4-(3-(2-PHENYLOXAZOL-4-YLMETHOXY)CYCLOHEXYLOXY)-BUTANOIC ACID DERIVATIVES AND RELATED COMPOUNDS AS PPAR MODULATORS FOR TREATING DIABETES TYPE 2 AND ATHEROSCLEROSIS

Description

Arylcycloalkyl-substituted alkanoic acid derivatives, processes for their preparation and their use as pharmaceuticals

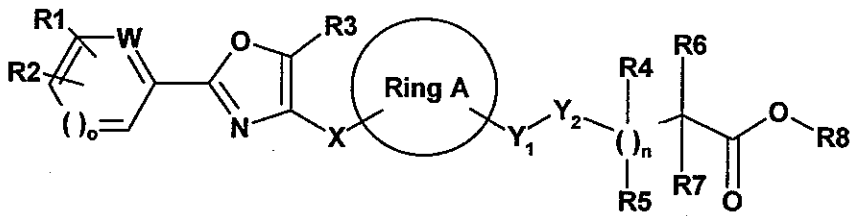
The invention relates to arylcycloalkyl-substituted alkanoic acid derivatives and to their physiologically acceptable salts and physiologically functional derivatives.

Compounds of a similar structure have already been described in the prior art for the treatment of hyperlipidemia and diabetes (WO 2000/64876).

It was an object of the invention to provide compounds which permit a therapeutically exploitable modulation of the lipid and/or carbohydrate metabolism and are thus suitable for the prevention and/or treatment of disorders such as type 2 diabetes and atherosclerosis and their multifarious sequelae.

Surprisingly, we have found a number of compounds which modulate the activity of PPAR receptors. The compounds are particularly suitable for activating PPARalpha and PPARgamma, where the extent of the relative activation may vary, depending on the compounds.

The invention thus relates to compounds of the formula I



I

in which:

Ring A	is (C3-C8)cycloalkanediyl or (C3-C8)cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one or more carbon atoms may be replaced by oxygen atoms;
R1, R2	independently of one another are H, F, Cl, Br, CF_3, OCF_3, (C1-C6)-alkyl, O-(C1-C6)-alkyl, SCF_3, SF_5, OCF_2-CHF_2, (C6-C10)-aryl, (C6-C10)-aryloxy, OH, NO_2; or
R1 and R2	together with the phenyl, pyridine, 1H-pyrrole, thiophene or furan ring form fused, partially or unsaturated bicyclic (C6-C10)-aryl, (C5-C11)-heteroaryl;
R3	is H, (C1-C6)-alkyl, (C3-C8)cycloalkyl, (C1-C3)-alkyl-(C3-C8)cycloalkyl, phenyl, (C1-C3)-alkyl-phenyl, (C5-C6)-heteroaryl, (C1-C3)-alkyl-(C5-C6)-heteroaryl or (C1-C3)-alkyl which is fully or partially substituted by F;
W	is CH or N if o = 1;
W	is O, S or NR9 if o = 0;
X	is (C1-C6)-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms;
Y1	is O;
Y2	is CR12R13, SO, SO2;
n	is 0-2;
R4	is H, F, (C1-C6)-alkyl;
R5	is H, F, (C1-C6)-alkyl;
R6	is H, (C1-C6)-alkyl; or F if n is not 0;
R7	is H, (C1-C6)-alkyl, (C2-C6)-alkenyl, (C2-C6)-alkynyl, O-(C1-

C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, (C3-C8)cycloalkyl, phenyl, (C5-C11)-heteroaryl, O-(C3-C8)cycloalkyl, O-phenyl, which may be substituted by OH, NR10R11, O-(C1-C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, O-(C3-C8)cycloalkyl, O-phenyl, O-(C5-C11)-heteroaryl, and where (C3-C8)cycloalkyl, phenyl, (C5-C11)-heteroaryl may additionally be substituted by (C1-C6)-alkyl, optionally fully or partially substituted by F, O-(C1-C6)-alkyl, optionally fully or partially substituted by F, Cl, Br, J, OH, NR10R11, CO-(C1-C6)-alkyl, CO-(C6-C10)-aryl, CO-(C1-C6)-alkyl-(C6-C10)-aryl, CO-(C5-C11)-heteroaryl, C(O)-O-(C1-C6)-alkyl, C(O)-O-(C1-C6)-alkyl-(C6-C10)-aryl, C(O)-O-(C6-C10)-aryl, C(O)-O-(C5-C11)-heteroaryl, SO2-(C1-C6)-alkyl, SO2-(C1-C6)-alkyl-(C6-C10)-aryl, SO2-(C1-C6)-alkyl-SO2-(C1-C6)-alkyl, SO2-(C6-C10)-aryl, SO2-(C5-C11)-heteroaryl;

R6 and R7 together with the carbon atom that carries them are (C3-C8)cycloalkyl;

R8 is H, (C1-C6)-alkyl;

R9 is H, (C1-C6)-alkyl, which is unsubstituted or substituted by phenyl;

R10 is H, (C1-C6)-alkyl, which is unsubstituted or substituted by phenyl;

R11 is H, (C1-C6)-alkyl, which is unsubstituted or substituted by phenyl;

R12 is H, (C1-C6)-alkyl;

R13 is H, (C1-C6)-alkyl;

and their physiologically acceptable salts.

Preference is given to compounds of the formula I in which

Ring A is (C_3-C_8)cycloalkanediyl or (C_3-C_8)cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one carbon atom may be replaced by an oxygen atom;

X is (C1-C6)-alkanediyl, where in the alkanediyl group the C1 or C2 carbon atom (to Ring A) may be replaced by an oxygen atom;

and their physiologically acceptable salts.

Particular preference is given to the compounds of the formula I in which one or more radicals are as defined below:

Ring A is cyclohexane-1,3-diyl; or

R1 is F, Br, CF_3, OCF_3, (C1-C6)-alkyl, O-(C1-C6)-alkyl, phenyl; or

R1 and R2 together with the phenyl ring = naphthyl; or

such in which the substituent

R1 is in the meta- or in the para-position; or

R2 is hydrogen; or

R3 is H, (C1-C6)-alkyl, (C3-C8)cycloalkyl, (C1-C3)-alkyl-(C5-C6)cycloalkyl, phenyl, (C1-C3)-alkyl-phenyl; or

W is CH if o = 1; or

X is CH_2-O or CH_2-O-CH_2; or

n is 0; or

R6 is H, (C1-C6)-alkyl; or

R7 is H, (C1-C6)-alkyl, (C2-C6)-alkenyl, (C2-C6)-alkynyl, O-(C1-C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, (C3-C8)cycloalkyl, phenyl, O-(C3-C8)cycloalkyl, O-phenyl, (C5-C11)-heteroaryl, which may be substituted by OH, NR10R11, O-(C1-C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, O-(C3-C8)cycloalkyl, O-phenyl, O-(C5-C11)-heteroaryl, and where (C3-C8)cycloalkyl, phenyl, (C5-C11)-heteroaryl may additionally be substituted by (C1-C6)-alkyl, optionally fully or partially substituted by F, O-(C1-C6)-alkyl, optionally fully or partially substituted by F, Cl, Br, J, OH, NR10R11; or

R6 and R7 together with the carbon atom that carries them are (C3-C6)cycloalkyl, in particular cyclopentyl; or

R10 and R11 are H, (C1-C6)-alkyl; or

R12 and R13 are hydrogen.

Particular preference is furthermore given to the compounds of the formula I in which

R7 is H, (C1-C6)-alkyl, (C2-C6)-alkenyl, (C2-C6)-alkynyl, O-(C1-C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, (C3-C8)cycloalkyl, phenyl, (C3-C8)cycloalkyl, phenyl, (C5-C11)-heteroaryl, which may be substituted by NR10R11, O-(C1-C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, O-(C3-C8)cycloalkyl, O-phenyl, O-(C5-C11)-heteroaryl, and where phenyl, (C5-C11)-heteroaryl may additionally be substituted by (C1-C6)-alkyl, optionally fully or partially substituted by F, O-(C1-C6)-alkyl, optionally fully or partially substituted by F, Cl, NR10R11;

and their physiologically acceptable salts.

Very particular preference is given to the compounds of the formula I

in which

Ring A	is cis-cyclohexane-1,3-diyl
R1, R2	independently of one another are H, F, CF3, (C1-C6)-alkyl, O-(C1-C6)-alkyl, phenyl, or
R1 and R2	together with the phenyl ring = naphthyl;
R3	is (C1-C6)-alkyl;
W	is CH if o = 1;
X	is (CH2)O, CH2-O-CH2;
Y1	is O;
Y2	is CH2;
n	is 0, 1;
R4	is H;
R5	is H;
R6	is H;
R7	is H, (C1-C6)-alkyl, O-(C1-C6)-alkyl, (C1-C6)-alkyl-O-(C1-C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, CH2NR10R11, where alkyl, O-alkyl and alkenyl may be substituted by phenyl or (C5-C6)-heteroaryl, which in turn may be substituted by (C1-

C6)-alkyl, O-(C1-C6)-alkyl, CF3;

R6 and R7 together with the carbon atom that carries them are (C3-C6)cycloalkyl;

R8 is H;

R10 is (C1-C6)-alkyl;

R11 is (C1-C6)-alkyl which is substituted by phenyl;

and their physiologically acceptable salts.

The alkyl, alkenyl and alkynyl radicals in the substituents R1, R2, R3, R4, R5 , R6, R7, R8, R9, R10, R11, R12 and R13 may be either straight-chain or branched.

Aryl means an aromatic carbocyclic mono- or bicyclic ring system which comprises 6 to 10 atoms in the ring or rings.

Heteroaryl is a mono- or bicyclic aromatic ring system having 4 to 11 ring members, in which at least one atom in the ring system is a heteroatom from the series N, O and S.

The compounds of the formula I comprise at least two centers of asymmetry and may comprise more in addition. The compounds of the formula I may therefore exist in the form of their racemates, racemic mixtures, pure enantiomers, diastereomers and mixtures of diastereomers. The present invention encompasses all these isomeric forms of the compounds of the formula I. These isomeric forms can be obtained by known methods even if not specifically described in some cases.

Pharmaceutically acceptable salts are, because their solubility in water is greater than that of the initial or basic compounds, particularly suitable for medical applications. These salts must have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of

the compounds of the invention are salts of inorganic acids such as hydrochloroic acid, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acid, and of organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic and tartaric acid. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts), alkaline earth metal salts (such as magnesium and calcium salts), and salts of trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine or ethylenediamine.

Salts with a pharmaceutically unacceptable anion such as, for example, trifluoroacetate likewise belong within the framework of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

The term "physiologically functional derivative" used herein refers to any physiologically tolerated derivative of a compound of the formula I of the invention, for example an ester, which on administration to a mammal such as, for example, a human is able to form (directly or indirectly) a compound of the formula I or an active metabolite thereof.

Physiologically functional derivatives also include prodrugs of the compounds of the invention, as described, for example, in H. Okada et al., Chem. Pharm. Bull. 1994, 42, 57-61. Such prodrugs can be metabolized in vivo to a compound of the invention. These prodrugs may themselves be active or not.

The compounds of the invention may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the invention belong within the framework of the invention and are a further aspect of the invention.

All references to "compound(s) of formula I" hereinafter refer to compound(s) of the formula I as described above, and their salts, solvates and physiologically functional derivatives as described herein.

Use

This invention relates further to the use of compounds of the formula I and their pharmaceutical compositions as PPAR ligands. The PPAR ligands of the invention are suitable as modulators of PPAR activity.

Peroxisome proliferator-activated receptors (PPAR) are transcription factors which can be activated by ligands and belong to the class of nuclear hormone receptors. There are three PPAR isoforms, PPARalpha, PPARgamma and PPARdelta, which are encoded by different genes (Peroxisome proliferator-activated receptor (PPAR): structure, mechanisms of activation and diverse functions: Motojima K, Cell Struct Funct. 1993 Oct; 18(5): 267-77).

Two variants of PPARgamma exist, PPARgamma$_1$ and gamma$_2$, which are the result of alternative use of promoters and differential mRNA splicing (Vidal-Puig et al. J. Clin. Invest., 97:2553-2561, 1996). Different PPARs have different tissue distribution and modulate different physiological functions. The PPARs play a key role in various aspects of the regulation of a large number of genes, the products of which genes are directly or indirectly crucially involved in lipid and carbohydrate metabolism. Thus, for example, PPARalpha receptors play an important part in the regulation of fatty acid catabolism or lipoprotein metabolism in the liver, while PPARgamma is crucially involved for example in regulating adipose cell differentiation. In addition, however, PPARs are also involved in the regulation of many other physiological processes, including those which are not directly connected with carbohydrate or lipid metabolism. The activity of different PPARs can be modulated by various fatty acids, fatty acid derivatives and synthetic compounds to varying extents. For relevant reviews about functions, physiological effect and pathophysiology, see: Joel Berger et al., Annu. Rev. Med. 2002, 53, 409 – 435; Timothy Wilson et al. J. Med. Chem., 2000, Vol. 43, No. 4, 527-550; Steven Kliewer et al., Recent Prog Horm Res. 2001; 56: 239-63.

The present invention relates to compounds of the formula I suitable for modulating the activity of PPARs, especially the activity of PPARalpha and PPARgamma. Depending on the modulation profile, the compounds of the formula I are suitable for the treatment, control and prophylaxis of the indications described hereinafter, and for a number of other pharmaceutical applications connected thereto (see, for example, Joel Berger et al., Annu. Rev. Med. 2002, 53, 409 – 435; Timothy Wilson et al. J. Med. Chem., 2000, Vol. 43, No. 4, 527-550; Steven Kliewer et al., Recent Prog Horm Res. 2001; 56: 239-63; Jean-Charles Fruchart, Bart Staels and Patrick Duriez:

PPARS, Metabolic Disease and Arteriosclerosis, Pharmacological Research, Vol. 44, No. 5, 345-52; 2001; Sander Kersten, Beatrice Desvergne & Walter Wahli: Roles of PPARs in health and disease, NATURE, VOL 405, 25 MAY 2000; 421-4; Ines Pineda Torra, Giulia Chinetti, Caroline Duval, Jean-Charles Fruchart and Bart Staels: Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice, Curr Opin Lipidol 12: 2001, 245-254).

Compounds of this type are particularly suitable for the treatment and/or prevention of

1. - disorders of fatty acid metabolism and glucose utilization disorders
   - disorders in which insulin resistance is involved

2. Diabetes mellitus, especially type 2 diabetes, including the prevention of the sequelae associated therewith.
   Particular aspects in this connection are
   - hyperglycemia,
   - improvement in insulin resistance,
   - improvement in glucose tolerance,
   - protection of the pancreatic ß cells
   - prevention of macro- and microvascular disorders
3. Dyslipidemias and their sequelae such as, for example, atherosclerosis, coronary heart disease, cerebrovascular disorders etc, especially those (but not restricted thereto) which are characterized by one or more of the following factors:
   - high plasma triglyceride concentrations, high postprandial plasma triglyceride concentrations,
   - low HDL cholesterol concentrations
   - low ApoA lipoprotein concentrations
   - high LDL cholesterol concentrations
   - small dense LDL cholesterol particles
   - high ApoB lipoprotein concentrations

4. Various other conditions which may be associated with the metabolic syndrome, such as:
   - obesity (excess weight), including central obesity
   - thromboses, hypercoagulable and prothrombotic states (arterial and venous)
   - high blood pressure
   - heart failure such as, for example (but not restricted thereto),

following myocardial infarction, hypertensive heart disease or cardiomyopathy

5. Other disorders or conditions in which inflammatory reactions or cell differentiation may for example be involved are:
   - atherosclerosis such as, for example (but not restricted thereto), coronary sclerosis including angina pectoris or myocardial infarction, stroke
   - vascular restenosis or reocclusion
   - chronic inflammatory bowel diseases such as, for example, Crohn's disease and ulcerative colitis
   - pancreatitis
   - other inflammatory states
   - retinopathy
   - adipose cell tumors
   - lipomatous carcinomas such as, for example, liposarcomas
   - solid tumors and neoplasms such as, for example (but not restricted thereto), carcinomas of the gastrointestinal tract, of the liver, of the biliary tract and of the pancreas, endocrine tumors, carcinomas of the lungs, of the kidneys and the urinary tract, of the genital tract, prostate carcinomas etc
   - acute and chronic myeloproliferative disorders and lymphomas
   - angiogenesis
   - neurodegenerative disorders
   - Alzheimer's disease
   - multiple sclerosis
   - Parkinson's disease
   - erythemato-squamous dermatoses such as, for example, psoriasis
   - acne vulgaris
   - other skin disorders and dermatological conditions which are modulated by PPAR
   - eczemas and neurodermitis
   - dermatitis such as, for example, seborrheic dermatitis or photodermatitis
   - keratitis and keratoses such as, for example, seborrheic keratoses, senile keratoses, actinic keratosis, photo-induced keratoses or keratosis follicularis
   - keloids and keloid prophylaxis
   - warts, including condylomata or condylomata acuminata

- human papilloma viral (HPV) infections such as, for example, venereal papillomata, viral warts such as, for example, molluscum contagiosum, leukoplakia
- papular dermatoses such as, for example, Lichen planus
- skin cancer such as, for example, basal-cell carcinomas, melanomas or cutaneous T-cell lymphomas
- localized benign epidermal tumors such as, for example, keratoderma, epidermal naevi
- chilblains
- high blood pressure
- syndrome X
- polycystic ovary syndrome (PCOS)
- asthma
- osteoarthritis
- lupus erythematosus (LE) or inflammatory rheumatic disorders such as, for example, rheumatoid arthritis
- vasculitis
- wasting (cachexia)
- gout
- ischemia/reperfusion syndrome
- acute respiratory distress syndrome (ARDS)

Formulations

The amount of a compound of formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.001 mg to 100 mg (typically from 0.01 mg to 50 mg) per day and per kilogram of bodyweight, for example 0.1-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.001 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. Thus, ampules for injections may contain, for example, from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, capsules or tablets, may contain, for example, from 0.05 to 1000 mg, typically from 0.5 to 600 mg. For the

therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions of the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of the condition to be treated and on the nature of the compound of formula I used in each case. Coated formulations and coated slow-release formulations also belong within the framework of the invention. Preference is given to acid- and gastric juice-resistant formulations. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical preparations for oral administration may be in the form of separate units such as, for example, capsules, cachets, suckable tablets or tablets, each of which contain a defined amount of the compound of formula I; as powders or granules, as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be

produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more) surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and is moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise suckable tablets which contain a compound of formula I with a flavoring, normally sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain from 0.1 to 5% by weight of the active compound.

Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of the formula I with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. Carriers which can be used are petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses can be in the form of single plasters which

are suitable for long-term close contact with the patient's epidermis. Such plasters suitably contain the active ingredient in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. A particular possibility is for the active ingredient to be released by electrotransport or iontophoresis as described, for example, in Pharmaceutical Research, 2(6): 318 (1986).

The compounds of the formula I are distinguished by favorable effects on metabolic disorders. They beneficially influence lipid and sugar metabolism, in particular they lower the triglyceride level and are suitable for the prevention and treatment of type II diabetes and arteriosclerosis and the diverse sequalae thereof.

Combinations with other medicaments

The compounds of the invention can be administered alone or in combination with one or more further pharmacologically active substances which have, for example, favorable effects on metabolic disturbances or disorders frequently associated therewith. Examples of such medicaments are

1. medicaments which lower blood glucose, antidiabetics,
2. active ingredients for the treatment of dyslipidemias,
3. antiatherosclerotic medicaments,
4. antiobesity agents,
5. antiinflammatory active ingredients
6. active ingredients for the treatment of malignant tumors
7. antithrombotic active ingredients
8. active ingredients for the treatment of high blood pressure
9. active ingredients for the treatment of heart failure and
10. active ingredients for the treatment and/or prevention of complications caused by diabetes or associated with diabetes.

They can be combined with the compounds of the invention of the formula I in particular for a synergistic improvement in the effect. Administration of the active ingredient combination can take place either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present

in one pharmaceutical preparation.

Examples which may be mentioned are:

Antidiabetics

Suitable antidiabetics are disclosed for example in the Rote Liste 2001, chapter 12 or in the USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2001. Antidiabetics include all insulins and insulin derivatives such as, for example, Lantus® (see www.lantus.com) or Apidra®, and other fast-acting insulins (see US 6,221,633), GLP-1 receptor modulators as described in WO 01/04146 or else, for example, those disclosed in WO 98/08871 of Novo Nordisk A/S. The orally effective hypoglycemic active ingredients include, preferably, sulfonylureas, biguanides, meglitinides, oxadiazolidinediones`, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, DPP-IV inhibitors, potassium channel openers such as, for example, those disclosed in WO 97/26265 and WO 99/03861, insulin sensitizers, inhibitors of liver enzymes involved in the stimulation of gluconeogenesis and/or glycogenolysis, modulators of glucose uptake, compounds which alter lipid metabolism and lead to a change in the blood lipid composition, compounds which reduce food intake, PPAR and PXR modulators and active ingredients which act on the ATP-dependent potassium channel of the beta cells.

In one embodiment of the invention, the compounds of the formula I are administered in combination with insulin.

In one embodiment of the invention, the compounds of the formula I are administered in combination with substances which influence hepatic glucose production such as, for example, glycogen phosphorylase inhibitors (see: WO 01/94300, WO 02/096864, WO 03/084923, WO 03/084922, WO 03/104188).

In one embodiment, the compounds of the formula I are administered in combination with a sulfonylurea such as, for example, tolbutamide, glibenclamide, glipizide or glimepiride.

In one embodiment, the compounds of the formula I are administered in combination with an active ingredient which acts on the ATP-dependent potassium channel of the beta cells, such as, for example, tolbutamide,

glibenclamide, glipizide, glimepiride or repaglinide.
In one embodiment, the compounds of the formula I are administered in combination with a biguanide such as, for example, metformin.

In a further embodiment, the compounds of the formula I are administered in combination with a meglitinide such as, for example, repaglinide.
In one embodiment, the compounds of the formula I are administered in combination with a thiazolidinedione such as, for example, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 of Dr. Reddy's Research Foundation, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy]phenyl]methyl]-2,4-thiazolidinedione.
In one embodiment, the compounds of the formula I are administered in combination with a DPPIV inhibitor as described, for example, in WO98/19998, WO99/61431, WO99/67278, WO99/67279, WO01/72290, WO 02/38541, WO03/040174, in particular P 93/01 (1-cyclopentyl-3-methyl-1-oxo-2-pentanammonium chloroide), P-31/98, LAF237 (1-[2-[3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2-(S)-carbonitrile), TS021 ((2S, 4S)-4-fluoro-1-[[(2-hydroxy-1,1-dimethylethyl)amino]-acetyl]pyrrolidine-2-carbonitrile monobenzenesulfonate).

In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPARgamma agonist such as, for example, rosiglitazone, pioglitazone.

In one embodiment, the compounds of the formula I are administered in combination with compounds with an inhibitory effect on SGLT-1 and/or 2, as disclosed directly or indirectly for example in PCT/EP03/06841, PCT/EP03/13454 and PCT/EP03/13455.

In one embodiment, the compounds of the formula I are administered in combination with an α-glucosidase inhibitor such as, for example, miglitol or acarbose.
In one embodiment, the compounds of the formula I are administered in combination with more than one of the aforementioned compounds, e.g. in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

Lipid modulators

In one embodiment of the invention, the compounds of the formula I are administered in combination with an HMGCoA reductase inhibitor such as lovastatin, fluvastatin, pravastatin, simvastatin, ivastatin, itavastatin, atorvastatin, rosuvastatin.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a bile acid reabsorption inhibitor (see, for example, US 6,245,744, US 6,221,897, US 6,277,831, EP 0683 773, EP 0683 774).

In one embodiment of the invention, the compounds of the formula I are administered in combination with a polymeric bile acid adsorbent such as, for example, cholestyramine, colesevelam.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a cholesterol absorption inhibitor as described for example in WO 0250027, or ezetimibe, tiqueside, pamaqueside.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an LDL receptor inducer (see, for example, US 6,342,512).

In one embodiment, the compounds of the formula I are administered in combination with bulking agents, preferably insoluble bulking agents (see, for example, carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6.) Caromax is a carob-containing product from Nutrinova, Nutrition Specialties & Food Ingredients GmbH, Industriepark Höechst, 65926 Frankfurt/Main)). Combination with Caromax® is possible in one preparation or by separate administration of compounds of the formula I and Caromax®. Caromax® can in this connection also be administered in the form of food products such as, for example, in bakery products or muesli bars.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPARalpha agonist.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a mixed PPAR alpha/gamma agonist such as, for example, AZ 242 (Tesaglitazar, (S)-3-(4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl)-2-ethoxypropionic acid), BMS 298585 (N-[(4-methoxyphenoxy)carbonyl]-N-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]glycine) or as described in WO 99/62872, WO 99/62871, WO 01/40171, WO 01/40169, WO96/38428, WO 01/81327, WO 01/21602, WO 03/020269, WO 00/64888 or WO 00/64876.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a fibrate such as, for example, fenofibrate, gemfibrozil, clofibrate, bezafibrate.

In one embodiment of the invention, the compounds of the formula I are administered in combination with nicotinic acid or niacin.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a CETP inhibitor, e.g. CP- 529, 414 (torcetrapib).

In one embodiment of the invention, the compounds of the formula I are administered in combination with an ACAT inhibitor.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an MTP inhibitor such as, for example, implitapide.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an antioxidant.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein lipase inhibitor.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an ATP citrate lyase inhibitor.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a squalene synthetase inhibitor.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein(a) antagonist.

Antiobesity agents

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipase inhibitor such as, for example, orlistat.

In one embodiment, the further active ingredient is fenfluramine or dexfenfluramine.
In another embodiment, the further active ingredient is sibutramine.

In a further embodiment, the compounds of the formula I are administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A, et al., M.: Hormone and Metabolic Research (2001), 33(9), 554-558), NPY antagonists, e.g. naphthalene-1-sulfonic acid {4-[(4-aminoquinazolin-2-ylamino)methyl]-cyclohexylmethyl}amide hydrochloroide (CGP 71683A)), MC4 agonists (e.g. 1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid [2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]-amide; (WO 01/91752)), orexin antagonists (e.g. 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea hydrochloroide (SB-334867-A)), H3 agonists (3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208)); TNF agonists, CRF antagonists (e.g. [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585)), CRF BP antagonists (e.g. urocortin), urocortin agonists, β3 agonists (e.g. 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)ethylamino]-ethanol hydrochloroide (WO 01/83451)), MSH (melanocyte-stimulating hormone) agonists, CCK-A agonists (e.g. {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)thiazol-2-ylcarbamoyl]-5,7-dimethylindol-1-yl}acetic acid trifluoroacetic acid salt (WO 99/15525)), serotonin reuptake inhibitors (e.g. dexfenfluramine), mixed serotoninergic and noradrenergic compounds (e.g. WO 00/71549), 5HT agonists e.g. 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111), bombesin agonists, galanin antagonists, growth hormone (e.g. human growth hormone), growth hormone-releasing compounds (6-benzyloxy-1-(2-

diisopropylaminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tertiary butyl ester (WO 01/85695)), TRH agonists (see, for example, EP 0 462 884), uncoupling protein 2 or 3 modulators, leptin agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. Drugs of the Future (2001), 26(9), 873-881), DA agonists (bromocriptine, Doprexin), lipase/amylase inhibitors (e.g. WO 00/40569), PPAR modulators (e.g. WO 00/78312), RXR modulators or TR-β agonists.

In one embodiment of the invention, the further active ingredient is leptin.

In one embodiment, the further active ingredient is dexamphetamine, amphetamine, mazindole or phentermine.

In one embodiment, the compounds of the formula I are administered in combination with medicaments having effects on the coronary circulation and the vascular system, such as, for example, ACE inhibitors (e.g. ramipril), medicaments which act on the angiotensin-renine system, calcium antagonists, beta blockers etc.

In one embodiment, the compounds of the formula I are administered in combination with medicaments having an antiinflammatory effect.

In one embodiment, the compounds of the formula I are administered in combination with medicaments which are employed for cancer therapy and cancer prevention.

It will be appreciated that every suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more other pharmacologically active substances is regarded as falling within the protection conferred by the present invention.

The activity of the compounds was tested as follows:

Determination of EC50 values of PPAR agonists in the cellular PPARalpha assay

Principle

The potency of substances which bind to human PPAR□ and activate in an agonistic manner is analyzed using a stably transfected HEK cell line (HEK= human embryo kidney) which is referred to here as PPARalpha reporter cell line. It contains two genetic elements, a luciferase reporter element (p□M-GAL4-Luc-Zeo) and a PPARalpha fusion protein (GR-GAL4-humanPPAR□-LBD) which mediates expression of the luciferase reporter element depending on a PPARalpha ligand. The stably and constitutively expressed fusion protein GR-GAL4-humanPPARalpha-LBD binds in the cell nucleus of the PPARalpha reporter cell line via the GAL4 protein portion to the GAL4 DNA binding motifs 5′-upstream of the luciferase reporter element which is integrated in the genome of the cell line. There is only little expression of the luciferase reporter gene without addition of a PPARalpha ligand if fatty acid-depleted fetal calf serum (cs-FCS) is used in the assay. PPAR□ ligands bind and activate the PPAR□ fusion protein and thereby bring about expression of the luciferase reporter gene. The luciferase which is formed can be detected by means of chemiluminescence via an appropriate substrate.

Construction of the cell line

The PPARalpha reporter cell line was prepared in 2 stages. Firstly, the luciferase reporter element was constructed and stably transfected into HEK cells. For this purpose, five binding sites of the yeast transcription factor GAL4 (each 5′-CGGAGTACTGTCCTCCGAG-3′) were cloned in 5′-upstream of a 68 bp-long minimal MMTV promoter (Genbank Accession # V01175). The minimal MMTV promoter section contains a CCAAT box and a TATA element in order to enable efficient transcription by RNA polymerase II. The cloning and sequencing of the GAL4-MMTV construct took place in analogy to the description of Sambrook J. *et. al.* (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Then the complete Photinus pyralis gene (Genbank Accession # M15077) was cloned in 3′-downstream of the GAL4-MMTV element. After sequencing, the luceriferase reporter element consisting of five GAL4 binding sites, MMTV promoter and luciferase gene was recloned into a plasmid which confers zeocin resistance in order to obtain the plasmid p□M-GAL4-Luc-Zeo. This vector was transfected into HEK cells in accordance with the statements in Ausubel, F.M. et al. (Current protocols in molecular biology, Vol. 1-3, John Wiley & Sons, Inc., 1995). Then zeocin-containing medium (0.5 mg/ml) was used to select a suitable stable cell clone which showed very low basal

expression of the luceriferase gene.

In a second step, the PPARalpha fusion protein (GR-GAL4-humanPPARalpha-LBD was introduced into the stable cell clone described. For this purpose, initially the cDNA coding for the N-terminal 76 amino acids of the glucocorticoid receptor (Genbank Accession # P04150) was linked to the cDNA section coding for amino acids 1-147 of the yeast transcription factor GAL4 (Genbank Accession # P04386). The cDNA of the ligand-binding domain of the human PPARalpha receptor (amino acids S167-Y468; Genbank Accession # S74349) was cloned in at the 3'-end of this GR-GAL4 construct. The fusion construct prepared in this way (GR-GAL4-humanPPARalpha-LBD) was recloned into the plasmid pcDNA3 (from Invitrogen) in order to enable constitutive expression therein by the cytomegalovirus promoter. This plasmid was linearized with a restriction endonuclease and stably transfected into the previously described cell clone containing the luciferase reporter element. The finished PPARalpha reporter cell line which contains a luciferase reporter element and constitutively expresses the PPARalpha fusion protein (GR-GAL4-human PPARalpha-LBD) was isolated by selection with zeocin (0.5 mg/ml) and G418 (0.5 mg/ml).

Assay procedure

The activity of PPARalpha agonists is determined in a 3-day assay which is described below:

Day 1

The PPAR□reporter cell line is cultivated to 80% confluence in DMEM (# 41965-039, Invitrogen) which is mixed with the following additions: 10% cs-FCS (fetal calf serum; #SH-30068.03, Hyclone), 0.5 mg/ml zeocin (#R250-01, Invitrogen), 0.5 mg/ml G418 (#10131-027, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). The cultivation takes place in standard cell culture bottles (# 353112, Becton Dickinson) in a cell culture incubator at 37°C in the presence of 5% CO_2. The 80%-confluent cells are washed once with 15 ml of PBS (#14190-094, Invitrogen), treated with 3 ml of trypsin solution (#25300-054, Invitrogen) at 37°C for 2 min, taken up in 5 ml of the DMEM described and counted in a cell counter. After dilution to 500.000 cells/ml, 35,000 cells are seeded in each well of a 96 well microtiter plate with a clear plastic base (#3610, Corning Costar). The

plates are incubated in the cell culture incubator at 37°C and 5% CO_2 for 24 h.

Day 2

PPARalpha agonists to be tested are dissolved in DMSO in a concentration of 10 mM. This stock solution is diluted in DMEM (#41965-039, Invitrogen) which is mixed with 5% cs-FCS (#SH-30068.03, Hyclone), 2 mM L-glutamine (#25030-024, Invitrogen) and the previously described antibiotics (zeocin, G418, penicillin and streptomycin).

Test substances are tested in 11 different concentrations in the range from 10 µM to 100 pM. More potent compounds are tested in concentration ranges from 1 µM to 10 pM or between 100 nM and 1 pM.

The medium of the PPARalpha reporter cell line seeded on day 1 is completely removed by aspiration, and the test substances diluted in medium are immediately added to the cells. The dilution and addition of the substances is carried out by a robot (Beckman FX). The final volume of the test substances diluted in medium is 100 µl per well of a 96 well microtiter plate. The DMSO concentration in the assay is less than 0.1 % v/v in order to avoid cytotoxic effects of the solvent.

Each plate was charged with a standard PPARalpha agonist, which was likewise diluted in 11 different concentrations, in order to demonstrate the functioning of the assay in each individual plate. The assay plates are incubated in an incubator at 37°C and 5% CO2 for 24 h.

Day 3

The PPARalpha reporter cells treated with the test substances are removed from the incubator, and the medium is aspirated off. The cells are lyzed by pipetting 50 µl of Bright Glo reagent (from Promega) into each well of a 96 well microtiter plate. After incubation at room temperature in the dark for 10 minutes, the microtiter plates are measured in the luminometer (Trilux from Wallac). The measuring time for each well of a microtiter plate is 1 sec.

Evaluation

The raw data from the luminometer are transferred into a Microsoft Excel file. Dose-effect plots and EC50 values of PPAR agonists are calculated using the XL.Fit program as specified by the manufacturer (IDBS).

The PPARalpha EC50 values for the compounds of Examples 1 to 91 in this assay are in the range from 0.6 nM to >10 µM.

The results for the activity of some compounds of the invention of the formula I are indicated in Table I below:

Table 1

Example No.	EC50 PPARalpha [nM]
1	41
5	69
8	24
18	1.5
22	43
25	6.2
35	84
36	14
47	0.8
52	22
60	26
81	0.6
93	78

It is evident from Table I that the compounds of the invention of the formula I activate the PPARalpha receptor and thus bring about for example in analogy to fibrates in clinical use a lowering of triglycerides in the body (see, for example, J.-Ch. Fruchard et al.: PPARS, Metabolic Disease and Atherosclerosis, Pharmacological Research, Vol. 44, No. 5, 345-52, 2001; S. Kersten et al.: Roles of PPARs in health and disease, NATURE, VOL 405, 25 MAY 2000, 421-4; I. Pineda et al.: Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice, Curr Opin Lipidol 12: 2001, 245-254).

