-Et	Ala-Et	++	++		–	–
Ala-Bu	Ala-Bu	++	+++	+	–	
Aba-Et	Aba-Et	+++	+++			
Aba-Bu	Aba-Bu	+++	+++	++	+	
Val-Et	Val-Et	+	+++	–	–	
Leu-Et	Leu-Et	++	+++			
Leu-Bu	Leu-Bu	++	++	+	+	
Phe-Et	Phe-Et		+++			
Phe-Bu	Phe-Bu		+++			

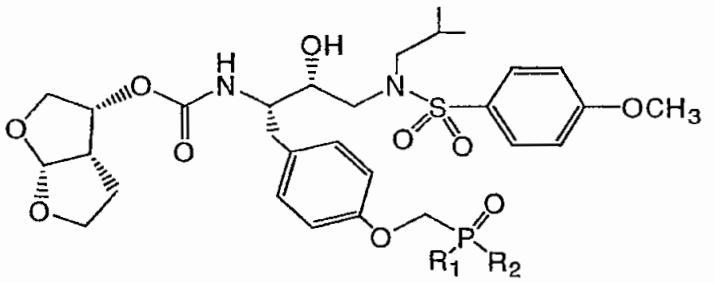
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P1-P-Bislactates



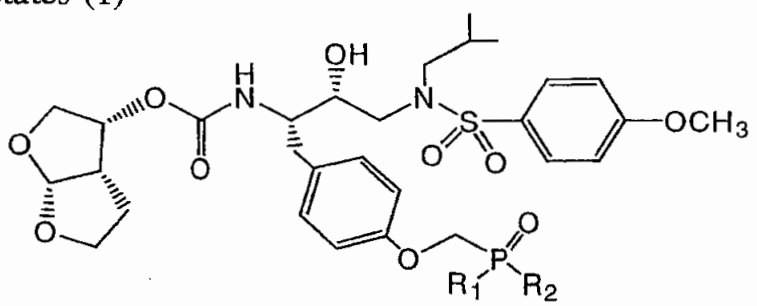
R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} μM
Glc-Et	Glc-Et	+++	+	–	–	
Lac-Et	Lac-Et	++	++	–	–	
Lac-iPr	Lac-iPr	++	+++		–	

P1-P-Monoamidates



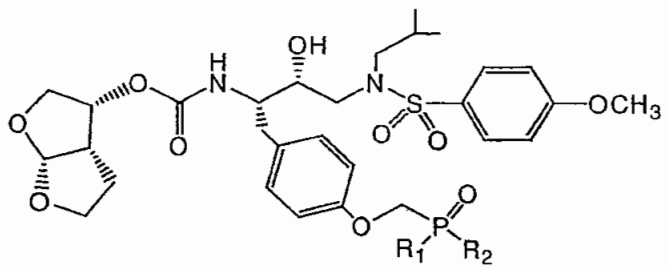
R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
OPh	Gly-Bu	++	++	_	_	
OPh	Ala-Me	++	+++		_	
OPh	Ala-Et	+++	+++	_	_	
OPh	Ala-iPr	++	+++	_	_	
OPh	Ala-iPr	+++	+++			
OPh	Ala-iPr	++	+++			
OPh	(D)Ala-iPr	++	+++		_	
OPh	(D)Ala-iPr	+++	+++			
OPh	(D)Ala-iPr	+++	+++			
OPh	Ala-Bu	++	+++	_	_	
OPh	Ala-Bu	++	+++	_		
OPh	Ala-Bu	++	+++	_		
OPh	Aba-Et		+++			
OPh	Aba-Et		+++	_	_	
OPh	Aba-Et		++			
OPh	Aba-Bu		+++	+	_	
OPh	Aba-Bu		++	_	_	
OBn	Ala-Et	+++	+++	_	_	
OH	Ala-OH	+++	_			
OH	Ala-Bu		_			

P1-P-Monolactates (1)



R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I50V (#2) fold change	I84V/L90M fold change	CC_{50} µM
OPh	Glc-Et	+++	+++	–		–	
OPh	Lac-Me		++	–			
OPh	Lac-Et		+++	–	+	–	+
OPh	Lac-Et	+++	+++	–		–	
OPh	Lac-Et	++	+++	–		–	
OPh	Lac-iPr	++	+++	–		–	
OPh	Lac-iPr	+++	+++				
OPh	Lac-iPr	++	+++				
OPh	Lac-Bu	++	++			–	
OPh	Lac-Bu	++	++				
OPh	Lac-Bu	++	++				
OPh	Lac-EtMor		–				
OPh	Lac-PrMor		–				
OPh	(R)Lac-Me	+++	+++				
OPh	(R)Lac-Et	+++	+++	–		–	
OEt	Lac-Et		++				
OCH_2CF_3	Lac-Et		++				
OBn	Lac-Bn	++	++				
OBn	(R)Lac-Bn						
OH	Lac-OH	+++	+			–	
OH	(R)Lac-OH	++	+			–	

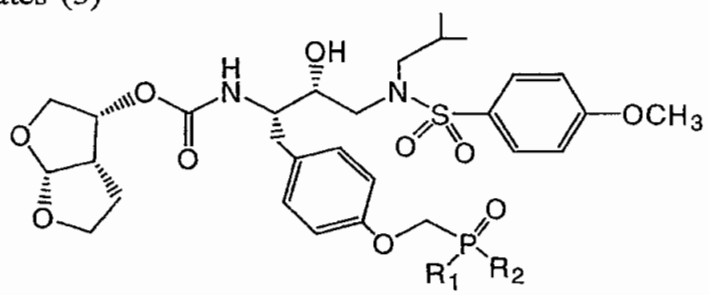
P1-P-Monolactates (2)



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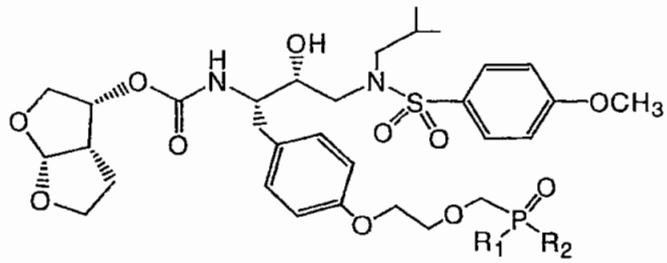
R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
OPh	mix-Hba-Et	++	+++	+	–	
OPh	(S)Hba-Et	+	+++			
OPh	(S)Hba-tBu		+++			
OH	(S)Hba-OH	++				
OPh	(R)Hba-Et		+++			
OPh	(S)MeBut-Et		+++			
OPh	(R)MeBut-Et		+++			
OPh	DiMePro-Me	++				
OPh	(S)Lac-EtMor		–			
OPh	(S)Lac-PrMor		–			
OPh	(S)Lac-EtPip		++	–	–	

P1-P-Monolactates (3)



R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
OPh—*o*-i-But	(S)Lac-Et		+++			
OPh—*p*-n-Oct	(S)Lac-Et		++			
OPh—*p*-n-But	(S)Lac-Et		+++			
OPh-*m*-COOBn	(S)Lac-Et		++			
OPh-*m*-COOH	(S)Lac-Et		++			
OPh-*m*-CH_2OH	(S)Lac-Et		++	–	–	
OPh-*m*-CH_2NH_2	(S)Lac-Et	++	++			
OPh-*m*-CH_2NMe_2	(S)Lac-Et		+			
OPh-*m*-CH_2Mor	(S)Lac-Et		++	–	–	
OPh-*m*-CH_2Pip	(S)Lac-Et		++			
OPh-*m*-CH_2NMeC2OM	(S)Lac-Et		++			
OPh-*o*-OEt	(S)Lac-Et		+++			
$ONMe_2$	(S)Lac-Et		++			
OPip	(S)Lac-Et		+			
OMor	(S)Lac-Et		–			

