PROCESS FOR THE PREPARATION OF ENTECAVIR AND NOVEL INTERMEDIATES THEREOF VIA CARBON-SILICON OXIDATION

RELATED APPLICATION

[0001] This application claims the priority benefit of U.S. Provisional Application No. 60/576899 filed June 4, 2004, the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Entecavir, [1*S*-(1α, 3α, 4β)]-2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one monohydrate, is currently being used as a drug for treating hepatitis B viral infections.

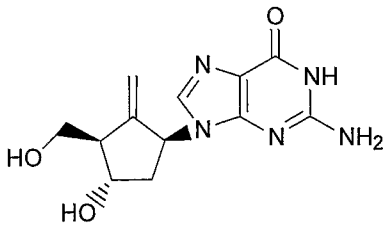
[0003] Entecavir and its use as an antiviral agent are described by Zahler *et al.* in U.S. Patent 5,206,244. Improved processes of preparing entecavir are described by Bisacchi *et al.*, in WO 98/09964, and by Pendri *et al.*, in WO2004/052310 and US20040192912. The disclosure of each of the foregoing patent or patent applications is herein incorporated by reference in its entirety.

[0004] Colonno *et al.* in WO 01/64221 describe compositions containing a low dose of entecavir administered on a daily basis to treat hepatitis B virus infection and/or co-infections.

[0005] The discussion of the background to the invention herein is included to explain the context of the invention This is not to be taken as an admission that any of the material referred to was prior art as at the priority date of any of the claims.

SUMMARY OF THE INVENTION

[0006] This invention is directed to various methods for preparing entecavir as recited in the claims appended hereto. Entecavir is the monohydrate of the compound of formula I, which has the structural formula shown below:



I (entecavir)

[0007] This invention is also directed to various intermediates useful in the preparation of entecavir and the methods of preparing such intermediates.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations

[0008] For ease of reference, the following abbreviations are used in this application and have the meanings given below:

AcOH	acetic acid
Ac_2O	acetic anhydride
AP	HPLC area percent
Bn	benzyl
BnBr	benzyl bromide
BHT	2,6-di-*tert*-butyl-4-methylphenol
CHP	cumene hydroperoxide, or α,α-dimethylbenzylhydroperoxide
CSA	(1*R*)-(-)-camphorsulfonic acid
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
(-)-DIPT	diisopropyl D-tartrate
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide or methyl sulfoxide
EtOAc	ethyl acetate
FMSA	fluoromethane sulfonic acid
KHMDS	potassium hexamethyldisilazide or potassium bis(trimethylsilyl)amide
KOtBu	potassium *tert*-butoxide
MCPBA	*meta*-chloroperbenzoic acid
MSA	methanesulfonic acid
NMP	1-methyl-2-pyrrolidinone

PMB	*para*-methoxybenzyl
PMBCl	*para*-methoxybenzyl chloride
PPTS	pyridinium 4-toluenesulfonate
PTSA	*para*-toluene sulfonic acid
RAP	relative area percent
TBAF	tetrabutylammonium fluoride
TBAHS	tetrabutylammonium hydrogensulfate
TBHP	*tert*-butyl hydroperoxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TFMSA	trifluoromethanesulfonic acid
$Ti(OiPr)_4$	titanium isopropoxide
TIOF	triisopropyl orthoformate

Definitions

[0009] The following terms shall have, for the purposes of this application, including the claims appended hereto, the respective meanings set forth below. It should be understood that when reference herein is made to a general term, such as acid, base, oxidizing agent, etc. one skilled in the field may make appropriate selections for such reagents from those given in the definitions below, as well as from additional reagents recited in the specification that follows, or from those found in literature references in the field.

[0010] "Anhydride" refers generally to compounds that will react with water or solvent to form an acid, e.g., including carboxylic acid anhydrides having the formula R-C(=O)-O-C(=O)R', wherein R and R' are selected from alkyl or aryl groups, as defined below, more preferably, wherein R and R' are selected from methyl and ethyl.

[0011] "Acid" refers to any compound that contains hydrogen and dissociates in water or solvent to produce positive hydrogen ions, as well as Lewis acids, including but not limited to acids such as hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, trihaloacetic acid (e.g.,TFA), hydrogen bromide, maleic acid, sulfonic acids such as toluenesulfonic acids and camphorsulfonic acids, propionic acids such as (*R*)-chloropropionic acid, phthalamic acids such as *N*-[(*R*)-1-(1-naphthyl) ethyl]

phthalamic acid, tartaric acids such as L-tartaric acid and dibenzyl-L-tartaric acid, lactic acids, camphoric acids, aspartic acids, citronellic acids, BCl_3, BBr_3, and so forth. Thus, the term includes weak acids such as ethanoic acid and hydrogen sulfide; strong organic acids such as methanesulfonic acid, trifluoroacetic acid, and so forth.

[0012] "Alkyl" as used herein includes linear or branched alkyl groups having from one to twelve carbon atoms, more preferably from one to eight carbon atoms, and most preferably, from one to four carbon atoms, unless otherwise specifically described. The term alkyl includes such groups optionally having up to four (more preferably 0 to 2), substituents selected from the group of non-interfering substituents recited below. The term lower alkyl refers to alkyl groups having from one to four carbon atoms. When a subscript is used with reference to an alkyl or other group, the subscript refers to the number of carbon atoms that the group may contain. For example, the term "C_1-C_4 alkyl" refers to alkyl groups of 1 to 4 carbon atoms, which include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, and t-butyl. Alkyl moieties incorporated in other radicals are also linear or branched, unless specifically described otherwise. When the term alkyl is used as a prefix in conjunction with another group, as in alkylaryl, this means the alkyl as defined above is present as a divalent moiety (i.e., alkylene), creating a linkage to the other named group. Thus, alkylaryl includes benzyl and the like.

[0013] "Alkoxy" as used herein includes alkyl groups as defined above, bonded through an oxygen atom, i.e., -O-alkyl. "C_1-C_4 alkoxy" refers to –O-C_1-C_4 alkyl.

[0014] "Alkali metal salt" refers to salts formed with alkali metals, preferably salts of sodium, lithium or potassium.

[0015] "Allyl" refers to the group $–CH_2-CH=CH_2$, as well as such groups optionally having one or more (preferably 0 to 1) non-interfering substituents as defined below.

[0016] "Anti-oxidant" refers to a chemical compound or complex that is effective to slow or inhibit the rate of an oxidation reaction. Exemplary anti-oxidants may include, without limitation, β-carotene, ZrO_2, aromatic amines, phenols, quinones including BHT, citric acid, ascorbic acid, vitamin E, benzoic acid, phosphoric acid, and so forth.

[0017] "Aryl" includes monocyclic or bicyclic aromatic groups having 6 to 12 carbon atoms in the ring portion, i.e., phenyl and naphthyl, as well as heteroaryl groups, e.g., 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic aromatic ring systems, which have at least one heteroatom and at least one carbon atom-containing ring. Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like. Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxaxolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, and the like. The term "aryl" includes aryl groups optionally having up to four (preferably 0 to 2) non-interfering substituents.