Determination of EC50 values of PPAR agonists in the cellular PPARgamma assay

Principle

A transient transfection system is employed to determine the cellular PPARgamma activity of PPAR agonists. It is based on the use of a luciferase reporter plasmid (pGL3basic-5xGAL4-TK) and of a PPARgamma expression plasmid (pcDNA3-GAL4-humanPPARgammaLBD). Both plasmids are transiently transfected into human embryonic kidney cells (HEK cells). There is then expression in these cells of the fusion protein GAL4-humanPPARgammaLBD which binds to the GAL4 binding sites of the reporter plasmid. In the presence of a PPARgamma-active ligand, the activated fusion protein GAL4-humanPPARgammaLBD induces expression of the luciferase reporter gene, which can be detected in the form of a chemiluminescence signal after addition of a luciferase substrate. As a difference from the stably transfected PPARalpha reporter cell line, in the cellular PPARγ assay the two components (luciferase reporter plasmid and PPARgamma expression plasmid) are transiently transfected into HEK cells because stable and permanent expression of the PPARgamma fusion protein is cytotoxic.

Construction of the plasmids

The luciferase reporter plasmid pGL3basic-5xGAL4-TK is based on the vector pGL3basic from Promega. The reporter plasmid is prepared by cloning five binding sites of the yeast transcription factor GAL4 (each binding site with the sequence 5′-CTCGGAGGACAGTACTCCG-3′), together with a 160 bp-long thymidine kinase promoter section (Genbank Accession # AF027128) 5'-upstream into pGL3basic. 3'-downstream of the thymidine kinase promoter is the complete luciferase gene from Photinus pyralis (Genbank Accession # M15077) which is already a constituent of the plasmid pGL3basic used. The cloning and sequencing of the reporter plasmid pGL3basic-5xGAL4-TK took place in analogy to the description in Sambrook J. *et. al.* (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989).

The PPARgamma expression plasmid pcDNA3-GAL4-humanPPARγLBD was prepared by first cloning the cDNA coding for amino acids 1-147 of the yeast transcription factor GAL4 (Genbank Accession # P04386) into the plasmid pcDNA3 (from Invitrogen) 3´-downstream of the cytomegalovirus promoter. Subsequently, the cDNA of the ligand-binding domain (LBD) of the human PPARγ receptor (amino acids I152-Y475; Accession # g1480099) 3'-downstream of the GAL4 DNA binding domain. Cloning and sequencing of the PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD again took place in analogy to the description in Sambrook J. *et. al.* (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Besides the luciferase reporter plasmid pGL3basic-5xGAL4-TK and the PPARγ expression plasmid pcDNA3-GAL4-humanPPARgammaLBD, also used for the cellular PPARgamma assay are the reference plasmid pRL-CMV (from Promega) and the plasmid pBluescript SK(+) from Stratagene. All four plasmids were prepared using a plasmid preparation kit from Qiagen, which ensured a plasmid quality with a minimal endotoxin content, before transfection into HEK cells.

Assay procedure

The activity of PPARgamma agonists is determined in a 4-day assay which is described below. Before the transfection, HEK cells are cultivated in DMEM (# 41965-039, Invitrogen) which is mixed with the following additions: 10% FCS (#16000-044, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen).

Day 1

Firstly, solution A, a transfection mixture which contains all four plasmids previously described in addition to DMEM, is prepared. The following amounts are used to make up 3 ml of solution A for each 96 well microtiter plate for an assay: 2622 µl of antibiotic- and serum-free DMEM (# 41965-039, Invitrogen), 100 µl of reference plasmid pRL-CMV (1 ng/µl), 100 µl of luciferase reporter plasmid pGL3basic-5xGAL4-TK (10 ng/µl), 100 µl of PPARγ expression plasmid pcDNA3-GAL4-humanPPARγLBD (100 ng/µl) and 78 µl of plasmid pBluescript SK(+) (500 ng/µl). Then 2 ml of solution B are prepared by mixing 1.9 ml of DMEM (# 41965-039, Invitrogen) with 100 µl of PolyFect transfection reagent (from Qiagen) for each 96 well microtiter

plate. Subsequently, 3 ml of solution A are mixed with 2 ml of solution B to give 5 ml of solution C, which is thoroughly mixed by multiple pipetting and incubated at room temperature for 10 min.

80%-confluent HEK cells from a cell culture bottle with a capacity of 175 cm^2 are washed once with 15 ml of PBS (#14190-094, Invitrogen) and treated with 3 ml of trypsin solution (#25300-054, Invitrogen) at 37°C for 2 min. The cells are then taken up in 15 ml of DMEM (# 41965-039, Invitrogen) which is mixed with 10% FCS (# 16000-044, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). After the cell suspension has been counted in a cell counter, the suspension is diluted to 250,000 cells/ml. 15 ml of this cell suspension are mixed with 5 ml of solution C for one microtiter plate. 200 µl of the suspension are seeded in each well of a 96 well microtiter plate with a clear plastic base (#3610, Corning Costar). The plates are incubated in a cell culture incubator at 37°C and 5% CO_2 for 24 h.

Day 2

PPAR agonists to be tested are dissolved in DMSO in a concentration of 10 mM. This stock solution is diluted in DMEM (# 41965-039, Invitrogen) which is mixed with 2% Ultroser (#12039-012, Biosepra), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). Test substances are tested in a total of 11 different concentrations in the range from 10 µM to 100 pM. More potent compounds are tested in concentration ranges from 1 µM to 10 pM.

The medium of the HEK cells transfected and seeded on day 1 is completely removed by aspiration, and the test substances diluted in medium are immediately added to the cells. The dilution and addition of the substances is carried out by a robot (Beckman FX). The final volume of the test substances diluted in medium is 100 µl per well of a 96 well microtiter plate. Each plate is charged with a standard PPARγ agonist, which is likewise diluted in 11 different concentrations, in order to demonstrate the functioning of the assay in each individual plate. The assay plates are incubated in an incubator at 37°C and 5% CO_2.

Day 4

After removal of the medium by aspiration, 50 µl of Dual-Glo™ reagent (Dual-Glo™ Luciferase Assay System; Promega) are added to each well in

accordance with the manufacturer's instructions in order to lyze the cells and provide the substrate for the firefly luciferase (Photinus pyralis) formed in the cells. After incubation at room temperature in the dark for 10 minutes, the firefly luciferase-mediated chemiluminescence is measured in a measuring instrument (measuring time/well 1 sec; Trilux from Wallac). Then 50 µl of the Dual-Glo™ Stop & Glo reagent (Dual-Glo™ Luciferase Assay System; Promega) is added to each well in order to stop the activity of the firefly luciferase and provide the substrate for the Renilla luciferase expressed by the reference plasmid pRL-CMV. After incubation at room temperature in the dark for a further 10 minutes, a chemiluminescence mediated by the Renilla luciferase is again measured for 1 sec/well in the measuring instrument.

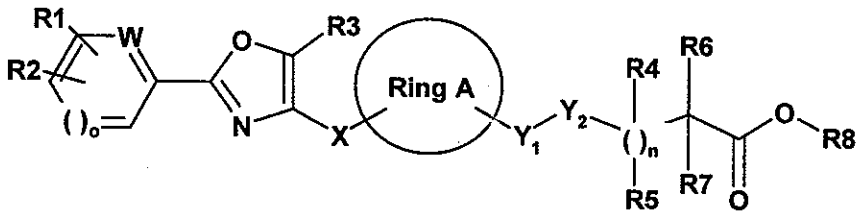
Evaluation

The crude data from the luminometer are transferred into a Microsoft Excel file. The firefly/Renilla luciferase activity ratio is determined for each measurement derived from one well of the microtiter plate. The dose-effect plots and EC50 values of PPAR agonists are calculated from the ratios by the XL.Fit program as specified by the manufacturer (IDBS).

PPARgamma EC50 values in the range from 6 nM to >10 µM were measured for the PPAR agonists described in this application.

The examples below serve to illustrate the invention, but without limiting it.

Table II:

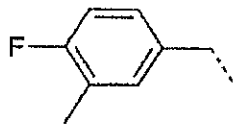
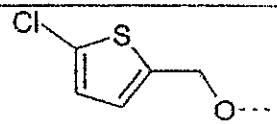


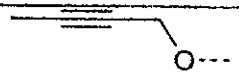
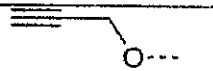
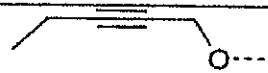
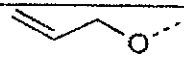
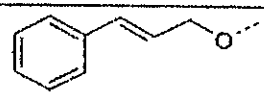
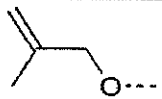
I

Hereinbelow:

Ring A = cis-cyclohexane-1,3-diyl, W = CH if o=1, R4 = R5 = R8 = H.

Ex.	R1	R2	R3	X	Y1	Y2	n	R6	R7	R9	R10
1	4-F	H	Me	CH2O	O	CH2	1	H	Et	–	–
2	4-F	H	Me	CH2O	O	CH2	1	H	n-Pr	–	–
3	4-F	H	Me	CH2O	O	CH2	1	H	H	–	–
4	4-F	H	Me	CH2O	O	CH2	1	H	Me	–	–
5	3-Me	H	Me	CH2O	O	CH2	0	cyclopropyl		–	–
6	3-Me	H	Me	CH2O	O	CH2	0	H	CH2NR9R10	Me	Bn
7	3-Me	H	Me	CH2O	O	CH2	0	H	CH2NR9R10	Me	PhCH2CH2

Ex.	R1	R2	R3	X	Y1	Y2	n	R6	R7	R9	R10
8	3-Me	H	Me	CH2O	O	CH2	0	H	MeOCH2	–	–
9	3-Me	H	Me	CH2O	O	CH2	0	H		–	–
10	3-Me	H	Me	CH2O	O	CH2	0	H	n-PrO	–	–
11	3-Me	H	Me	CH2O	O	CH2	0	H	4-CF_3-(C6H4)-CH2O	–	–
12	3-Me	H	Me	CH2O	O	CH2	0	H	MeO	–	–
13	3-Me	H	Me	CH2O	O	CH2	0	H	4-CF_3-(C6H4)-CH2O	–	–
14	3-Me	H	Me	CH2O	O	CH2	0	H	3-CF_3-(C6H4)-CH2O	–	–
15	3-Me	H	Me	CH2O	O	CH2	0	H	3-MeO-(C6H4)-CH2O	–	–
16	3-Me	H	Me	CH2O	O	CH2	0	H	2-Me-4-Me-(C6H4)-CH2O	–	–
17	3-Me	H	Me	CH2O	O	CH2	0	H	4-Me-(C6H4)-CH2O	–	–
18	3-Me	H	Me	CH2O	O	CH2	0	H	4-^{t}Bu--(C6H4)-CH2O	–	–
19	3-Me	H	Me	CH2O	O	CH2	0	H	2-CF_3-(C6H4)-CH2O	–	–
20	3-Me	H	Me	CH2O	O	CH2	0	H		–	–

Ex.	R1	R2	R3	X	Y1	Y2	n	R6	R7	R9	R10
21	3-Me	H	Me	CH2O	O	CH2	0	H		–	–
22	3-Me	H	Me	CH2O	O	CH2	0	H		–	–
23	3-Me	H	Me	CH2O	O	CH2	0	H		–	–
24	3-Me	H	Me	CH2O	O	CH2	0	H		–	–
25	3-Me	H	Me	CH2O	O	CH2	0	H		–	–
26	3-Me	H	Me	CH2O	O	CH2	0	H		–	–
27	3-Me	H	Me	CH2O	O	CH2	0	H	BnO	–	–
28	H	H	Me	CH2O	O	CH2	0	H	MeO	–	–
29	3-CF3	H	Me	CH2O	O	CH2	0	H	MeO	–	–
30	3-OCF3	H	Me	CH2O	O	CH2	0	H	MeO	–	–
31	4-CF3	H	Me	CH2O	O	CH2	0	H	MeO	–	–

Ex.	R1	R2	R3	X	Y1	Y2	n	R6	R7	R9	R10
32	4-Me	H	Me	CH2O	O	CH2	0	H	MeO	–	–
33	2-Me	6-Me	Me	CH2O	O	CH2	0	H	MeO	–	–
34	2-CF3	H	Me	CH2O	O	CH2	0	H	MeO	–	–
35	2-naphthyl		Me	CH2O	O	CH2	0	H	MeO	–	–
36	2-Me	4-Me	Me	CH2O	O	CH2	0	H	MeO	–	–
37	4-Ph	H	Me	CH2O	O	CH2	0	H	MeO	–	–
38	3-OMe	H	Et	CH2O	O	CH2	0	H	MeO	–	–
39	4-Me	H	Et	CH2O	O	CH2	0	H	MeO	–	–
40	2-CF3	H	Et	CH2O	O	CH2	0	H	MeO	–	–
41	2-Me	6-Me	Et	CH2O	O	CH2	0	H	MeO	–	–
42	H	H	Me	CH2O	O	CH2	0	H	n-PrO	–	–
43	3-Me	H	Me	CH2O	O	CH2	0	H	n-PrO	–	–
44	3-OCF3	H	Me	CH2O	O	CH2	0	H	n-PrO	–	–
45	3-OMe	H	Me	CH2O	O	CH2	0	H	n-PrO	–	–

Ex.	R1	R2	R3	X	Y1	Y2	n	R6	R7	R9	R10
46	4-CF3	H	Me	CH2O	O	CH2	0	H	n-PrO	–	–
47	4-Me	H	Me	CH2O	O	CH2	0	H	n-PrO	–	–
48	4-CF3	H	Me	CH2O	O	CH2	0	H	n-PrO	–	–
49	4-i-Pr	H	Me	CH2O	O	CH2	0	H	n-PrO	–	–
50	2-CF3	H	Me	CH2O	O	CH2	0	H	n-PrO	–	–
51	2-naphthyl		Me	CH2O	O	CH2	0	H	n-PrO	–	–
52	3-CF3	H	Me	CH2O	O	CH2	0	H	n-PrO	–	–
53	3-OMe	H	Et	CH2O	O	CH2	0	H	n-PrO	–	–
54	4-Me	H	Et	CH2O	O	CH2	0	H	n-PrO	–	–
55	2-CF3	H	Et	CH2O	O	CH2	0	H	n-PrO	–	–
56	2-Me	6-Me	Et	CH2O	O	CH2	0	H	n-PrO	–	–
57	3-CF3	H	Me	CH2O	O	CH2	0	H	EtO	–	–
58	3-OCF3	H	Me	CH2O	O	CH2	0	H	EtO	–	–
59	4-CF3	H	Me	CH2O	O	CH2	0	H	EtO	–	–
60	4-OCF3	H	Me	CH2O	O	CH2	0	H	EtO	–	–

Ex.	R1	R2	R3	X	Y1	Y2	n	R6	R7	R9	R10
61	4-i-Pr	H	Me	CH2O	O	CH2	0	H	EtO	–	–
62	2-CF3	H	Me	CH2O	O	CH2	0	H	EtO	–	–
63	2-Me	4-Me	Me	CH2O	O	CH2	0	H	EtO	–	–
64	4-Ph	H	Me	CH2O	O	CH2	0	H	EtO	–	–
65	4-Me	H	Et	CH2O	O	CH2	0	H	EtO	–	–
66	4-i-Pr	H	Et	CH2O	O	CH2	0	H	EtO	–	–
67	2-CF3	H	Et	CH2O	O	CH2	0	H	EtO	–	–
68	2-Me	6-Me	Et	CH2O	O	CH2	0	H	EtO	–	–
69	4-i-Pr	H	Et	CH2O	O	CH2	0	H	n-PrO	–	–
70	H	H	Me	CH2O	O	CH2	0	H	EtO	–	–
71	3-Me	H	Me	CH2O	O	CH2	0	H	EtO	–	–
72	3-OMe	H	Me	CH2O	O	CH2	0	H	EtO	–	–
73	4-Me	H	Me	CH2O	O	CH2	0	H	EtO	–	–
74	2-naphthyl		Me	CH2O	O	CH2	0	H	EtO	–	–
75	3-OMe	H	Et	CH2O	O	CH2	0	H	EtO	–	–
76	3-Me	H	Me	CH2O	O	CH2	0	H	4-CF3-(C6H4)-CH2O	–	–

Ex.	R1	R2	R3	X	Y1	Y2	n	R6	R7	R9	R10
77	3-CF3	H	Me	CH2O	O	CH2	0	H	4-CF3-(C6H4)-CH2O	–	–
78	3-OCF3	H	Me	CH2O	O	CH2	0	H	4-CF3-(C6H4)-CH2O	–	–
79	4-i-Pr	H	Me	CH2O	O	CH2	0	H	4-CF3-(C6H4)-CH2O	–	–
80	2-naphthyl		Me	CH2O	O	CH2	0	H	4-CF3-(C6H4)-CH2O	–	–
81	4-Me	H	Me	CH2O	O	CH2	0	H	4-CF3-(C6H4)-CH2O	–	–
82	4-OCF3	H	Me	CH2O	O	CH2	0	H	4-CF3-(C6H4)-CH2O	–	–
83	4-CF3	H	Me	CH2O	O	CH2	0	H	4-CF3-(C6H4)-CH2O	–	–
84	3-OMe	H	Me	CH2O	O	CH2	0	H	4-CF3-(C6H4)-CH2O	–	–
85	3-CF3	H	Me	CH2O	O	CH2	0	H	i-BuO	–	–
86	3-OMe	H	Me	CH2O	O	CH2	0	H	i-BuO	–	–
87	4-Me	H	Me	CH2O	O	CH2	0	H	i-BuO	–	–
88	4-i-Pr	H	Me	CH2O	O	CH2	0	H	i-BuO	–	–
89	3-Me	H	Me	CH2OCH2	O	CH2	0	H	4-CF3-(C6H4)-CH2O	–	–
90	3-Me	H	Me	CH2OCH2	O	CH2	0	H	4-CF3-(C6H4)-CH2O	–	–

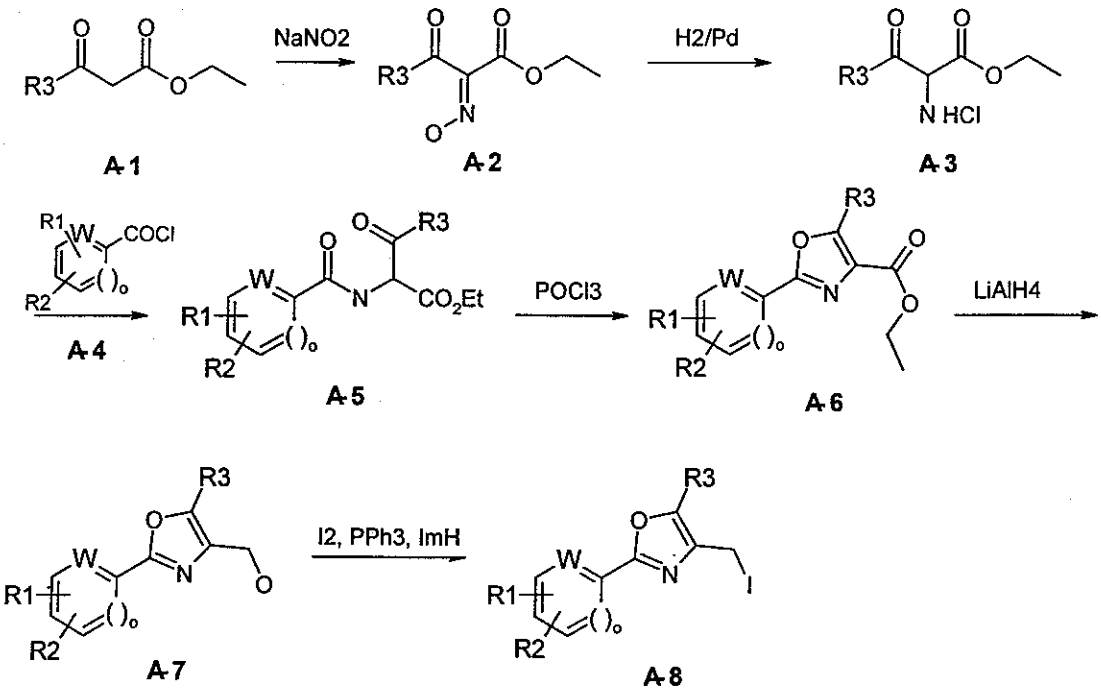
Ex.	R1	R2	R3	X	Y1	Y2	n	R6	R7	R9	R10
91	3-Me	H	Me	CH2O	O	CH2	1	H	m-CF3-(C6H4)-CH2	–	–

The broken line indicates the point of attachment.

The compounds of the formula I according to the invention can be obtained according to the reaction schemes below:

Process A:

This process serves for the synthesis of the building block A-A where R1, R2, W and R3 are as defined above.



The ester A-1 in which R3 is as defined above is reacted with sodium nitrite and hydrochloroic acid to give the oxime A-2 which is reduced by hydrogenation with hydrogen over palladium/carbon to give the amine A-3.

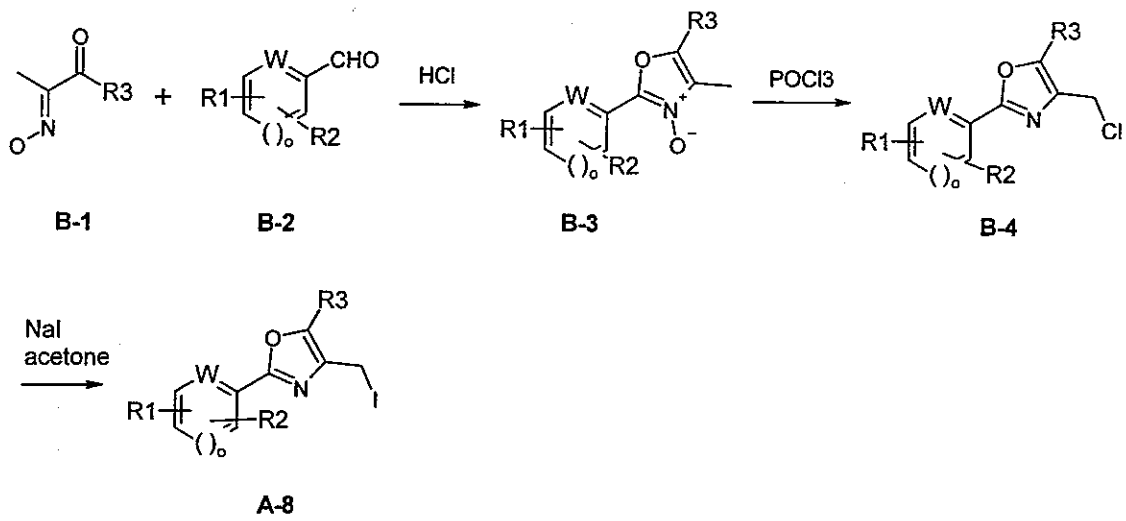
The compound A-3 is reacted with acid chloroides of the formula A-4 in which R1, W and R2 are as defined above and base (for example triethylamine) to give the compound A-5.

The compound A-5 is converted by heating in phosphoryl chloroide into the compound A-6.

The ester A-6 is reduced with lithium aluminum hydride in diethyl ether to give the alcohol A-7. This is converted with iodine, imidazole (ImH) and triphenylphosphine into the iodide A-8.

Process B:

This process serves for the synthesis of the building block A-8 in which R1, R2, W and R3 are as defined above.



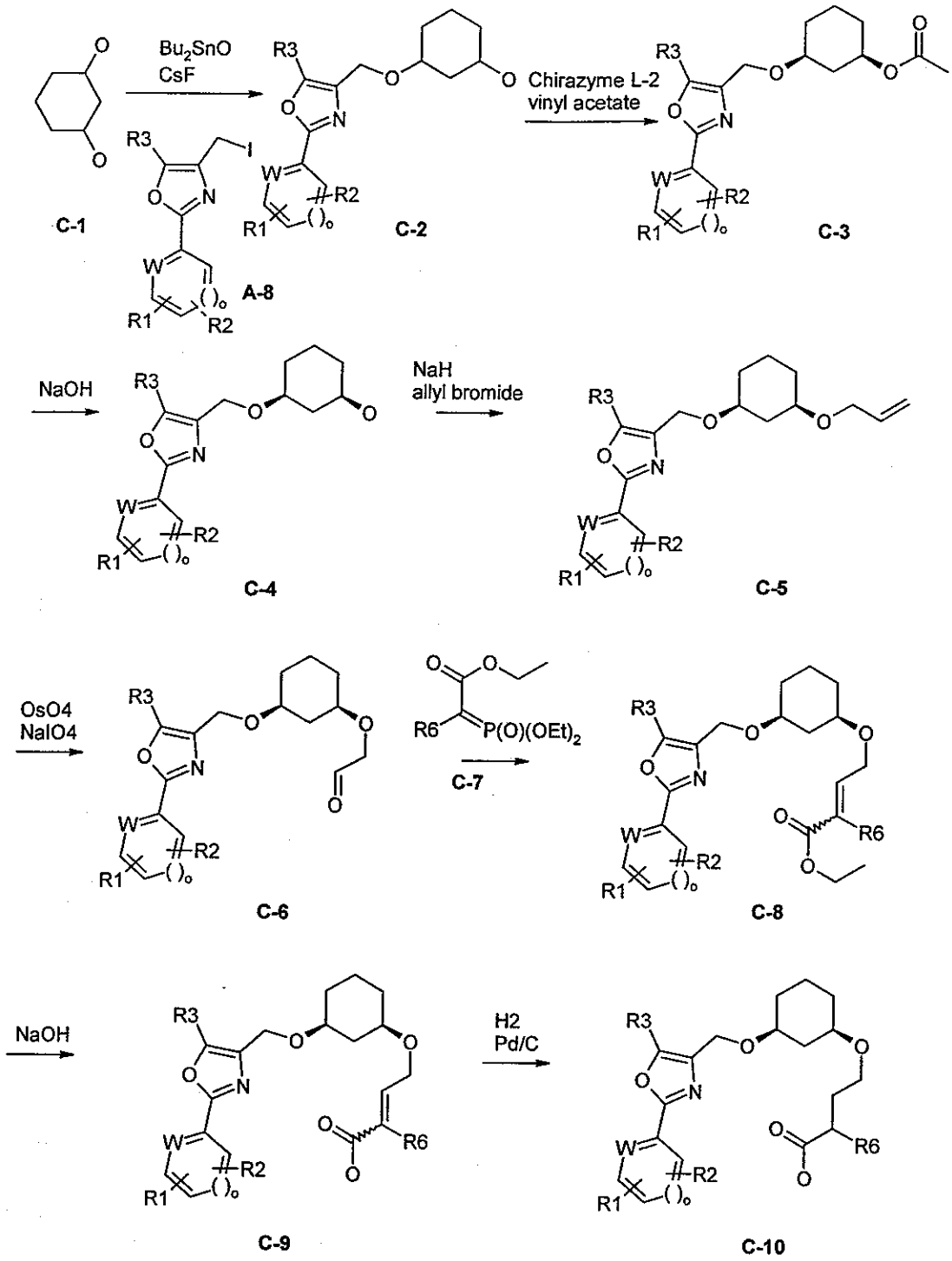
B-1 B-2 B-3 B-4

A-8

The compound B-1 is reacted with the aldehyde B-2 in which R1, R2, W and R3 are as defined above in ethanol with hydrogen chloroide to give the compound B-3.

The compound B-3 is heated to the boil in phosphoryl chloroide, which gives the compound B-4. This is heated with sodium iodide in acetone to the boil. This gives the compound A-8.

Process C:



The compound C-1 is boiled with dibutyltin oxide in toluene under reflux on a water separator. After addition of dimethylformamide, cesium fluoride and the compound A-8 (see process A), the suspension is stirred at room temperature. This gives the compound C-2. This is converted with Chirazyme L-2 in vinyl acetate into the enantiomerically enriched acetate C-3. Using sodium hydroxide in methanol, the acetate C-3 is converted into the alcohol C-4.

At room temperature, the compound C-4 is reacted with sodium hydride

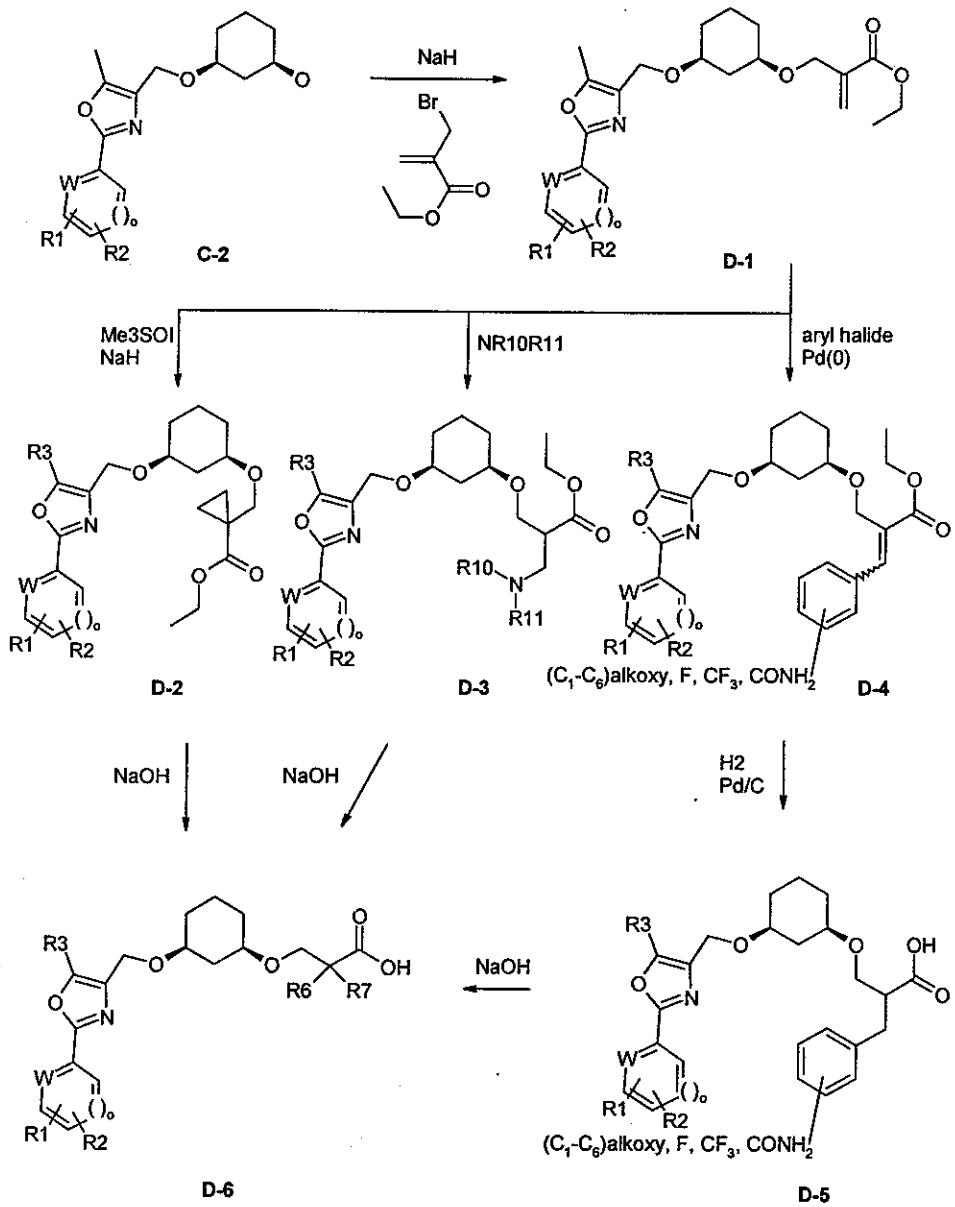
and allyl bromide and dimethylformamide to give the compound C-5.

The compound C-5 is reacted with osmium tetroxide and sodium periodate in diethyl ether to give the compound C-6. In a Horner-Emmons-Wadsworth reaction, this is converted with sodium hydride and the compound C-7 into the compound C-8.

The compound C-8 is hydrolyzed to the free acid by stirring for a number of hours with sodium hydroxide in methanol at room temperature. The resulting compound C-9 is hydrogenated with hydrogen over palladium/ carbon to give the compound C-10.

Using this process, it is possible to synthesize examples 1 to 4.

Process D:



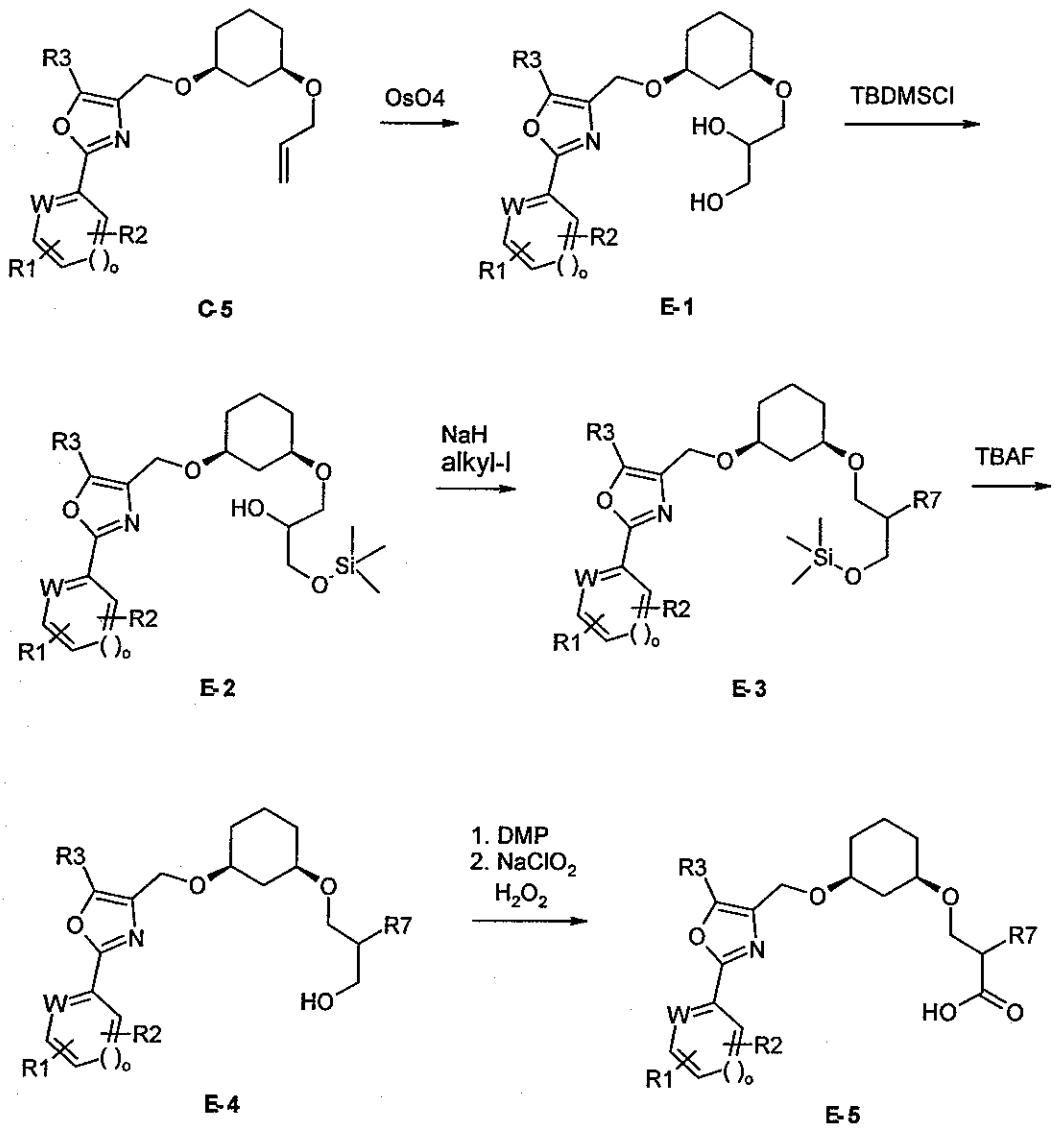
The compound C-2 is reacted with sodium hydride and ethyl 2-bromomethylacrylate in dimethylformamide at 0°C, to give the compound D-1.