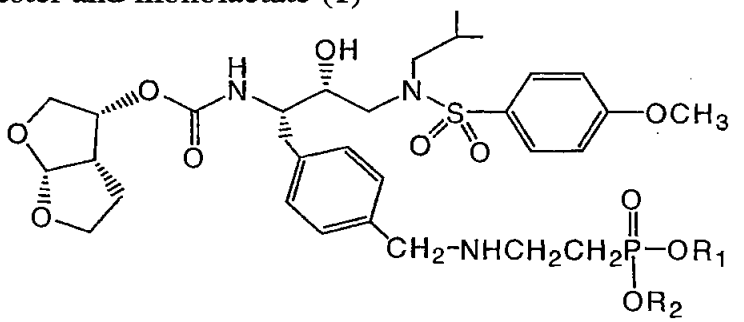
P1-C_2H_4-P-Monolactates



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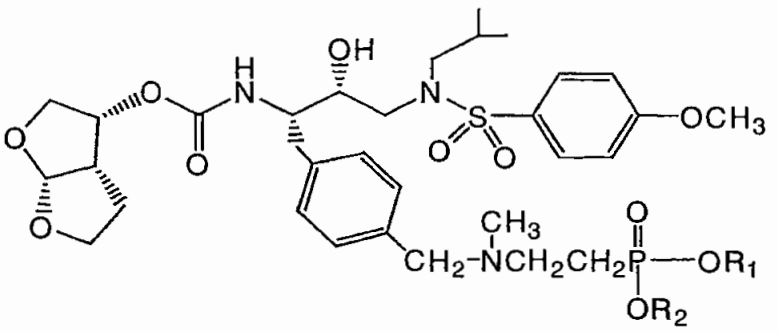
R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
-OC_2H_4OBn			+++			
OEt	OEt		+++	–	–	
OPh	Lac-Et		++	–	–	
OH	OH	++				
OH	Lac	++				

P1-CH_2N-P-diester and monolactate (1)



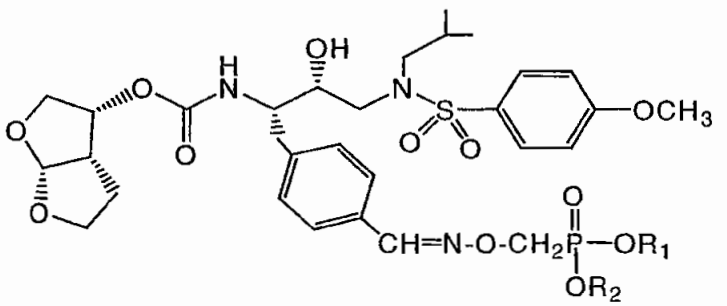
R_1	R_2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I50V (#2) fold change	I84V/L9M fold change	CC_{50} µM
Et	Et	++	+++		–		
H	H	++	-		+		
Ph	Lac-Et		++	–	++	–	
Ph	Lac-Et		+		+	–	–
Ph	Lac-Et		+		++	–	
Ph	Aba-Et		+		+	–	
Ph-oEt	Lac-Et	++	++	–	++	–	
Ph-dM	Lac-Et		+++		+	+	
Ph-dM	Lac-Pr		+++				
H	Lac	++					
Ph	Hba-Et		++		++	–	
Ph	Hba-Et		++		++	–	+
Ph	Hba-Et		++		++	–	
H	Hba	+					

P1-CH_2N-P-diester and monolactate (2)



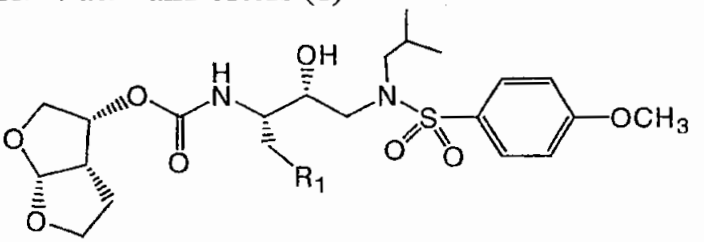
R_1	R_2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
Ph	Lac-Et	+	++	+	+	
H	H	++				

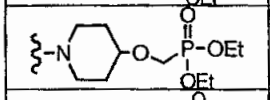
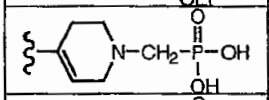
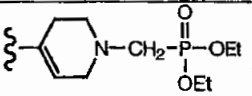
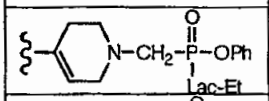
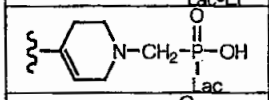
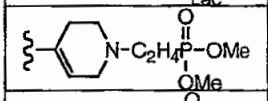
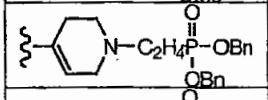
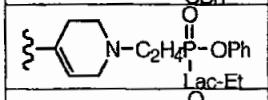
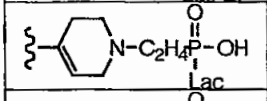
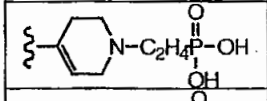
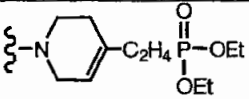
P1-CH_2N-P-diester and monolactate (3)



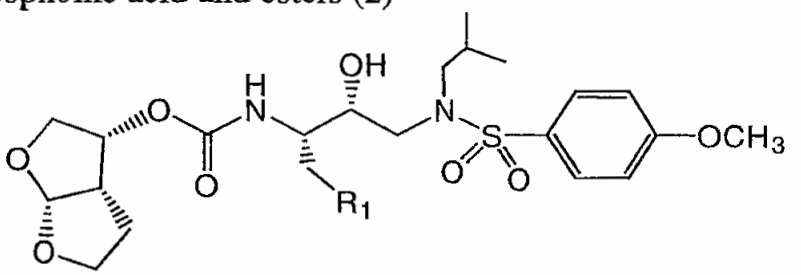
R_1	R_2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50}µM
Et	Et	++	+++		–	

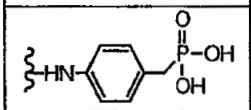
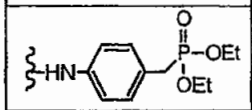
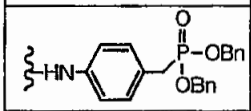
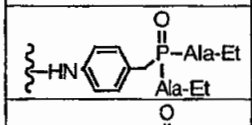
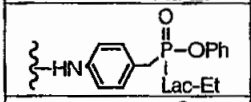
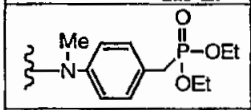
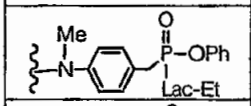
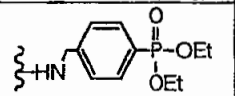
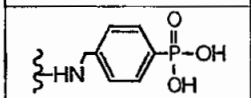
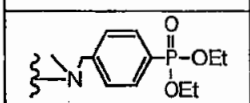
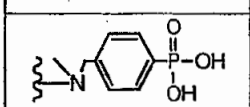
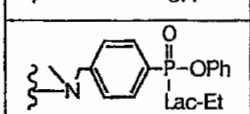
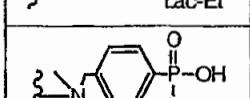
P1-N-P1-Phosphonic acid and esters (1)



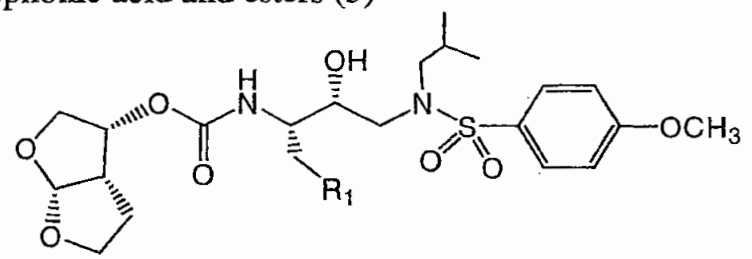
R1	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
	–	++			
	–	++			
	–				
	++	+++		+	
		–			
	–				
	+	++			
	++	+++		+	
		–			
		–			
	–				
	+	+++		+	

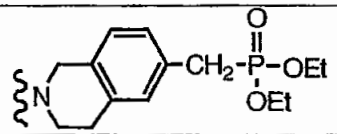
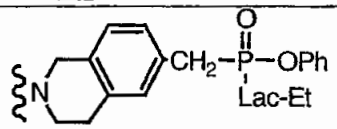
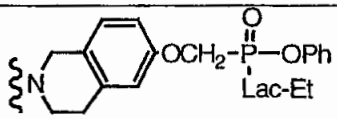
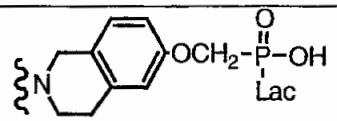
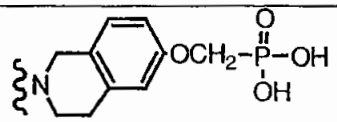
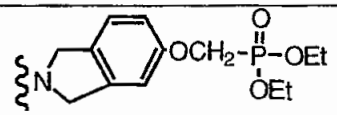
P1-N-P1-Phosphonic acid and esters (2)