[0018] "Base" when used herein includes hydroxides or alkoxides, hydrides, or compounds such as amine and its derivatives, that accept protons in water or solvent. Thus, exemplary bases include, but are not limited to, alkali metal hydroxides and alkoxides (i.e., MOR, wherein M is an alkali metal such as potassium, lithium, or sodium, and R is hydrogen or alkyl, as defined above, more preferably where R is straight or branched chain $C_{1\text{-}5}$ alkyl, thus including, without limitation, potassium hydroxide, potassium *tert*-butoxide, potassium *tert*-pentoxide, sodium hydroxide, sodium *tert*-butoxide, lithium hydroxide, etc.); other hydroxides such as magnesium hydroxide ($Mg(OH)_2$) or calcium hydroxide ($Ca(OH)_2$), barium hydroxide ($Ba(OH)_2$); alkali metal hydrides (i.e., MH, wherein M is as defined above, thus including, without limitation, sodium, potassium, and lithium hydrides); alkylated disilazides, such as, for example, potassium hexamethyldisilazide and lithium hexamethyldisilazide; carbonates such as potassium carbonate (K_2CO_3), sodium carbonate (Na_2CO_3), potassium bicarbonate ($KHCO_3$), and sodium bicarbonate ($NaHCO_3$), alkyl ammonium hydroxides such as tetrabutyl ammonium hydroxide (TBAH) and so forth. Aqueous bases include metal hydroxides, for example, hydroxides of Group 1 / Group 2 metals such as Li, Na, K, Mg, Ca, etc. (e.g., aqueous LiOH, NaOH, KOH, etc.), alkyl ammonium hydroxides, and aqueous carbonates. Non-aqueous bases include but not limited to, amines and their derivatives, for example, trialkyl amine (e.g., Et_3N, diisopropylethyl amine, etc.), and aromatic amine

(e.g., Ph-NH_2, PhN(Me)H, etc.); alkali metal alkoxides; alkali metal hydrides; alkylated disilazides; and non-aqueous carbonates.

[0019] "Benzyl" includes the group $-CH_2$-phenyl, as well as such groups optionally containing non-interfering substituents on the methyl or phenyl portions of the benzyl, unless otherwise indicated.

[0020] "Benzyl halide" refers to a benzyl group having a halide substituent on the alkyl portion of the benzyl group, i.e., Ph-CH_2-X, wherein X is halide, and Ph denotes a phenyl ring as defined below.

[0021] "Benzyloxy" refers to the group -O-benzyl, wherein the benzyl moiety is as described immediately above.

[0022] "Diastereoselective epoxidation" refers to a reaction wherein one diastereomeric epoxide is preferentially formed. The term "diastereoselective epoxidation" thus includes Sharpless epoxidations wherein epoxidation of an allylic alcohol preferentially gives one enantiomer. However, the term "diastereoselective epoxidation" as used herein also more broadly covers the epoxidation of a diastereomeric compound, or the epoxidation of an otherwise non-racemic compound. The term "diastereoselective epoxidation" is intended to include enantioselective oxidation of olefins as described in Bonini and Righi, "A Critical Outlook And Comparison of Enantioselective Oxidation Methodologies of Olefins", Tetrahedron, Vol. 58 (2002), at pp. 4981-5021, incorporated herein by reference.

[0023] "Halide" or "halo" refers to F, Cl, Br, or I..

[0024] "Halogenated methanesulfonic acid" refers to methanesulfonic acid substituted with one, two or three halogens, for example, monofluromethanesulfonic acid, difluromethanesulfonic acid, trifluromethanesulfonic acid, monochloromethanesulfonic acid, dichloromethanesulfonic acid, trichloromethanesulfonic acid, monobromomethanesulfonic acid, dibromomethanesulfonic acid, tribromomethanesulfonic acid, monoiodomethanesulfonic acid, and diiodomethanesulfonic acid.

[0025] "Hydride reagent" refers to reagents that are capable of delivering H^- ions. Exemplary hydride reagents include, but are not limited to, lithium aluminum hydride ($LiAlH_4$), sodium borohydride ($NaBH_4$), Red-Al® (sodium bis[2-methoxyethoxyaluminum] hydride), zinc borohydride, diisobutylaluminum hydride,

sodium borohydride-cerium chloride, lithium triethylborohydride, lithium 9-BBN hydride, 9-BBN pyridine, borane-sulfide complex, 5,5-diphenyl-2-methyl-3,4-propan-1,3,2-oxazaborolidine (Corey Reagent), lithium tri-*tert*-butoxyaluminum hydride, sodium cyanoborohydride, lithium tri-*sec*-butyl borohydride (L-Selectride®), diisobutylaluminum chloride, borane-tetrahydrofuran complex, and the like.

[0026] "Hydroperoxide" means a compound or complex comprising the hydroperoxide moiety HO_2^-, such as compounds having the formula (R^pOOH), wherein R^p can be hydrogen (e.g., hydrogen peroxide H_2O_2), or can be an alkyl, substituted alkyl, aryl, alkylaryl, substituted aryl, or substituted alkylaryl or other moiety (including without limitation compounds wherein the methyl moiety of the benzyl group is optionally substituted). Hydroperoxides thus include α,α-dimethylbenzylhydroperoxide, *tert*-butylhydroperoxide, and the like.

[0027] "Hydroxy protecting groups" means those groups that one skilled in the field would recognize as being suitable to protect the –OH substituent on an alkyl or ringed system as described herein and which may be removed under deprotection conditions known to those skilled in the field as set forth, for example, in the latest edition of Greene and Wuts, Protecting Groups in Organic Synthesis, incorporated herein. As an illustration, nonlimiting examples of hydroxy protecting groups include ether protecting groups (e.g. benzyl ethers, silyl ethers such as tert-butyldimethylsilyl ether), esters (e.g., benzoate, acetate), and acetals (e.g., MOP).

[0028] "Homochiral diester of tartaric acid" as used herein includes single diastereomers of alkyl tartrates including diethyl tartrate and diisopropyl tartrate.

[0029] "Metal catalyst" refers to compounds and complexes including metallic elements that are effective as catalysts and encompasses, without limitation, "transition metal catalysts." Metal catalysts include, without limitation, titanium (IV) isopropoxide, palladium salts such as palladium (0) catalyst, e.g., tetrakis(triphenylphosphine)palladium, copper(I)triflate, rhodium(II) acetate, $Rh_6(CO)_{16}$, and so forth.

[0030] "Non-interfering substituent" refers to a substituent that is bonded to a compound or complex identified herein that does not render the compound or complex inoperable, with regard to the functionality or object to be achieved with the particular compound or complex, and which is compatible with the reaction sequences

detailed herein. Such substituents may be selected by one skilled in the field depending on the particular reaction step and function to be achieved. Exemplary non-interfering substituents may include without limitation groups such as alkyl, halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, -OR, -SR, -C(=O)R, $-CO_2R$, aryl, alkylaryl, C_{3-7}cycloalkyl, $-NRR'_2$, $-NRC(=O)R'$, $-SO_{(q)}R''$, $-NRSO_{(q)}R''$, $-SO_{(q)}R''$, $-C(=O)NRR'$, and the like; and alkyl groups substituted with one to four (preferably 1 to 2) of halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, -OR, -SR, -C(=O)R, $-CO_2R$, aryl, alkylaryl, C_{3-7}cycloalkyl, $-NRR'_2$, $-NR-C(=O)R'$, $-SO_{(q)}R''$, $-NRSO_{(q)}R''$, $-SO_{(q)}R''$, $-C(=O)NRR'$, and the like, wherein R and R' are hydrogen, alkyl, benzyl, or aryl, as defined above, R" is alkyl, benzyl, or aryl, as defined above, and q is 1, 2 or 3.