The compound D-1 is then reacted either with trimethylsulfonium iodide and sodium hydride in dimethyl sulfoxide to give the compound D-2, or with a secondary amine NR10R11, where R10 and R11 are as defined above, to give the compound D-3, or with an aryl halide and a palladium(0) catalyst in a Heck reaction to give the compound D-4. The compound D-4 is then hydrogenated using hydrogen over palladium-on-carbon to give the compound D-5.

Using sodium hydroxide, the compounds D-2, D-3 and D-5 are converted into compounds of the formula D-6, where R6 and R7 are as defined above.

Using this process, it is possible to synthesize examples 5 to 9.

Process E:



C-5 E-1 E-2 E-3 E-4 E-5

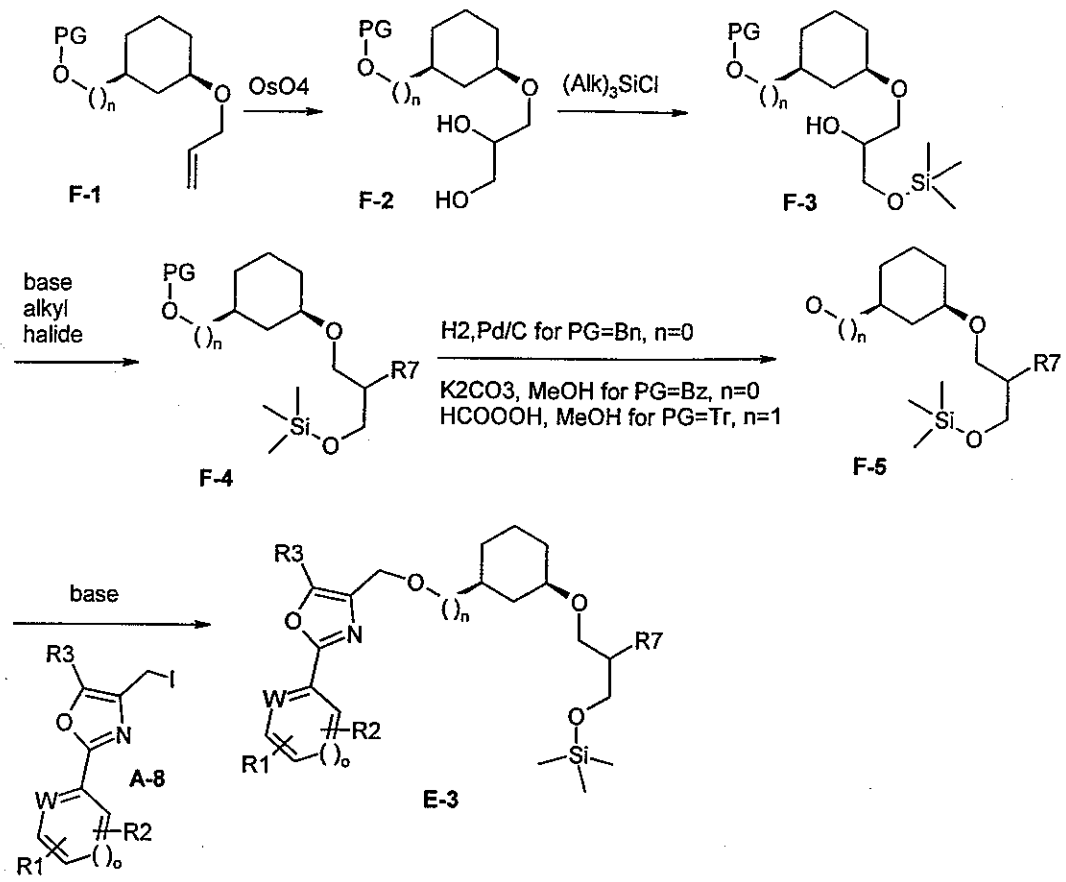
Using osmium tetroxide, 1,5-diazabicyclo[2.2.2]octane (DABCO) and N-methylmorpholine-N-oxide, the compound C-5 is dihydroxylated to the compound E-1. The primary hydroxyl group is then protected as trialkylsilyl ether E-2 by stirring the compound E-1 with a trialkylchlorosilane (for example tert-butyldimethylsilyl chloroide) and imidazole as base in dimethylformamide at room temperature. The compound E-2 is then reacted with a strong base (for example sodium hydride or potassium tert-butoxide) and an alkyl halide to give the compound E-3 where R7 is as defined above. Using tetrabutylammonium fluoride in tetrahydrofuran, the silyl protective group is removed, giving the compound E-4.

The compound E-4 is stirred at room temperature with Dess-Martin Periodinane (DMP) in dichloromethane for a number of hours, worked up and then reacted with sodium chloroite and hydrogen peroxide in acetonitrile to give the compound E-5. Alternatively, E-5 can be synthesized from E-4 by direct oxidation of E-4 using a chromium(VI) compound (for example CrO_3 in sulfuric acid).

Using this process, it is possible to synthesize examples 10 to 27.

Process F:

This process serves as an alternative preparation of intermediates E-3 (see process E)



The racemic or enantiomerically pure compound F-1 in which PG is as defined in the scheme is dihydroxylated to the compound F-2 using osmium tetroxide, 1,5-diazabicyclo[2.2.2]octane (DABCO) and N-methyl-morpholine-N-oxide.

The primary hydroxyl group is then protected as trialkylsilyl ether F-3 by stirring the compound F-2 at room temperature with a trialkylchlorosilane (for example tert-butyldimethylsilyl chloroide) and imidazole as base in dimethylformamide. The compound F-3 is then reacted with a strong base (for example sodium hydride or potassium tert-butoxide) and an alkyl halide to give the compound F-4 in which R7 is as defined above. The benzyl protective group is removed hydrolytically using hydrogen over Pd (10% on carbon), the benzoyl protective group is cleaved using potassium carbonate in methanol and the trityl group is removed using formic acid in methanol, which gives the compound F-5.

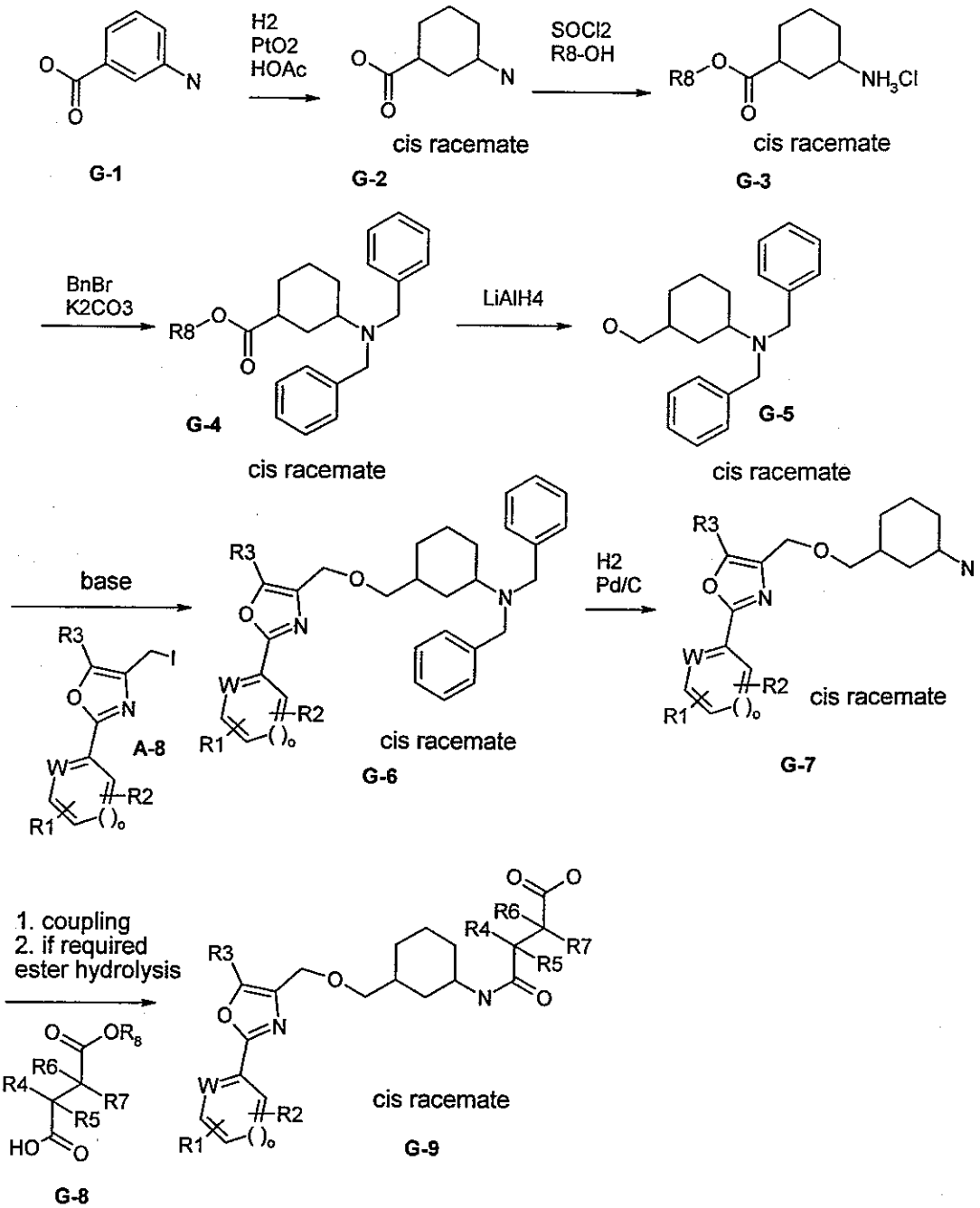
The compound F-5 is reacted with the alkyl iodide A-8 in the presence of a strong base (for example sodium hydride or potassium tert-butoxide) in an inert solvent (for example MTBE, chlorobenzene) to give the compound E-3 in which R1, R2, R3, R7 and W are as defined above.

The subsequent conversions of E-3 to E-5 are carried out as described

under process E.

Using this process, it is possible to synthesize examples 28 to 90.

Process G:



The compound G-1 (3-aminobenzoic acid) is hydrogenated in acetic acid using hydrogen over platinum dioxide under elevated pressure, which gives the compound G-2. Using thionyl chloroide in an alcohol R8OH in which R8 is as defined above (except for R8 = H), this is converted into an ester, which gives the compound G-3. The compound G-3 is then reacted with

benzyl bromide and potassium carbonate to give the dibenzylamine G-4. Reduction of G-4 with LiAlH4 affords the alcohol G-5.

Using an alkyl iodide A-8, the compound G-5 is converted into the compound G-6 in which R1, R2, W and R3 are as defined above. The compound G-6 is hydrogenated using hydrogen over palladium to give the compound G-7 in which R1, R2, W and R3 are as defined above.

The compound G-7 is coupled with carboxylic acid derivatives G-8 in which R4, R5, R6 and R7 are as defined above. If dicarboxylic acid monoesters G-8 are used, the coupling is followed by ester hydrolysis (using, for example, LiOH in THF/methanol/water for R8 = methyl or ethyl). This gives the compound G-9 in which R1, R2, W, R3, R4, R5, R6 and R7 are as defined above.

Using this process, it is possible to synthesize examples 28 to 90.

The abbreviations used denote:

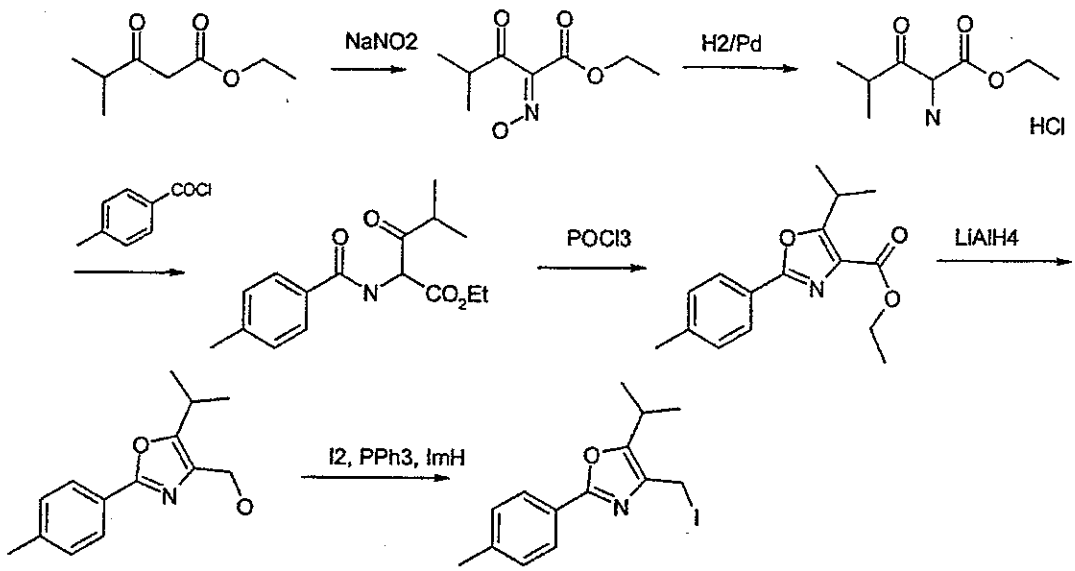
Ac	Acetyl
Bn	Benzyl
^{i}Bu	Isobutyl
^{t}Bu	tert-Butyl
BuLi	n-Butyllithium
Bz	Benzoyl
Cy	Cyclohexyl
TLC	Thin-layer chromatography
DCI	Direct chemical ionization (in MS)
DCM	Dichloromethane
DMAP	4-N,N-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
EA	Ethyl acetate
EDC	N'-(3-Dimethylaminopropyl)-N-ethylcarbodiimide x HCl

EI	Electron impact ionization (in MS)
eq	Equivalent
ESI	Electrospray ionization (in MS)
Et	Ethyl
sat.	Saturated
h	Hour
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBt	1-Hydroxy-1H-benzotriazole x H_2O
HPLC	High pressure, high performance liquid chromatography
LC-MS	Liquid chromatography-coupled mass spectroscopy
Me	Methyl
MS	Mass spectroscopy
MsCl	Methanesulfonyl chloroide
NMR	Nuclear magnetic resonance spectroscopy
Pd/C	Palladium on carbon
^{i}Pr	Isopropyl
^{n}Pr	n-Propyl
R_f	Retention time (in TLC)
RT	Room temperature
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPSCl	tert-Butyldiphenylsilyl chloroide
TBDMSCl	tert-Butyldimethylsilyl chloroide
THF	Tetrahydrofuran
Tr	Trityl

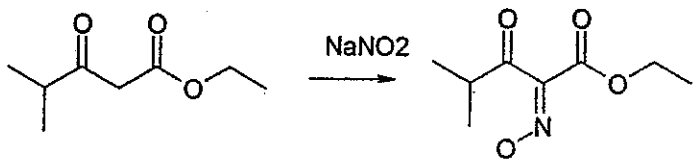
It is possible to prepare other compounds by the processes mentioned above.

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Building block synthesis according to process A:



Ethyl 2-hydroxyimino-4-methyl-3-oxopentanoate



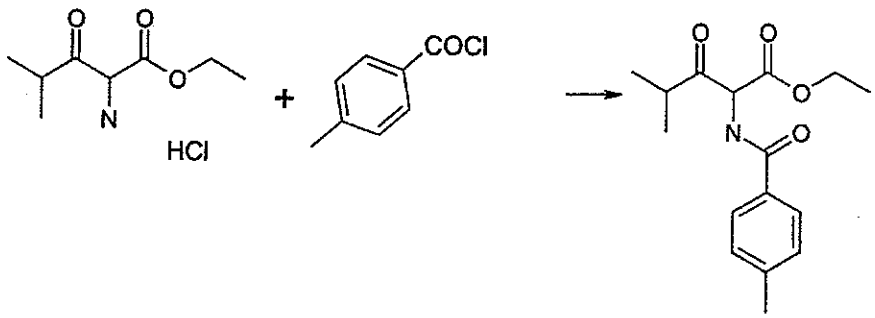
42.4 g of ethyl 4-methyl-3-oxopentanoate are dissolved in 100 ml of glacial acetic acid, and 21 g of sodium nitrite, dissolved in 100 ml of water, are added at 5°C. Over a period of one hour, the mixture is allowed to warm to room temperature, 100 ml of water are added and the mixture is stirred at room temperature for another hour. The mixture is extracted three times with in each case 150 ml of methyl tert-butyl ether, 200 ml of water are added to the combined organic phases and the mixture is neutralized by addition of solid NaHCO3. The organic phase is removed, washed with saturated NaCl solution and dried over MgSO4, and the solvent is removed under reduced pressure. This gives 46 g of ethyl 2-hydroxyimino-4-methyl-3-oxopentanoate as an oil. C8H13NO4 (187.20), MS (ESI) = 188 ($M+H^+$).

Ethyl 2-amino-4-methyl-3-oxopentanoate hydrochloroide



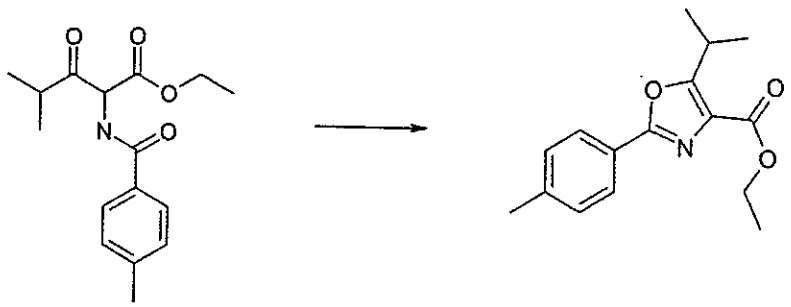
10 g of HCl are introduced into 200 ml of ethanol. 46 g of ethyl 2-hydroxy-imino-4-methyl-3-oxopentanoate are dissolved in this mixture, 5 g of Pd (10% on carbon) are added and the mixture is stirred under atmosphere of hydrogen (5 bar) for 8 hours. The reaction mixture is filtered through Celite and the solvent is removed under reduced pressure. This gives 45 g of ethyl 2-amino-4-methyl-3-oxopentanoate hydrochloroide as a white solid. C8H15NO3*HCl (209.5), MS(ESI) = 188 ($M+H^+$).

Ethyl 4-methyl-2-(4-methylbenzoylamino)-3-oxopentanoate



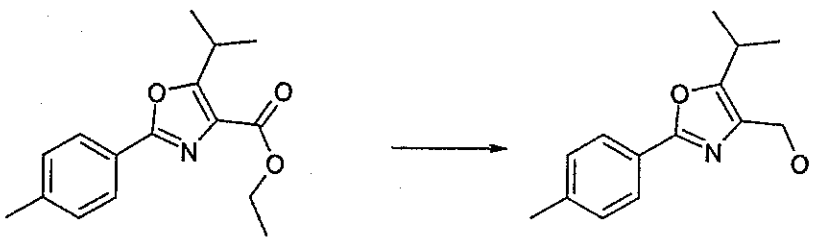
10 g of ethyl 2-amino-4-methyl-3-oxopentanoate hydrochloroide and 7.4 g of 4-methylbenzoyl chloroide are dissolved in 250 ml of dichloromethane, and 13.3 ml of triethylamine are slowly added dropwise at 0°C. The mixture is stirred at room temperature for one hour and then washed with water, the organic phase is separated off and dried over MgSO4 and the solvent is then removed under reduced pressure. This gives 13 g of ethyl 4-methyl-2-(4-methylbenzoylamino)-3-oxopentanoate as an oil.
C16H21NO4 (291.35), MS(ESI) = 292 ($M+H^+$).

Ethyl 5-isopropyl-2-p-tolyloxazole-4-carboxylate



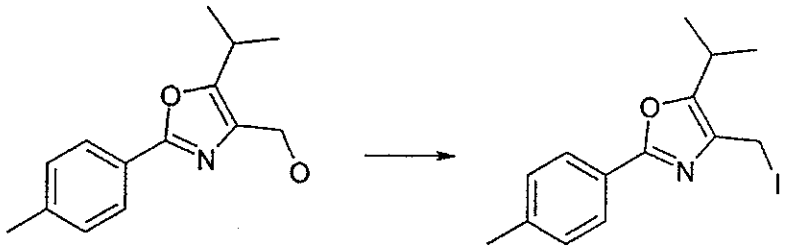
13 g of ethyl 4-methyl-2-(4-methylbenzoylamino)-3-oxopentanoate in 80 ml of phosphorus oxychloroide are heated to the boil under reflux for 2 h. The phosphorus oxychloroide is removed under reduced pressure and the resulting residue is dissolved in 200 ml of dichloromethane, washed three times with saturated $NaHCO_3$ solution and dried over MgSO4, and the solvent is then removed under reduced pressure. This gives 11 g of ethyl 5-isopropyl-2-p-tolyloxazole-4-carboxylate as a brownish sold. C16H19NO3 (273.33), MS(ESI) = 292 ($M+H^+$), Rf(n-heptane:ethyl acetate) = 2:1) = 0.43.

(5-Isopropyl-2-p-tolyloxazol-4-yl)methanol



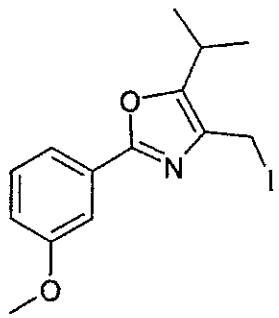
11 g of ethyl 5-isopropyl-2-p-tolyloxazole-4-carboxylate are dissolved in 100 ml of tetrahydrofuran, and 40 ml of a 1 molar solution of lithium aluminum hydride in tetrahydrofuran are added at 0°C. After 30 min, 1N of HCl are added to the reaction mixture, and the mixture is extracted five times with ethyl acetate. The combined organic phases are dried over MgSO4 and the solvent is then removed under reduced pressure. The residue is purified on silica gel using the mobile phase n-heptane:ethyl acetate = 6:1 => 1:1. This gives 4.3 g of (5-isopropyl-2-p-tolyloxazol-4-yl)methanol as a light-yellow solid.
C14H17NO2 (231.30), MS(ESI) = 232 ($M+H^+$), Rf(n-heptane:ethyl acetate) = 1:1) = 0.17.

4-Iodomethyl-5-isopropyl-2-p-tolyloxazole



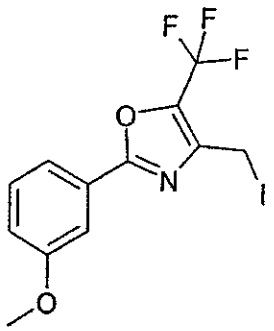
500 mg of (5-isopropyl-2-p-tolyloxazol-4-yl)methanol, together with 690 mg of triphenylphosphine and 600 mg of imidazole, are dissolved in 20 ml of toluene. 715 mg of iodine are added, and the mixture is stirred at room temperature for 1 hour. 10 ml of saturated sodium carbonate solution and 500 mg of iodine are then added. After 10 minutes, the organic phase is separated off, washed twice with saturated Na2S2O3 solution and dried over MgSO4, and the solvents are then removed under reduced pressure. The residue is purified on silica gel using the mobile phase n-heptane:ethyl acetate = 10:1. This gives 400 mg of 4-iodomethyl-5-isopropyl-2-p-tolyl-oxazole as a white solid. C14H16INO (341.19), MS(ESI): 342 ($M+H^+$), Rf(n-heptane:ethyl acetate = 1:1) = 0.75.

Analogously to the building block synthesis according to process K, ethyl 2-amino-4-methyl-3-oxopentanoate hydrochloroide and 3-methoxybenzoyl chloroide gave 4-iodomethyl-2-(3-methoxyphenyl)-5-isopropyloxazole.



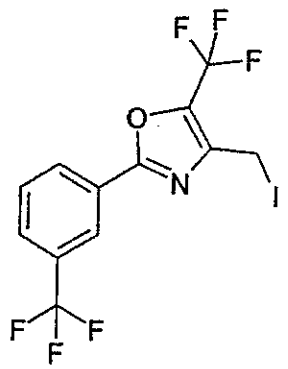
C14H16INO2 (357.19), MS(ESI): 358 ($M+H^+$), Rf(n-heptane:ethyl acetate = 1:1) = 0.60.

Analogously to the building block synthesis of 4-iodomethyl-5-isopropyl-2-p-tolyloxazole, ethyl 4,4,4-trifluoro-3-oxobutyrate and 3-methoxybenzoyl chloroide gave 4-iodomethyl-2-(3-methoxyphenyl)-5-trifluoromethyloxazole.



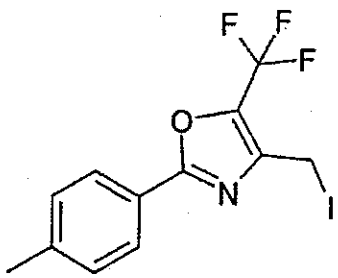
C12H9F3INO2 (383.11), MS(ESI): 384 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-isopropyl-2-p-tolyloxazole, ethyl 4,4,4-trifluoro-3-oxobutyrate and 3-trifluoromethyl-benzoyl chloroide gave 4-iodomethyl-2-(3-trifluoromethylphenyl)-5-trifluoro-methyloxazole.



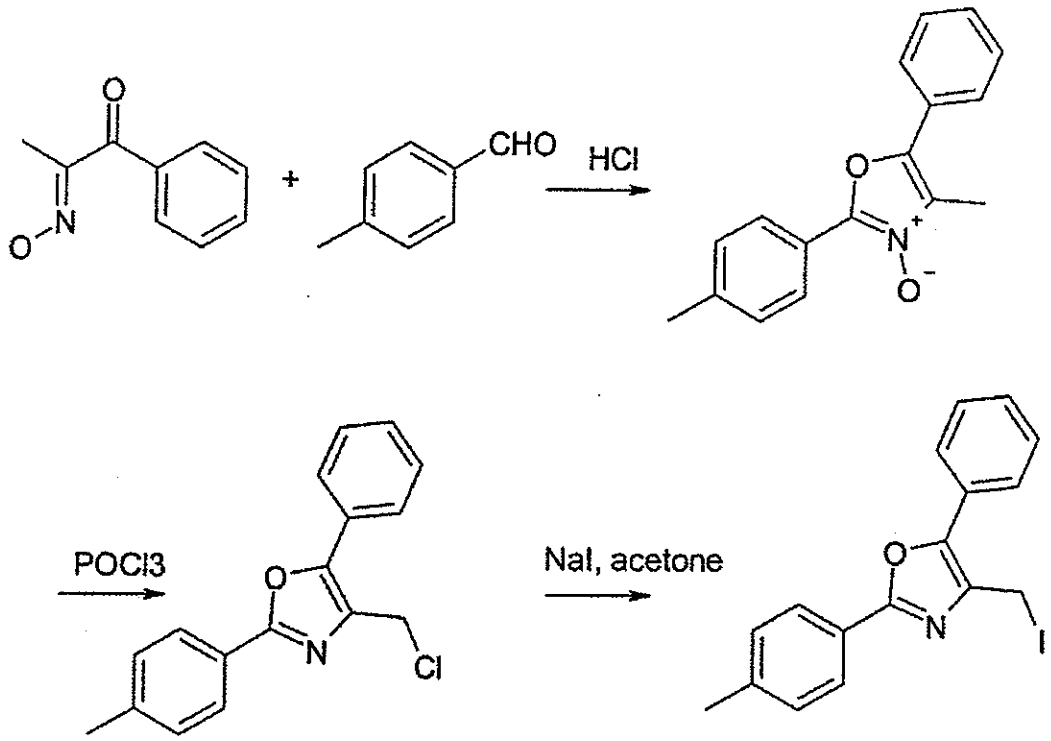
C12H6F6INO (421.08), MS(ESI): 422 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-isopropyl-2-p-tolyloxazole, ethyl 4,4,4-trifluoro-3-oxobutyrate and 4-methylbenzoyl chloroide gave 4-iodomethyl-5-trifluoromethyl-2-p-tolyloxazole.

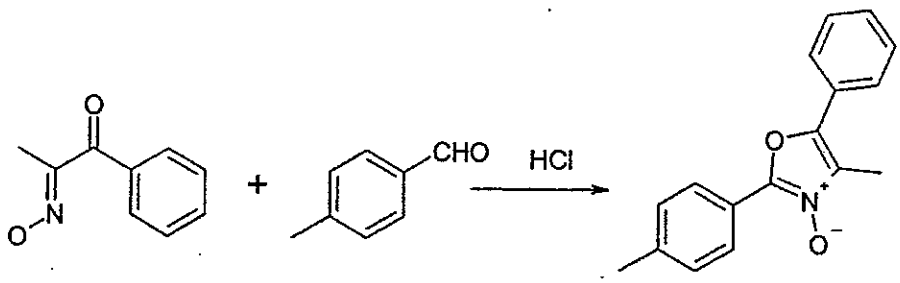


C12H9F3INO (367.11), MS(ESI): 368 ($M+H^+$).

Building block synthesis according to process B:



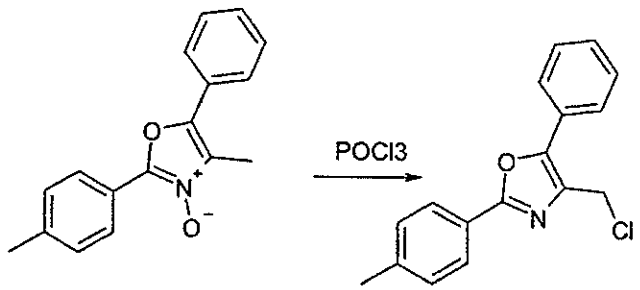
4-Methyl-5-phenyl-2-p-tolyloxazole 3-oxide



12.5 g of 1-phenyl-1,2-propanedione-2-oxime and 10 ml of p-tolualdehyde are added to 50 ml of glacial acetic acid, and HCl gas is introduced for 30 minutes, with ice-cooling. The product is precipitated as the hydrochloroide by addition of methyl tert-butyl ether and filtered off with suction, and the precipitate is washed with methyl tert-butyl ether. The precipitate is suspended in water and the pH is made alkaline using ammonia. The mixture is extracted three times with in each case 200 ml of dichloromethane, the combined organic phases are dried over MgSO4 and

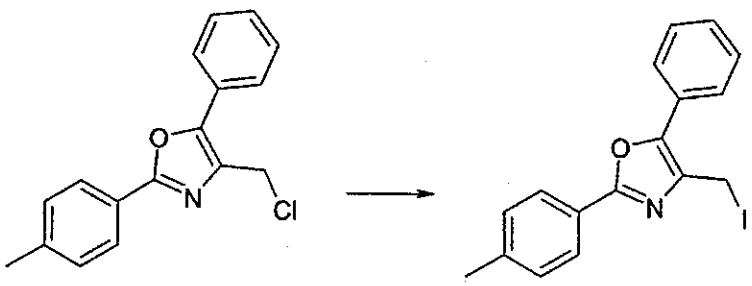
the solvent is then removed under reduced pressure. This gives 6.4 g of 4-methyl-5-phenyl-2-p-tolyloxazole 3-oxide as a white solid. C17H15NO2 (265.31), MS(ESI) = 266 ($M+H^+$).

4-Chloromethyl-5-phenyl-2-p-tolyloxazole



6.4 g of 4-methyl-5-phenyl-2-p-tolyloxazole 3-oxide are dissolved in 50 ml of chloroform, 2.4 ml of phosphorus oxychloroide are added and the mixture is, under reflux, heated at the boil for 30 minutes. The reaction mixture is cooled to 0°C, the pH is made slightly alkaline using ammonia and the mixture is extracted three times with in each case 100 ml of ethyl acetate. The combined organic phases are washed with water and dried over MgSO4, and the solvent then removed under reduced pressure. This gives 5.4 g of 4-chloromethyl-5-phenyl-2-p-tolyloxazole as a yellow solid. C17H14ClNO (283.76), MS(ESI) = 284 ($M+H^+$), Rf(n-heptane:ethyl acetate) = 7:1) = 0.41

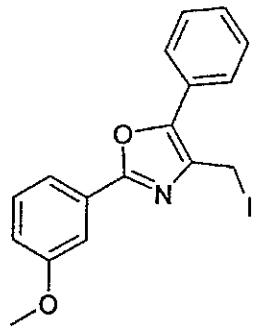
4-Iodomethyl-5-phenyl-2-p-tolyloxazole



Together with 3 g of sodium iodide, 1.8 g of 4-chloromethyl-5-phenyl-2-p-tolyloxazole are, in 150 ml of acetone, heated at the boil under reflux for 2 hours. After cooling of the reaction mixture, 300 ml of methyl tert-butyl ether are added, the mixture is washed three times with saturated Na2S2O3 solution and dried over MgSO4 and the solvents are then

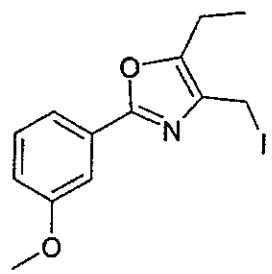
removed under reduced pressure. This gives 2.7 g of 4-iodomethyl-5-phenyl-2-p-tolyloxazole as a light-yellow solid.
C17H14INO (375.21), MS(ESI): 376 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, 1-phenyl-1,2-propanedione-2-oxime and m-anisaldehyde gave 4-iodomethyl-2-(3-methoxyphenyl)-5-phenyloxazole.



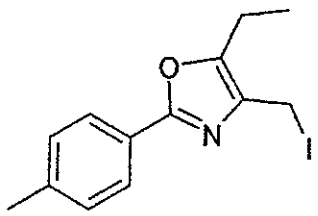
C17H14INO2 (391.21), MS(ESI): 392 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, 1-ethyl-1,2-propanedione-2-oxime and m-anisaldehyde gave 4-iodomethyl-5-ethyl-2-(3-methoxyphenyl)oxazole.



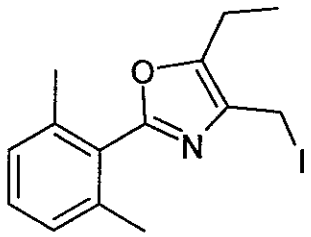
C13H14INO2 (343.17), MS(ESI): 344 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, 1-ethyl-1,2-propanedione-2-oxime and p-tolualdehyde gave 4-iodomethyl-5-ethyl-2-p-tolylazole.



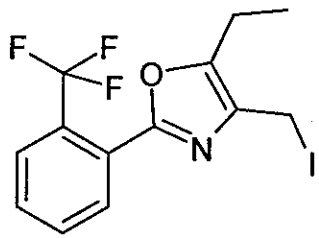
C13H14INO (327.17), MS(ESI): 328 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, 1-ethyl-1,2-propanedione-2-oxime and 2,6-dimethyl-benzaldehyde gave 4-iodomethyl-5-ethyl-2-(2,6-dimethylphenyl)oxazole.



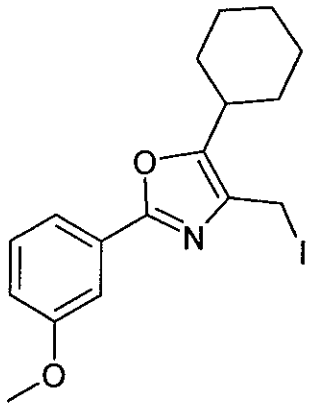
C14H16INO (341.19), MS(ESI): 342 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, 1-ethyl-1,2-propanedione-2-oxime and 2-trifluoromethyl-benzaldehyde gave 4-iodomethyl-5-ethyl-2-(2-trifluoromethylphenyl)-oxazole.