R1	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
	+	+		+	
	++	+++		+	
	++	+++			
	++	++		–	
		+++			
	++	+++		+	
		+++		–	
	–	+++		++	
	–				
	+	+++	+++	–	
	–				
		+++	++	+	
	–				

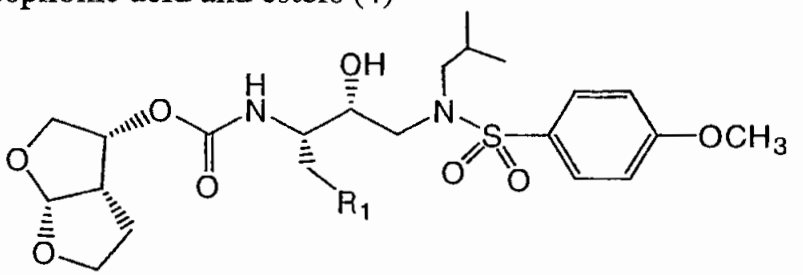
P1-N-P1-Phosphonic acid and esters (3)

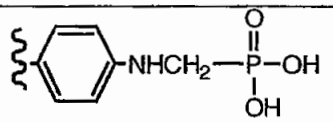
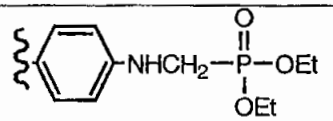
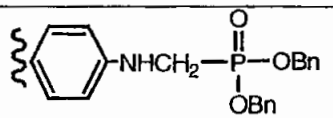
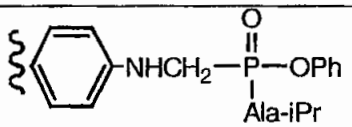
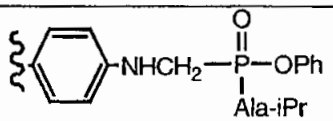
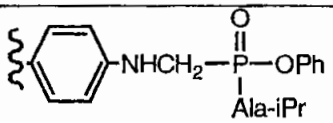
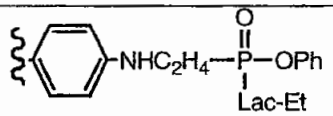
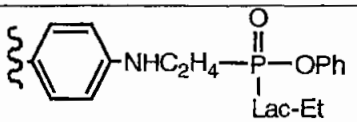
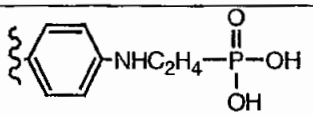
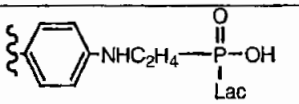


R1	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
	++	+++	+	+	
	+	++	+	+	
	+	++	+	+	
	+				
					
	–	–			

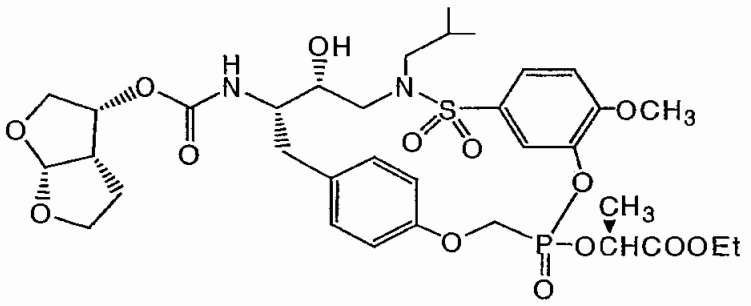
5

P1-N-P1-Phosphonic acid and esters (4)



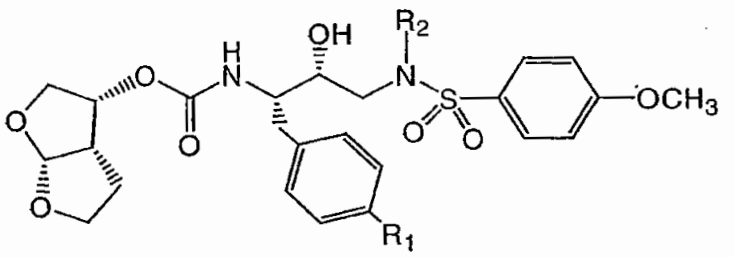
R1	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
	+++				
	+++	+++	–	–	
	++	+++	+	–	
	++	+++			
	++	++			
	+++	+++			
		+++	++	–	
		+++	++	–	
	++				
	++				

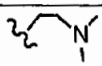
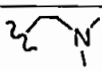
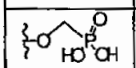
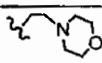
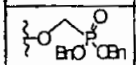
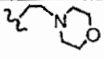
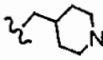
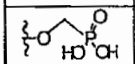
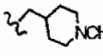
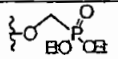
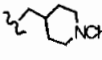
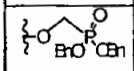
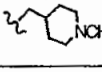
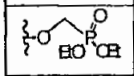
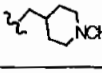
P1- P-cyclic monolactate



R_1	R_2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	$CC_{50}\mu M$
		nd	nd			
		nd	nd			

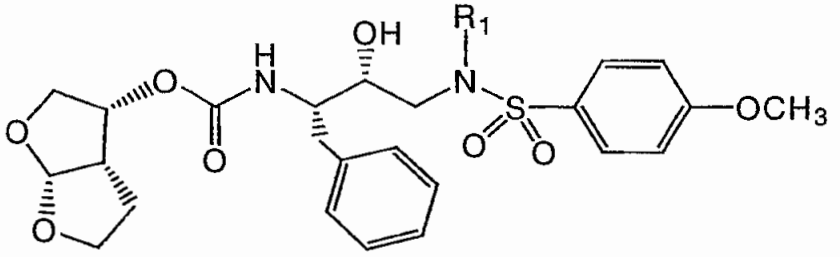
P1'-N-P1-Phosphonic acid and esters

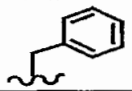
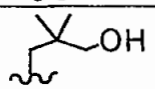
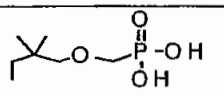
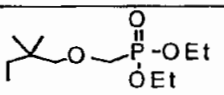
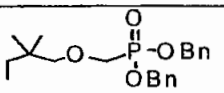
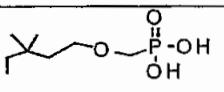
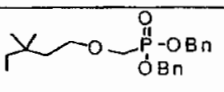


R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
CH_3		++	+++	++	+	
OH			+++	–	–	
CH_2OH		+++	+++	–	–	
OBn		+++	+++	–	–	
OH		–	++	–	–	
OBn		–	+++		–	
		–	–	+	+	
		+	++	+	+	
OH		–	–			
		++	–			
		++	–			
		++	++			
		+	–			

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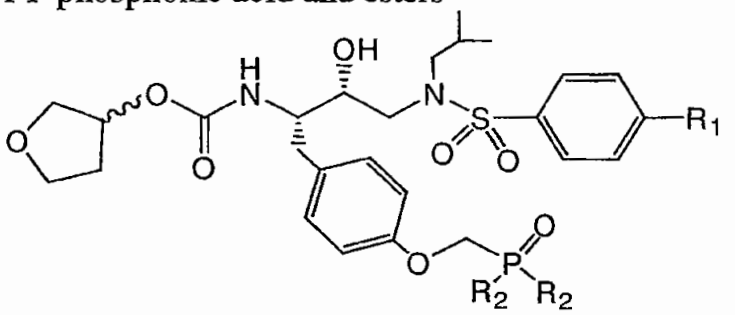
P1'-Phosphonic acid and esters



R1	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
	++	+++	+++	+++	
	+++	+++	+++	+++	
	++	+		+++	
	+++	+++		+++	
	+++	+++		++	
	++	++	++	++	
	++	+++	+++	+++	

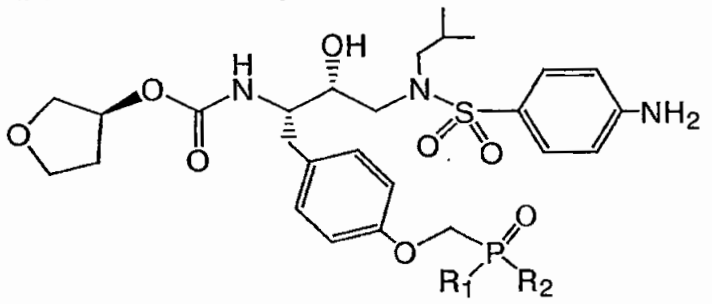
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P2-Monofuran-P1-phosphonic acid and esters