[0031] "Orthoformate derivatives" means reagents effective for the preparation of dioxolanes from vicinal diol moieties, or for the preparation of imidazole rings from vicinal diamines on, for example 5,6-diaminopyrimidine derivatives. Non-limiting examples include triethylorthoformate, trimethylorthoformate, triisopropylorthoformate, diethoxymethyl acetate, and di-isopropyloxymethylacetate.

[0032] "Oxidizing agent," or "oxidizing source" refers to any compound or complex that is known in the field for its effects in converting a functional group in a molecule from a lower oxidation state to a higher oxidation state. For example, oxidizing agents may include, without limitation, *m*-CPBA, hydrogen peroxide, AcOOH in AcOH, potassium peroxymonosulfate, sodium periodate, sodium percarbonate, potassium permanganate, ruthenium oxide, and the like. Oxidizing agents may be used in the presence of one or more additives, such as KF, $KHCO_3$, NEt_3, AcONa, and the like. As one skilled in the field will appreciate, additives may be selected depending on the particular oxidizing agents used and the reaction conditions.

[0033] "Per-acid" as used herein includes without limitation, magnesium monoperoxyphthalate (MPPA), perbenzoic acids, and peracetic acid.

[0034] "Peroxohydrates" are crystalline adducts containing molecular hydrogen peroxide, for example, sodium carbonate peroxohydrate (known commercially as sodium percarbonate, e.g., $Na_2CO_3 \cdot 1.5\ H_2O_2$), urea peroxohydrate ($CO(NH_2)_2 \cdot H_2O_2$),

the peroxohydrate of melamine, ($C_3H_6N_6 \cdot H_2O_2$), sodium pyrophosphate peroxohydrate ($Na_4P_2O_7 \cdot 2\ H_2O_2$), sodium sulfate peroxohydrate hydrate (2 $Na_2SO_4 \cdot H_2O_2 \cdot 2\ H_2O$), potassium carbonate peroxohydrates, rubidium carbonate peroxohydrates, and cesium carbonate peroxohydrates (the last three have the general formula $M_2CO_3 \cdot 3H_2O_2$).

[0035] "Phenyl" includes phenyl rings optionally substituted with up to four (preferably 0 to 2) non-interfering substituents as defined above. When the term phenyl is used as a suffix following another term, as in alkylphenyl, or alkoxy phenyl, this means the phenyl group is connected via a divalent moiety of the other, specifically-named group. Thus, alkylphenyl includes benzyl, phenylethyl, and the like.

[0036] "Protecting group" includes without limitation such groups as are set forth, for example, in the latest edition of Greene and Wuts, Protecting Groups in Organic Synthesis, incorporated herein by reference.

[0037] "Reducing reagent" refers to any compound or complex that is known in the field for its effects in converting a functional group in a molecule from one oxidation state to a lower oxidation state. Exemplary reducing reagents include, without limitation, $NaBH_4$, LAH, lithium borohydride, diisobutylaluminum hydride, sodium bis(2-methoxyethoxyaluminum) hydride, and the like. The term "reducing reagent" will include "hydride reagents" as recited above.

[0038] "Strong non-nucleophilic base" means a non-aqueous base that does not act as a nucleophile, such as lithium, sodium or potassium bistrimethylsilylamide, lithium diisopropylamide, potassium, lithium, or sodium hydride.

[0039] "Tertiary amine base" means a trialkylamine, such as triethylamine, *N,N*-dimethylethylamine, diisopropylethylamine (Hunig's base) or tetramethylenediamine (TMEDA), or a nitrogen containing heterocycle, such as pyridine.

[0040] "Trimethylsilylating reagent" means a reagent effective to prepare a trimethylsilyl ether from an alcohol. Non-limiting examples include chlorotrimethylsilane, trimethylsilyl trifluoromethanesulfonate, and the like.

[0041] Additionally, it should be understood in the methods of preparation and claims herein, that the pronoun "a", when used to refer to a reagent, such "a base", "a

metal catalyst", "a hydroperoxide" and so forth, is intended to mean "at least one" and thus, include, where suitable, single reagents as well as mixtures of reagents. Thus, for example, a reaction step involving use of "a base" , or for example, involving use of "a base selected from one of potassium hydroxide, potassium *tert*-butoxide, potassium *tert*-pentoxide, sodium hydroxide, sodium *tert*-butoxide, lithium hydroxide," encompasses use of potassium hydroxide as a base, or, where appropriate, mixtures of potassium hydroxide plus one or more additional bases set forth in the group from which a selection may be made. One skilled in the field may make appropriate selections given the reactions steps and conditions and result to be achieved.

Methods of Preparation

[0042] The compound entecavir and novel intermediates therefore may be prepared by the exemplary processes described in the following reaction Schemes. Exemplary reagents and procedures for these reactions appear hereinafter or are described above. Starting materials can be readily prepared according to methods described in WO2004/052310 and US20040192912. Solvents, temperatures, pressures, starting materials having the desired groups, and other reaction conditions, may be readily selected as appropriate by one of ordinary skill in the art.

[0043] The compound of formula I (entecavir) can be prepared from an alcohol of formula **1a** according to Scheme 1. In the alcohol of formula **1a**, R^a is allyl, phenyl, or phenyl substituted with one, two or three C_1-C_4 alkyl or C_1-C_4 alkoxy, preferably R^a is phenyl; and each R^b is independently C_1-C_4 alkyl, preferably methyl. The definitions of R^a and R^b are the same as hereinabove throughout the specification, unless otherwise indicated. The primary alcohol moiety of the compound of formula **1a** is protected with a PMB protecting group by treatment with PMB-halide (e.g., PMB-Cl), and in the presence of a base and optionally a catalyst (e.g., TBAHS), in an organic solvent such as toluene, to yield a compound of formula **1b**. The compound of formula **1b** can be converted to a compound of formula **1c** via protodesilylation. The protodesilylation step can be achieved via reaction with boron trifluoride-acetic acid complex, or a Bronsted acid such as TFA, MSA, FMSA, or tetrafluoroboric acid in an inert solvent, *e.g.*, DCM. Alternatively, protodesilylation can be achieved with a

base (e.g., a hydroxide such as NaOH or KOH, an alkoxide such as KOtBu) or a strong acid (e.g., TFA), in a polar aprotic solvent such as DMF, DMSO, or NMP, to give the compound of formula **1c**. The compound of formula **1c** is further oxidized using an oxidizing reagent, for example, H_2O_2, in the presence of KF and $KHCO_3$ to afford an alcohol of formula **1d**. In addition, other methods may also be useful in the transformation of the silyl group to the hydroxyl group, see, e.g., Fleming, I. (*Chemtracts-Organic Chemistry* **1996**, *9*, 1-64) and Jones, G.R. *et al.* (*Tetrahedron*, **1996**, *52*, 7599-7662), both of which are herein incorporated by reference.