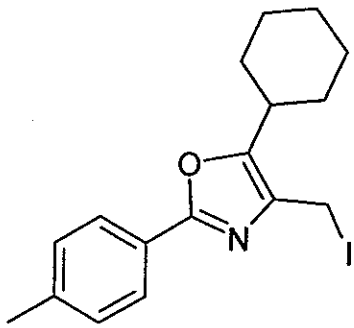
C13H11F3INO (381.14), MS(ESI): 382 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, 1-cyclohexyl-1,2-propanedione-2-oxime and m-anis-aldehyde gave 4-iodomethyl-5-cyclohexyl-2-(3-methoxyphenyl)oxazole.



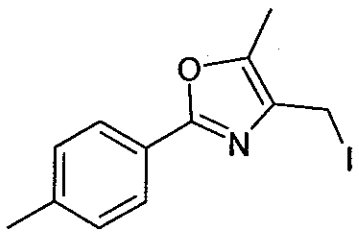
C17H20INO2 (397.26), MS(ESI): 398 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, 1-cyclohexyl-1,2-propanedione-2-oxime and p-toluene-aldehyde gave 4-iodomethyl-5-cyclohexyl-2-p-tolyloxazole.



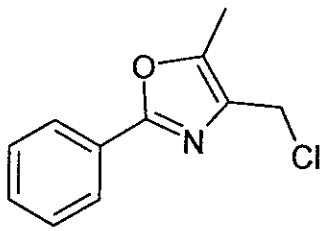
C17H20INO (381.26), MS(ESI): 382 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and p-toluenealdehyde gave 4-iodo-methyl-5-methyl-2-p-tolyloxazole.



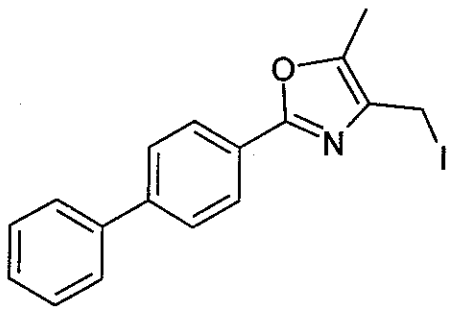
C12H12INO (313.14), MS(ESI): 314 ($M+H^+$).

Analogously to the building block synthesis of 4-chloromethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and benzaldehyde gave 4-chloromethyl-5-methyl-2-phenyloxazole.



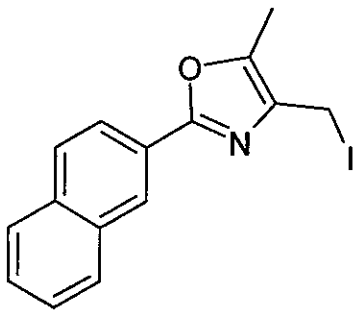
C11H10INO (207.66), MS(ESI): 208 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-biphenyloxazole, diacetylmonoxime and p-biphenylcarbaldehyde gave 4-iodomethyl-5-methyl-2-p-biphenyloxazole.



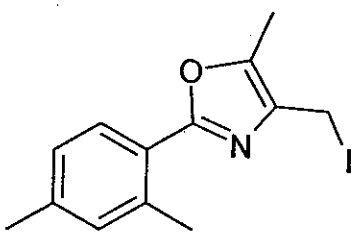
C12H12INO (375.21), MS(ESI): 376 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and 2-naphthalenecarbaldehyde gave 4-iodomethyl-5-methyl-2-naphthyloxazole.



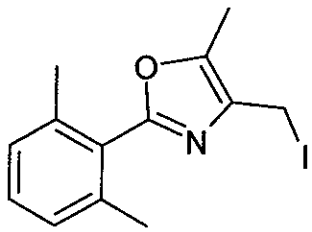
C12H12INO (349.17), MS(ESI): 350 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and 2,4-dimethylbenzaldehyde gave 4-iodomethyl-5-methyl-2-(2,4-dimethylphenyl)oxazole.



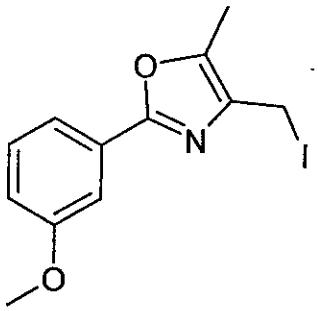
C13H14INO (327.17), MS(ESI): 328 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and 2,6-dimethylbenzaldehyde gave 4-iodomethyl-5-methyl-2-(2,6-dimethylphenyl)oxazole.



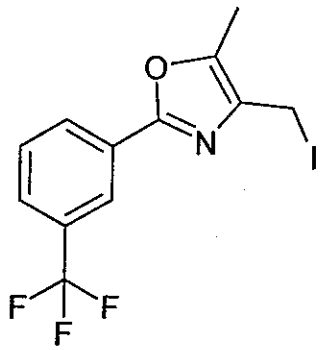
C13H14INO (327.17), MS(ESI): 328 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and m-anisaldehyde gave 4-iodomethyl-2-(3-methoxyphenyl)-5-methyloxazole.



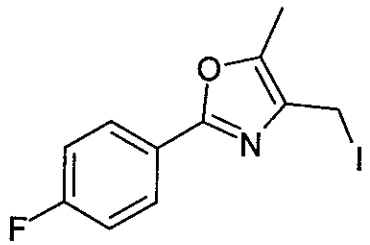
C12H12INO2 (329.14), MS(ESI): 330 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and 3-trifluoromethylbenzaldehyde gave 4-iodomethyl-5-methyl-2-(3-trifluoromethylphenyl)oxazole.



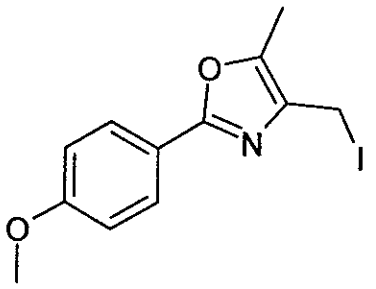
C12H9F3INO (367.11), MS(ESI): 368 ($M+H^+$).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and 4-fluorobenzaldehyde gave 2-(4-fluorophenyl)-4-iodomethyl-5-methyloxazole.



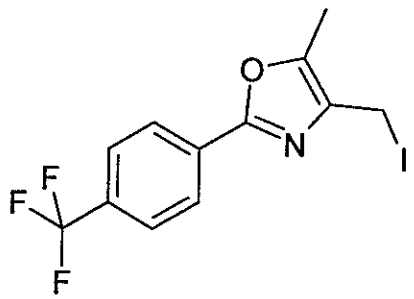
C11H9FINO (317.10), MS(ESI):318 (M+H+).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and 4-methoxybenzaldehyde gave 4-iodomethyl-2-(4-methoxyphenyl)-5-methyloxazole.



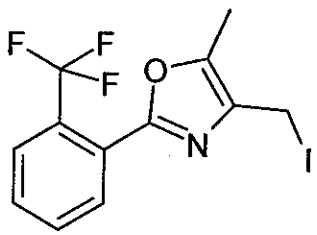
C12H12INO2 (329.14), MS(ESI):330 (M+H+).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and 4-trifluoromethylbenzaldehyde gave 4-iodomethyl-5-methyl-2-(4-trifluoromethylphenyl)oxazole.



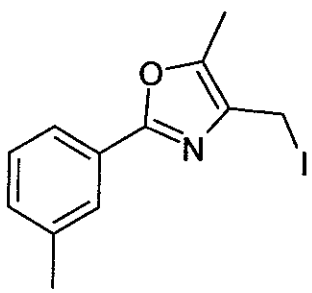
C12H9F3INO (367.11), MS(ESI):368 (M+H+).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and 2-trifluoromethylbenzaldehyde gave 4-iodomethyl-5-methyl-2-(2-trifluoromethylphenyl)oxazole.



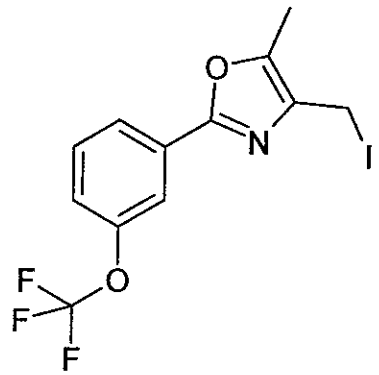
C12H9F3INO (367.11), MS(ESI):368 (M+H+).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and m-toluenealdehyde gave 4-iodomethyl-5-methyl-2-m-tolyloxazole.



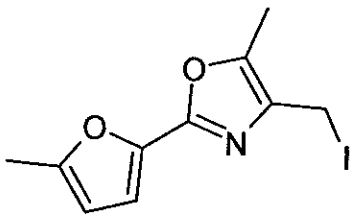
C12H12INO (313.14), MS(ESI):314 (M+H+).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and 3-trifluoromethoxybenzaldehyde gave 4-iodomethyl-5-methyl-2-(3-trifluoromethoxyphenyl)oxazole.



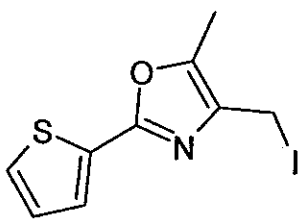
C12H9F3INO2 (383.11), MS(ESI):384 (M+H+).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and 5-methylfuran-2-carbaldehyde gave 4-iodomethyl-5-methyl-2-(5-methylfuran-2-yl)oxazole.



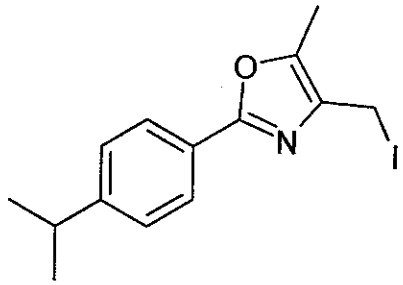
C10H10INO2 (303.11), MS(ESI):304 (M+H+).

Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and thiophene-2-carbaldehyde gave 4-iodomethyl-5-methyl-2-thiophen-2-yloxazole.



C9H8INOS (305.14), MS(ESI):306 (M+H+).

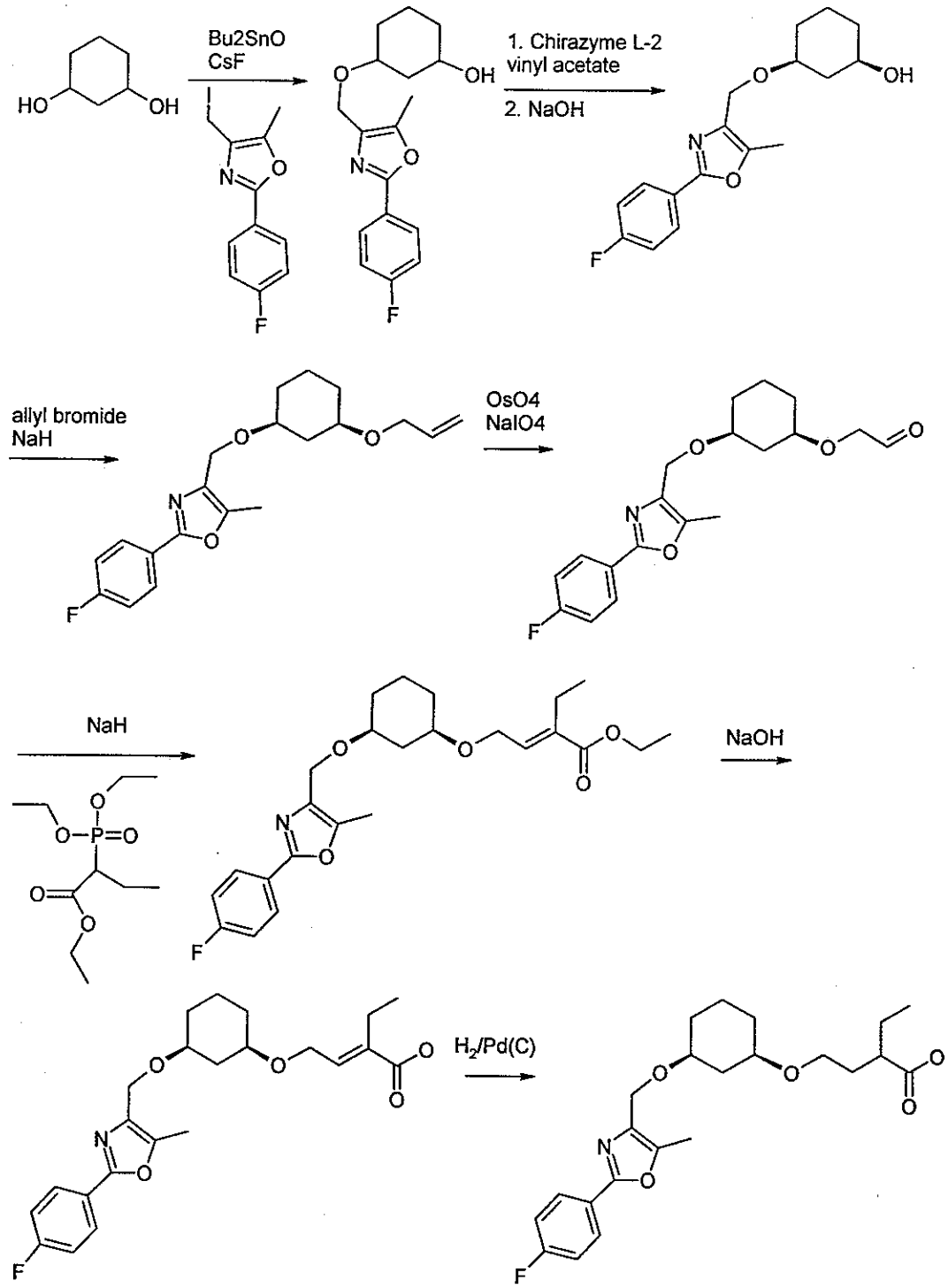
Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-p-tolyloxazole, diacetylmonoxime and 4-isopropylbenzaldehyde gave 4-iodomethyl-2-(4-isopropylphenyl)-5-methyloxazole.



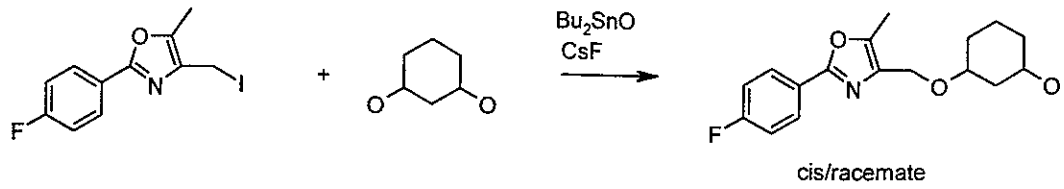
C14H16INO (341.19), MS(ESI):342 (M+H+).

Example 1:

2-Ethyl-4-{(1R,3S)-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}butanoic acid

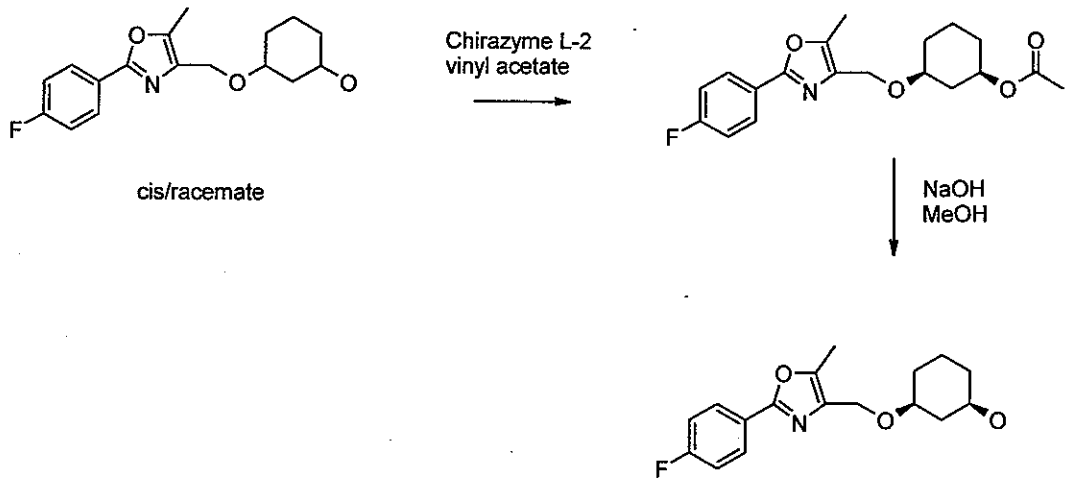


rac-3-(cis-5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol



21.7 g of 1,3-cyclohexanediol and 30.3 g of dibutyltin oxide are dissolved in 450 ml of toluene and, under reflux on a water separator, heated to the boil. During the duration of the reaction, the reaction volume is reduced to half of the original volume. After 3 hours, the reaction mixture is cooled to room temperature, and 300 ml of dimethylformamide, 29 g of 2-(4-fluorophenyl)-4-iodomethyl-5-methyloxazole and 23.5 g of cesium fluoride are added. The mixture is stirred at room temperature for another 18 hours. The reaction mixture is diluted by addition of ethyl acetate and washed with saturated sodium chloroide solution. The organic phase is dried over magnesium sulfate, the solvent is removed under reduced pressure and the residue is purified by flash chromatography on silica gel (n-heptane/ ethyl acetate = 10:1 → 1:4). This gives 58 g of rac-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol as a yellowish solid which is recrystallized from n-heptane/ethyl acetate. C17H20FNO3 (305.35), MS (ESI): 306 (M + H+).

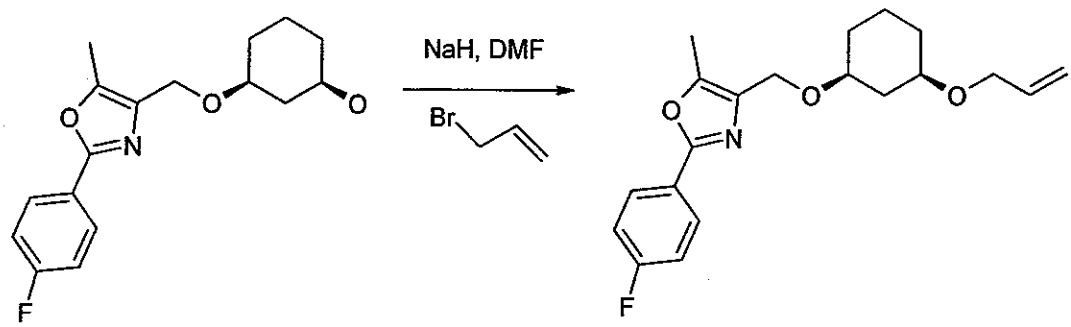
3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol



25 g of rac-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol are dissolved in 320 ml of vinyl acetate, and 1.3 g of Chirazyme L-2 Lyo (Boehringer Mannheim) are added. After about three hours of stirring at room temperature (LC-MS control for 40-45% conversion), the enzyme is

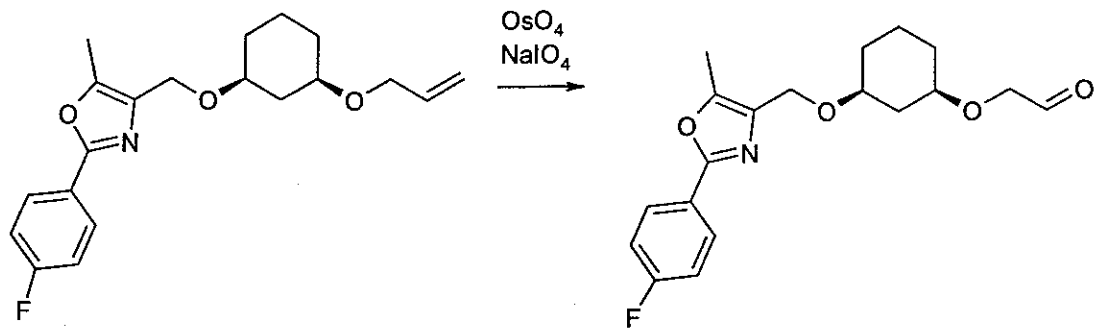
filtered off and rinsed with ethyl acetate, and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 3:1). This gives 8 g of the acetate as a colorless oil. C19H22FNO4 (347.39), MS (ESI): 348 (M + H+). The acetate is taken up in 170 ml of methanol and, after addition of 27 ml of 2N NaOH, stirred at room temperature for one hour. Most of the solvent is removed under reduced pressure. After addition of in each case 150 ml of water and ethyl acetate, the organic phase is washed with sodium chloroide solution. The organic phase is dried over magnesium sulfate and the solvent is removed under reduced pressure. This gives 6.7 g of 3-((1R,3S)-cis-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol as a yellowish solid. C17H20FNO3 (305.35), MS (ESI): 306 (M + H+).

4-(3-Allyloxycyclohexyloxymethyl)-2-(4-fluorophenyl)-5-methyloxazole



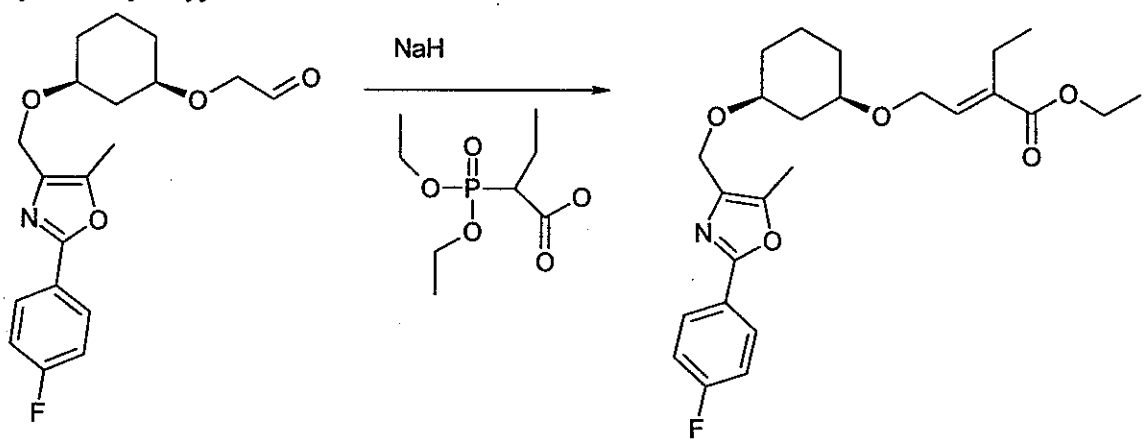
2 g of the 3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol are dissolved in 15 ml of dimethylformamide, and 0.3 g of sodium hydride is added. After 30 minutes, 2.4 g of allyl bromide are added dropwise. The mixture is stirred at room temperature for 5 hours. 15 ml of 1N HCl are then added to the reaction mixture, and the mixture is washed three times with 15 ml of ethyl acetate. The organic phase is dried over magnesium sulfate, and the solvent is then removed under reduced pressure. The residue is purified by RP-HPLC. This gives 2.4 g of 4-(3-allyloxycyclohexyloxymethyl)-2-(4-fluorophenyl)-5-methyloxazole as a yellowish oil. C20H24FNO3 (345.42) MS(ESI): 346 (M+H+)

[3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl]acetaldehyde



2.0 g of 4-(3-allyloxycyclohexyloxymethyl)-2-(4-fluorophenyl)-5-methyloxazole are dissolved in 50 ml of diethyl ether, and 3.8 g of sodium periodate, dissolved in 50 ml of water, are added. At 0°C, 1 ml of an osmium tetroxide solution (2.5% by weight in tert-butanol) is added, and the mixture is stirred vigorously at room temperature. After 8 h, 100 ml of methyl tert-butyl ether are added, and the mixture is washed with a saturated sodium thiosulfate solution. The organic phase is dried over magnesium sulfate and the solvent is removed under reduced pressure. The residue is purified on silica gel (n-heptane:ethyl acetate = 1:1 → 1:5). This gives 1.4 g of [3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl]acetaldehyde as a yellow-brown oil. C20H25NO4 (343.42), MS(ESI): 344 (M+H+), Rf(n-heptane:ethyl acetate = 1:1) = 0.25.

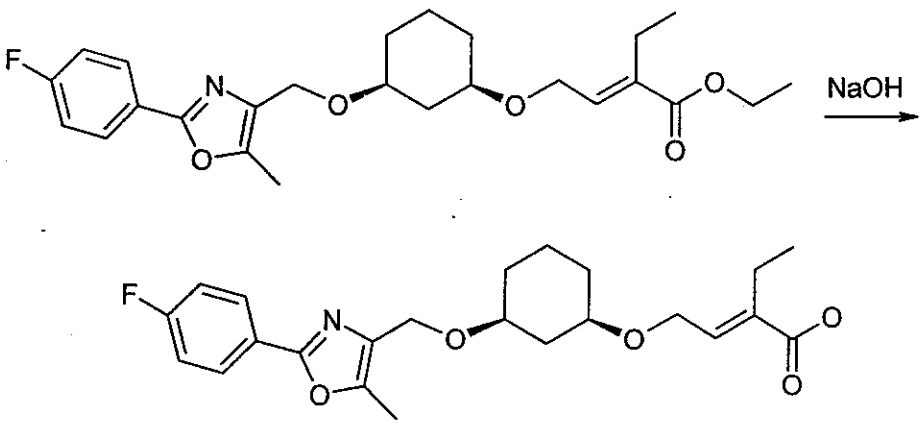
Ethyl 2-ethyl-4-{(1R,3S)-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]-cyclohexyloxy}but-2-enoate



0.58 g of ethyl 2-(diethoxyphosphoryl)butanoate is dissolved in tetrahydrofuran (20 ml), and 0.06 g of sodium hydride is added at 0°C. The suspension is stirred at 0°C for 30 min and at room temperature for 30 min

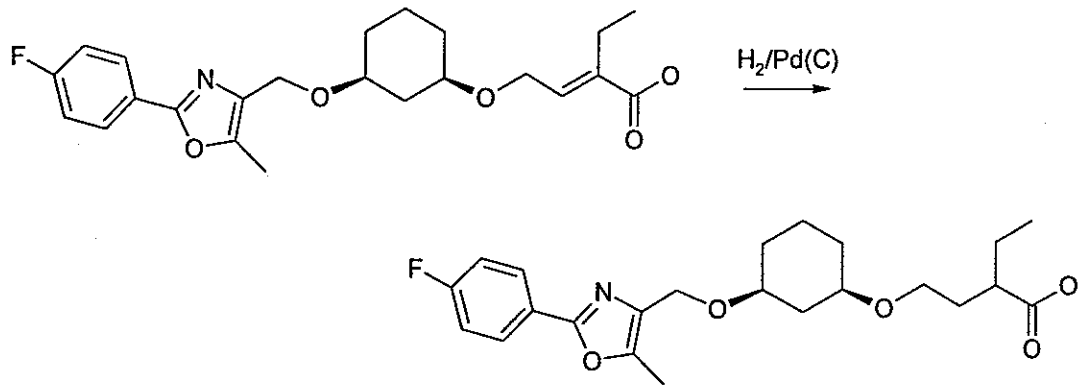
and then cooled to -70°C. After addition of 0.4 g of 2-((1R,3S)-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]acetaldehyde (dissolved in 5 ml of tetrahydrofuran), the mixture is stirred at -70°C for 60 min and then at room temperature for 12 h. 10 ml of water are added, the mixture is extracted with ethyl acetate (3 × 10 ml) and the combined organic phases are washed with saturated sodium chloroide solution (10 ml). The solvent is removed under reduced pressure and the residue is purified by HPLC. This gives 0.32 g of ethyl 2-ethyl-4-{(1R,3S)-3-[2-(4-fluorophenyl)-5-methyl-oxazol-4-ylmethoxy]cyclohexyloxy}but-2-enoate C25H32FNO5 (445.54) MS(ESI): 446 (M + H+)

2-Ethyl-4-{(1R,3S)-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]-cyclohexyloxy}but-2-enoic acid



0.5 g of ethyl 2-ethyl-4-{(1R,3S)-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}but-2-enoate is dissolved in 5 ml of methanol, and 2.5 ml of 1N aqueous sodium hydroxide solution are added. After 12 h of stirring at room temperature, the mixture is acidified with 3 ml of 1N hydrochloroic acid and the resulting precipitate is taken up in ethyl acetate. The solvent is removed under reduced pressure and the residue of the ester hydrolysis, 2-ethyl-4-{(1R,3S)-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}but-2-enoic acid, is obtained as 0.45 g of a white solid. $C_{23}H_{28}FNO_5$ (417.48) MS(ESI): 418 ($M + H^+$)

2-Ethyl-4-{(1R,3S)-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclo-hexyloxy}butanoic acid

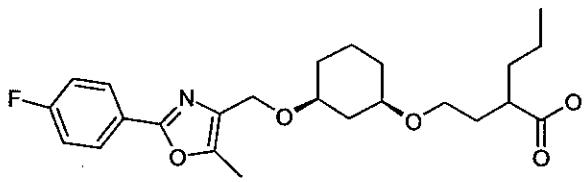


0.3 g of 2-ethyl-4-{(1R,3S)-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}but-2-enoic acid is dissolved in a solvent mixture of 2 ml of ethyl acetate and 1 ml of methanol, and 0.05 g of palladium (10% on carbon) is added. The mixture is then hydrogenated at a hydrogen pressure of 1 bar for 3 h.

The palladium is filtered off and the solvent mixture is then removed under reduced pressure and the residue is recrystallized from acetonitrile. This gives 0.25 g of 2-ethyl-4-{(1R,3S)-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}butanoic acid as a white solid. $C_{23}H_{30}FNO_5$ (419.49), MS(ESI): 420 ($M + H^+$)

Example 2:

Using reaction conditions similar to those of example 1, 2-((1R,3S)-[3-(2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy)cyclohexyloxy]acetaldehyde and ethyl 2-(diethoxyphosphoryl)pentanoate give 2-propyl-4-[3-(2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy)cyclohexyloxy]butanoic acid.

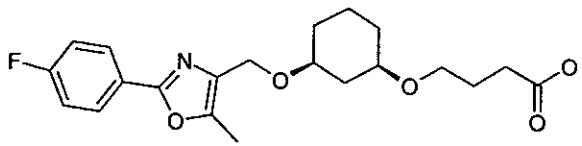


$C_{24}H_{32}FNO_5$ (433.52) MS(ESI): 434 ($M+H^+$)

Example 3:

Using reaction conditions similar to those of example 1, 2-((1R,3S)-[3-(2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy)cyclohexyloxy]acetaldehyde and

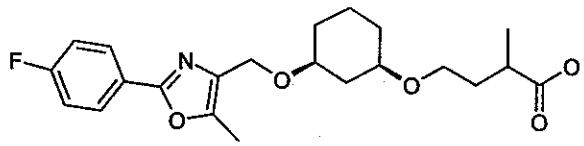
ethyl 2-(diethoxyphosphoryl)acetate give 4-{3-[2-(4-fluorophenyl)-5-methyl-oxazol-4-ylmethoxy]cyclohexyloxy}butanoic acid



$C_{21}H_{26}FNO_5$ (391.44) MS(ESI): 392 ($M + H^+$)

Example 4:

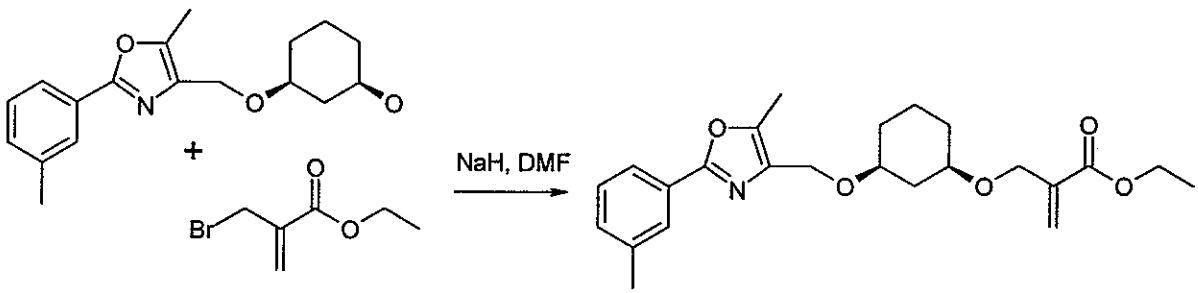
Using reaction conditions similar to those of example 1, 2-((1R,3S)-[3-(2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy)cyclohexyloxy]acetaldehyde and ethyl 2-(diethoxyphosphoryl)propionate give 4-{3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}-2-methylbutanoic acid



C22H28FNO5 (405.47) MS(ESI): 406 (M + H+)

Example 5:

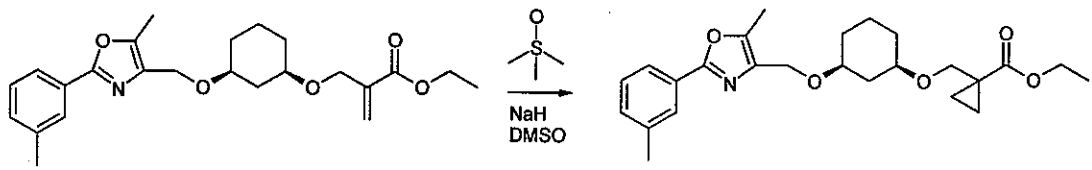
Ethyl ((1R,3S)-2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy-methyl]acrylate



200 mg of a 60% strength sodium hydride suspension are added at room temperature to a solution of 754 mg of 3-((1R,3S)-cis-5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol in 10 ml of dimethylformamide/5 ml of tetrahydrofuran, and the mixture is stirred at room temperature for

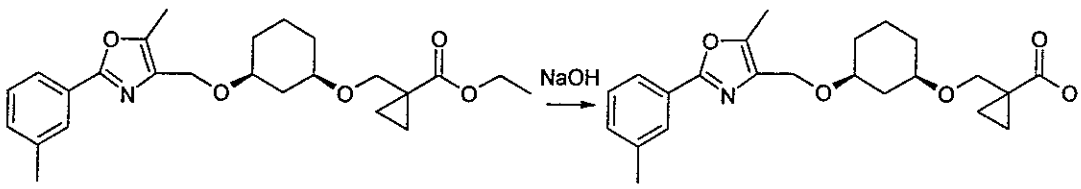
20 minutes. At 0°C, 1 g of ethyl 2-bromomethylacrylate is then added, and the mixture is stirred at this temperature for 2 h. 100 ml of ethyl acetate and 150 ml of saturated NaCl solution are added. The organic phase is dried over sodium sulfate, the solvent is removed under reduced pressure and the residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 2:1). This gives 1.18 g of ethyl ((1R,3S)-2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]acrylate as a colorless oil. $C_{24}H_{31}NO_5$ (413.52), MS (ESI): 414 ($M + H^+$).

Ethyl ((1R,3S)-1-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]cyclopropanecarboxylate



At room temperature, 12 mg of a 60% strength sodium hydride suspension are added to a suspension of 55 mg of trimethylsulfonium iodide in 2 ml of DMSO, and the mixture is stirred at room temperature for 20 min. At 10°C, 100 mg of ethyl ((1R,3S)-2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]acrylate, dissolved in 2 ml of DMSO, are then added, and the mixture is stirred at room temperature for 90 min. The mixture is poured into ice-water and extracted with methyl tert-butyl ether. The organic phase is dried over sodium sulfate, the solvent is removed under reduced pressure and the residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 2:1). This gives ethyl ((1R,3S)-1-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]cyclopropanecarboxylate as a colorless oil. $C_{25}H_{33}NO_5$ (427.55), MS (ESI): 428 ($M + H^+$).