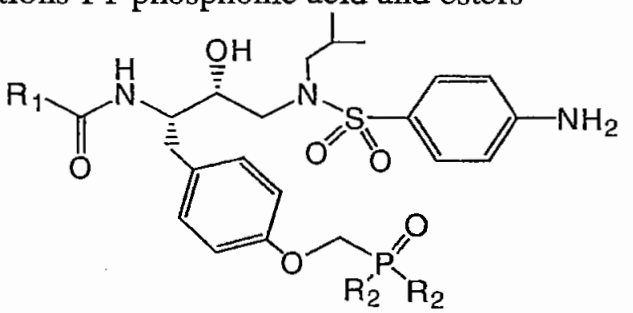
R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
OMe	OH		–	+++	+++	
OMe	OEt	+++	+++	+++	++	
OMe	OBn		+++	++	++	
OMe	phenol	+++	+++	+++	+	
OMe	OEt	++	+++	+++	++	
NH_2	phenol	+	++	+	–	
NH_2	OH		–		+	
NH_2	OBn	++	++		+	

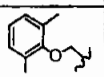
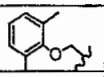
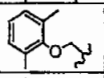
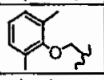
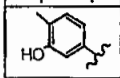
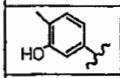
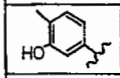
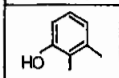
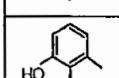
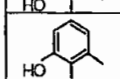
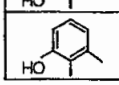
P2-Monofuran-P1-P-monoamidates



R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
OPh	Ala-iPr	++	++		+	
OPh	Ala-iPr	++	++			
OPh	Ala-iPr	+	++			

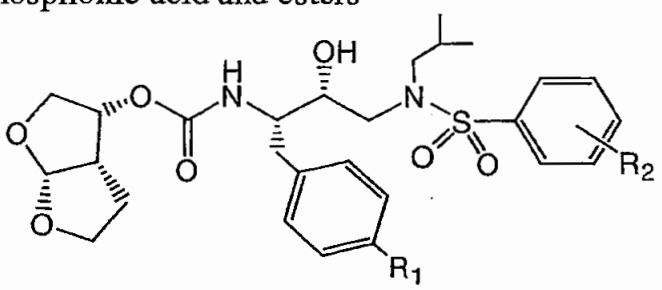
P2-Other modifications-P1-phosphonic acid and esters



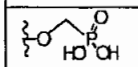
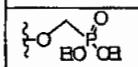
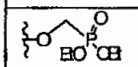
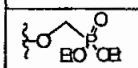
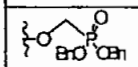
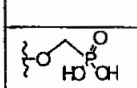
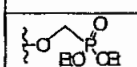
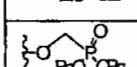
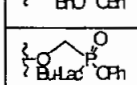
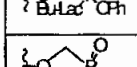
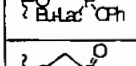
R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
	phenyl	+	+++	+++	++	
	phenol	+	++	++	+	
	OH	–	–	++	–	
	OBn	+	++	+	–	
	phenyl	+	++	+++	+	
	OH	+	–	++	+	
	OBn	+	++	+++	+	
	phenyl	–	++		++	
	phenol	+	+		–	
	OH	+	–	–	–	
	OBn	++	++	+	–	

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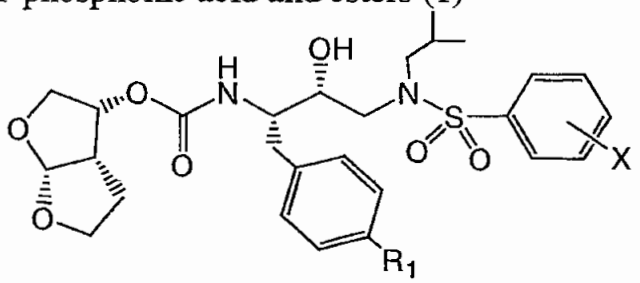
P2'-Amino-P1-phosphonic acid and esters

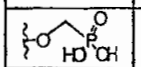
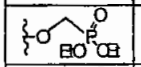
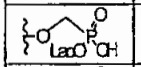
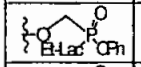
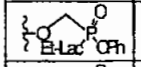
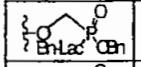
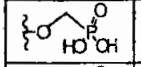
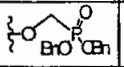
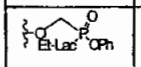
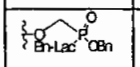
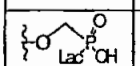
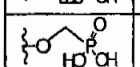
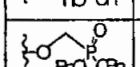
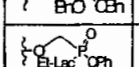
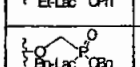
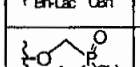
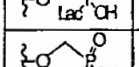
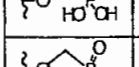
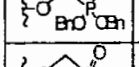
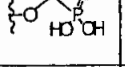


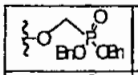
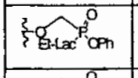
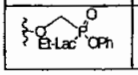
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R1	R2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
OH	*p*-NH_2	++	++	–	–	
	*p*-NH_2	++	–	+	–	
	*p*-NH_2	++	+++		–	
	*p*-NO_2	++	+++		–	
	*p*-NHEt	++	+++		–	
	*p*-NH_2	++	+++	–	–	
OH	*m*-NH_2	++	++		–	
	*m*-NH_2	++	+		–	
	*m*-NH_2	++	++		–	
	*m*-NH_2	++	+++	–	–	
	*m*-NH_2	+	++	–	–	
	*m*-NH_2	++	++			
	*m*-NH_2	+	++			

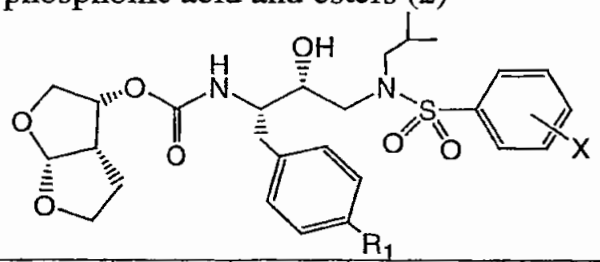
P2'-Substituted-P1-phosphonic acid and esters (1)

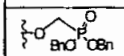
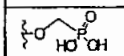
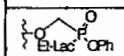
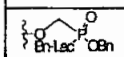
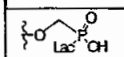
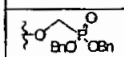
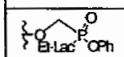
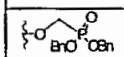
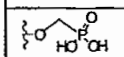
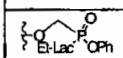
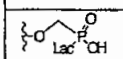
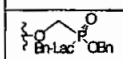
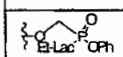
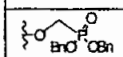
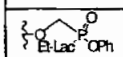
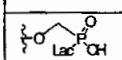
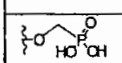
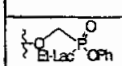
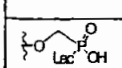
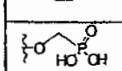


R1	X	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
	*p*-OH	+++	+			
	*p*-OH	+++	+++			
	*p*-OH	++				
	*p*-OH		+++		–	
	*p*-OBn		++			
	*p*-OBn		–			
	*p*-H	++	–			
	*p*-H	++	+++		+	
	*p*-H		+++	+	+	
	*p*-H		++			
	*p*-H	++				
	*p*-F	++	+			
	*p*-F	++	+++		+	
	*p*-F		+++	+	+	
	*p*-F		++	+	+	
	*p*-F	++				
	*p*-CF_3	+++	+			
	*p*-CF_3	++	+++		–	
	*p*-OCF_3	++	+			
	*p*-OCF_3	++	+++		+	

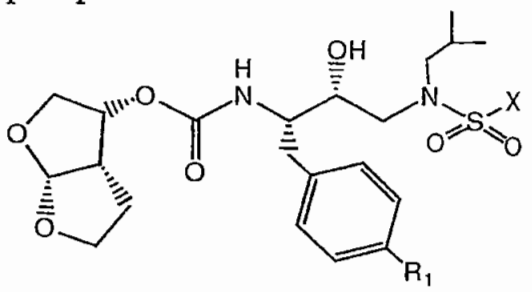
	*p*-CN	++	+++		–	
	*p*-Pip	–	–			
	*p*-Pip-Me	–	–			