[0044] The alcohol of formula **1d** is protected as a benzyl ether of formula **1e** using a benzyl halide, such as BnBr, in the presence of a base, such as KHMDS or NaH, and in an organic solvent, such as toluene. The PMB group in the compound of formula **1e** can be removed upon treatment with DDQ in an organic solvent such as CH_2Cl_2 in the presence of water to yield a compound of formula **1f**.

[0045] The compound of formula **1f** can then be diastereoselectively epoxidized. For example, the epoxidation can be accomplished using a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst, such as a transition metal catalyst, to yield a cyclopentane epoxide of formula **1g**. In one embodiment, the homochiral diester is (-)-diisopropyl tartrate [(-)-DIPT], the hydroperoxide is TBHP or CHP, and the metal catalyst is titanium (IV) isopropoxide. Preferably, the reaction is carried out in an inert solvent such as DCM or toluene.

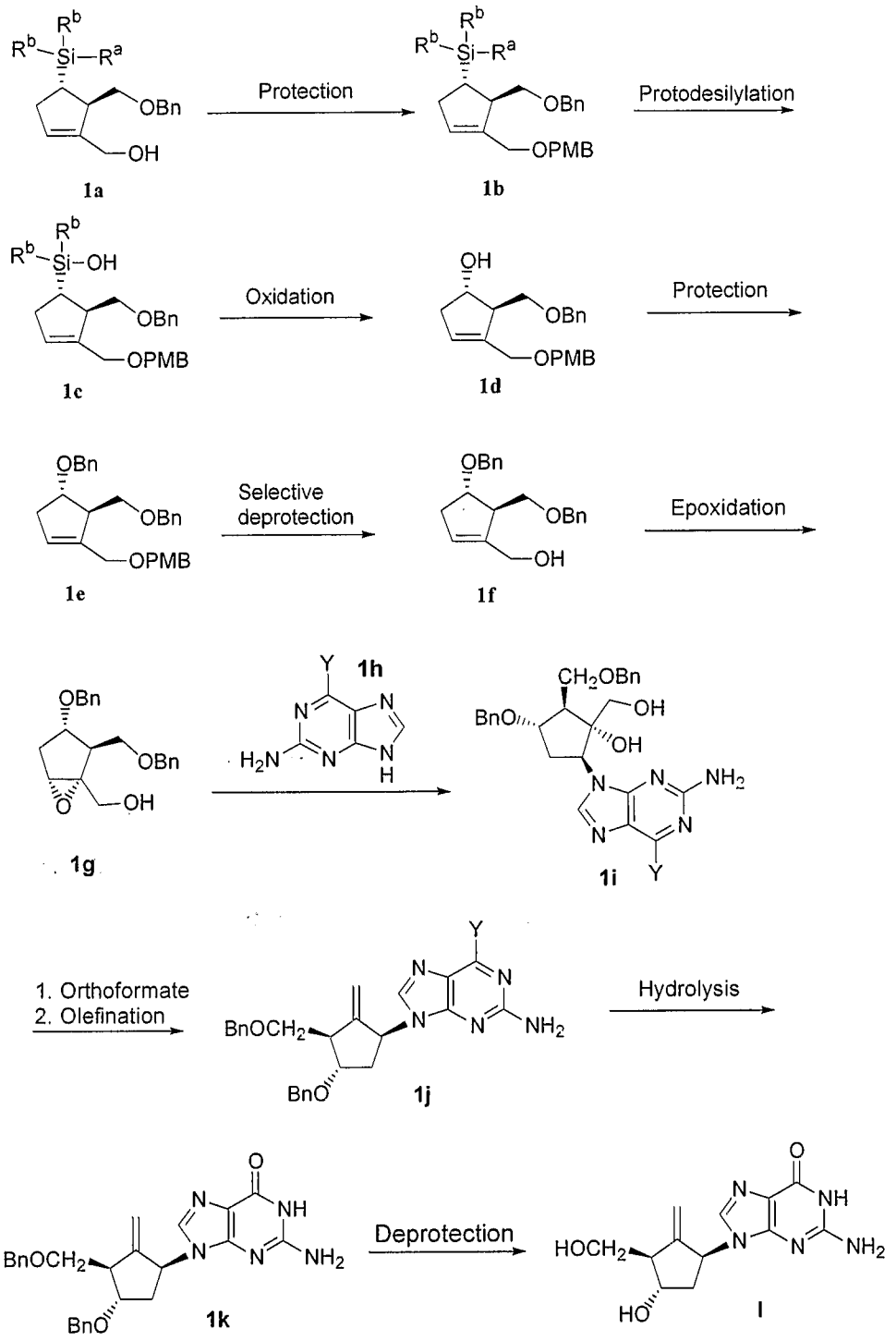
[0046] The epoxide of formula **1g** can be subsequently coupled to an alkali metal salt (e.g., lithium) of a purine compound of formula **1h**, wherein Y is Cl, Br, I or BnO, in a dipolar aprotic solvent such as DMF to afford a compound of formula **1i**. The compound of formula 1h can be prepared according to methods disclosed by Igi *et al.*, in EP 543095 (1993), and by Lolli *et al.*, in J. Labelled Compounds & Radiopharmaceuticals, 41(3), 243-252 (1998). Preferably the coupling of the cyclopentane epoxide of the formula **1g** is conducted with the lithium salt of 2-amino-6-benzyloxypurine. The compound of formula **1i**, wherein Y is benzyloxy, can be purified by crystallization from solvents such as ethyl acetate and hexanes.

[0047] The vicinal diol moiety of the compound of formula **1i** can then be converted to an alkene moiety. In one embodiment, the compound of formula **1i** can

be treated with an orthoformate derivative, e.g, trimethyl orthoformate, in the presence of a catalytic amount of an acid such as TFA or PTSA, or acid catalyst such as PPTS. The resulting mixture of dioxolanes (preferably as a crude mixture) is heated with a mixture of acetic anhydride and optionally acetic acid to provide a methylene compound of formula **1j**. Alternatively, this reaction can be performed in the presence of antioxidant such as BHT.

[0048] A compound of **1k** can be prepared from the compound of formula **1j** *via* hydrolysis. In one embodiment wherein Y is OBn, the 6-*O*-benzyloxy group can be hydrolyzed (as well as any pendant 2-acetamide group formed from the acetylation of the 2-amino group of the purine during the acetic anhydride treatment step) by heating the compound of formula **1j** with aqueous mineral acid, such as 2 N HCl to give the methylene compound of formula **1k**. In another embodiment wherein Y is Cl, Br or I, the 6-halo group can be hydrolyzed by treatment with aqueous base (e.g., aqueous hydroxide solution). Finally, removal of the remaining benzyl ether protecting group in the compound of formula **1k** upon treatment with a Lewis acid such as BCl_3, BBr_3, etc., or a Bronsted acid such as MSA, TFMSA, etc., in an inert solvent such as DCM, provides the compound of formula I.