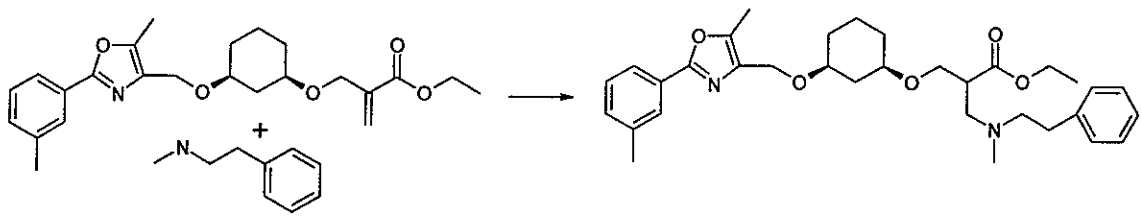
((1R,3S)-1-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-cyclopropanecarboxylic acid



56 mg of ethyl ((1R,3S)-1-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]cyclopropanecarboxylate are dissolved in 3 ml of methanol, 0.5 ml of 5 N NaOH are added and the mixture is stirred at room temperature for 18 h. The solvent is removed under reduced pressure and the residue is acidified with trifluoroacetic acid and purified by RP-HPLC. This gives ((1R,3S)-1-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]cyclopropane carboxylic acid as a colorless oil. $C_{23}H_{29}NO_5$ (399.49), MS (ESI): 400 ($M + H^+$).

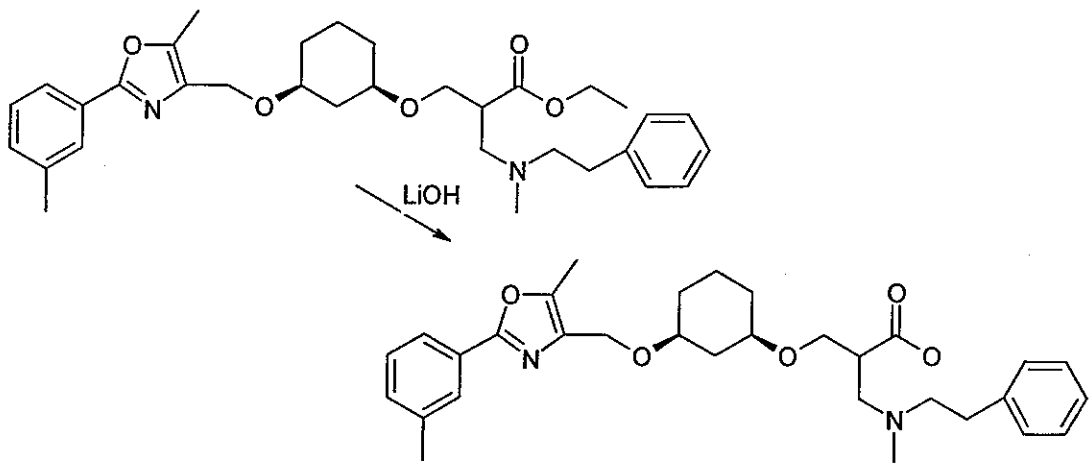
Example 6:

Ethyl 2R/S-((1R′,3S′)-2-[(methylphenethylamino)methyl]-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propionate



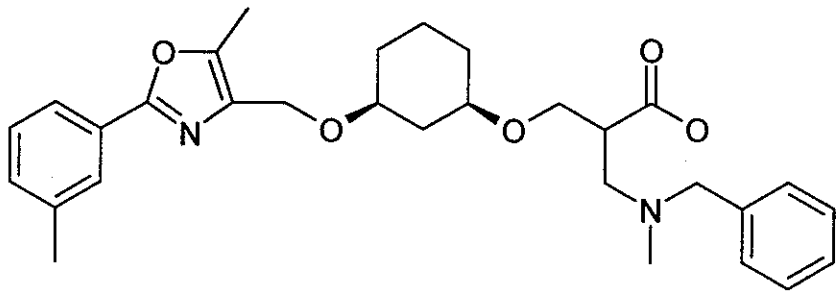
50 mg of ethyl ((1R,3S)-2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]acrylate are dissolved in 5 ml of ethanol, 95 mg of N-methylhomobenzylamine are added and the mixture is stirred at room temperature for 18 h. The solvent is removed under reduced pressure and the residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 1:1 + 3% NEt_3). This gives ethyl 2R/S-((1R′,3S′)-2-[(methylphenethylamino)methyl]-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propionate as a colorless oil. $C_{33}H_{44}N_2O_5$ (548.73), MS (ESI): 549 ($M + H^+$).

((1R′,3S′)-2R/S-[(Methylphenethylamino)methyl]-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propionic acid



65 mg of ethyl 2R/S-((1R´,3S´)-2-[(methylphenethylamino)methyl]-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propionate are dissolved in 3 ml of tetrahydrofuran/methanol 3:1, 0.6 ml of 1 N LiOH is added and the mixture is stirred at room temperature for 6 h. The solvent is removed under reduced pressure and the residue is acidified with trifluoroacetic acid and purified by RP-HPLC. This gives 2R/S-((1R´,3S´)-[(methylphenethylamino)methyl]-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-propionic acid as a colorless oil. $C_{31}H_{40}N_2O_5$ (520.67), MS (ESI): 521 ($M + H^+$).

Example 7:



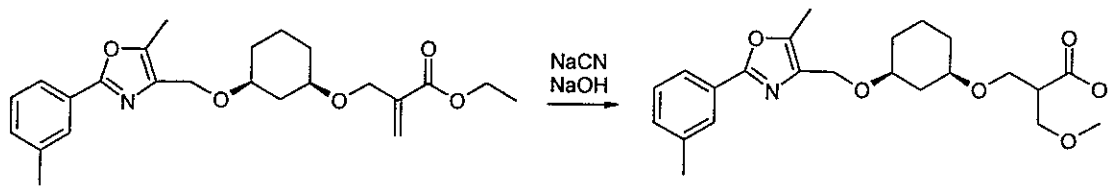
(1R´,3S´)-2R/S-[(Benzylmethylamino)methyl]-3-[3-(5-methyl-2-m-tolyl-oxazol-4-ylmethoxy)cyclohexyloxy]propionic acid

Using reaction conditions similar to those of example 100, ethyl ((1R,3S)-2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]acrylate and N-methylbenzylamine give (1R´,3S´)-2R/S-[(benzylmethylamino)methyl]-3-

[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propionic acid of molecular weight 506.65 ($C_{30}H_{38}N_2O_5$), MS(ESI): 507.20 ($M + H^+$).

Example 8:

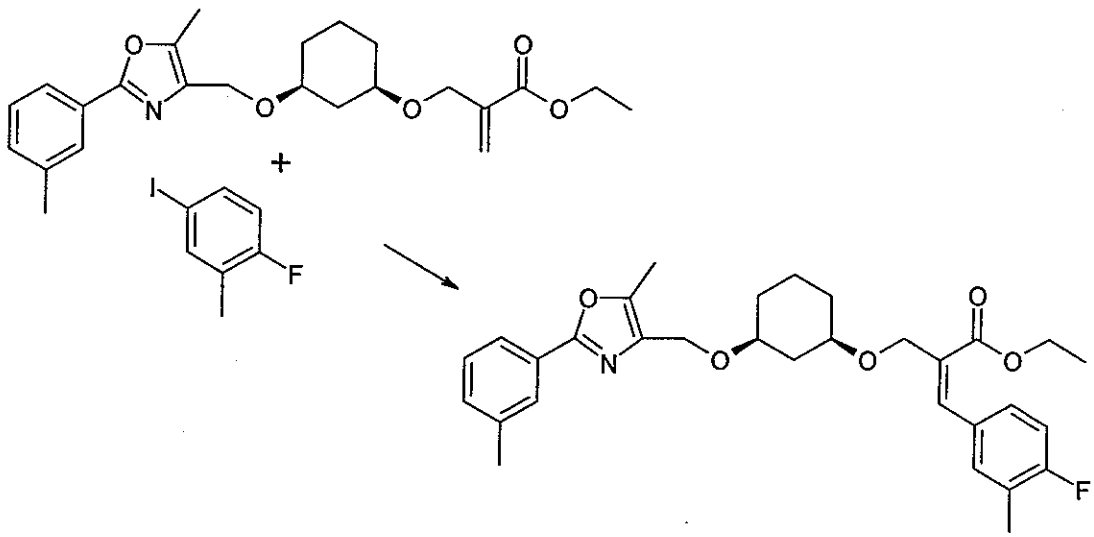
((1R´,3S´)-2R/S-Methoxymethyl-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propionic acid



56 mg of ethyl ((1R,3S)-2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]acrylate are dissolved in 3 ml of methanol, 49 mg of sodium cyanide and 0.25 ml of 2N NaOH are added and the mixture is stirred at room temperature for 18 h. The solvent is removed under reduced pressure and the residue is acidified with trifluoroacetic acid and purified by RP-HPLC. This gives ((1R´,3S´)-2R/S-methoxymethyl-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propionic acid as a colorless oil. $C_{23}H_{31}NO_6$ (417.51), MS (ESI): 418.15 ($M + H^+$).

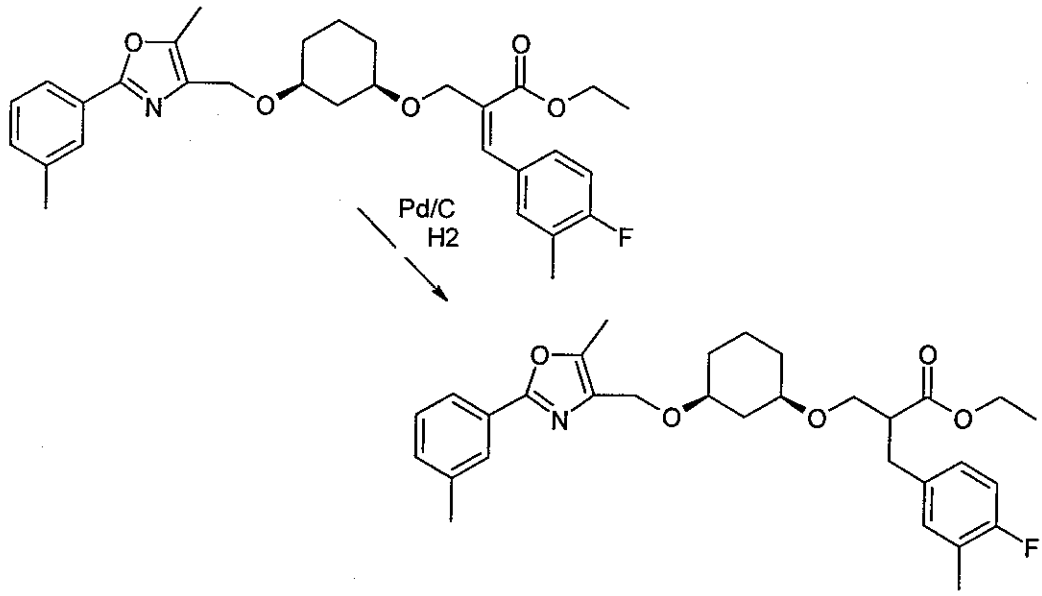
Example 9:

Ethyl Z-((1R´,3S´)-3-(4-fluoro-3-methylphenyl)-2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]acrylate



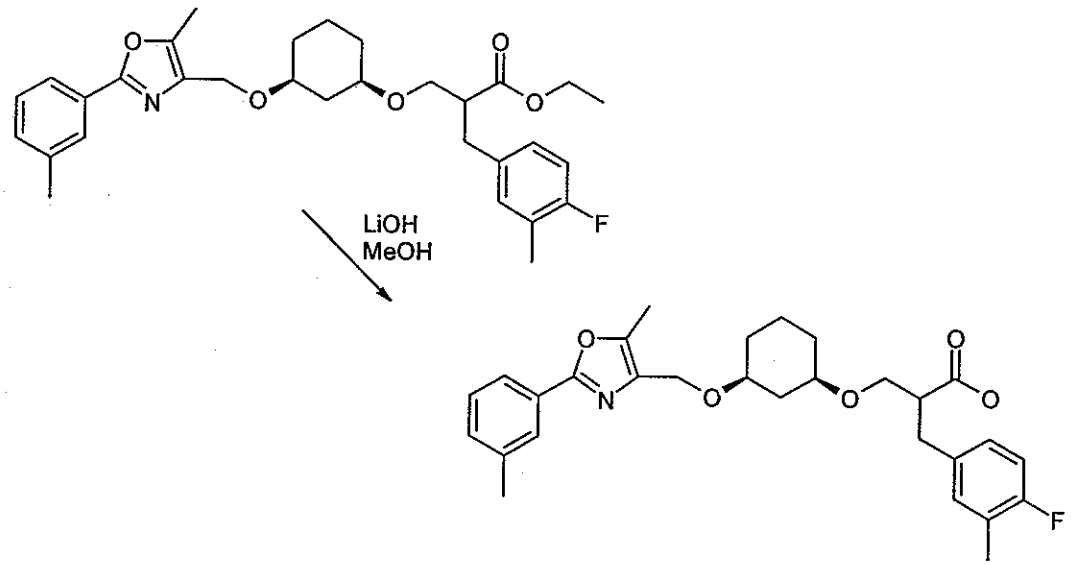
220 mg of tetrabutylammonium chloroide and 332 mg of potassium carbonate are suspended in 4 ml of dimethylformamide and stirred intimately for 20 min. 400 mg of ethyl ((1R,3S)-2-[3-(5-methyl-2-m-tolyl-oxazol-4-ylmethoxy)cyclohexyloxymethyl]acrylate, 25 mg of triphenylphosphine and 212 mg of 4-fluoro-3-methyliodobenzene are added, the mixture is degassed and flushed with argon and 10 mg of palladium acetate and 0.2 mol of water are added. The mixture is heated at 60°C for 4 h. After cooling, 20 ml of ethyl acetate and 50 ml of saturated NaCl solution are added. The organic phase is dried over sodium sulfate, the solvent is removed under reduced pressure and the residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 4:1). This gives ethyl Z-((1R´,3S´)-3-(4-fluoro-3-methylphenyl)-2-[3-(5-methyl-2-m-tolyl-oxazol-4-ylmethoxy)cyclohexyloxymethyl]acrylate as a colorless oil. $C_{31}H_{38}FNO_5$ (523.65), MS (ESI): 524 ($M + H^+$).

Ethyl 2R/S-(4-fluoro-3-methylbenzyl)-(1R´,3S´)-3-[3-(5-methyl-2-m-tolyl-oxazol-4-ylmethoxy)cyclohexyloxy]propionate



80 mg of ethyl Z-((1R′,3S′)-3-(4-fluoro-3-methylphenyl)-2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]acrylate are dissolved in 15 ml of ethyl acetate and, after addition of 30 mg of Pd/C 10%, stirred under 1 bar of H_2 for 24 h. The catalyst is filtered off and the solvent is evaporated. This gives ethyl 2R/S-(4-fluoro-3-methylbenzyl)-(1R′,3S′)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propionate as a colorless oil. $C_{31}H_{38}FNO_5$ (521.63), MS (ESI): 522 ($M + H^+$).

(2R/S)-(4-Fluoro-3-methylbenzyl)-(1R′,3S′)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propionic acid

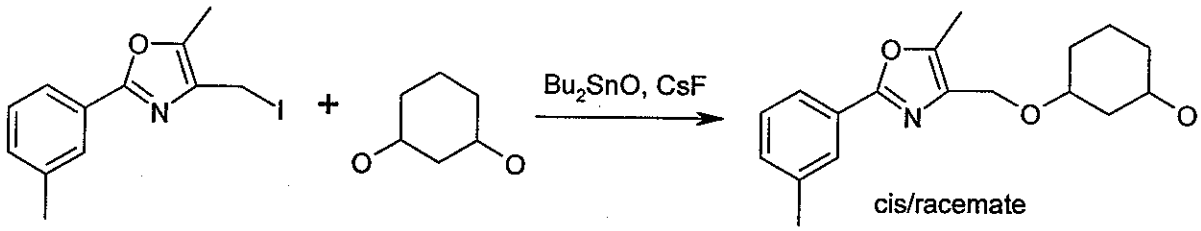


70 mg of ethyl 2R/S-(4-fluoro-3-methylbenzyl)-(1R′,3S′)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propionate are dissolved in 3 ml

of tetrahydrofuran/methanol 3:1, 0.1 ml of 1 N LiOH is added and the mixture is stirred at room temperature for 18 h. The solvent is removed under reduced pressure and the residue is acidified with trifluoroacetic acid and purified by RP-HPLC. This gives 2R/S-(4-fluoro-3-methylbenzyl)-(1R´,3S´)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-propionic acid as a colorless oil. $C_{29}H_{34}FNO_5$ (495.60), MS (ESI): 496.20 ($M + H^+$).

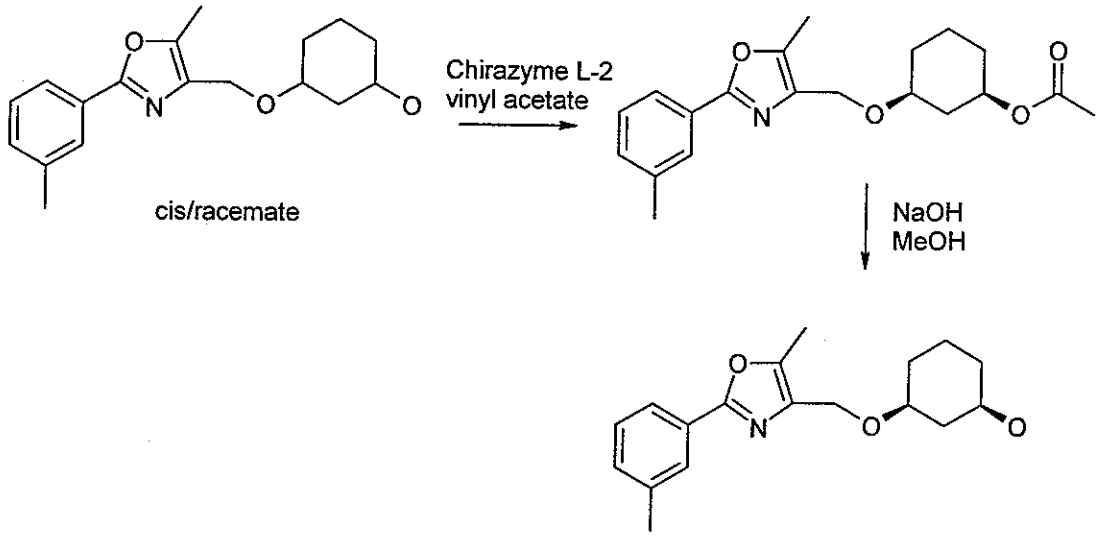
Example 10:

rac-3-(cis-5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol



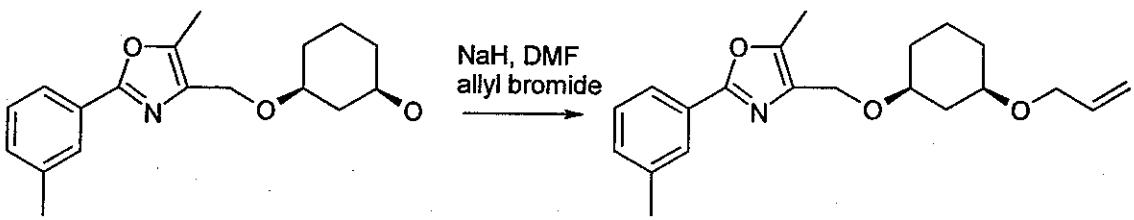
21.7 g of 1,3-Cyclohexanediol and 30.3 g of dibutyltin oxide are dissolved in 450 ml of toluene and, under reflux on a water separator, heated to the boil. During the reaction, the volume of the mixture is reduced to half of the original volume. After 3 hours, the reaction mixture is cooled to room temperature and 300 ml of dimethylformamide, 29 g of 4-iodomethyl-5-methyl-2-m-tolyloxazole 1 and 23.5 g of cesium fluoride are added. The mixture is stirred at room temperature for 18 hours. The reaction mixture is diluted by addition of ethyl acetate and washed with saturated NaCl solution. The organic phase is dried over magnesium sulfate, the solvent is removed under reduced pressure and the residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 10:1 → 1:4). This gives 58 g of rac-3-(cis-5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol as a yellowish solid which is recrystallized from n-heptane/ethyl acetate. C18H23NO3 (301.39), MS (ESI): 302 (M + H+).

3-((1R,3S)-cis-5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol 4



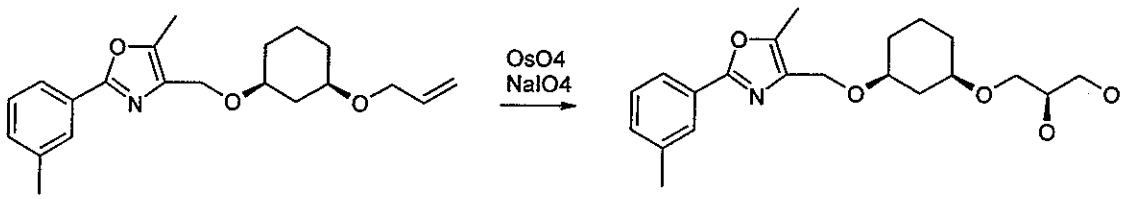
25 g of rac-3-(cis-5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol are dissolved in 320 ml of vinyl acetate and 1.3 g of Chirazyme L-2 Lyo (Boehringer Mannheim) are added. The mixture is stirred at room temperature for about 3 hours (LC-MS control for 40-45% conversion), the enzyme is then filtered off and washed with ethyl acetate and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 3:1). This gives 8 g of acetate 3 as a colorless oil. C20H25NO4 (343.43), MS (ESI): 344 (M + H+). The acetate is taken up in 170 ml of methanol and, after addition of 27 ml of 2N NaOH, stirred at room temperature for 1 hour. Most of the solvent is removed under reduced pressure. After addition of in each case 150 ml of water and ethyl acetate, the org. phase is washed with NaCl solution. The organic phase is dried over magnesium sulfate and the solvent is removed under reduced pressure. This gives 6.7 g of 3-((1R,3S)-cis-5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol as a yellowish solid. C18H23NO3 (301.39), MS (ESI): 302 (M + H+).

4-((1R,3S)-3-Allyloxycyclohexyloxymethyl)-5-methyl-2-m-tolyloxazole 5



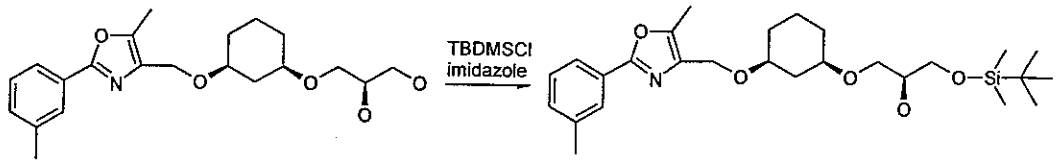
At room temperature, 470 mg of 60% strength sodium hydride suspension are added to a solution of 2.2 g of 3-((1R,3S)-cis-5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol in 30 ml of dimethylformamide, and the mixture is stirred at room temperature for 10 min. 1.36 ml of allyl bromide are then added and the mixture is stirred at 40°C until the conversion is complete; if required, further sodium hydride and allyl bromide are added. After complete conversion (LC-MS control), 100 ml of ethyl acetate and 150 ml of saturated NaCl solution are added. The organic phase is dried over magnesium sulfate, the solvents are removed under reduced pressure and the residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 3:1). This gives 2.3 g of 4-((1R,3S)-3-allyloxycyclohexyloxymethyl)-5-methyl-2-m-tolyloxazole 5 as a colorless oil. C21H27NO3 (341.45), MS (ESI): 342 (M + H+).

(1R′,3S′)-3-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propane-1,2-diol



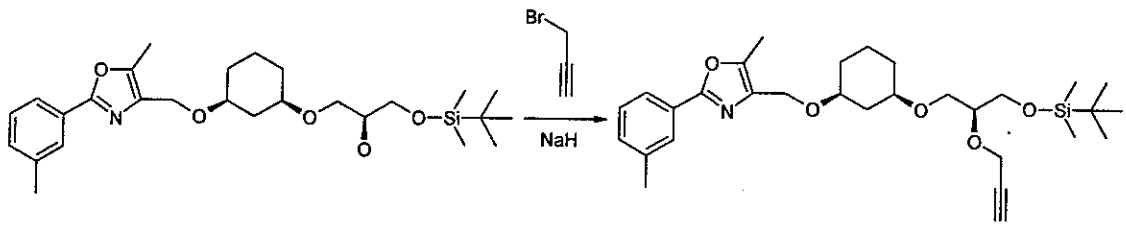
At 0°C, 225 mg of DABCO, 1.4 g of anhydrous N-methylmorpholine N-oxide and 350 µl of osmium tetroxide, 2.5% in tert-butanol, were added to 2.8 g of 4-((1R,3S)-3-allyloxycyclohexyloxymethyl)-5-methyl-2-m-tolyloxazole in 9 ml of acetone/water 10:1. After 24 h of stirring at room temperature, 2.4 g of sodium metabisulfite were added, and after 10 min, the mixture was diluted with 25 ml of CH2Cl2. The mixture was filtered and the solvent was removed under reduced pressure. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 1:3). This gives 2.5 g of 2R-(1R′,3S′)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propane-1,2-diol as a colorless oil. $C_{21}H_{29}NO_5$ (375.47), MS (ESI): 376 ($M + H^+$).

2S-(1S′,3R′)-1-(tert-Butyldimethylsilanyloxy)-3-[3-(5-methyl-2-m-tolyl-oxazol-4-ylmethoxy)cyclohexyloxy]propan-2-ol



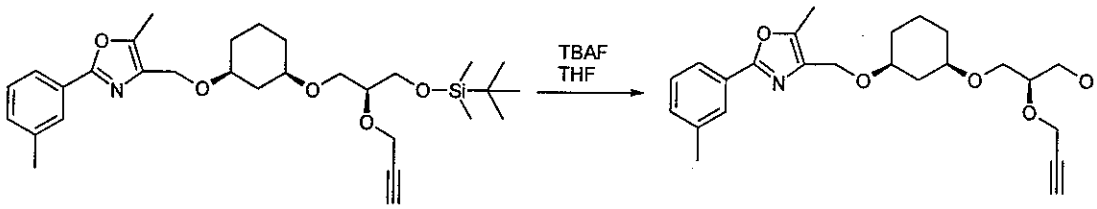
At 0°C, 500 mg of imidazole, 1.02 g of tert-butyldimethylsilyl chloride and 50 mg of tetrabutylammonium iodide are added to 2.5 g of 2R-(1R′,3S′)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propane-1,2-diol in 30 ml of dichloromethane. Over a period of 18 h, the mixture is allowed to warm to room temperature and then poured onto ice. The mixture is extracted with dichloromethane, the extract is dried over sodium sulfate and filtered and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 2:1 → 1:2). This gives 2S-(1S′,3R′)-1-(tert-butyldimethylsilanyloxy)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-propan-2-ol as a colorless oil. $C_{27}H_{43}NO_5Si$ (489.73), MS (ESI): 490 ($M + H^+$).

2S′-(1S,3R)4-{3-[3-(tert-Butyldimethylsilanyloxy)-2-prop-2-ynyloxypropoxy]-cyclohexyloxymethyl}-5-methyl-2-m-tolyloxazole



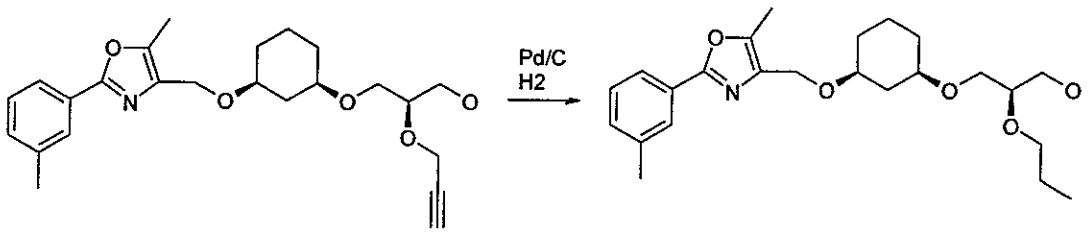
25 mg of 60% strength sodium hydride suspension are added to 245 mg of 2S-(1S′,3R′)-1-(tert-butyldimethylsilanyloxy)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propan-2-ol in 3 ml of dimethylformamide, and the mixture is stirred at room temperature for 20 min. 200 mg of propargyl bromide are then added, and the mixture is stirred at room temperature until the conversion is complete. The mixture is taken up in saturated NaCl solution/ethyl acetate, the organic phase is dried over sodium sulfate and filtered and the solvent is removed under reduced pressure. This gives 2S′-(1S,3R)4-{3-[3-(tert-butyldimethylsilanyloxy)-2-prop-2-ynyloxypropoxy]cyclohexyloxymethyl}-5-methyl-2-m-tolyloxazole as a colorless oil. $C_{30}H_{45}NO_5Si$ (527.78), MS (ESI): 528 ($M + H^+$).

(1R′,3S′)-2R-3-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-prop-2-ynyloxypropan-1-ol



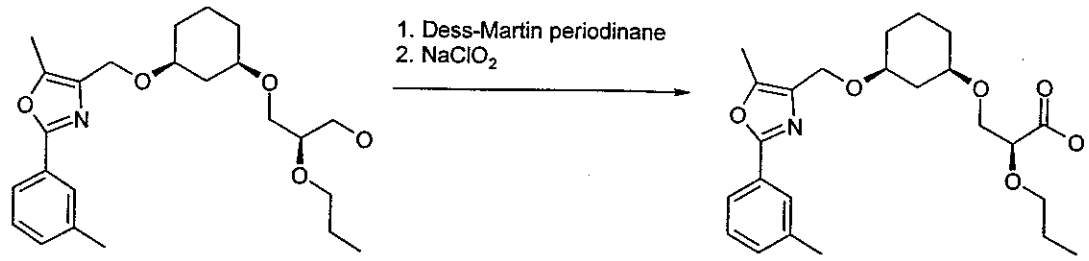
2 ml of tetrabutylammonium fluoride, 1M in tetrahydrofuran, are added to 200 mg of 2S′-(1S,3R)4-{3-[3-(tert-butyldimethylsilanyloxy)-2-prop-2-ynyloxypropoxy]cyclohexyloxymethyl}-5-methyl-2-m-tolyloxazole in 2 ml of tetrahydrofuran, and the mixture is stirred at room temperature for 2 h. The mixture is taken up in saturated NaCl solution/ethyl acetate, the organic phase is dried over sodium sulfate and filtered and the solvent is removed under reduced pressure. This gives (1R′,3S′)-2R-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-prop-2-ynyloxypropan-1-ol as a colorless oil. $C_{24}H_{31}NO_5$ (413.53), MS (ESI): 414 ($M + H^+$).

2R-(1R′,3S′)-3-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-propoxypropan-1-ol



50 mg of Pd/C 10% are added to crude (1R′,3S′)-2R-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-prop-2-ynyloxypropan-1-ol dissolved in 20 ml of methanol, and the mixture is stirred under a hydrogen pressure of 1 bar for 3 h. The catalyst is filtered off and the solvent is removed under reduced pressure. This gives 2R-(1R′,3S′)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-propoxypropan-1-ol as a colorless oil. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 1:1). $C_{24}H_{35}NO_5$ (417.55), MS (ESI): 418 ($M + H^+$).

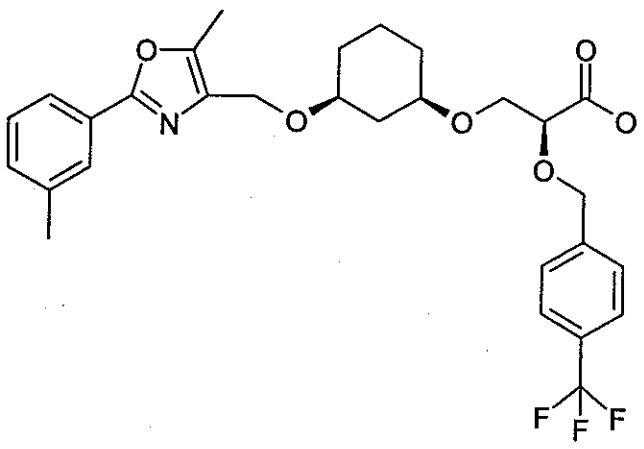
2R-(1R′,3S′)-2-(2-Propoxy)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propionic acid



180 mg of Dess-Martin periodinane are added to 90 mg of 2R-(1R′,3S′)-2-propoxy-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propan-1-ol in 1.5 ml of dichloromethane, and the mixture is stirred at room temperature for 2 h. 41 mg of $Na_2S_2O_3$ in 3 ml of 5% strength $NaHCO_3$ solution are then added, and the mixture is stirred at room temperature for 10 min. The organic phase is separated off, dried over $MgSO_4$ and concentrated. The residue is taken up in 2 ml of acetonitrile, and 1.5 ml of 0.65 M NaH_2PO_4 solution and 48 µl of 35% strength H_2O_2 solution are added. At 0°C, 30 mg of $NaClO_2$ in 2 ml of water are added dropwise over a period of 1 h. The mixture is stirred at this temperature for 3 h. Na_2SO_3 solution, 10% strength HCl and 10 ml of CH_2Cl_2 are then added, the phases are separated and the organic phase is dried over $MgSO_4$ and concentrated. Purification of the residue by HPLC gives 1.2 mg of 2R-(1R′,3S′)-2-(2-methylpropoxy)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propionic acid.

Example 11:

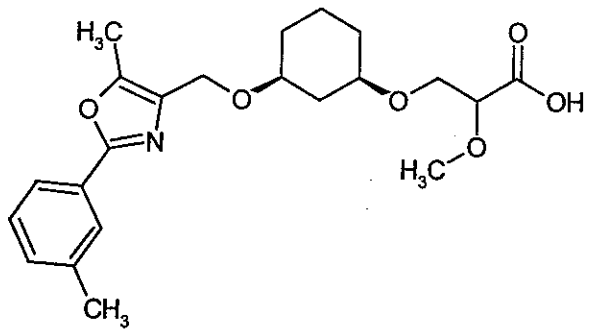
2R-(1R′,3S′)-3-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propanoic acid



Using reaction conditions similar to those of example 10, 2S-(1R′,3S′)-1-(tert-butyldimethylsilanyloxy)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and 4-trifluoromethylbenzyl bromide give 2R-(1R′,3S′)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid.

Example 12:

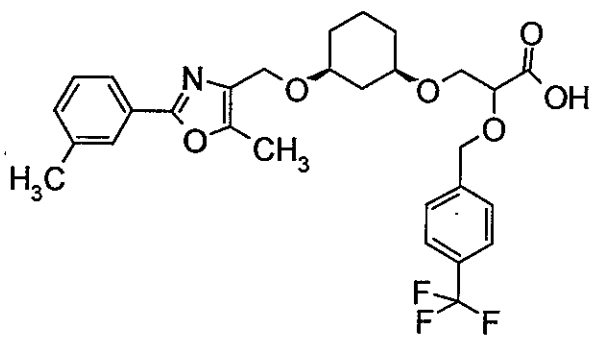
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-methoxypropionic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and methyl iodide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-methoxypropionic acid.

Example 13:

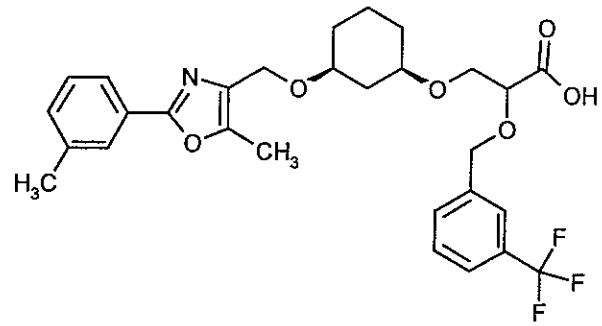
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propanoic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and 4-trifluoromethylbenzyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propanoic acid.