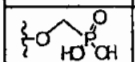
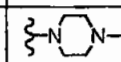
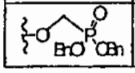
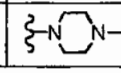
P2'-Substituted-P1-phosphonic acid and esters (2)



R1	X	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
	*m*-Py	++	+++			
	*m*-Py	++				
	*m*-Py	++	++	+	–	
	*m*-Py	++	++			
	*m*-Py	++				
	*m*-Py-Me^+		+			
	*m*-Py-Me^+		++			
	*m*-Py-oxide		++			
	*m*-Py-oxide	++				
	*m*-Py-oxide	++	++		–	
	*m*-Py-oxide	+				
	*m*-Py-oxide		–			
p-Py-oxide	*p*-OMe	++	–			
	*p*-CHO		+++			
	*p*-CHO		+++			
	*p*-CH2 OH		+++	–	–	
	*p*-CH2 OH	++				
	*p*-CH2 OH	++				
	*p*-CH2 Mor		++	–	–	
	*p*-CH2 Mor	–				
	*p*-CH2 Mor	–				

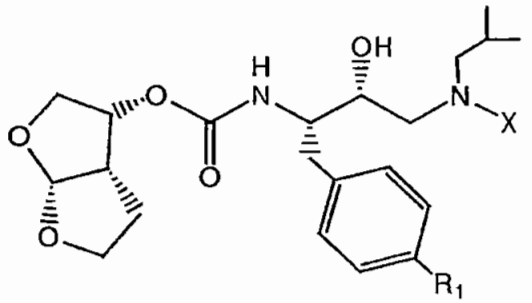
P2'-Alkylsulfonyl-P1-phosphonic acid and esters

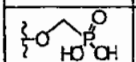
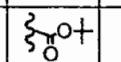
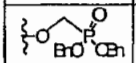
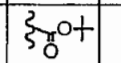
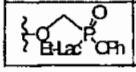
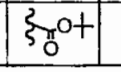


R1	X	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
		–	–			
		+	++			

5

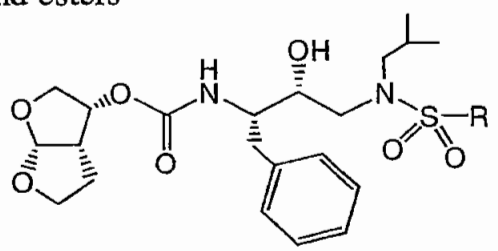
P2'-Carbonyl-substituted-P1-phosphonic acid and esters

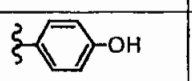
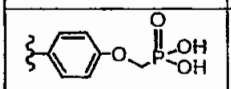
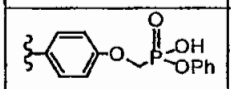
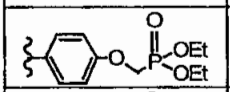
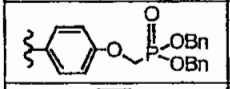
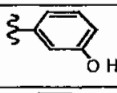
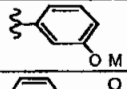
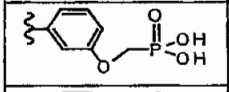
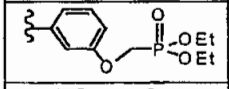
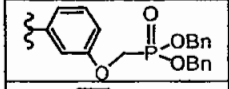
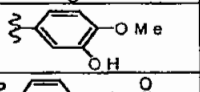
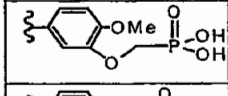
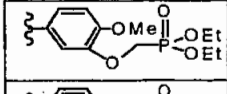
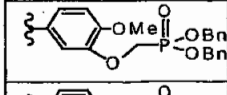
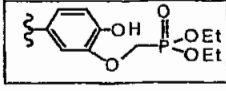


R1	X	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
		–				
		–	++			
			+			

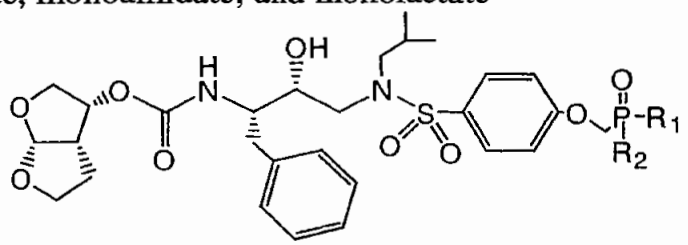
10

P2'-Phosphonic acid and esters



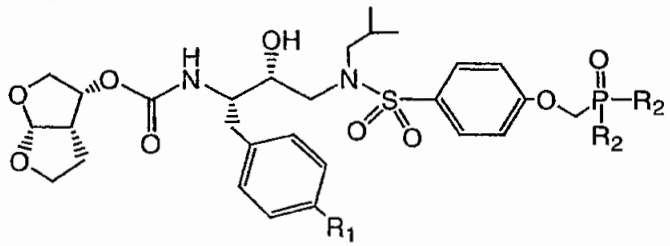
R	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
	+++	+++	–	–	
	+++	+	–	–	
	++	–			
	++	+++	++	++	
	+	++	+++	+++	
	+++	+++	+	+	
	+++	+++	+++	++	
	++	++	++	+	
	+++	+++	+++	++	
	++	+++	++	++	
	+++	+++	–	–	
	+++	++	+	–	
	+	++	+	+	
	–	+	+++	++	
	+	++	+	–	

P2'-P-Bisamidate, monoamidate, and monolactate



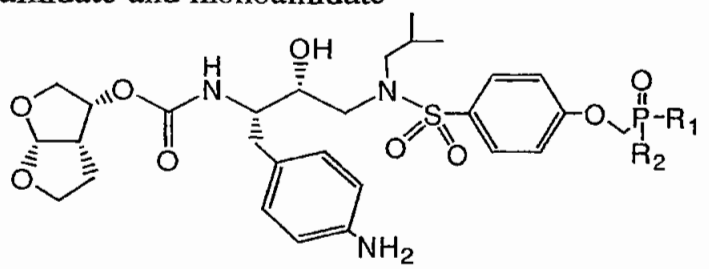
R_1	R_2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
Ala-Bu	Ala-Bu	+	++	+	+	
OPh	Ala-iPr	++	++			
OPh	Lac-iPr	+	+			
OH	Ala-OH	++				

P1-N-P2'-Phosphonic acid and esters



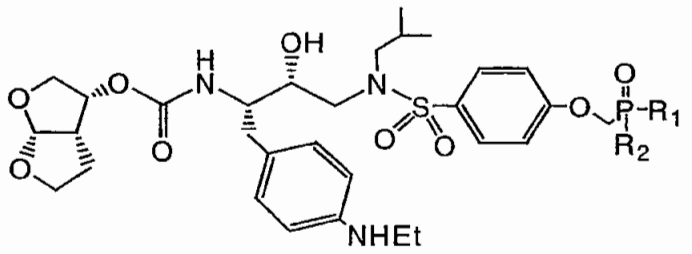
R_1	R_2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
NO_2	phenol		+++	–		
NH_2	OH	++	-			
NH_2	OEt	+	++		++	
NH_2	OBn	+	+		+	
NMe_2	OEt	++	+++		++	
OH	OH	++	-			
OH	OBn	++	++			
$OC_2H_4NMe_2$	OH	+++	+			
OC_2H_4-NMe_2	OBn	++	++			

P1-N-P2'-P-Bisamidate and monoamidate



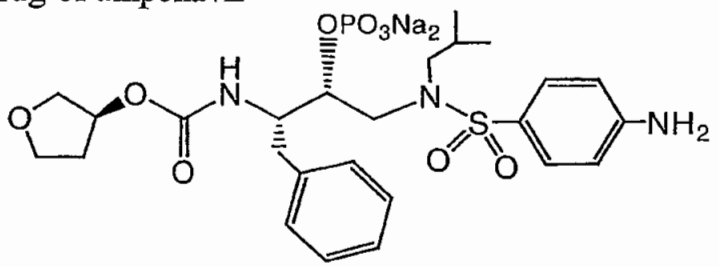
R_1	R_2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
Ala-Bu	Ala-Bu	+	+			
OPh	Ala-iPr	+	–			
OPh	Ala-iPr	++	–			