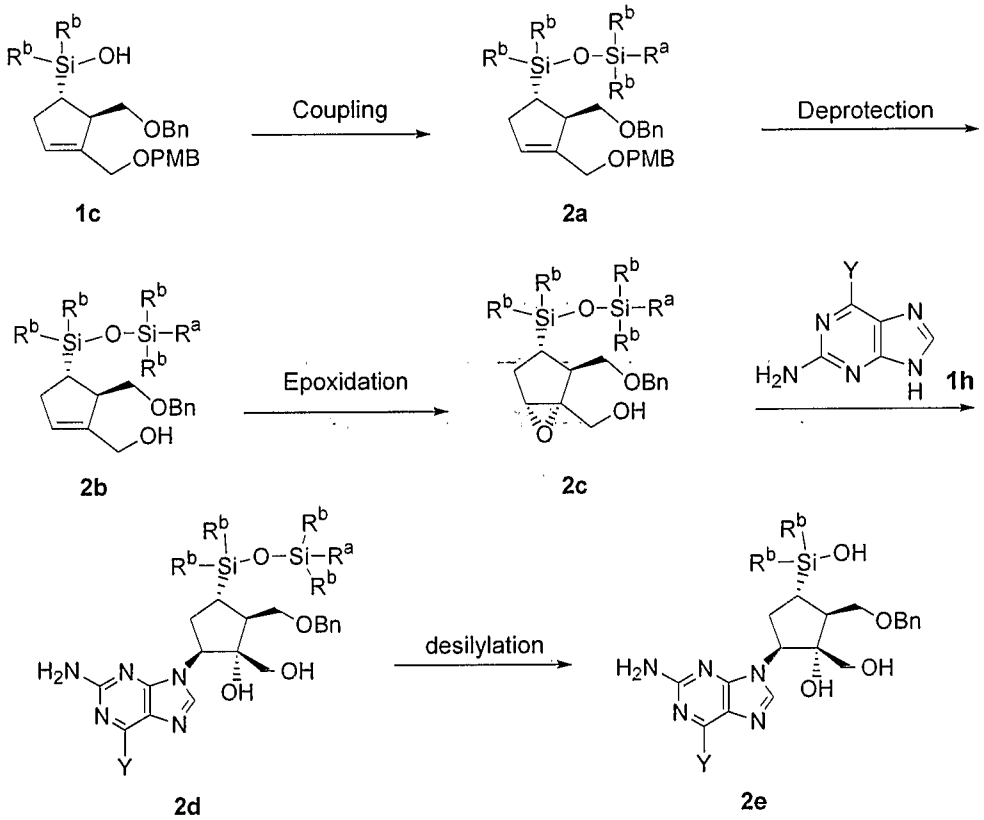
Scheme 1



[0049] Alternative syntheses of the compound of formula I are described in Schemes 2 and 3. In Scheme 2, the compound of formula **1c** can also be converted to a compound of formula **2a** upon treatment with a silylating reagent $R^aSi(R^b)_2$-halide, wherein said silylating reagent is preferably phenyldimethylchlorosilane, in presence of a base, such as imidazole. Deprotection of the PMB group in the compound of

formula **2a** can be achieved using DDQ in an organic solvent such as CH_2Cl_2 in the presence of water to yield an allylic alcohol of formula **2b**, which can be converted to a compound of formula **2c** via epoxidation as described in Scheme 1. Coupling of the compound of formula **2c** with a compound of formula **1h,** wherein Y is defined as above, in the presence of an alkali metal base (e.g., LiOH), and in a dipolar aprotic solvent such as DMF, provides a compound of formula **2d**, which can be subsequently transformed to a compound of formula **2e** through desilylation, which can be achieved with a base such as KOtBu, in a polar aprotic solvent such as DMSO.

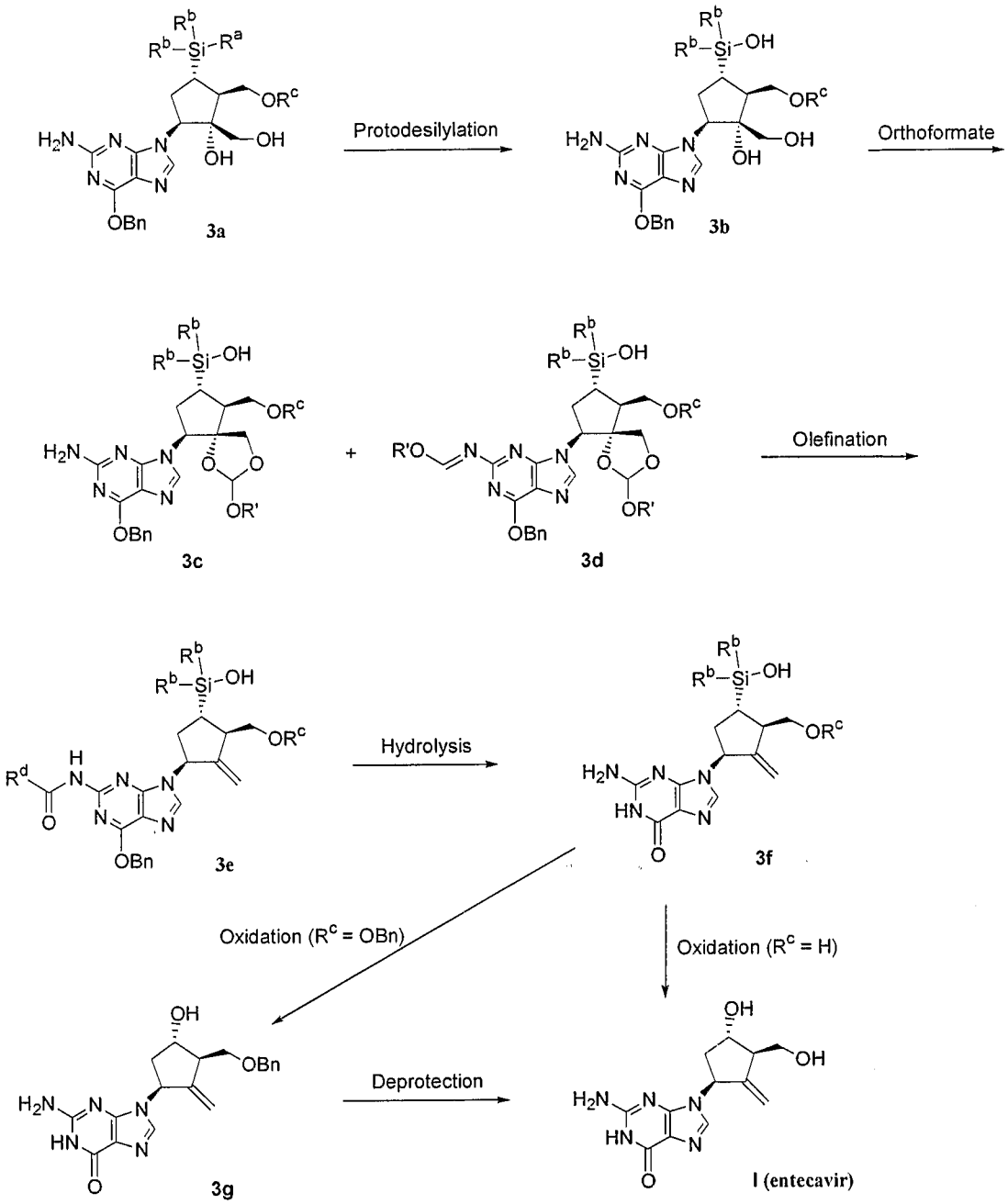
Scheme 2



[0050] As shown in Scheme 3, the compound of formula I can also be prepared from a compound of formula **3a**, which is disclosed as compounds of formula **78A** and **73** in WO 2004/052310. A compound of formula **3b** can be prepared from the compound of formula **3a** via protodesilylation as described in Scheme 1. The compound of formula **3b** can be further converted to a mixture of a compound of formula **3c** and a compound of formula **3d** upon treatment with an orthoformate derivative, e.g, trimethyl orthoformate, in the presence of a catalytic amount of an acid