Example 14:

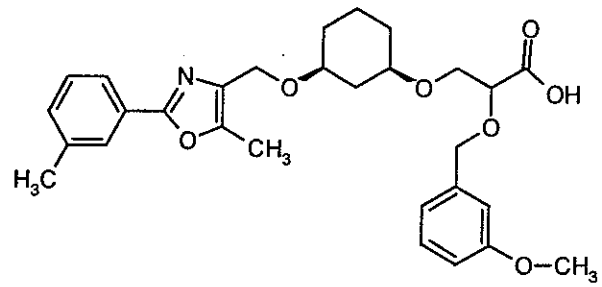
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(3-trifluoromethylbenzyloxy)propanoic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyldimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propan-2-ol and 3-trifluoromethylbenzyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(3-trifluoromethylbenzyloxy)propanoic acid.

Example 15:

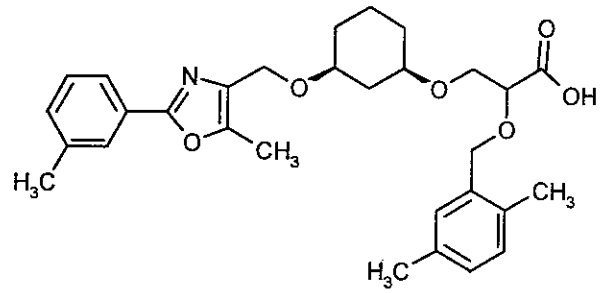
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(3-methoxybenzyloxy)propanoic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyldimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and 3-methoxybenzyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(3-methoxybenzyloxy)propanoic acid.

Example 16:

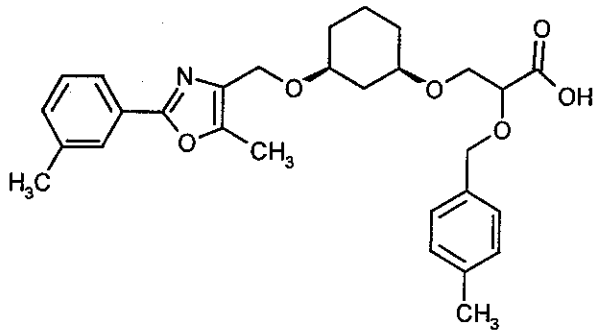
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2,5-dimethylbenzyloxy)propanoic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and 2,5-dimethylbenzyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2,5-dimethylbenzyloxy)propanoic acid.

Example 17:

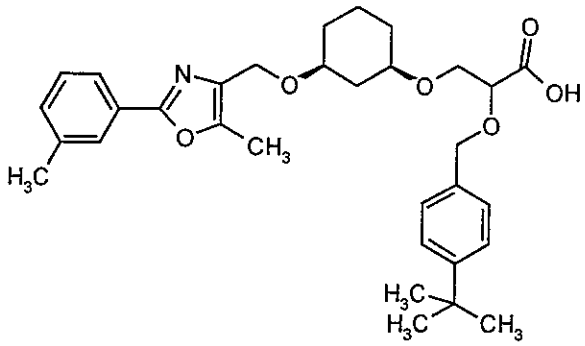
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-methylbenzyloxy)propanoic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and 4-methylbenzyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-methylbenzyloxy)propanoic acid.

Example 18:

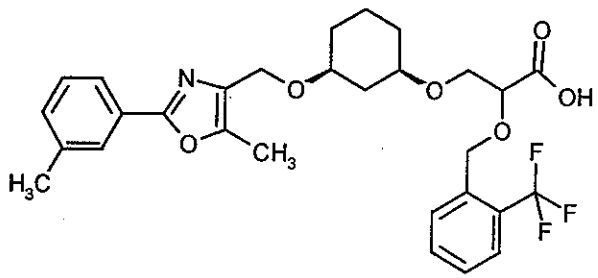
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-tert-butylbenzyloxy)propanoic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and 4-tert-butylbenzyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-tert-butyl-benzyloxy)propanoic acid.

Example 19:

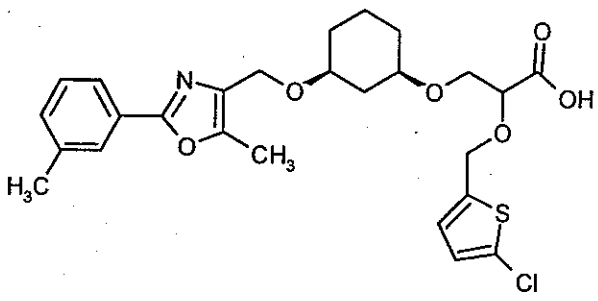
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-trifluoromethylbenzyloxy)propanoic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and 2-trifluoromethylbenzyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-trifluoromethylbenzyloxy)propanoic acid.

Example 20:

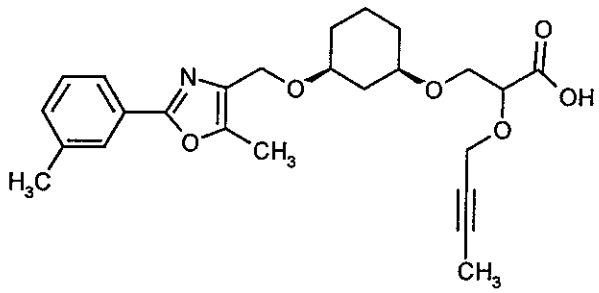
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-chlorothien-5-ylmethoxy)propionic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and 2-chlorothien-5-ylmethyl chloride give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-chlorothien-5-ylmethoxy)propionic acid.

Example 21:

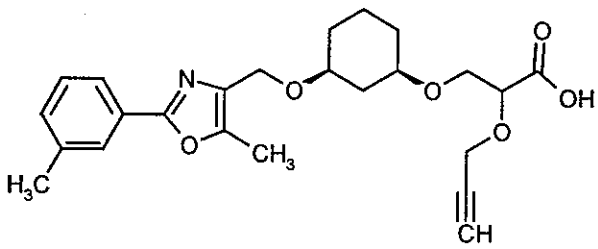
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-butynoxy)propionic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and 2-butynyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-butynoxy)propionic acid.

Example 22:

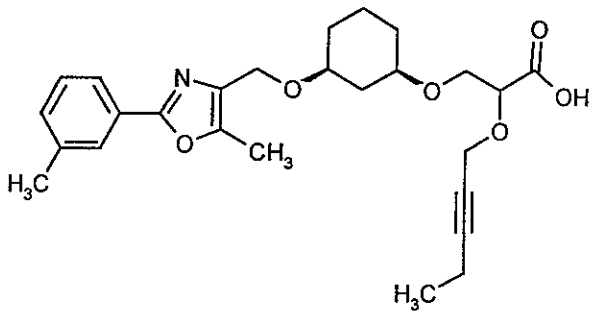
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-propynoxy)propionic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and 2-propynyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-propynoxy)-propionic acid.

Example 23:

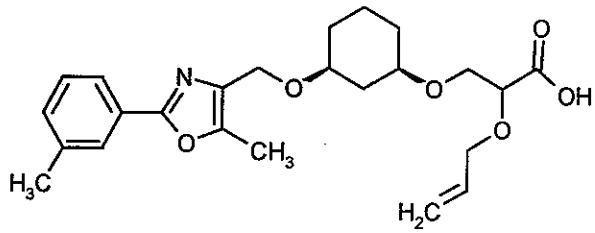
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-pentynoxy)propionic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and 2-pentynyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-pentynoxy)-propionic acid.

Example 24:

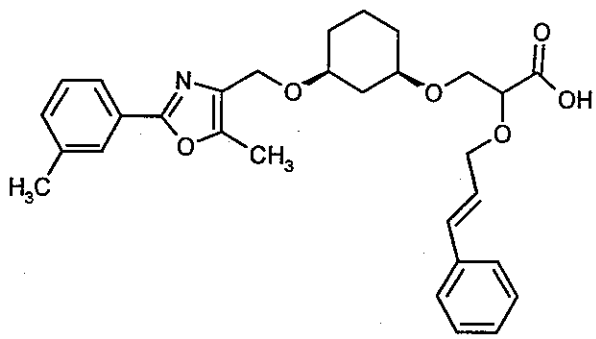
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-propenoxy)propionic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and allyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-propenoxy)propionic acid.

Example 25:

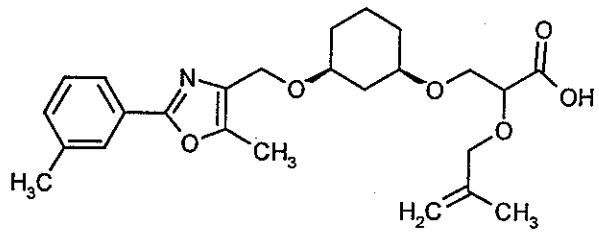
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(3-phenyl-2-propenoxy)propionic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and 3-phenyl-2-propenyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(3-phenyl-2-propenoxy)propionic acid.

Example 26:

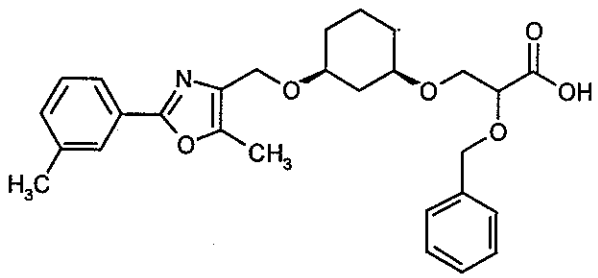
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-methyl-2-propenoxy)propionic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and isobutenyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(2-methyl-2-propen-oxy)propionic acid.

Example 27:

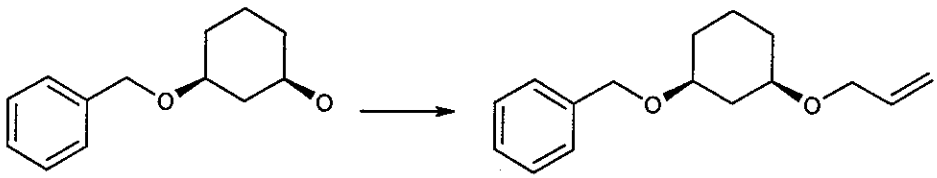
3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-benzyloxypropionic acid



Using reaction conditions similar to those of example 10, 1-(tert-butyl-dimethylsilanyloxy)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propan-2-ol and benzyl bromide give 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-benzyloxypropionic acid.

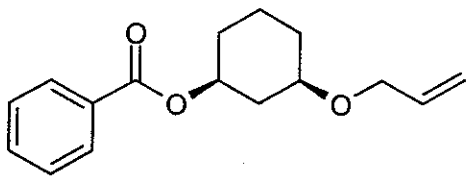
Example 28:

Benzyl [(1S,3R)-3-allyloxycyclohex-1-yl] ether



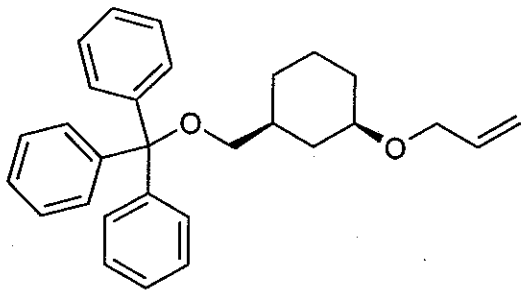
Under an atmosphere of argon, 12 g of sodium hydride (55-65%) are initially charged in 200 ml of abs DMF and stirred at RT for 10 min. With ice cooling, 54 g of benzyl [(1S,3R)-3-hydroxycyclohex-1-yl] ether in 70 ml of DMF are added dropwise. The mixture is stirred at RT for 90 min. With ice cooling, 50 g of allyl bromide are slowly added dropwise. After the addition is complete, the mixture is stirred at 45°C for 1 h. According to TLC, the reaction has gone to completion. The reaction solution is quenched with 15 ml of iPrOH, diluted with water and saturated NaCl solution and extracted with MTBE. The combined organic phases are washed with water and NaCl solution, dried over MgSO4 and concentrated. This gives 60 g of benzyl [(1S,3R)-3-allyloxycyclohex-1-yl] ether as a light-beige oil. C16H22O2 (246.35), MS (ESI): 247 ($M + H^+$).

(1S,3R)-3-Allyloxycyclohex-1-yl benzoate



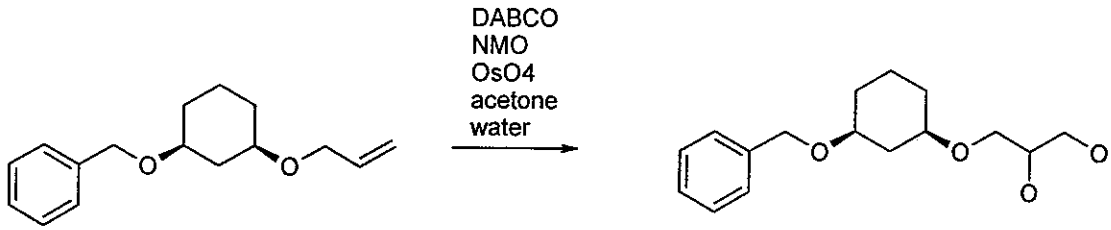
Analogously to benzyl (1S,3R)-3-allyloxycyclohex-1-yl ether, (1S,3R)-3-hydroxycyclohex-1-yl benzoate and allyl bromide give (1S,3R)-3-allyloxycyclohex-1-yl benzoate. C16H20O3 (260.37), MS (ESI): 261 ($M + H^+$).

Allyl (1R,3S)-3-trityloxymethylcyclohex-1-yl ether



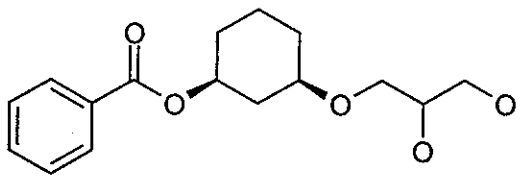
Analogously to benzyl (1S,3R)-3-allyloxycyclohex-1-yl ether, (1R,3S)-3-trityloxymethylcyclohexanol and allyl bromide give allyl (1R,3S)-3-trityloxymethylcyclohex-1-yl ether.

(2R/2S)-3-[(1S,3R)-3-Benzyloxycyclohexyloxy]propane-1,2-diol



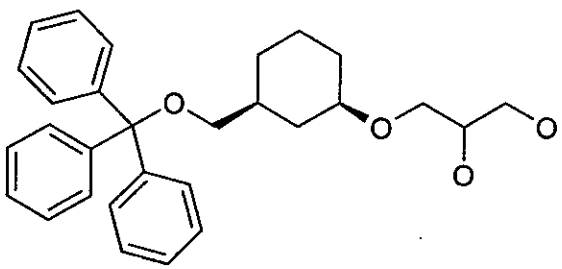
At 0°C, 6.8 g of DABCO, 42.8 g of NMO and 8.0 ml of osmium tetroxide solution (2.5% in tert-butanol) are added successively to 60 g of benzyl (1S,3R)-3-allyloxycyclohex-1-yl ether in 200 ml of acetone/water (10:1). The solution is stirred at RT overnight. After 24 h, another 5 ml of osmium tetroxide solution are added, and the solution is stirred at RT overnight. The reaction is then complete. Sodium sulfite solution and water are added, and the mixture is extracted with dichloromethane. The organic phase is dried over Na2SO4 and concentrated, which gives 65 g of (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]propane-1,2-diol as a brown oil. C16H24O4 (280.37), MS (ESI): 281 ($M + H^+$).

(2R/2S)-3-[(1R,3S)-1-Benzoyloxycyclohex-3-yloxy]propane-1,2-diol



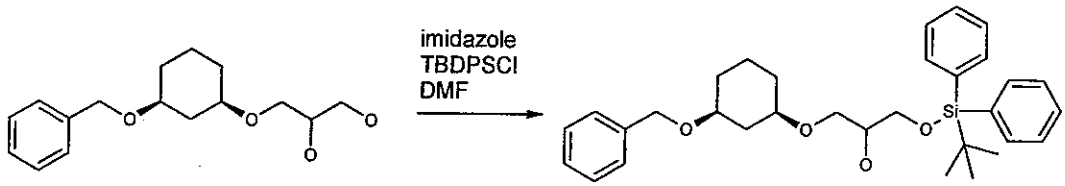
Analogously to (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]propane-1,2-diol, (1S,3R)-3-hydoxycyclohex-1-yl benzoate, NMO, DABCO and osmium tetroxide give (2R/2S)-3-[(1R,3S)-1-benzoyloxycyclohex-3-yloxy]propane-1,2-diol. C16H22O5 (294.35), MS (ESI): 295 ($M + H^+$).

(2R/2S)-3-[(1R,3S)-3-Trityloxymethylcyclohexyloxy]propane-1,2-diol



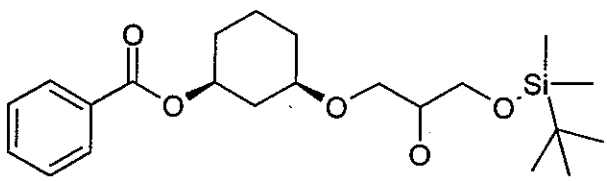
Analogously to (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]propane-1,2-diol, allyl (1R,3S)-3-trityloxymethylcyclohex-1-yl ether, NMO, DABCO and osmium tetroxide give ((2R/2S)-3-[(1R,3S)-3-trityloxymethylcyclohexyloxy]-propane-1,2-diol.

(2R/2S)-3-[(1S,3R)-3-Benzyloxycyclohexyloxy]-2-hydroxypropyl tert-butyl-diphenylsilyl ether



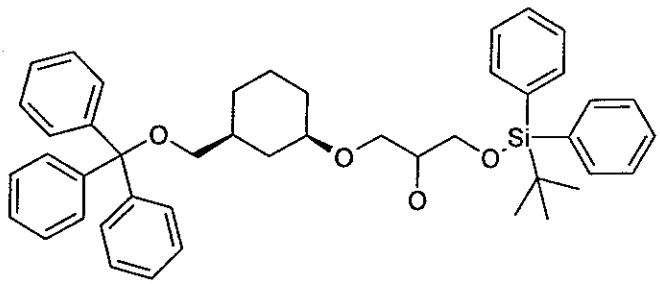
20 g of (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]propane-1,2-diol are dissolved in 100 ml of DMF, 12 g of imidazole and then 20.6 g of TBDPSCl are added and the mixture is stirred at RT. After 3 h, the reaction is complete. The solution is diluted with water/saturated NaCl solution and extracted with MTBE and the organic phase is dried over MgSO4 and concentrated, which gives 35 g of (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-hydroxypropyl tert-butyldiphenylsilyl ether as a yellow oil. C32H42O4Si (518.78), MS (ESI): 519 ($M + H^+$).

(2R/2S)-3-[(1R,3S)-1-Benzoyloxycyclohex-1-yloxy]-2-hydroxypropyl tert-butyldimethylsilyl ether



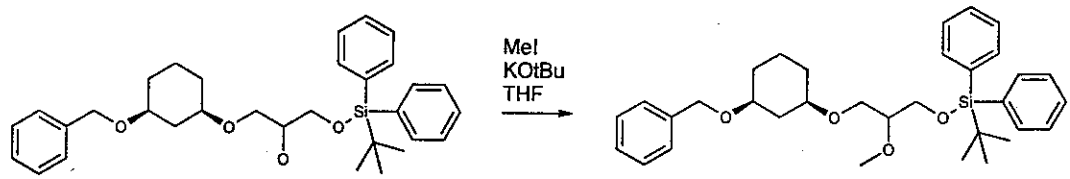
Analogously to (2R/2S)-3-[(1S,3R)-3-benzoyloxycyclohex-1-yloxy]-2-hydroxypropyl tert-butyldiphenylsilyl ether, (2R/2S)-3-[(1R,3S)-1-benzoyloxycyclohex-3-yloxy]propane-1,2-diol, imidazole and TBDMSCl give (2R/2S)-3-[(1S,3R)-1-benzoyloxycyclohex-1-yloxy]-2-hydroxypropyl tert-butyldimethylsilyl ether. C22H36O5Si (408.62), MS (ESI): 409 ($M + H^+$).

(2R/2S)-3-[(1R,3S)-3-Trityloxymethylcyclohexyloxy]-2-hydroxypropyl tert-butyldiphenylsilyl ether



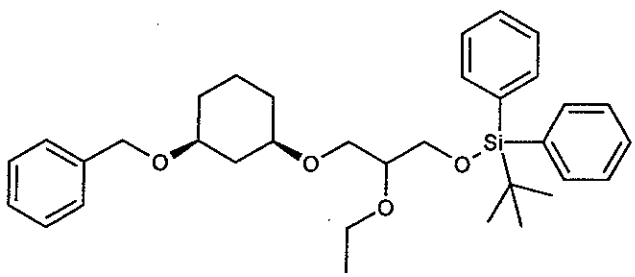
Analogously to (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-hydroxypropyl tert-butyldiphenylsilyl ether, (2R/2S)-3-[(1R,3S)-3-trityloxymethylcyclohexyloxy]propane-1,2-diol, imidazole and TBDPSCl give (2R/2S)-3-[(1R,3S)-3-trityloxymethylcyclohexyloxy]-2-hydroxypropyl tert-butyldiphenylsilyl ether.

(2R/2S)-3-[(1S,3R)-3-Benzyloxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether



10 g of (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-hydroxypropyl tert-butyldiphenylsilyl ether and 8.5 g of iodomethane are dissolved in 100 ml of THF. At RT, 3.3 g of KOtBu are added, and the suspension is stirred at RT for 1 h. Saturated NH4Cl solution and water are then added, and the solution is extracted with MTBE. The combined organic phases are dried over MgSO4 and concentrated. The residue is chromatographed on silica gel (heptane/ethyl acetate 5:1 → 1:1), which gives 7.2 g of (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether as a light-yellow oil.

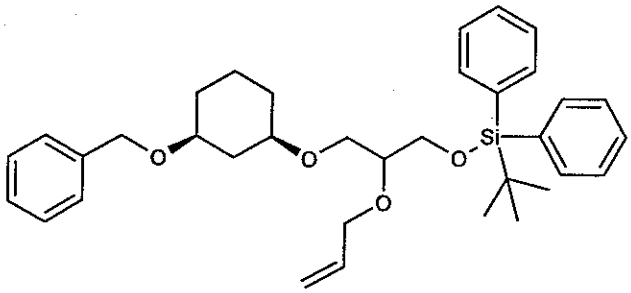
(2R/2S)-3-[(1S,3R)-3-Benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether



Analogously to (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether, (2R/2S)-3-[(1S,3R)-3-benzyloxy-

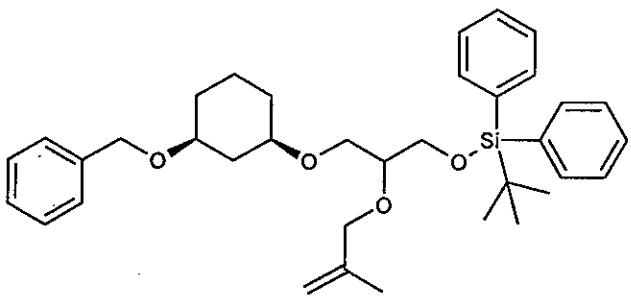
cyclohexyloxy]-2-hydroxypropyl tert-butyldiphenylsilyl ether and iodoethane give (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether.

(2R/2S)-3-[(1S,3R)-3-Benzyloxycyclohexyloxy]-2-allyloxypropyl tert-butyldiphenylsilyl ether



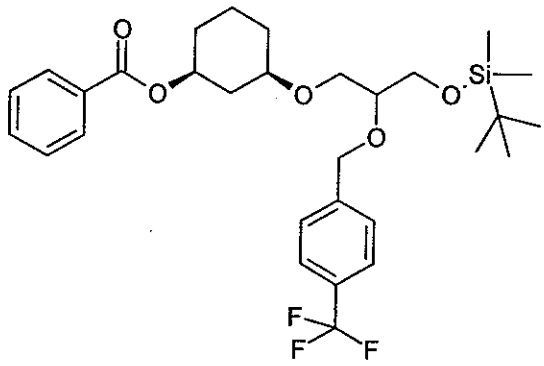
Analogously to (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilylether, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-hydroxypropyl tert-butyldiphenylsilylether and allyl bromide give (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-allyloxypropyl tert-butyldiphenylsilyl ether.

(2R/2S)-3-[(1S,3R)-3-Benzyloxycyclohexyloxy]-2-(2-methyl-2-propenloxy)propyl tert-butyldiphenylsilyl ether



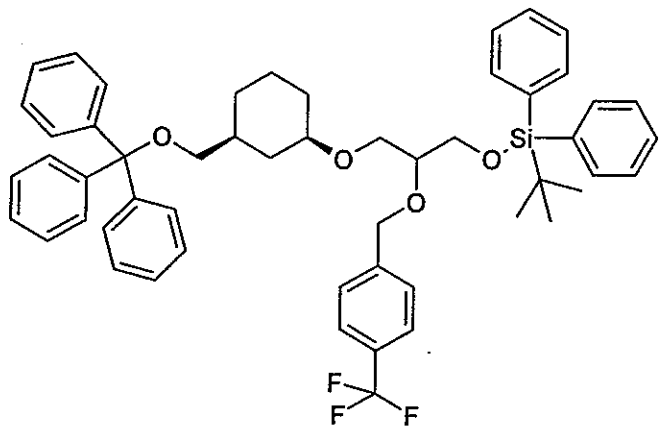
Analogously to (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-hydroxypropyl tert-butyldiphenylsilyl ether and isobutenyl bromide give (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-(2-methyl-2-propenloxy)propyl tert-butyldiphenylsilyl ether.

(2R/2S)-3-[(1R,3S)-3-Benzoyloxycyclohex-1-yloxy]-2-(4-trifluoromethylbenzyloxy)propyl tert-butyldimethylsilyl ether



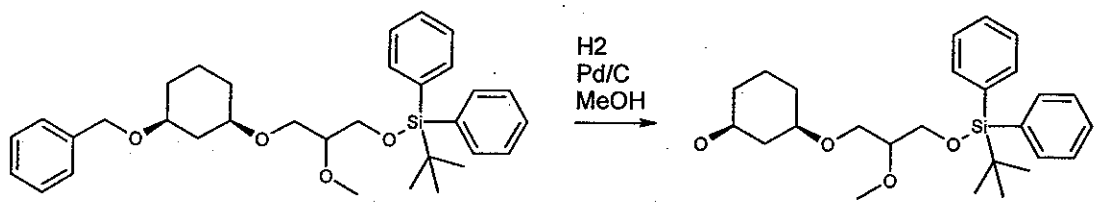
Analogously to (2R/2S)-3-[(1S,3R)-3-benzoyloxycyclohex-1-yloxy]-2-(4-trifluoromethylbenzyloxy) tert-butyldimethylsilyl ether, (2R/2S)-3-[(1R,3S)-1-benzoyloxycyclohex-3-yloxy]-2-hydroxypropyl tert-butyldiphenylsilyl ether and 4-trifluoromethylbenzyl bromide give (2R/2S)-3-[(1R,3S)-3-benzoyloxycyclohex-1-yloxy]-2-(4-trifluoromethylbenzyloxy)propyl tert-butyldimethylsilyl ether.

(2R/2S)-3-[(1R,3S)-3-Trityloxymethylcyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propyl tert-butyldiphenylsilyl ether



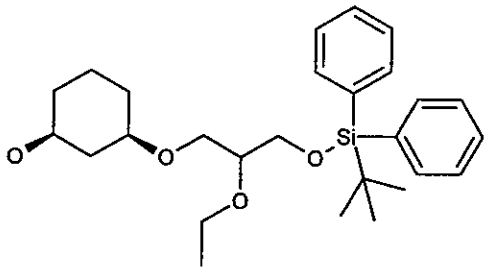
Analogously to (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether, (2R/2S)-3-[(1R,3S)-3-trityloxymethylcyclohexyloxy]-2-hydroxypropyl tert-butyldiphenylsilyl ether and 4-trifluoromethylbenzyl bromide give (2R/2S)-3-[(1R,3S)-3-trityloxymethylcyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propyl tert-butyldiphenylsilyl ether.

(2R/2S)-3-[(1S,3R)-3-Hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether



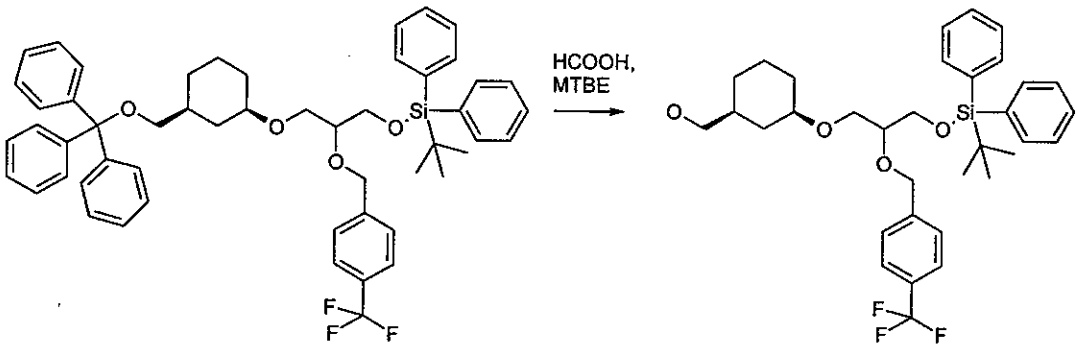
7.2 g of (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether are dissolved in 40 ml of methanol, 4 g of Pd/C (10%) are added and the mixture is hydrogenated at RT and a super-atmospheric pressure of 5 bar for 15 h. The catalyst is filtered off, the residue is washed with dichloromethane and the filtrate is concentrated, which gives 6.0 g of (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether as a colorless oil. C26H38O4Si (442.68), MS (ESI): 443 ($M + H^+$).

(2R/2S)-3-[(1S,3R)-3-Hydroxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether



Analogously to (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether gives (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether. C27H40O4Si (456.70), MS (ESI): 457 ($M + H^+$).

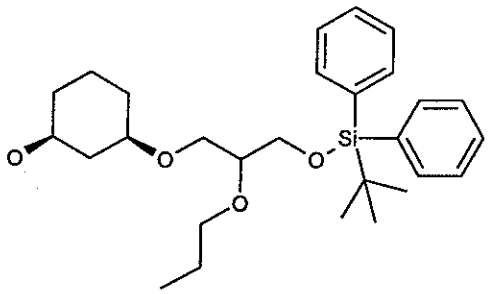
(2R/2S)-3-[(1R,3S)-3-Hydroxymethylcyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propyl tert-butyldiphenylsilyl ether



3.5 g of (2R/2S)-3-[(1R,3S)-3-trityloxymethylcyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propyl tert-butyldiphenylsilyl ether are dissolved in 100 ml of MTBE, 58 g of formic acid are added and the mixture is stirred at RT. The solution is concentrated and the residue is chromatographed on silica gel, which gives 170 mg of (2R/2S)-3-[(1R,3S)-3-

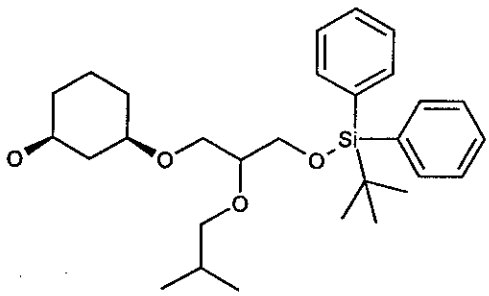
hydroxymethylcyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propyl tert-butyldiphenylsilyl ether as a colorless oil.

(2R/2S)-3-[(1S,3R)-3-Hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether



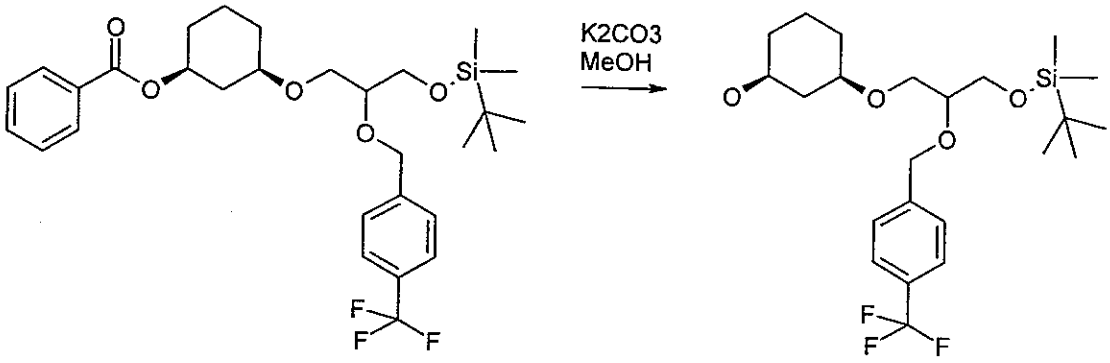
Analogously to (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether gives (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether.
C28H42O4Si (470.73), MS (ESI): 471 ($M + H^+$).

(2R/2S)-3-[(1S,3R)-3-Hydroxycyclohexyloxy]-2-isobutoxypropyl tert-butyldiphenylsilyl ether



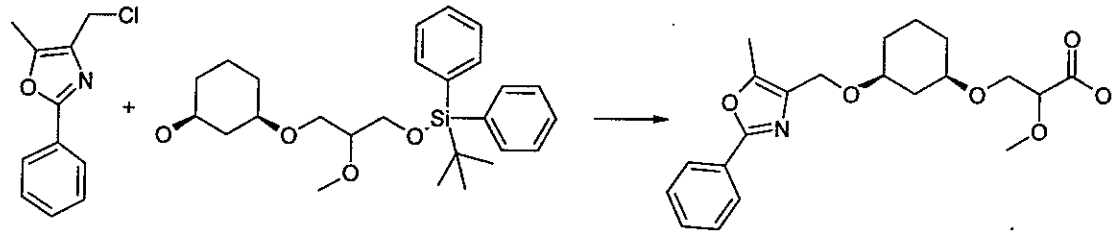
Analogously to (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-isobutoxypropyl tert-butyldiphenylsilyl ether gives (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-isobutoxypropyl tert-butyldiphenylsilyl ether. C29H44O4Si (484.76), MS (ESI): 485 ($M + H^+$).

(2R/2S)-3-[(1R,3S)-1-Hydroxycyclohex-1-yloxy]-2-(4-trifluoromethylbenzyloxy) tert-butyldimethylsilyl ether



4.6 g of (2R/2S)-3-[(1S,3R)-1-benzoyloxycyclohex-3-yloxy]-2-(4-trifluoromethoxybenzyloxy) tert-butyldimethylsilyl ether are dissolved in 20 ml of methanol, 2.2 g of K2CO3 are added and the mixture is stirred at RT for 72 h. The K2CO3 is filtered off, the residue is washed with methanol and the filtrate is concentrated, which gives 0.85 g of (2R/2S)-3-[(1R,3S)-3-hydroxycyclohexyloxy]-2-(4-trifluoromethylbenzyloxy) tert-butyldimethylsilyl ether as a colorless oil. C23H37F3O4Si (462.63), MS (ESI): 463 ($M + H^+$).