P1-NEt-P2'-P-Bisamidate and monoamidate



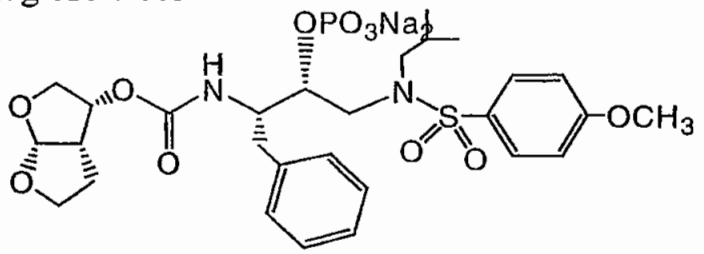
R_1	R_2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
OPh	Ala-iPr	+	+			
OPh	Ala-iPr	+	+	–	–	

Phosphate prodrug of ampenavir



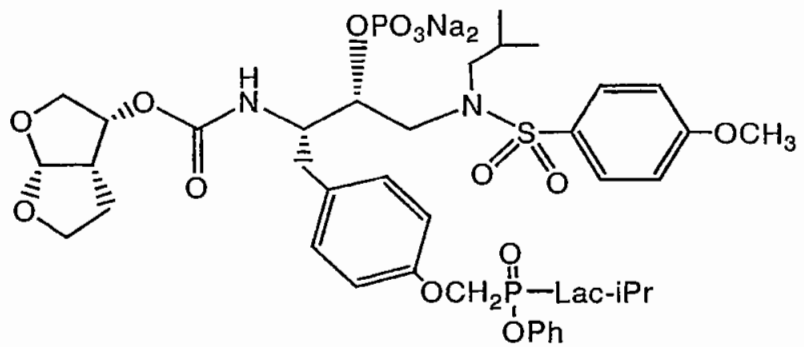
R_1	R_2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
			++			

Phosphate prodrug of 94-003



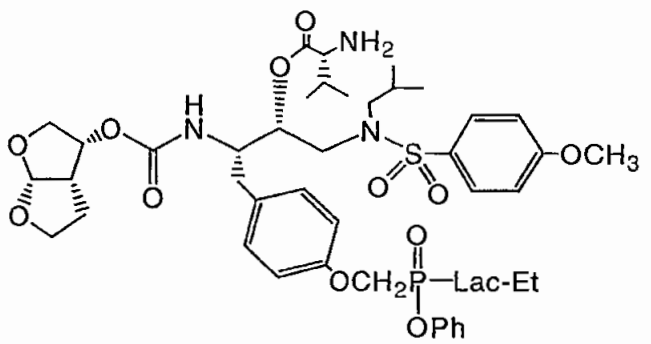
R_1	R_2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
			+++			

Phosphate prodrug of GS77366 (P1-mono(S)Lac-iPr)



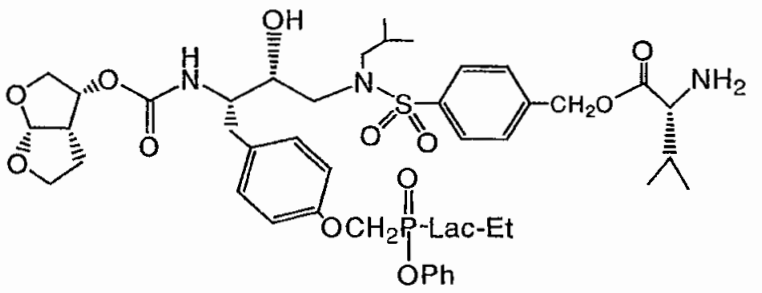
R_1	R_2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
			+++			

Valine prodrug of (P1-mono(S)Lac-Et)



R_1	R_2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
			++			

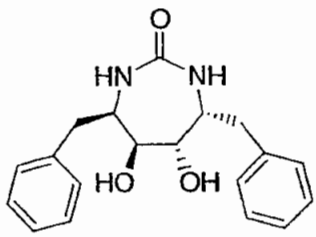
Valine prodrug of GS278053 (P1-mono(S)Lac-Et,P2'-CH_2OH)



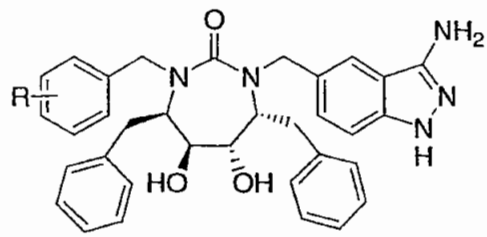
R_1	R_2	Ki (pM)	EC_{50} (nM)	I50V (#1) fold change	I84V/L90M fold change	CC_{50} µM
			++			

Table 11: Enzymatic and Cellular Activity Data

Formula VIIIa CCLPPI activity

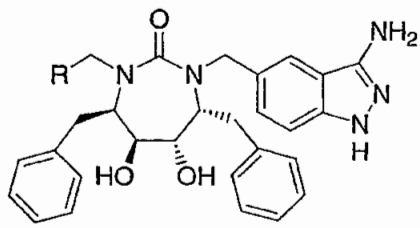


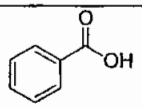
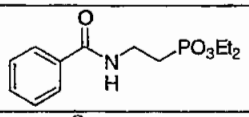
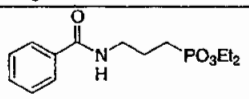
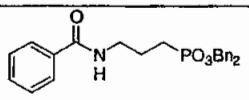
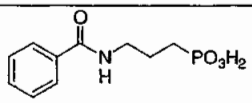
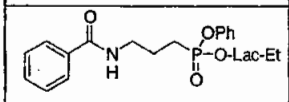
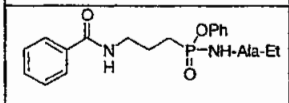
DMP-850

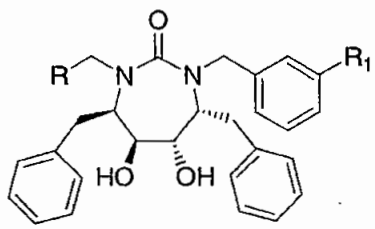


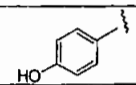
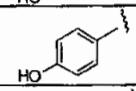
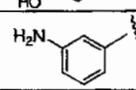
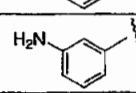
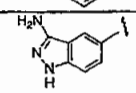
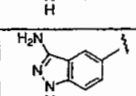
Structure, R	Enzymatic assay			Cell-based assay (MT-4) EC_{50} / nM						
	K_i (nM)	WT IC_{50}/ nM	84V90M IC_{50} / nM	WT	84V90M	30N82I88D	48V54V82A	48V54V82S	48V82A90M	46I50V
H (DMP-850)	0.033	3.0	9.1	165	819	82	82	73	45	88
p-OH	0.029	3.0	12	149	143	79	32	39	19	55
p-OBn	>5	353	781	2123	5312	1548	ND	ND	ND	ND
p-$OCH_2PO_3Bn_2$	>5	276	2042	2697	4963	2119	ND	ND	ND	ND
p-$OCH_2PO_3Et_2$	>5	627	1474	2480	>6000	1340	ND	ND	ND	ND
p-$OCH_2PO_3H_2$	>5	551	1657	>12000	ND	ND	ND	ND	ND	ND
m-OH	0.128	1.6	12	151	475	249	84			104
m-OBn	0.253	6.9	27	218	2422	82	709	ND	ND	601
m-$OCH_2PO_3Bn_2$ (N-iPr indazole)	1.54[a]	31	72	489	514	237	159	171	168	708
m-$OCH_2PO_3Bn_2$	0.177	18	43	898	>6000	705	2597	ND	ND	3121
m-$OCH_2PO_3Et_2$	1.93[a]	70	169	665	3005	93	513	ND	ND	857
m-$OCH_2PO_3H_2$	0.254	8.3	33	>12000	ND	ND	ND	ND	ND	ND