such as TFA or PTSA, or an acid catalyst such as PPTS. The next olefination step was achieved by treating the resulting mixture of compounds **3c** and **3d** with an acid anhydride having a formula of R^d-C(=O)-O-C(=O)-R^d, wherein R^d is C_1-C_4 alkyl, preferably methyl; and optionally an acid having a formula of R^d-C(=O)OH, wherein R^d is C_1-C_4 alkyl, preferably methyl; and preferably in the presence of an antioxidant such as BHT, to yield a compound of formula **3e**. The definition of R^d is the same as hereinabove throughout the specification, unless otherwise indicated. Hydrolysis of the compound of formula **3e** with an aqueous mineral acid, such as 6M HCl, in an organic solvent, such as MeOH, provides a compound of formula **3f**. Subsequent oxidation of the compound of formula **3f** using the method as described in Scheme 1 affords the compound of formula I (entecavir) when R^c is H; or a compound of formula **3g** when R^c is Bn, which can be converted to the compound of formula I (entecavir) by removing the OBn protecting group using the method as described in Scheme 1.

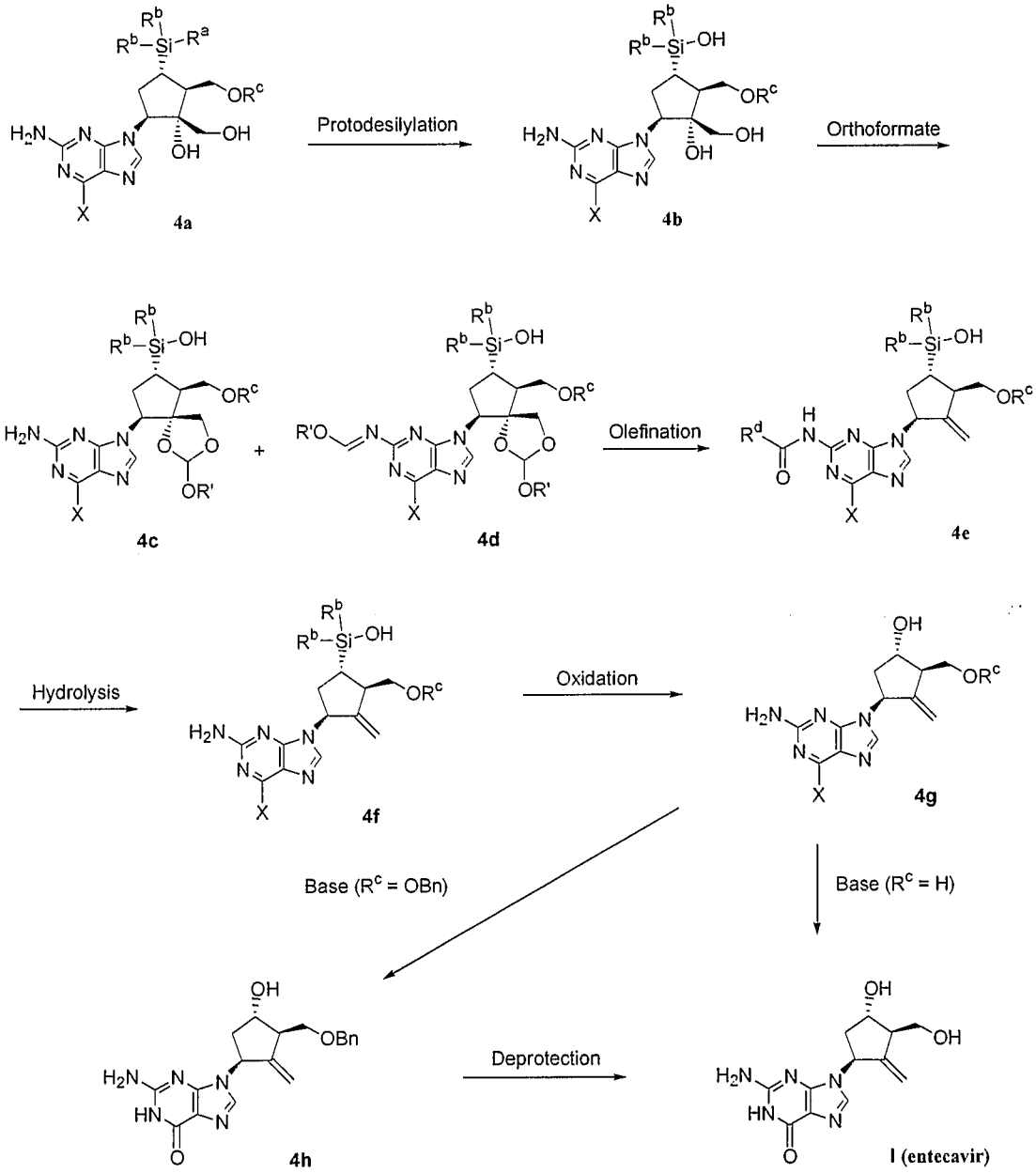
Scheme 3



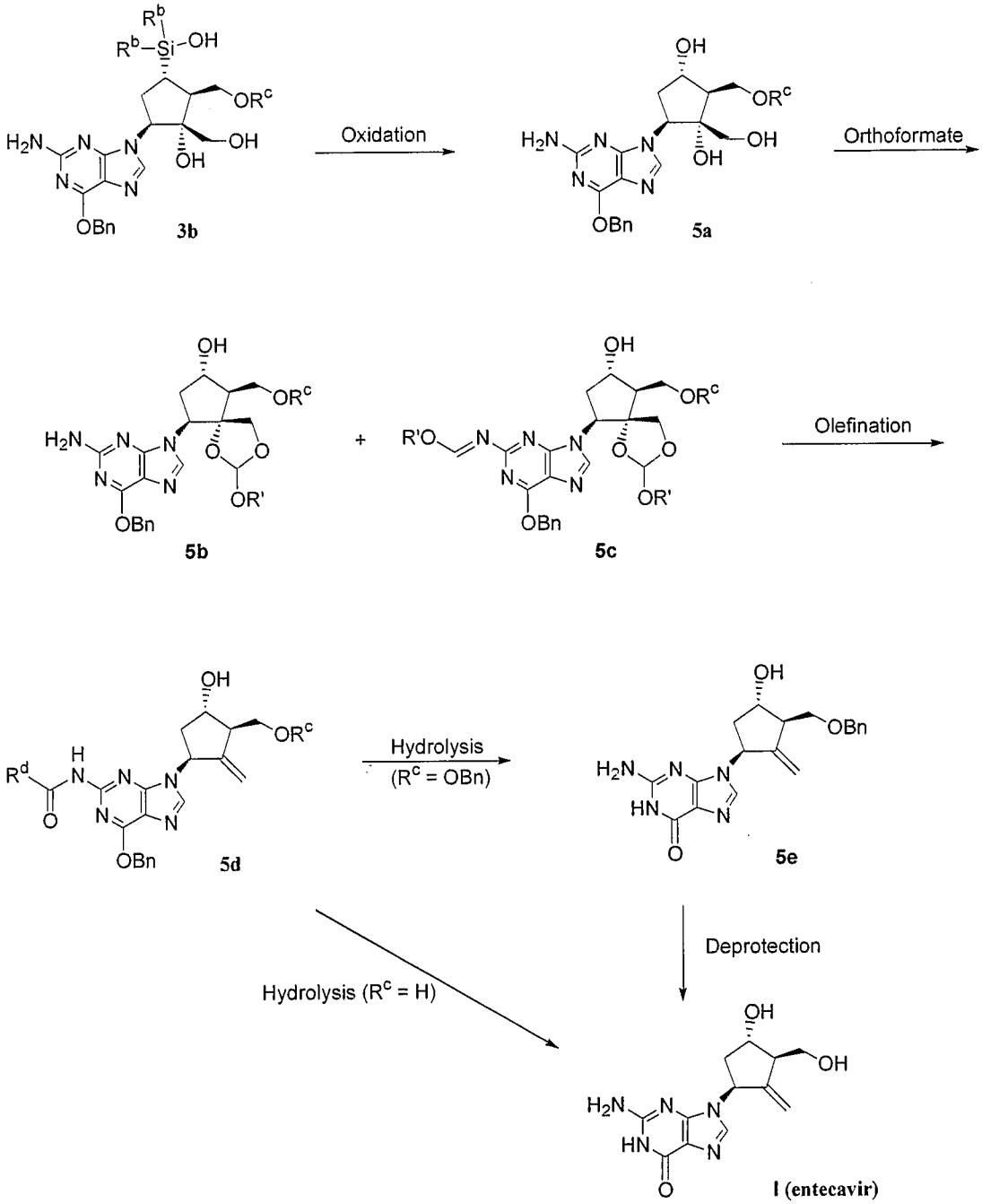