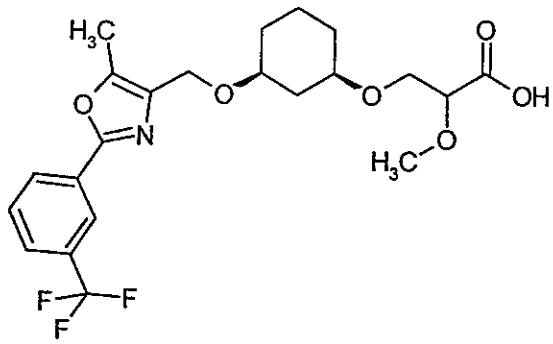
2-Methoxy-3-[(1R,3S)-3-(5-methyl-2-phenyloxazol-4-ylmethoxy)cyclohexyloxy]propanoic acid



100 mg of (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether are dissolved in 2 ml of THF, and 83 mg of 2-phenyl-5-methyloxazol-4-ylmethyl chloride and 51 mg of KOtBu are added successively. At RT, the reaction mixture is shaken overnight. 214 mg of TBAF are added, and the suspension is allowed to stand overnight. After addition of water and MBTE, the organic phase is separated off and concentrated. The residue is taken up in acetone, and 1 ml of 1.92 M Jones reagent is added. The reaction solution is shaken overnight. The solution is diluted with 3 ml of water and poured onto an extraction cartridge (kieselguhr, for 20 ml aqueous phases). The product is then eluted with ethyl acetate and the solution obtained is concentrated and purified by HPLC. This gives 5 mg of 2-methoxy-3-[(1R,3S)-3-(5-methyl-2-phenyloxazol-4-ylmethoxy)cyclohexyloxy]propanoic acid as a yellow oil.

Example 29:

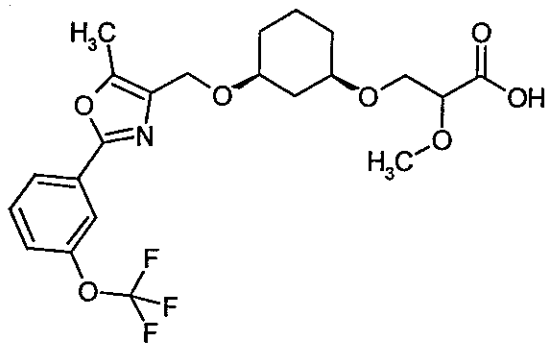
2-Methoxy-3-{(1R,3S)-3-[5-methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give 2-methoxy-3-{(1R,3S)-3-[5-methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid.

Example 30:

2-Methoxy-3-{(1R,3S)-3-[5-methyl-2-(3-trifluoromethoxyphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid

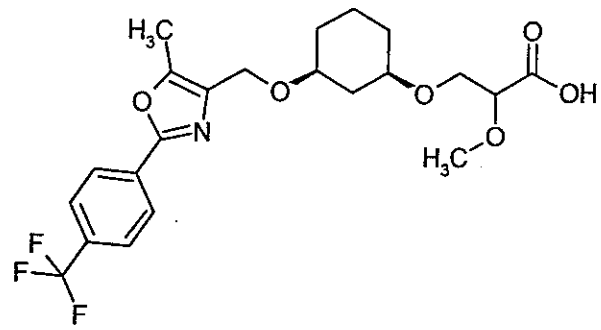


Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(3-trifluoromethoxyphenyl)oxazol-4-ylmethyl iodide give 2-methoxy-3-{(1R,3S)-3-[5-methyl-2-(3-trifluoromethoxyphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid

.

Example 31:

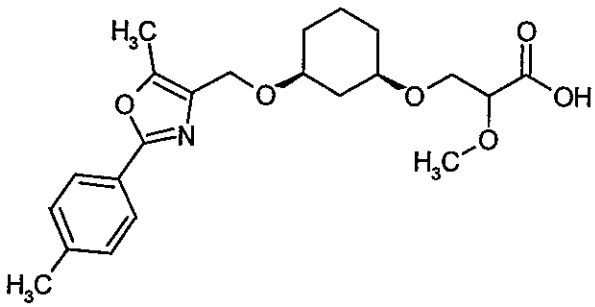
2-Methoxy-3-{(1R,3S)-3-[5-methyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give 2-methoxy-3-{(1R,3S)-3-[5-methyl-2-(4-trifluoromethylphenyl)oxazol-4-yl-methoxy]cyclohexyloxy}propionic acid.

Example 32:

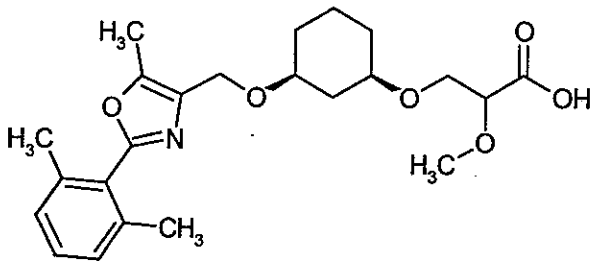
2-Methoxy-3-{(1R,3S)-3-[5-methyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(4-methylphenyl)oxazol-4-ylmethyl iodide give 2-methoxy-3-{(1R,3S)-3-[5-methyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid

Example 33:

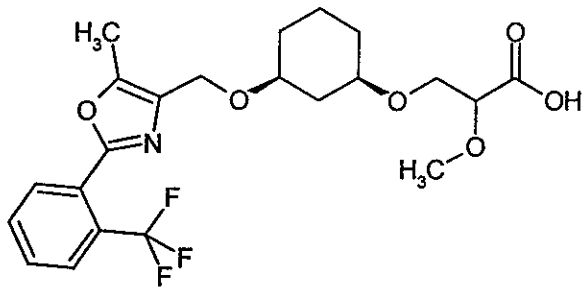
2-Methoxy-3-{(1R,3S)-3-[5-methyl-2-(2,6-dimethylphenyl)oxazol-4-yl-methoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(2,6-dimethylphenyl)oxazol-4-ylmethyl iodide give 2-methoxy-3-{(1R,3S)-3-[5-methyl-2-(2,6-dimethylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid.

Example 34:

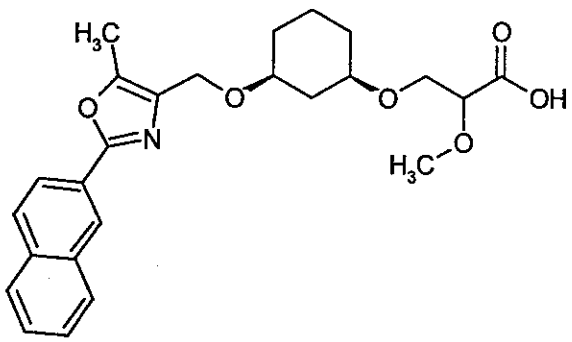
2-Methoxy-3-{(1R,3S)-3-[5-methyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give 2-methoxy-3-{(1R,3S)-3-[5-methyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid.

Example 35:

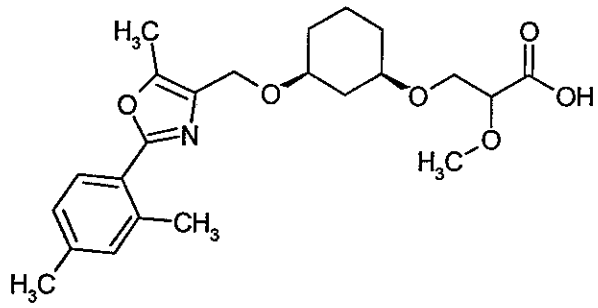
2-Methoxy-3-{(1R,3S)-3-[5-methyl-2-(3-naphthyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(2-naphthyl)oxazol-4-ylmethyl iodide give 2-methoxy-3-{(1R,3S)-3-[5-methyl-2-(3-naphthyl)oxazol-4-ylmethoxy]cyclohexyloxy}-propionic acid.

Example 36:

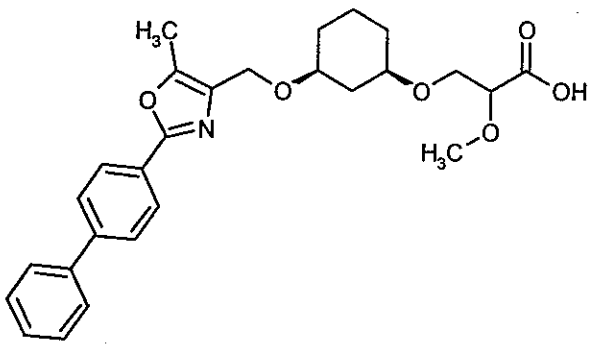
2-Methoxy-3-{(1R,3S)-3-[5-methyl-2-(2,4-dimethylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(2,4-dimethylphenyl)oxazol-4-ylmethyl iodide give 2-methoxy-3-{(1R,3S)-3-[5-methyl-2-(2,4-dimethylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid.

Example 37:

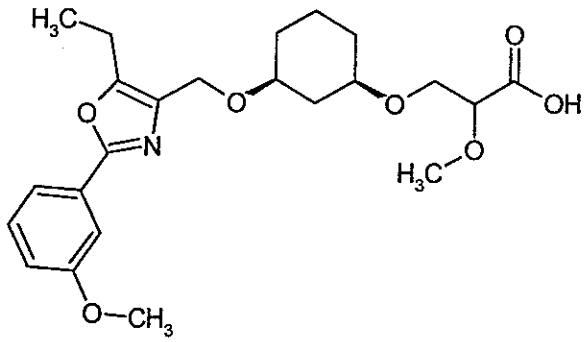
2-Methoxy-3-{(1R,3S)-3-[5-methyl-2-(4-biphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(4-biphenyl)oxazol-4-ylmethyl iodide give 2-methoxy-3-{(1R,3S)-3-[5-methyl-2-(4-biphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-propionic acid.

Example 38:

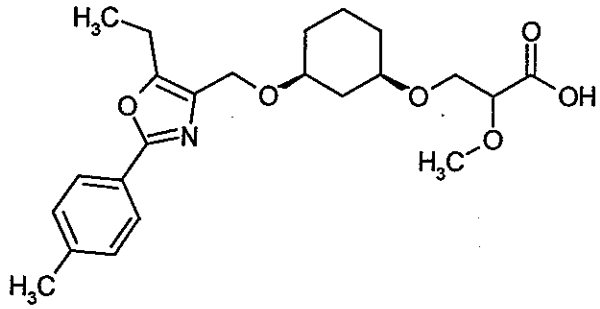
2-Methoxy-3-{(1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether and 5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethyl iodide give 2-methoxy-3-{(1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid.

Example 39:

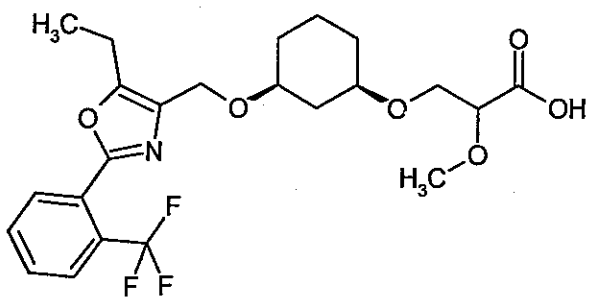
2-Methoxy-3-{(1R,3S)-3-[5-ethyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether and 5-ethyl-2-(4-methylphenyl)oxazol-4-ylmethyl iodide give 2-methoxy-3-{(1R,3S)-3-[5-ethyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid.

Example 40:

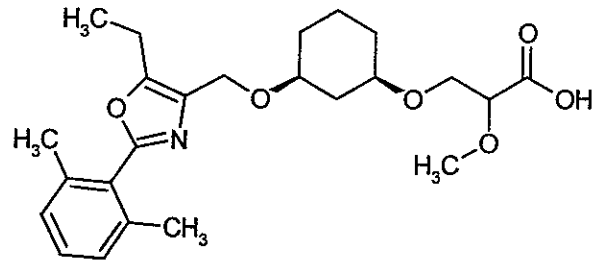
2-Methoxy-3-{(1R,3S)-3-[5-ethyl-2-(2-trifluoromethylphenyl)oxazol-4-yl-methoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether and 5-ethyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give 2-methoxy-3-{(1R,3S)-3-[5-ethyl-2-(2-trifluoromethylphenyl)oxazol-4-yl-methoxy]cyclohexyloxy}propionic acid.

Example 41:

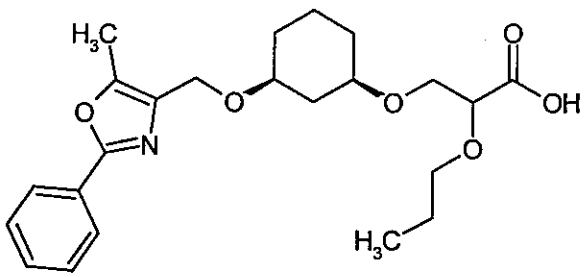
2-Methoxy-3-{(1R,3S)-3-[5-ethyl-2-(2,6-dimethylphenyl)oxazol-4-ylmeth-oxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-methoxypropyl tert-butyldiphenylsilyl ether and 5-ethyl-2-(2,6-methylphenyl)oxazol-4-ylmethyl iodide give 2-methoxy-3-{(1R,3S)-3-[5-ethyl-2-(2,6-dimethylphenyl)oxazol-4-ylmeth-oxy]cyclohexyloxy}propionic acid.

Example 42:

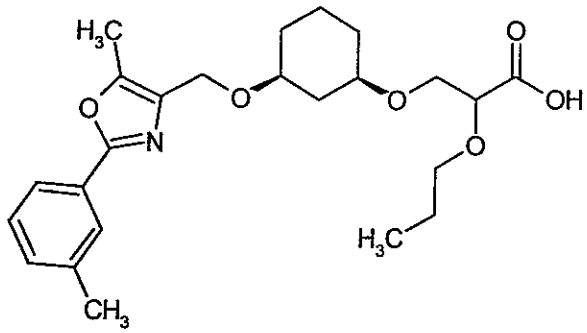
3-[(1R,3S)-3-(5-Methyl-2-phenyloxazol-4-ylmethoxy)cyclohexyloxy]-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-phenyloxazol-4-ylmethyl iodide give 3-[(1R,3S)-3-(5-methyl-2-phenyloxazol-4-ylmethoxy)cyclohexyloxy]-2-propoxypropionic acid.

Example 43:

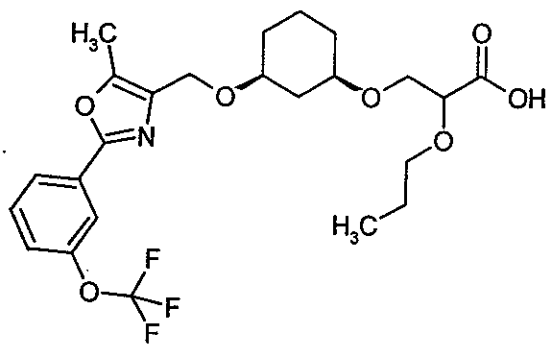
3-[(1R,3S)-3-(5-Methyl-2-(3-tolyl)oxazol-4-ylmethoxy)cyclohexyloxy]-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(3-tolyl)oxazol-4-ylmethyl iodide give 3-[(1R,3S)-3-(5-methyl-2-(3-tolyl)oxazol-4-ylmethoxy)cyclohexyloxy]-2-propoxypropionic acid.

Example 44:

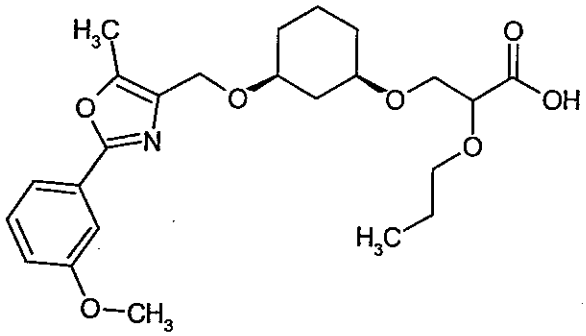
3-{(1R,3S)-3-[5-Methyl-2-(3-trifluoromethoxyphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether 2-(3-trifluoromethoxyphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-methyl-2-(3-trifluoromethoxyphenyl)oxazol-4-ylmethoxy]cyclohexyl-oxy}-2-propoxypropionic acid.

Example 45:

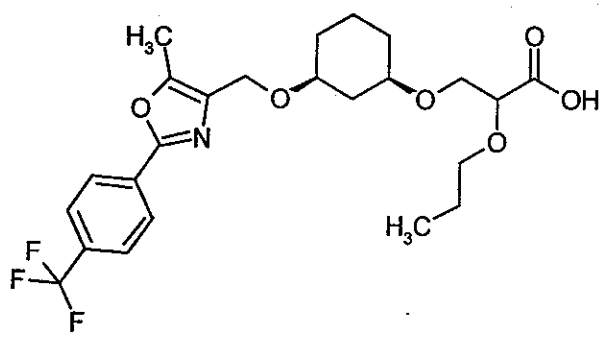
3-{(1R,3S)-3-[5-Methyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexyl-oxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 2-(3-methoxyphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-methyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-2-propoxypropionic acid.

Example 46:

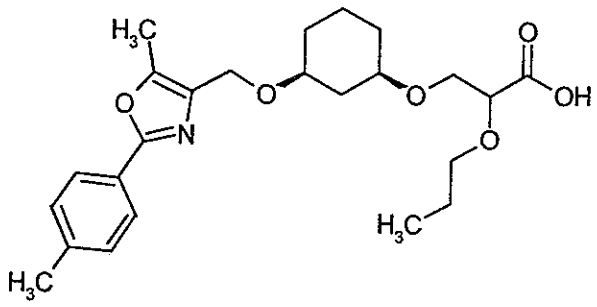
3-{(1R,3S)-3-[5-Methyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 2-(4-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-methyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}-2-propoxypropionic acid.

Example 47:

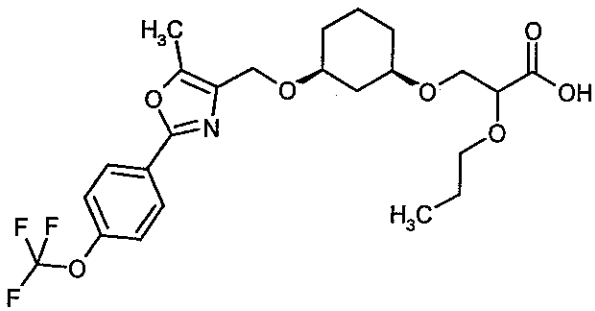
3-{(1R,3S)-3-[5-Methyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]cyclohexyl-oxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 2-(4-methylphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-methyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-2-propoxy-propionic acid.

Example 48:

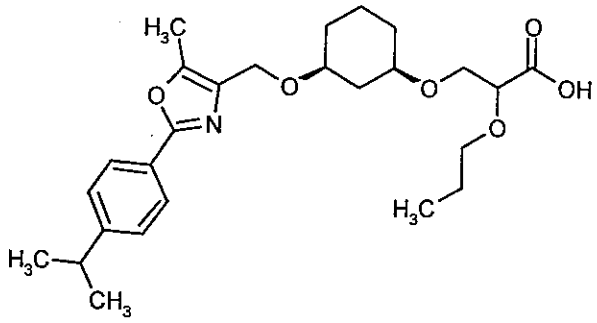
3-{(1R,3S)-3-[5-Methyl-2-(4-trifluoromethoxyphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 2-(4-trifluoromethoxyphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-methyl-2-(4-trifluoromethoxyphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}-2-propoxypropionic acid.

Example 49:

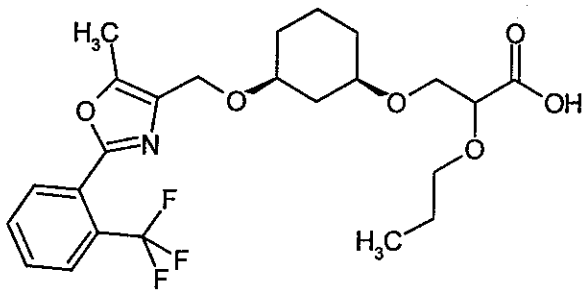
3-{(1R,3S)-3-[5-Methyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclo-hexyloxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 2-(4-isopropylphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-methyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-2-propoxypropionic acid.

Example 50:

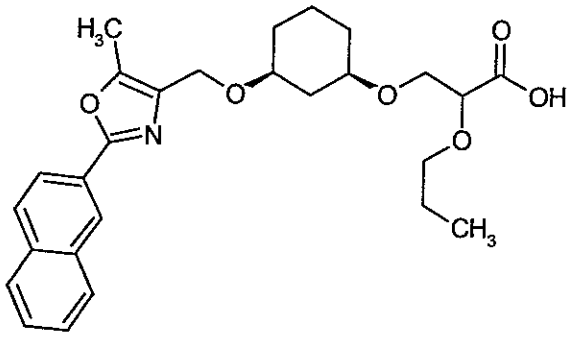
3-{(1R,3S)-3-[5-Methyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 2-(2-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-methyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}-2-propoxypropionic acid.

Example 51:

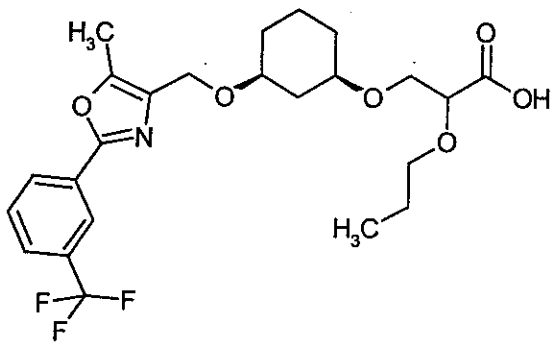
3-{(1R,3S)-3-[5-Methyl-2-(2-naphthylphenyl)oxazol-4-ylmethoxy]cyclo-hexyloxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 2-(2-naphthyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-methyl-2-(2-naphthylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-2-propoxy-propionic acid.

Example 52:

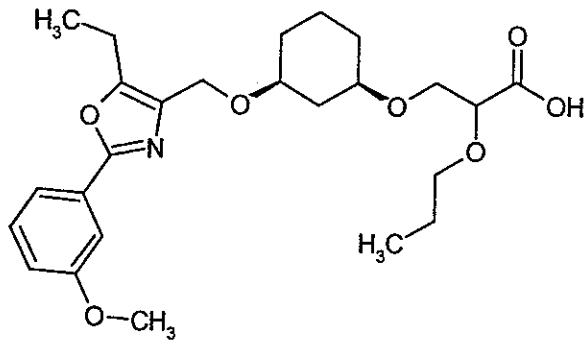
3-{(1R,3S)-3-[5-Methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 2-(3-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}-2-propoxypropionic acid.

Example 53:

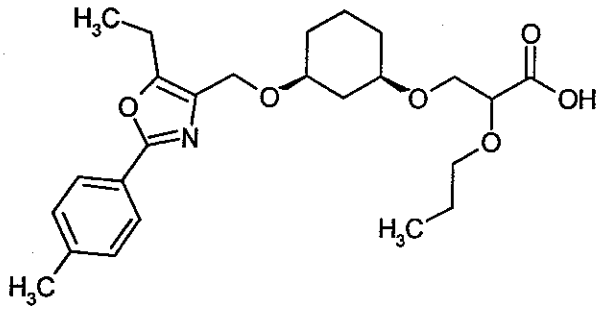
3-{(1R,3S)-3-[5-Ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclo-hexyloxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexyl-oxy}-2-propoxypropionic acid.

Example 54:

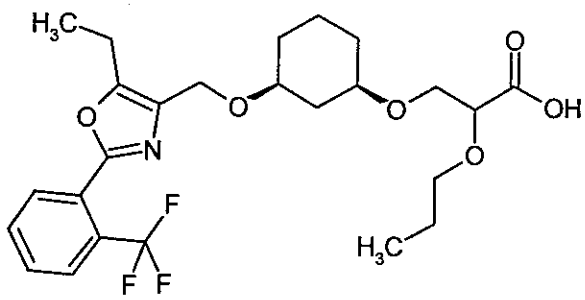
3-{(1R,3S)-3-[5-Ethyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]cyclohexyl-oxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 5-ethyl-2-(4-methylphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-ethyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]cyclohexyl-oxy}-2-propoxypropionic acid.

Example 55:

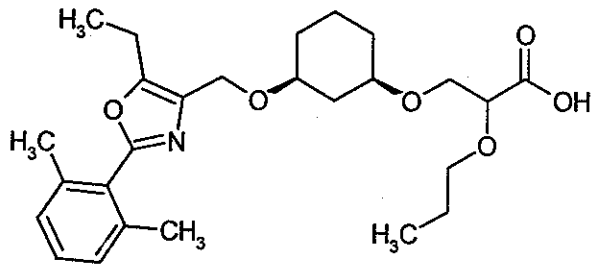
3-{(1R,3S)-3-[5-Ethyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclo-hexyloxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 5-ethyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-ethyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-2-propoxypropionic acid.

Example 56:

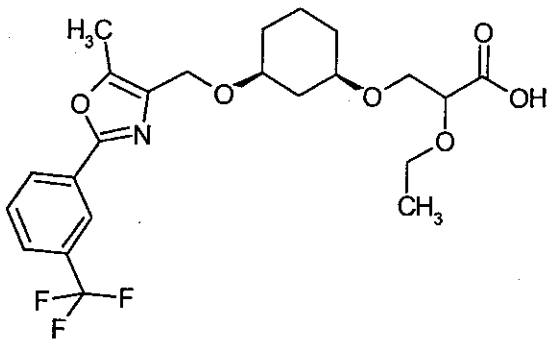
3-{(1R,3S)-3-[5-Ethyl-2-(2,6-dimethylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 5-ethyl-2-(2,6-dimethylphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-ethyl-2-(2,6-dimethylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-2-propoxypropionic acid.

Example 57:

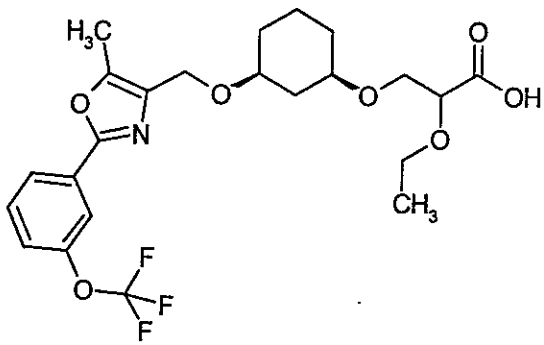
2-Ethoxy-3-{(1R,3S)-3-[5-methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-{(1R,3S)-3-[5-methyl-2-(3-trifluoromethylphenyl)oxazol-4-yl-methoxy]cyclohexyloxy}propionic acid.

Example 58:

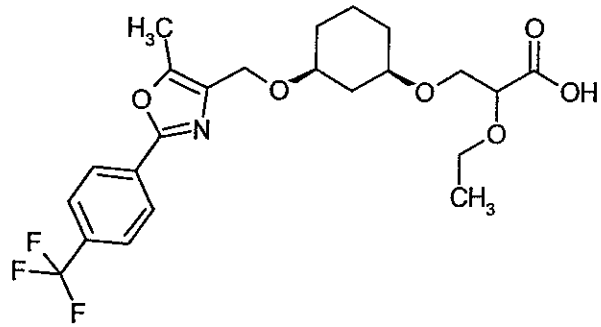
2-Ethoxy-3-{(1R,3S)-3-[5-methyl-2-(3-trifluoromethoxyphenyl)oxazol-4-yl-methoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(3-trifluoromethoxyphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-{(1R,3S)-3-[5-methyl-2-(3-trifluoromethoxyphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid.

Example 59:

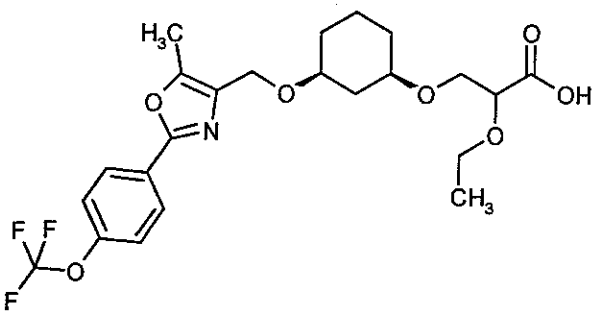
2-Ethoxy-3-{(1R,3S)-3-[5-methyl-2-(4-trifluoromethylphenyl)oxazol-4-yl-methoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-{(1R,3S)-3-[5-methyl-2-(4-trifluoromethylphenyl)oxazol-4-yl-methoxy]cyclohexyloxy}propionic acid.

Example 60:

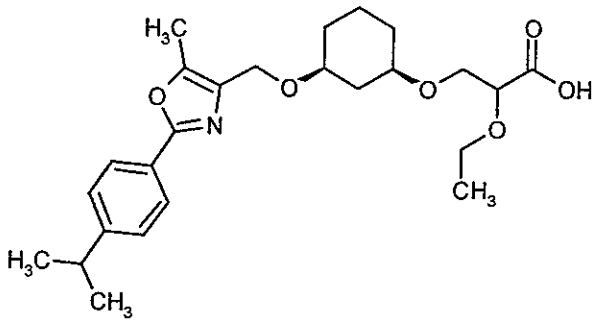
2-Ethoxy-3-{(1R,3S)-3-[5-methyl-2-(4-trifluoromethoxyphenyl)oxazol-4-yl-methoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(4-trifluoromethoxyphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-{(1R,3S)-3-[5-methyl-2-(4-trifluoromethoxyphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid.

Example 61:

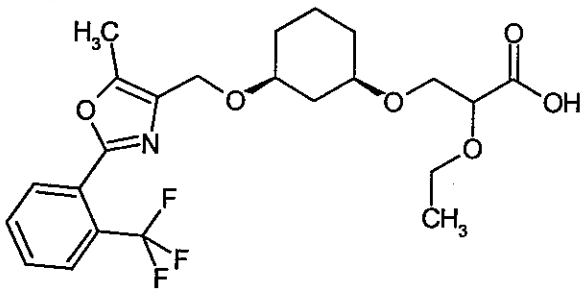
2-Ethoxy-3-{(1R,3S)-3-[5-methyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(4-isopropylphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-{(1R,3S)-3-[5-methyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid.

Example 62:

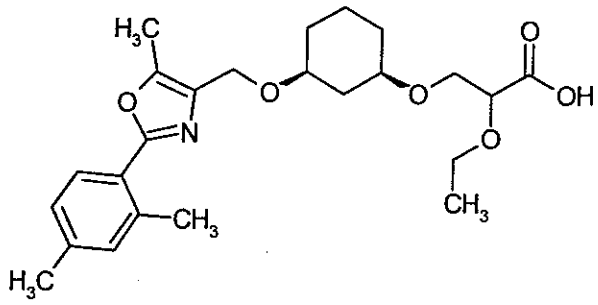
2-Ethoxy-3-{(1R,3S)-3-[5-methyl-2-(2-trifluoromethylphenyl)oxazol-4-yl-methoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-{(1R,3S)-3-[5-methyl-2-(2-trifluoromethylphenyl)oxazol-4-yl-methoxy]cyclohexyloxy}propionic acid.

Example 63:

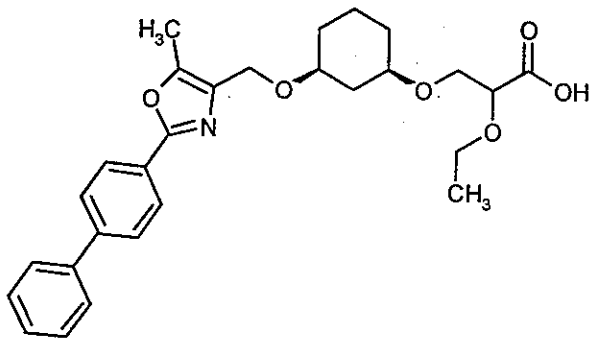
2-Ethoxy-3-{(1R,3S)-3-[5-methyl-2-(2,4-dimethylphenyl)oxazol-4-yl-methoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(2,4-dimethylphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-{(1R,3S)-3-[5-methyl-2-(2,4-dimethylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid.

Example 64:

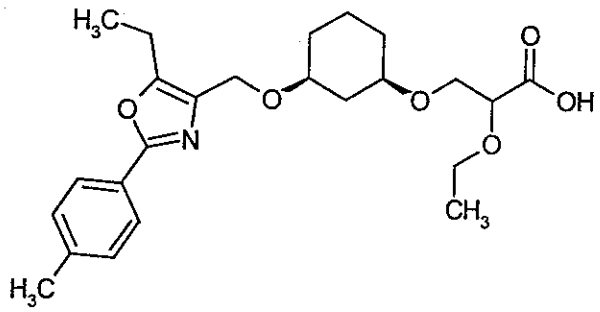
2-Ethoxy-3-{(1R,3S)-3-[5-methyl-2-(4-biphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(4-biphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-{(1R,3S)-3-[5-methyl-2-(4-biphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-propionic acid.

Example 65:

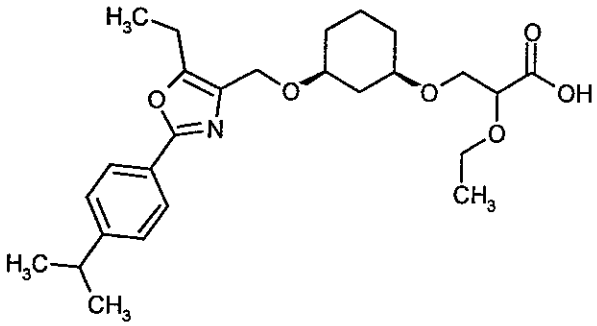
2-Ethoxy-3-[(1R,3S)-3-(5-ethyl-2-(2-tolyl)oxazol-4-ylmethoxy)cyclohexyloxy]propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(4-methylphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-[(1R,3S)-3-(5-ethyl-2-(2-tolyl)oxazol-4-ylmethoxy)cyclohexyl-oxy]propionic acid.

Example 66:

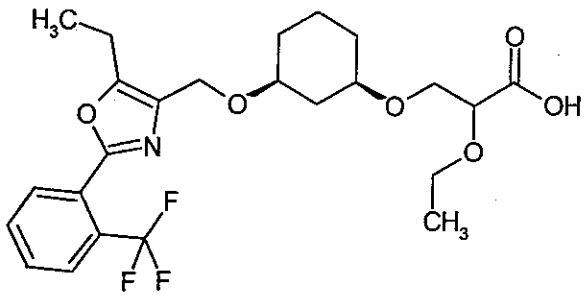
2-Ethoxy-3-[(1R,3S)-3-(5-ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy)-cyclohexyloxy]propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(4-isopropylphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-[(1R,3S)-3-(5-ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy)cyclohexyloxy]propionic acid.

Example 67:

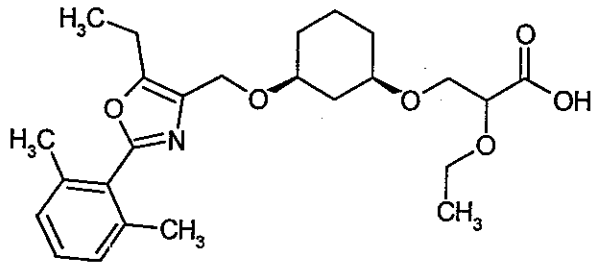
2-Ethoxy-3-[(1R,3S)-3-(5-ethyl-2-(2-trifluoromethylphenyl)oxazol-4-yl-methoxy)cyclohexyloxy]propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-[(1R,3S)-3-(5-ethyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethoxy)cyclohexyloxy]propionic acid.

Example 68:

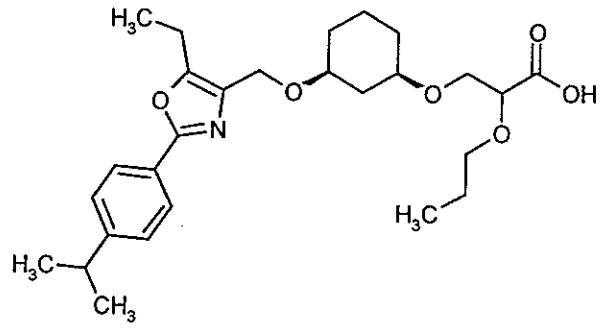
2-Ethoxy-3-[(1R,3S)-3-(5-ethyl-2-(2,4-dimethylphenyl)oxazol-4-ylmethoxy)-cyclohexyloxy]propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(2,4-dimethylphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-[(1R,3S)-3-(5-ethyl-2-(2,4-dimethylphenyl)oxazol-4-ylmethoxy)-cyclohexyloxy]propionic acid.