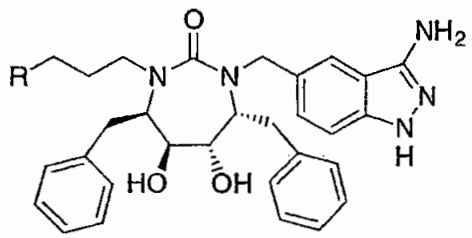
m-$OCH_2PO_3Ph_2$	0.543[a]	10	42	1349	>6000	1541	2183	ND	ND	3380
m-OCH_2PO_3HPh	0.644	17	65	1745	>6000	ND	ND	ND	ND	ND
m-mono-Ala-Bu	0.858[a]	6.6	39	1042	>6000	425	790	ND	ND	797
m-mono-Ala-Et[¶]		35	68	1436	>6000	219	734	ND	ND	1350
m-mono-Lac-Bu		15	34	2663	>6000	1089	ND	ND	ND	ND
m-mono-Lac-Et		23	80	2609	>6000	516	5923	ND	ND	>6000
m-bis-Ala-Bu	1.279[a]	18	103	1079	>6000	2362	1854	ND	ND	1536
m-bis-Ala-Et	1.987[a]	31	202	5620	>6000	1852	ND	ND	ND	ND



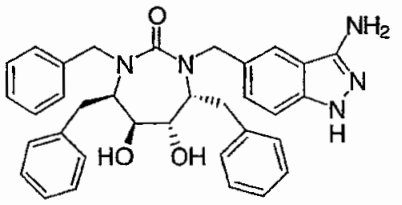
Structure, R	Enzymatic assay			Cell-based assay (MT-4) EC_{50} / nM						
	K_i (nM)	WT IC_{50} / nM	84V90M IC_{50} / nM	WT	84V90M	30N 82I88D	48V54V82A	48V54V82S	48V82A90M	46I50V
H (DMP-850)	0.033	3.0	9.1	165	819	82	82	73	45	88
	0.091	3.4	27	1548	>6000	>6000	ND	ND	ND	ND
	0.354	3.3	25	168	909	750	277			489
	0.157	1.6	10	188	476	666	240			319
	0.044	5.0	27	491	387	234	238			192
	0.362	7.3	70	5141	>6000	4480	ND	ND	ND	ND
	0.112	1.4	6.4	603	1276	678	208			209
	<0.03	1.3	7.5	625	708	899	301			398



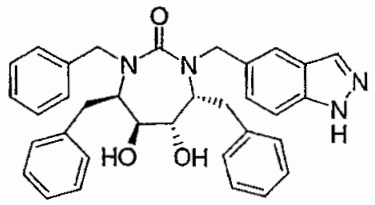
		Enzymatic assay			Cell-based assay (MT-4) EC_{50}/ nM						
Structure, R1	Structure, R	K_i (nM)	WT IC_{50}/ nM	84V90M IC_{50}/ nM	WT	84V90M	30N82I88D	48V54V82A	48V54V82S	48V82A90M	46I50V
CO_2H			15	174	3055	>6000	887	ND	ND	ND	ND
$CONH(CH_2)_3PO_3Et_2$		0.009	1.1	12	65	311	74	80	75	74	85
CO_2H			18	299	2344	>6000	3360	ND	ND	ND	ND
$CONH(CH_2)_3PO_3Et_2$		<0.004	2.3	29	176	824	171	233	ND	ND	195
CO_2H		0.091	3.4	27	1548	>6000	>6000	ND	ND	ND	ND
$CONH(CH_2)_3PO_3Et_2$		0.157	1.6	10	188	476	666	240			319



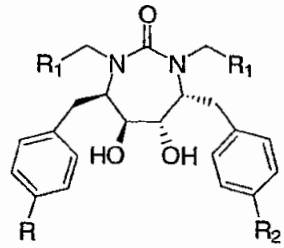
	Enzymatic assay			Cell-based assay (MT-4) EC_{50}/ nM						
Structure, R	K_i (nM)	WT IC_{50}/ nM	84V90M IC_{50} / nM	WT	84V90M	30N 82I88D	48V5 4V82A	48V5 4V82S	48V82 A90M	46I50V
CH_3 (DMP-851)	0.033	3.8	9.4	54	918	69	33	30	22	17
OH	0.65[a]	6.1	77	356	2791	669	294	ND	ND	683
$OCH_2PO_3Et_2$	1.230[a]	23	157	356	>6000	145	175	ND	ND	138
$OCH_2PO_3H_2$	0.809	59	137	1074	>6000	ND	ND	ND	ND	ND
O-mono-Lac-Et	>2.0	93	553	>6000	>6000	ND	ND	ND	ND	ND
O-mono-Lac-Bu	>2.0	25	249	>6000	>6000	ND	ND	ND	ND	ND
CH_2OH	0.017	2.8	31	253	1106	486	413	ND	ND	524
$CH_2OCH_2PO_3Et_2$	2.8	13	123	119	3295	267	430	ND	ND	789
CH_2 $OCH_2PO_3H_2$		42	205	1757	>4243	ND	ND	ND	ND	ND



77546

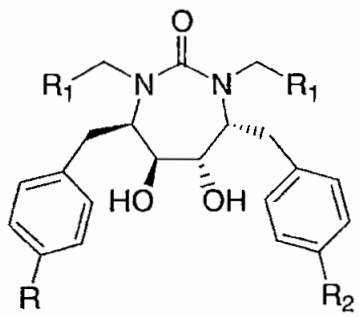


277735



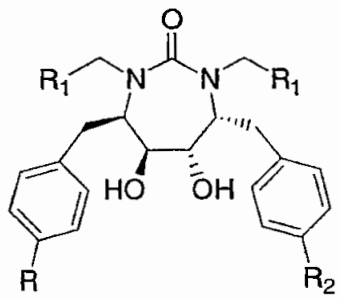
			Enzymatic assay			Cell-based assay (MT-4) EC_{50} / nM						
R	R1	R2	K_i (nM)	WT IC_{50}/ nM	84V90M IC_{50} / nM	WT	84V90M	30N82I88D	48V54V82A	48V54V82S	48V82A90M	46I50V
---	----	-----	0.033	3.0	9.1	165	819	82	82	73	45	88
---	---	---	0.374	5.8	43.3	193	2312	281	705	ND	ND	772
H	Ph	H		34	631	2492	>600	3360	ND	ND	ND	ND
OH	Ph	OH		31	397	117	5609	756	2266	ND	ND	928
OH	Ph	OCH_2PO_3		9	40	33	791	92	807	1103	1429	53
H	Ph	OCH_2PO_3	0.656	3.9	48	107	2456	293	1438	1899	3292	589
H	Indazol	H	<0.01	2.5	13	11	22	<8	5.5	8	4	4.0
OH	Indazol	OH	0.012	0.6	3.5	>600	2728	7224	ND	ND	ND	ND
OH	Indazol	OCH_2PO_3	0.137	1.1	5.5	1698	1753	1998	ND	ND	ND	ND
H	Indazol	OCH_2PO_3	0.028	1.4	6.2	57	40	68	28	26	32	27

5



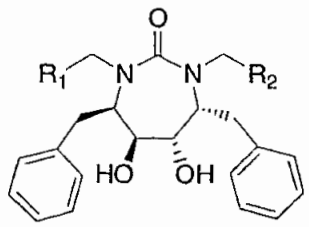
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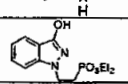
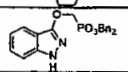
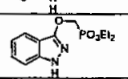
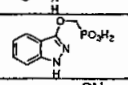
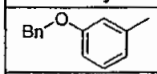
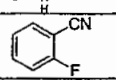
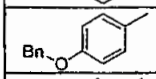
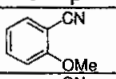
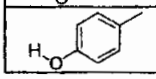
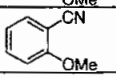
			Enzymatic		Cell-based assay (MT-4) EC_{50}/ nM							
R	R1	R2	K_i (nM)	WT IC_{50}/ nM	84V90M IC_{50}/ nM	WT	84V90M	30N82I8D	48V54V82A	48V54V82S	48V82A90M	46I50V
---	----	----	0.033	3.0	9.1	165	819	82	82	73	45	88
OH	Ph	$OCH_2PO_3Et_2$		9	40	33	791	92	807	1103	1429	53
H	Ph	$OCH_2PO_3Et_2$	0.656	3.9	48	107	2456	293	1438	1899	3292	589
OCH_3	Ph	$OCH_2PO_3Et_2$										
OH	Ph-pOH	$OCH_2PO_3Et_2$	<0.01	2.6	18	285	1912	211	986	ND	ND	1107
H	Ph-pOH	$OCH_2PO_3Et_2$	0.319	2.1	33	65	272	90	128	198	126	144
OCH_3	Ph-pOH	$OCH_2PO_3Et_2$	0.045	1.8	17	29	146	23	67	106	48	68
OH	Ph-mNH_2 /NHEt	$OCH_2PO_3Et_2$		8.7	67	286	1902	562	789	1781	684	239
H	Ph-mNH_2	$OCH_2PO_3Et_2$	0.126	3.4	39	65	328	16	168	146	74	46
OCH_3	Ph-mNH_2	$OCH_2PO_3Et_2$	<0.01	3.6	56	63	535	18	202	117	102	36
OCH_3	m-pyridine	$OCH_2PO_3Et_2$				115	765	106	1019	970	480	352