[0051] Similarly, the compound of formula I can be prepared from a compound of formula **4a**, wherein X is Cl, Br, or I (iodo), in accordance with Scheme 4. The compound of formula **4a** is disclosed as compounds of formula **78B** and **73** in WO 2004/052310. The transformation from the compound of formula **4a** to a compound of **4f** is analogous to the method described in Scheme 3. A compound of formula **4g** can be obtained from the compound of formula **4f** via oxidation using the method as described in Scheme 1. Hydrolysis of the compound of formula **4g** upon

treatment with an aqueous base provides the compound of formula I (entecavir) when R^c is H; or a compound of formula **4h** when R^c is Bn, which can be further converted to the compound of formula I by removing the benzyl group as described in Scheme 1.

Scheme 4



Scheme 5

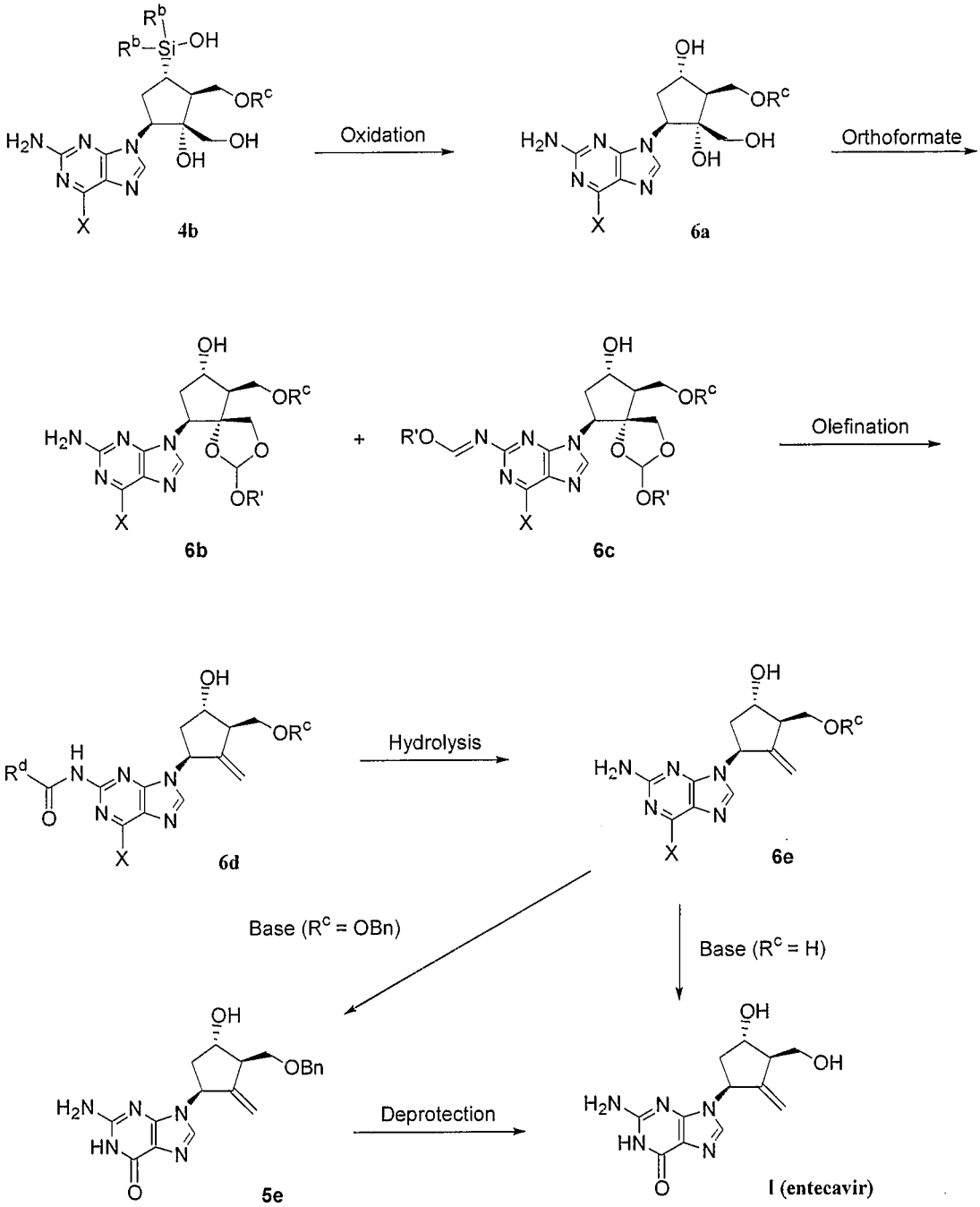


[0052] Scheme 5 describes an alternative synthesis of entecavir from the compound of formula **3b**. A compound of formula **5a** can be obtained from the compound **3b** via the oxidation method as described in Scheme 1. A compound of formula **5d** can be prepared from the compound of formula **5a** via the steps of orthoformate and olefination as described above. Subsequent hydrolysis of the compound of formula **5d** with an aqueous mineral acid, such as 6M HCl, in an organic solvent, such as MeOH, provides the compound of formula I (entecavir) when