Example 69:

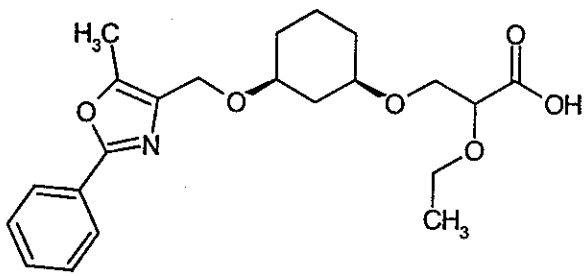
3-{(1R,3S)-3-[5-Ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 5-ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexyl-oxy}-2-propoxypropionic acid.

Example 70:

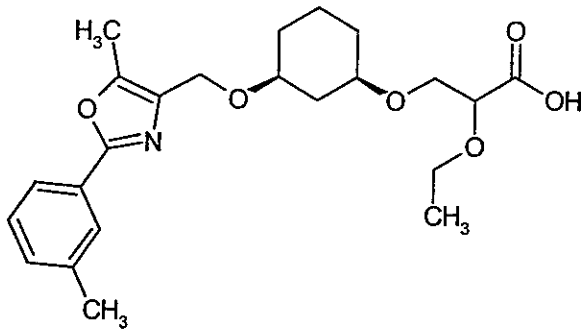
2-Ethoxy-3-{(1R,3S)-3-[5-methyl-2-phenyloxazol-4-ylmethoxy]cyclohexyl-oxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-phenyloxazol-4-ylmethyl iodide give 2-ethoxy-3-{(1R,3S)-3-[5-methyl-2-phenyloxazol-4-ylmethoxy]cyclohexyloxy}propionic acid.

Example 71:

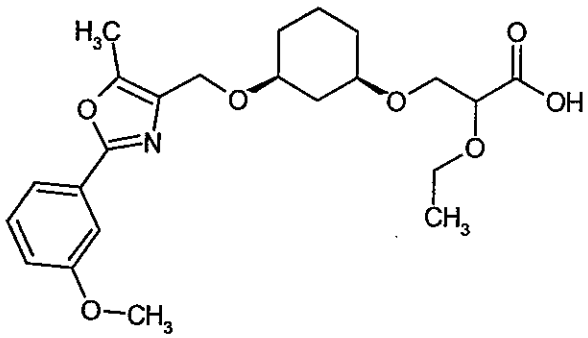
2-Ethoxy-3-{(1R,3S)-3-[5-methyl-2-(3-methylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(3-methylphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-{(1R,3S)-3-[5-methyl-2-(3-methylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid.

Example 72:

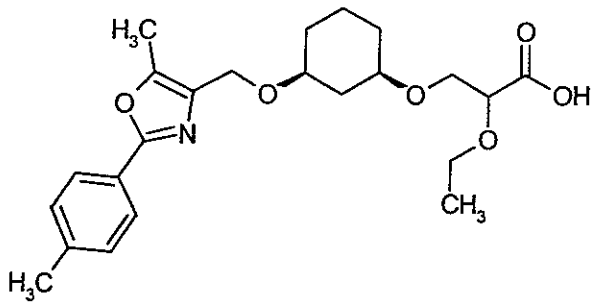
2-Ethoxy-3-{(1R,3S)-3-[5-methyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(3-methoxyphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-{(1R,3S)-3-[5-methyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid.

Example 73:

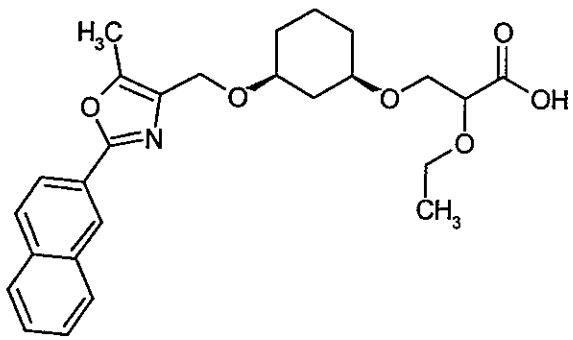
2-Ethoxy-3-{(1R,3S)-3-[5-methyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(4-methylphenyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-{(1R,3S)-3-[5-methyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}propionic acid.

Example 74:

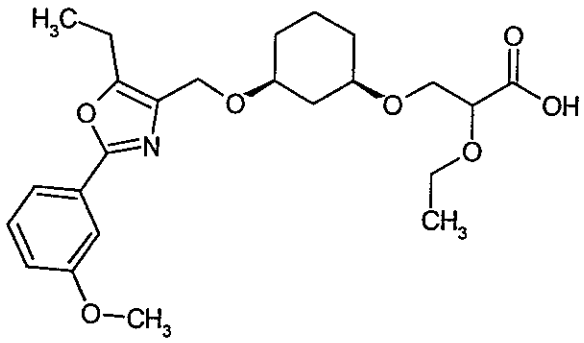
2-Ethoxy-3-{(1R,3S)-3-[5-methyl-2-(2-naphthyl)oxazol-4-ylmethoxy]cyclo-hexyloxy}propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-benzyloxycyclohexyloxy]-2-ethoxypropyl tert-butyldiphenylsilyl ether and 5-methyl-2-(2-naphthyl)oxazol-4-ylmethyl iodide give 2-ethoxy-3-{(1R,3S)-3-[5-methyl-2-(2-naphthyl)oxazol-4-ylmethoxy]cyclohexyloxy}-propionic acid.

Example 75:

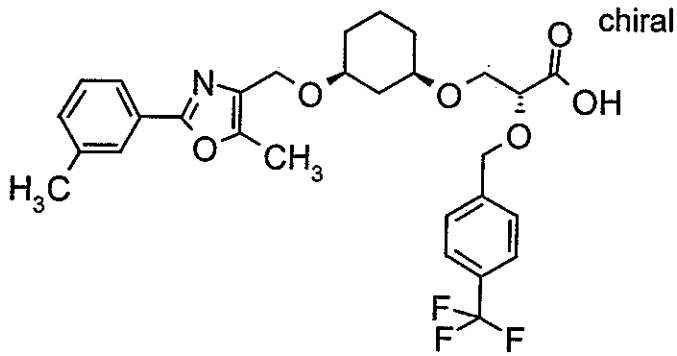
3-{(1R,3S)-3-[5-Ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexyl-oxy}-2-propoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-propoxypropyl tert-butyldiphenylsilyl ether and 5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-2-propoxypropionic acid.

Example 76:

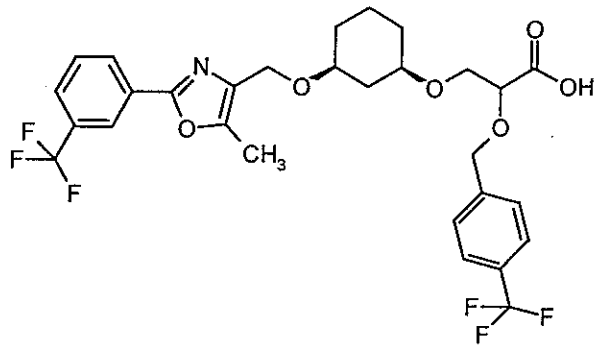
(R)-3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid



Separation of 3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propanoic acid (example 13) by chiral HPLC affords, in addition to enantiomerically pure (S)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid (example 10), (R)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid.

Example 77:

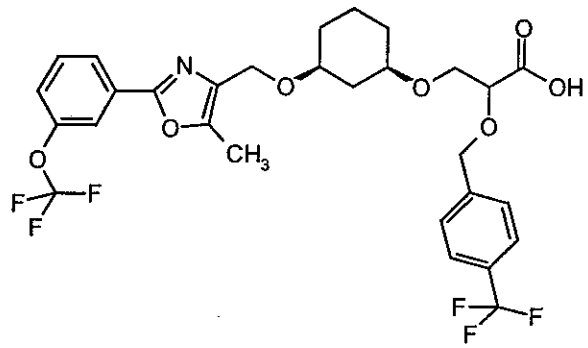
(R)-3-[(1R,3S)-3-(5-Methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1R,3S)-1-hydroxycyclohex-1-yloxy]-2-(4-trifluoromethylbenzyloxy) tert-butyldimethylsilyl ether and 5-methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give (R)-3-[(1R,3S)-3-(5-methyl-2-(3-trifluoromethylphenyl)-oxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid.

Example 78:

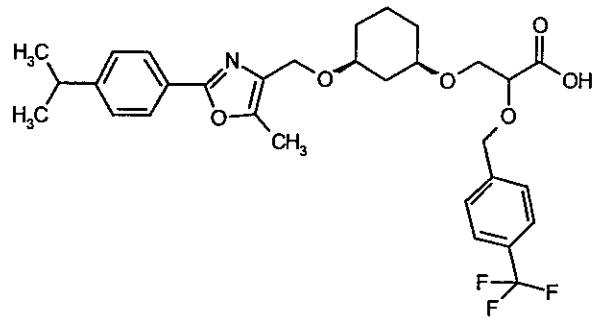
(R)-3-[(1R,3S)-3-(5-Methyl-2-(4-trifluoromethoxyphenyl)oxazol-4-ylmeth-oxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1R,3S)-1-hydroxycyclohex-1-yloxy]-2-(4-trifluoromethylbenzyloxy) tert-butyldimethylsilyl ether and 5-methyl-2-(3-trifluoromethoxyphenyl)oxazol-4-ylmethyl iodide give (R)-3-[(1R,3S)-3-(5-methyl-2-(4-trifluoromethoxy-phenyl)oxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)-propionic acid.

Example 79:

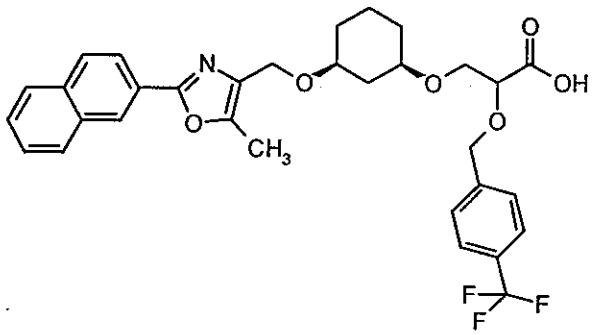
(R)-3-[(1R,3S)-3-(5-Methyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy)-cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1R,3S)-1-hydroxycyclohex-1-yloxy]-2-(4-trifluoromethylbenzyloxy) tert-butyldimethylsilyl ether and 5-methyl-2-(4-isopropylphenyl)oxazol-4-ylmethyl iodide give (R)-3-[(1R,3S)-3-(5-methyl-2-(4-isopropylphenyl)-oxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid.

Example 80:

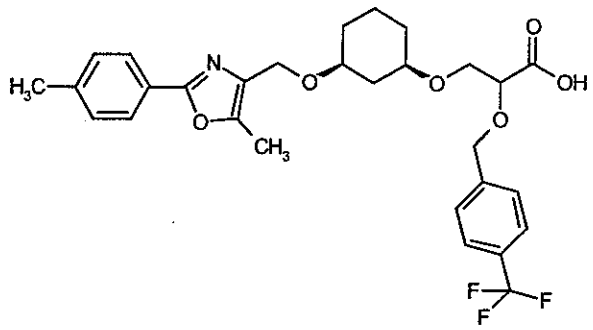
(R)-3-[(1R,3S)-3-(5-Methyl-2-(2-naphthyl)oxazol-4-ylmethoxy)cyclohexyl-oxy]-2-(4-trifluoromethylbenzyloxy)propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1R,3S)-1-hydroxycyclohex-1-yloxy]-2-(4-trifluoromethylbenzyloxy) tert-butyldimethylsilyl ether and 5-methyl-2-(2-naphthyl)oxazol-4-ylmethyl iodide give (R)-3-[(1R,3S)-3-(5-methyl-2-(2-naphthyl)oxazol-4-ylmethoxy)cyclo-hexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid.

Example 81:

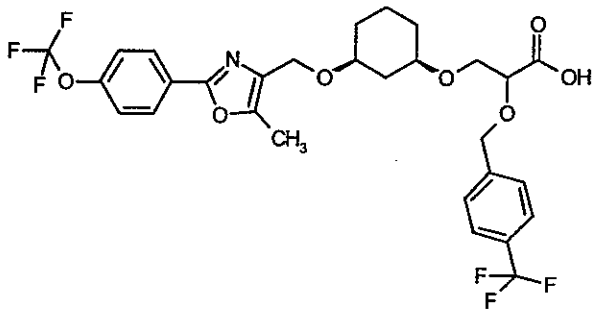
(R)-3-[(1R,3S)-3-(5-Methyl-2-(4-methylphenyl)oxazol-4-ylmethoxy)cyclo-hexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1R,3S)-1-hydroxycyclohex-1-yloxy]-2-(4-trifluoromethylbenzyloxy) tert-butyldimethylsilyl ether and 5-methyl-2-(4-methylphenyl)oxazol-4-ylmethyl iodide give (R)-3-[(1R,3S)-3-(5-methyl-2-(4-methylphenyl)oxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid.

Example 82:

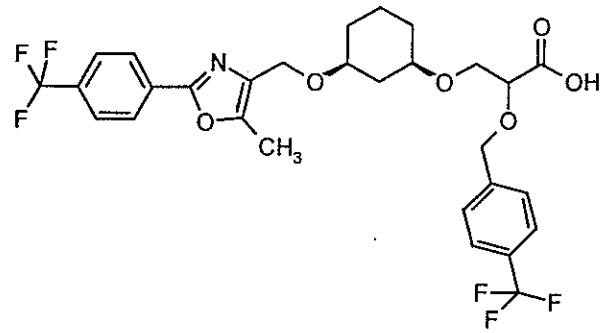
(R)-3-[(1R,3S)-3-(5-Methyl-2-(4-trifluoromethoxyphenyl)oxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1R,3S)-1-hydroxycyclohex-1-yloxy]-2-(4-trifluoromethylbenzyloxy) tert-butyldimethylsilyl ether and 5-methyl-2-(4-trifluoromethoxyphenyl)oxazol-4-ylmethyl iodide give (R)-3-[(1R,3S)-3-(5-methyl-2-(4-trifluoromethoxyphenyl)oxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)-propionic acid.

Example 83:

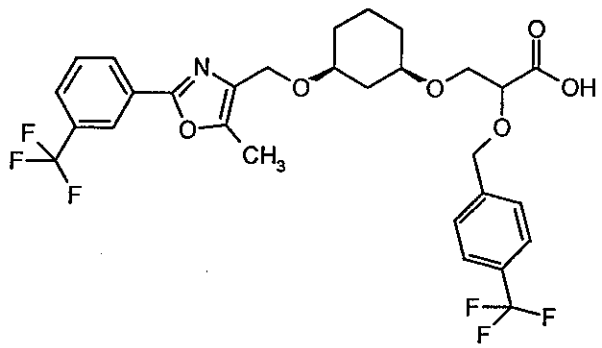
(R)-3-[(1R,3S)-3-(5-Methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy)-cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1R,3S)-1-hydroxycyclohex-1-yloxy]-2-(4-trifluoromethylbenzyloxy) tert-butyldimethylsilyl ether and 5-methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give (R)-3-[(1R,3S)-3-(5-methyl-2-(3-trifluoromethylphenyl)-oxazol-4-ylmethoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid.

Example 84:

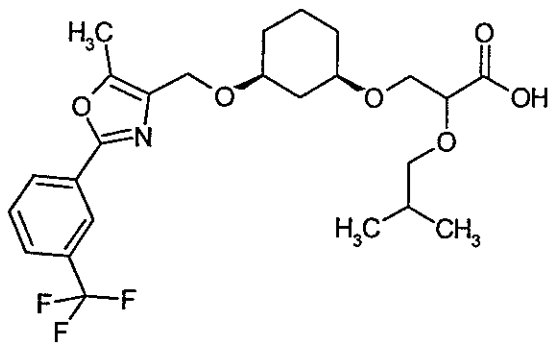
(R)-3-[(1R,3S)-3-(5-Methyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy)cyclo-hexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1R,3S)-1-hydroxycyclohex-1-yloxy]-2-(4-trifluoromethylbenzyloxy) tert-butyldimethylsilyl ether and 5-methyl-2-(3-methoxyphenyl)oxazol-4-ylmethyl iodide give (R)-3-[(1R,3S)-3-(5-methyl-2-(3-methoxyphenyl)oxazol-4-yl-methoxy)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid.

Example 85:

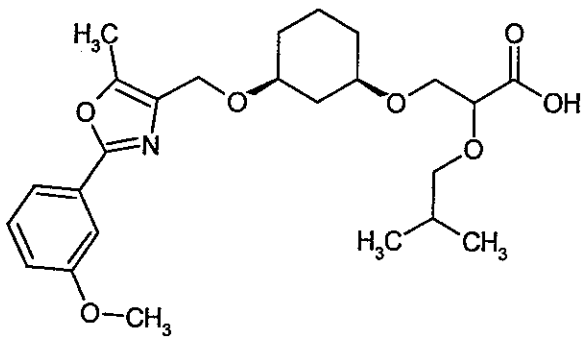
3-{(1R,3S)-3-[5-Methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}-2-isobutoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-isobutoxypropyl tert-butyldiphenylsilyl ether and 2-(3-trifluoromethylphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyloxy}-2-isobutoxypropionic acid.

Example 86:

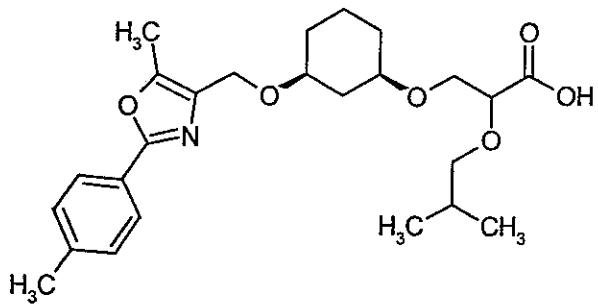
3-{(1R,3S)-3-[5-Methyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexyl-oxy}-2-isobutoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-isobutoxypropyl tert-butyldiphenylsilyl ether and 2-(3-methoxyphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-methyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-2-isobut-oxypropionic acid.

Example 87:

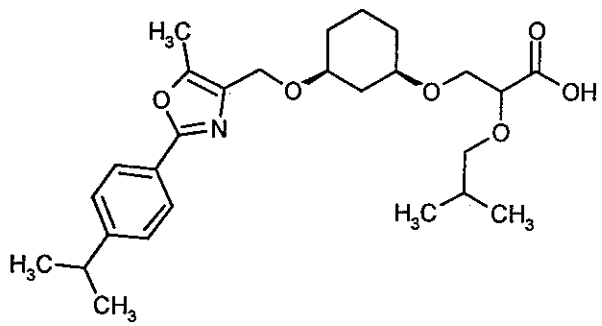
3-{(1R,3S)-3-[5-Methyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]cyclohexyl-oxy}-2-isobutoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-isobutoxypropyl tert-butyldiphenylsilyl ether and 2-(4-methylphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-methyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-2-isobutoxypropionic acid.

Example 88:

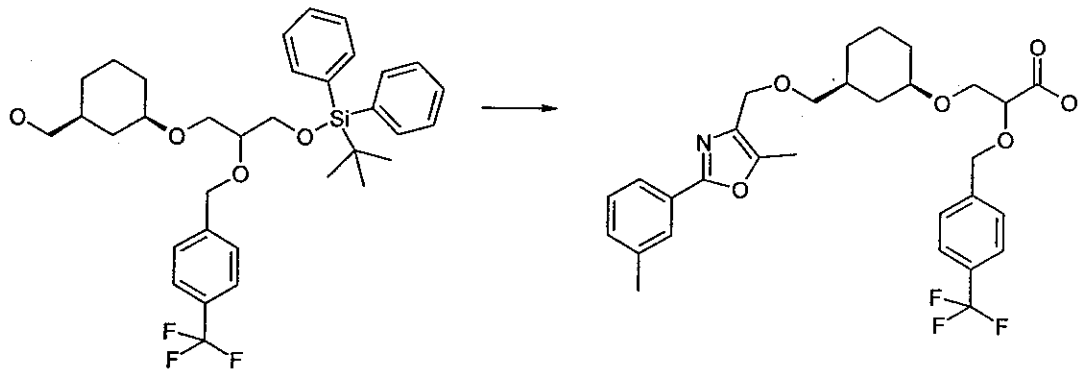
3-{(1R,3S)-3-[5-Methyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-2-isobutoxypropionic acid



Using reaction conditions similar to those of example 28, (2R/2S)-3-[(1S,3R)-3-hydroxycyclohexyloxy]-2-isobutoxypropyl tert-butyldiphenylsilyl ether and 2-(4-isopropylphenyl)oxazol-4-ylmethyl iodide give 3-{(1R,3S)-3-[5-methyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-2-isobutoxypropionic acid.

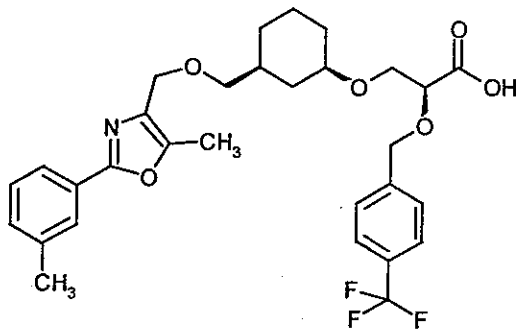
Example 89:

(2R/2S)-3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid



333 mg of (2R/2S)-3-[(1R,3S)-3-hydroxymethylcyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propyl tert-butyldiphenylsilyl ether are dissolved in MTBE, 125 mg of potassium tert-butoxide and 347 mg of 5-methyl-2-(3-methylphenyl)oxazol-4-ylmethyl iodide are added successively and the mixture is stirred at RT. After the reaction has gone to completion, water and MTBE are added and the organic phase is separated off, dried over MgSO4 and concentrated. The residue is chromatographed on silica gel (Flash-Master, heptane/ethyl acetate 1:0 → 1:1 → 0:1). The product-containing fractions are concentrated, the residue (420 mg) is dissolved in 10 ml of THF and 174 mg of TBAF are added. The mixture is stirred for 72 h, water and MTBE are then added and the organic phase is separated off, washed with NaCl solution, dried over MgSO4 and concentrated. The residue is dissolved in 2 ml of acetone, 0.5 ml of 1.9M Jones reagent is added and the mixture is stirred at RT overnight. Water and MTBE are added, and the organic phase is then separated off, dried over MgSO4 and concentrated. The residue is purified by HPLC, which gives 200 mg of (2R/2S)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid. C30H34F3NO6 (561.6), MS (ESI): 562 (M + H+).

(S)-3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid

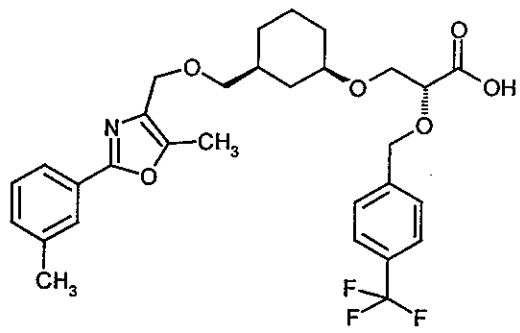


Separation of (2R/2S)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy-methyl)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid by chiral HPLC affords (2S)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy-methyl)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid.

C30H34F3NO6 (561.6), MS (ESI): 562 (M + H+).

Example 90:

(R)-3-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyl-oxy]-2-(4-trifluoromethylbenzyloxy)propionic acid

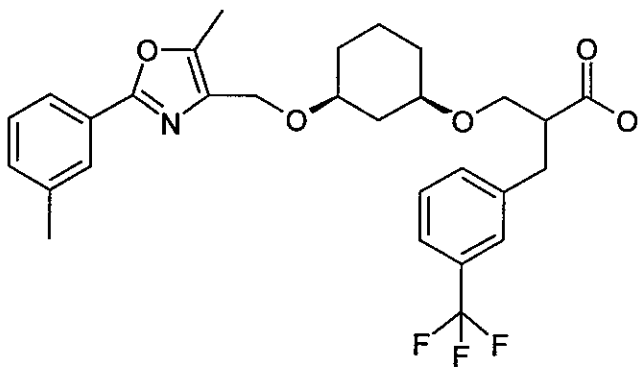


Separation of (2R/2S)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy-methyl)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid by chiral HPLC gives (2R)-3-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy-methyl)cyclohexyloxy]-2-(4-trifluoromethylbenzyloxy)propionic acid.

C30H34F3NO6 (561.6), MS (ESI): 562 (M + H+).

Example 91:

2-[(1R,3S)-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-3-(3-trifluoromethylphenyl)propionic acid



Analogously to example 9, ethyl ((1R,3S)-2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]acrylate and 3-bromobenzotrifluoride give 2-[(1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-3-(3-trifluoromethylphenyl)propionic acid.

Characterization of the examples by mass spectroscopy:

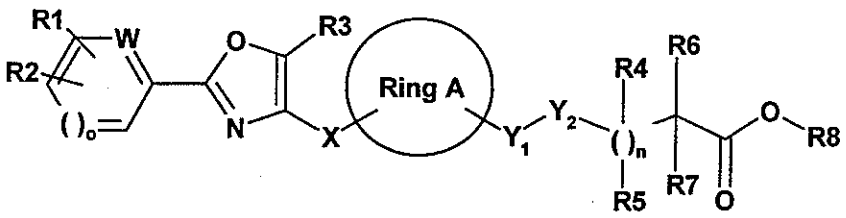
Example	Empirical formula	Monoisotope mass	Found by MS (ESI) as ($M + H^+$)
1	C23H30FNO5	419.49	420
2	C24H32FNO5	433.52	434
3	C21H26FNO5	391.44	392
4	C22H28FNO5	405.47	406
5	C23H29NO5	399.49	400
6	C31H40N2O5	520.67	521
7	C30H38N2O5	506.65	507
8	C23H31NO6	417.51	418
9	C29H34FNO5	495.60	496
10	C24H33NO6	431.53	432
11	C29H32F3NO6	547.58	548
12	C22H29NO6	403.48	404
13	C29H32F3NO6	547.58	548
14	C29H32F3NO6	547.58	548
15	C29H35NO7	509.61	510
16	C30H37NO6	507.63	508
17	C29H35NO6	493.61	494
18	C32H41NO6	535.69	536
19	C29H32F3NO6	547.58	548
20	C26H30ClNO6S	520.05	521
21	C25H31NO6	441.53	442
22	C24H29NO6	427.50	428
23	C26H33NO6	455.56	456
24	C24H31NO6	429.52	430
25	C30H35NO6	505.62	506
26	C25H33NO6	443.55	444
27	C28H33NO6	479.58	480
28	C21H27NO6	389.45	390
29	C22H26F3NO6	457.45	458
30	C22H26F3NO7	473.45	474
31	C22H26F3NO6	457.45	458
32	C22H29NO6	403.48	404
33	C23H31NO6	417.51	418
34	C22H26F3NO6	457.45	458
35	C25H29NO6	439.51	440

36	C23H31NO6	417.51	418
37	C27H31NO6	465.55	466
38	C23H31NO7	433.51	434
39	C23H31NO6	417.51	418
40	C23H28F3NO6	471.48	472
41	C24H33NO6	431.53	432
42	C23H31NO6	417.51	418
43	C24H33NO6	431.53	432
44	C24H30F3NO7	501.50	502
45	C24H33NO7	447.53	448
46	C24H30F3NO6	485.51	486
47	C24H33NO6	431.53	432
48	C24H30F3NO7	501.50	502
49	C26H37NO6	459.59	460
50	C24H30F3NO6	485.51	486
51	C27H33NO6	467.57	468
52	C24H30F3NO6	485.51	486
53	C25H35NO7	461.56	462
54	C25H35NO6	445.56	446
55	C25H32F3NO6	499.53	500
56	C26H37NO6	459.59	460
57	C23H28F3NO6	471.48	472
58	C23H28F3NO7	487.48	488
59	C23H28F3NO6	471.48	472
60	C23H28F3NO7	487.48	488
61	C25H35NO6	445.56	446
62	C23H28F3NO6	471.48	472
63	C24H33NO6	431.53	432
64	C28H33NO6	479.58	480
65	C24H33NO6	431.53	432
66	C26H37NO6	459.59	460
67	C24H30F3NO6	485.51	486
68	C25H35NO6	445.56	446
69	C27H39NO6	473.62	474
70	C22H29NO6	403.48	404
71	C23H31NO6	417.51	418
72	C23H31NO7	433.51	434
73	C23H31NO6	417.51	418

74	C26H31NO6	453.54	454
75	C24H33NO7	447.53	448
76	C29H32F3NO6	547.58	548
77	C29H29F6NO6	601.55	602
78	C29H29F6NO7	617.55	618
79	C31H36F3NO6	575.63	576
80	C32H32F3NO6	583.61	584
81	C29H32F3NO6	547.58	548
82	C29H29F6NO7	617.55	618
83	C29H29F6NO6	601.55	602
84	C29H32F3NO7	563.58	564
85	C25H32F3NO6	499.53	500
86	C25H35NO7	461.56	462
87	C25H35NO6	445.56	446
88	C27H39NO6	473.62	474
89	C30H34F3NO6	561.60	562
90	C30H34F3NO6	561.60	562
91	C29H32F3NO5	531.58	532

Patent Claims:

1. A compound of the formula I



I

in which:

Ring A	is (C3-C8)cycloalkanediyl or (C3-C8)cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one or more carbon atoms may be replaced by oxygen atoms;
R1, R2	independently of one another are H, F, Cl, Br, CF_3, OCF_3, (C1-C6)-alkyl, O-(C1-C6)-alkyl, SCF_3, SF_5, OCF_2-CHF_2, (C6-C10)-aryl, (C6-C10)-aryloxy, OH, NO_2; or
R1 and R2	together with the phenyl, pyridine, 1H-pyrrole, thiophene or furan ring form fused, partially or unsaturated bicyclic (C6-C10)-aryl, (C5-C11)-heteroaryl;
R3	is H, (C1-C6)-alkyl, (C3-C8)cycloalkyl, (C1-C3)-alkyl-(C3-C8)cycloalkyl, phenyl, (C1-C3)-alkyl-phenyl, (C5-C6)-heteroaryl, (C1-C3)-alkyl-(C5-C6)-heteroaryl or (C1-C3)-alkyl which is fully or partially substituted by F;
W	is CH or N if o = 1;
W	is O, S or NR9 if o = 0;
X	is (C1-C6)-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms;

Y1	is O;
Y2	is CR12R13, SO, SO2;
n	is 0-2;
R4	is H, F, (C1-C6)-alkyl;
R5	is H, F, (C1-C6)-alkyl;
R6	is H, (C1-C6)-alkyl; or F if n is not 0;
R7	is H, (C1-C6)-alkyl, (C2-C6)-alkenyl, (C2-C6)-alkynyl, O-(C1-C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, (C3-C8)-cycloalkyl, phenyl, (C5-C11)-heteroaryl, O-(C3-C8)-cycloalkyl, O-phenyl, which may be substituted by OH, NR10R11, O-(C1-C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, O-(C3-C8)-cycloalkyl, O-phenyl, O-(C5-C11)-heteroaryl, and where (C3-C8)-cycloalkyl, phenyl, (C5-C11)-heteroaryl may additionally be substituted by (C1-C6)-alkyl, optionally fully or partially substituted by F, O-(C1-C6)-alkyl, optionally fully or partially substituted by F, Cl, Br, J, OH, NR10R11, CO-(C1-C6)-alkyl, CO-(C6-C10)-aryl, CO-(C1-C6)-alkyl-(C6-C10)-aryl, CO-(C5-C11)-heteroaryl, C(O)-O-(C1-C6)-alkyl, C(O)-O-(C1-C6)-alkyl-(C6-C10)-aryl, C(O)-O-(C6-C10)-aryl, C(O)-O-(C5-C11)-heteroaryl, SO2-(C1-C6)-alkyl, SO2-(C1-C6)-alkyl-(C6-C10)-aryl, SO2-(C1-C6)-alkyl-SO2-(C1-C6)-alkyl, SO2-(C6-C10)-aryl, SO2-(C5-C11)-heteroaryl;
R6 and R7	together with the carbon atom that carries them are (C3-C8)cycloalkyl;
R8	is H, (C1-C6)-alkyl;
R9	is H, (C1-C6)-alkyl, which is unsubstituted or substituted by phenyl;

R10 is H, (C1-C6)-alkyl, which is unsubstituted or substituted by phenyl;

R11 is H, (C1-C6)-alkyl, which is unsubstituted or substituted by phenyl;

R12 is H, (C1-C6)-alkyl;

R13 is H, (C1-C6)-alkyl;

and its physiologically acceptable salts.

2. A compound of the formula I as claimed in claim 1 in which

Ring A is (C_3-C_8)cycloalkanediyl or (C_3-C_8)cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one carbon atom may be replaced by an oxygen atom;

X is (C1-C6)-alkanediyl, where in the alkanediyl group the C1 or C2 carbon atom (to Ring A) may be replaced by an oxygen atom;

and its physiologically acceptable salts.

3. A compound of the formula I as claimed in one or more of claims 1 to 2, in which

Ring A is cis-cyclohexane-1,3-diyl

R1, R2 independently of one another are H, F, CF3, (C1-C6)-alkyl, O-(C1-C6)-alkyl, phenyl, or

R1 and R2 together with the phenyl ring = naphthyl;

R3 is (C1-C6)-alkyl;

W is CH if o = 1;

X is (CH2)O, CH2-O-CH2;

Y1 is O;

Y2 is CH2;

n is 0, 1;

R4 is H;

R5 is H;

R6 is H;

R7 is H, (C1-C6)-alkyl, O-(C1-C6)-alkyl, (C1-C6)-alkyl-O-(C1-C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, CH2NR10R11, where alkyl, O-alkyl and alkenyl may be substituted by phenyl or (C5-C6)-heteroaryl, which in turn may be substituted by (C1-C6)-alkyl, O-(C1-C6)-alkyl, CF3;

R6 and R7 together with the carbon atom that carries them are (C3-C6)cycloalkyl;

R8 is H;

R10 is (C1-C6)-alkyl;

R11 is (C1-C6)-alkyl which is substituted by phenyl;

and its physiologically acceptable salts.

4. A pharmaceutical, comprising one or more compounds of formula I as claimed in one or more of claims 1 to 3.

5. A pharmaceutical, comprising one or more compounds of the

formula I as claimed in one or more of claims 1 to 3 and one or more active compounds having favorable effects on metabolic disorders or diseases associated therewith.

6. A pharmaceutical, comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 3 and one or more antidiabetics.

7. A pharmaceutical, comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 3 and one or more lipid modulators.

8. The use of the compounds of the formula I as claimed in one or more of claims 1 to 3 for the treatment and/or prevention of disorders of the fatty acid metabolism and glucose utilization disorders.

9. The use of the compounds of the formula I as claimed in one or more of claims 1 to 3 for the treatment and/or prevention of disorders where insulin resistance is involved.

10. The use of the compounds of the formula I as claimed in one or more of claims 1 to 3 for the treatment and/or prevention of diabetes mellitus and its sequelae.

11. The use of the compounds of the formula I as claimed in one or more of claims 1 to 3 for the treatment and/or prevention of dyslipidemias and their sequelae.

12. The use of the compounds of the formula I as claimed in one or more of claims 1 to 3 for the treatment and/or prevention of states associated with metabolic syndrome.

13. The use of the compounds as claimed in one or more of claims 1 to 3 in combination with at least one further active compound for the treatment and/or prevention of disorders of the fatty acid metabolism and glucose utilization disorders.

14. The use of the compounds as claimed in one or more of claims 1 to 3 in combination with at least one further active compound for the treatment

and/or prevention of disorders in which insulin resistance is involved.

15. A process for preparing a pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 3, which comprises mixing the active compound with a pharmaceutically acceptable carrier and bringing this mixture into a form suitable for administration.