			Enzymatic assay		Cell-based assay (MT-4) EC_{50} / nM							
R	R1	R2	K_i (nM)	WT IC_{50}/ nM	84V90M IC_{50}/ nM	WT	84V90M	30N82I88D	48V54V82A	48V54V82S	48V82A90M	46I50V
---	----	-----	0.033	3.0	9.1	165	819	82	82	73	45	88
H	Ph-mNH$_2$	OCH$_2$PO$_3$Et$_2$	0.126	3.4	39	65	328	16	168	146	74	46
OCH$_3$	Ph-mNH$_2$	OCH$_2$PO$_3$Et$_2$	<0.01	3.6	56	63	535	18	202	117	102	36
OCH$_3$	Ph-mNH$_2$	O(CH$_2$)$_2$PO$_3$Et$_2$										
OCH$_3$	Ph-mNH$_2$	OCONH(CH$_2$)$_2$PO$_3$Et$_2$		11.3	116	74	2265	77	262	214	215	184
OCH$_3$	Ph-mNH$_2$	OCONH(CH$_2$)PO$_3$Et$_2$		9.9	85	58	2151	68	223	203	185	104
H	Ph-pOH	OCH$_2$PO$_3$Et$_2$	0.319	2.1	33	65	272	90	128	222	146	144
OCH$_3$	Ph-pOH	OCH$_2$PO$_3$Et$_2$	0.045	1.8	17	30	148	25	70	129	54	90
OCH$_3$	Ph-pOH	OCONH(CH$_2$)$_2$PO$_3$Et$_2$		6.6	49	33	495	31	74	51	55	223
---	----	-----	0.033	3.0	9.1	165	819	82	82	73	45	88
H	Ph	OCH$_2$PO$_3$Et$_2$	0.656	3.9	48	107	2456	293	1438	1899	3292	589
H	Ph	OH	0.330	15	162	1261	>6000	2952	>6000			
H	Ph	OCH$_2$PO$_3$Bn$_2$	0.125	7.4	158	1769	>6000	3135	>6000			
H	Ph	OCH$_2$PO$_3$H$_2$	0.386	9.7	210	>600	>600	ND	ND			

						0	0					
H	Ph	Mono-lac-Et	0.120	6.6	56	1726	>6000	2793	>6000			
H	Ph	Mono-Ala-Et		5	50	310	2943	238	2851	1948	2450	1250



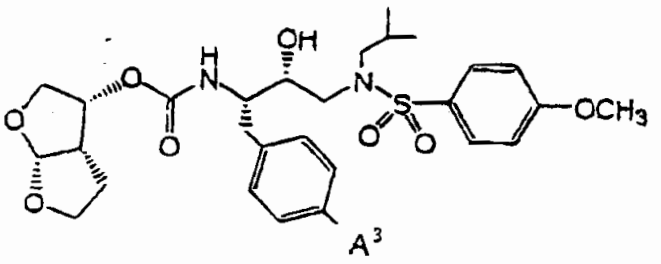
		Enzymatic assay			Cell-based assay (MT-4) EC_{50} / nM						
R1	R2	K_i (nM)	WT IC_{50} / nM	84V 90M IC_{50} / nM	WT	84V 90M	30N 82I88D	48V 54V 82A	48V54 V82S	48V82 A90M	46I5 0V
Phenyl		0.03	3.0	9.1	165	819	82	82	73	45	88
Phenyl		0.42	6.6	85	1226	>600	869	774	ND	ND	937
Phenyl		0.37	5.8	43.3	193	2312	281	705	ND	ND	772
Phenyl			109	>25	>6000	ND	ND	ND	ND	ND	ND
Phenyl											
Phenyl											
Phenyl											
		1.43	302	114	>6000	>600	ND	ND	ND	ND	ND
		>5	>25	ND	5949	ND	ND	ND	ND	ND	ND
		>5	130	348	2006	3121	ND	ND	ND	ND	ND

All publications and patent applications cited herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Although certain embodiments have been described in detail above, those having ordinary skill in the art will clearly understand that many modifications are possible in the embodiments without departing from the teachings thereof. All such modifications are intended to be encompassed within the claims of the invention.

Claims:

1. A compound having the formula



wherein

A^3 is a) $-OCH_2P(O)R_1R_2$;

b) $-P(O)R_1R_2$;

c) $-CH_2P(O)R_1R_2$;

wherein in radicals a), b) and c) R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyloxymethyl;

d) $-OCH_2P(O)R_1R_2$, wherein R_1 and R_2 are independently selected from Gly-Et, Ala-Et, Aba-Et, Val-Et, Leu-Et, Phe-Bu, and Phe-Et;

e) $-OCH_2P(O)R_1R_2$;

f) $-OCH_2CH_2OCH_2P(O)R_1R_2$

wherein in radicals e) and f) R_1 is hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, or benzyloxy, and R_2 is Glc-Et, Lac-Me, Lac-Et, Lac-iPr, Lac-Bu, Lac-EtMor, Lac-Me, Lac-Et, Lac-Bn, Lac-OH, Hba-Et, Hba-tBu, Hba-OH, MeBut-Et, or DiMePro-Me.

g) $-OCH_2P(O)R_1R_2$

wherein R_1 is phenoxy, benzyloxy, ethoxy, trifluoroethoxy, or hydroxyl; and R_2 is selected from Gly-Bu, Ala-Me, Ala-Et, Ala-iPr, (D)Ala-iPr, Ala-Bu, Aba-Et, Aba-Bu, and Ala-OH;

h) $-CH_2NHCH_2CH_2P(O)R_1R_2$

wherein R_1 is hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy or benzyloxy, and R_2 is selected from Glc-Et, Lac-Me, Lac-Et,

Lac-iPr, Lac-Bu, Lac-EtMor, Lac-Bn, Lac-OH, Hba-Et, Hba-tBu, Hba-OH, MeBut-Et, DiMePro-Me, Gly-Bu, Ala-Me, Ala-Et, Ala-iPr, (D)Ala-iPr, Ala-Bu, Aba-Et, Aba-Bu, and Ala-OH, and

the enantiomers and diastereomers as well as the physiologically acceptable salts, hydrates and prodrugs thereof.

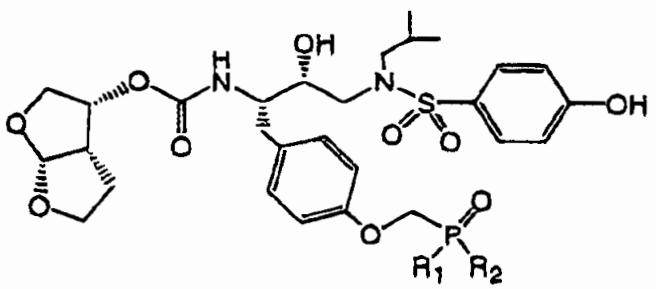
2. The compounds of claim 1, wherein A^3 is $-OCH_2P(O)R_1R_2$ or $-OCH_2CH_2OCH_2P(O)R_1R_2$ (radicals e) and f)) and wherein the lactate ester groups have (R) configuration.

3. The compounds of claim 1, wherein A^3 is $-OCH_2P(O)R_1R_2$ or $-OCH_2CH_2OCH_2P(O)R_1R_2$ (radicals e) and f)) and the lactate ester groups have (S) configuration.

4. The compounds of claim 1, wherein A^3 is $-OCH_2P(O)R_1R_2$ and R_1 and R_2 are independently selected from hydroxy and ethoxy.

5. The compounds of claim 4, wherein R_1 and R_2 are hydroxy or ethoxy.

6. A compound having the formula



wherein R_1 and R_2 are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyloxymethyl.

7. The use of a compound according to any one of claims 1 to 6 in the manufacture of a medicament for the treatment of HIV infection.

8. The use of a compound according to any one of claims 1 to 6 in the manufacture of a medicament for the treatment of disorders affecting white blood cells.

9. A pharmaceutical composition comprising a compound according to anyone of claims 1 to 6 and conventional carriers and excipients.