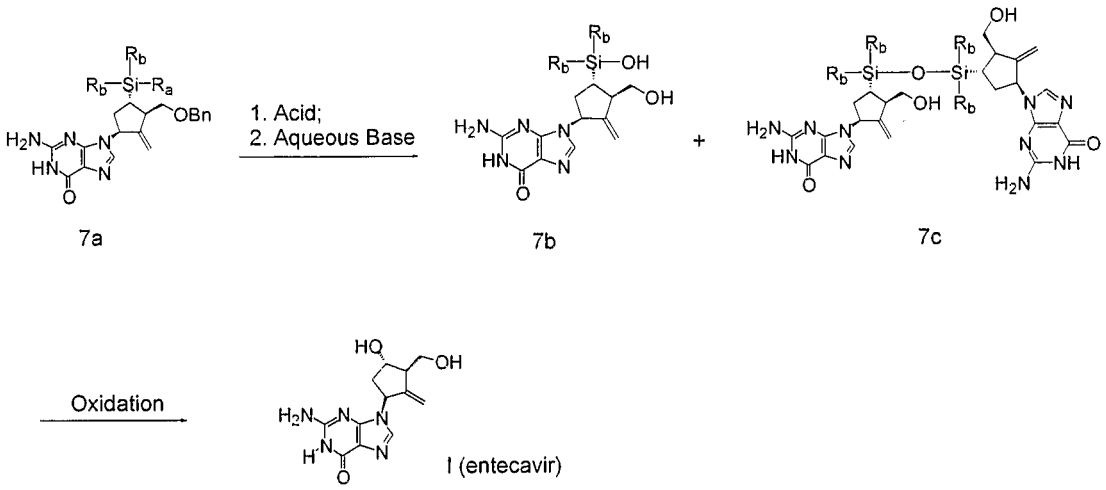
R^c is H; or a compound of formula **5e** when R^c is Bn, which can be converted to the compound of formula I (entecavir) via deprotection as described above.

[0053] Similarly, the compound of formula I can be prepared from a compound of formula **4b**, wherein X is Cl, Br, or I (iodo), in accordance with Scheme 6. The transformation from the compound of formula **4b** to a compound of **6d** is analogous to the method described in Scheme 5. Hydrolysis of the compound of formula **6d** upon treatment with an aqueous mineral acid, such as 6M HCl, in an organic solvent, such as MeOH, affords a compound of formula **6e**. Treating the compound of formula **6e** with an aqueous base provides the compound of formula I (entecavir) when R^c is H; or the compound of formula **5e** when R^c is Bn, which can be further converted to the compound of formula I by removing the benzyl group as described in Scheme 1.

Scheme 6


Oxidation
Orthoformate
Olefination
Hydrolysis
Base (R^C = OBn)
Base (R^C = H)
Deprotection
4b
6a
6b
6c
6d
6e
5e
I (entecavir)

Scheme 7



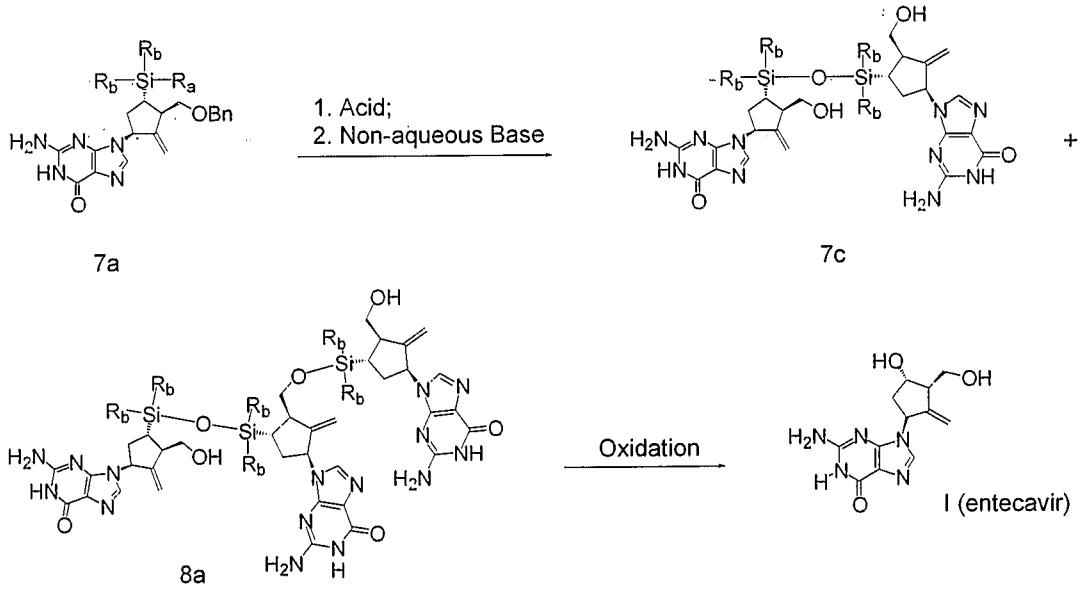
[0054] Scheme 7 further describes the synthesis of the compound of formula I from compound **7a**, which can be prepared according to a procedure reported by Pendri *et al* in WO 2004/052310. Treatment of compound **7a** with at least one acid selected from: (i) halogenated methanesulfonic acids; and (ii) optionally methanesulfonic acid; preferably a mixture of acids such as trifluromethanesulfonic acid / methanesulfonic acid, or monofluromethanesulfonic acid / methanesulfonic acid; followed by treatment with at least one aqueous base (e.g., LiOH, NaOH, KOH, etc.) to provide the compound of formula **7b** as the major product (typically about 85% to about 95% yield). The compound of formula **7c** (dimer of compound **7b**) may also be produced and may account for about 5% to about 15 % of the total yield (for example, 9.5% and 14.5%).

[0055] When a halogenated methanesulfonic acid alone is used, the amount can be less than about 20 mole equivalent, based on 1 mole equivalent of the compound **7a** used. For example, the amount of said halogenated methanesulfonic acid can be less than about 10 mole equivalent (e.g., 6 equivalent of monofluromethanesulfonic acid), based on 1 mole equivalent of the compound **7a** used. When a mixture of acids such as methanesulfonic acid / trifluromethanesulfonic acid is used, the amount of said methanesulfonic acid can be less than about 10 mole equivalent and said trifluromethanesulfonic acid can be less than about 10 mole equivalent, based on 1 mole equivalent of the compound **7a** used. For example, the amount of said methanesulfonic acid can be less than about 7 mole equivalent (e.g., about 1 to about 7 equivalent, or about 1.5 to about 6.7 equivalent, or about 2 equivalent) and said

trifluromethanesulfonic acid can be less than about 5 mole equivalent (e.g., about 1 to about 5 equivalent, or about 2.5 to about 3.5 equivalent), based on 1 mole equivalent of the compound **7a** used.

[0056] Oxidation of compound **7b** or a mixture of compound **7b** and **7c** affords the compound of formula I. The oxidation step may be achieved using at least one oxidizing agent such as peroxohydrates. Peroxohydrates are crystalline adducts containing molecular hydrogen peroxide, for example, sodium carbonate peroxohydrate (known commercially as sodium percarbonate, e.g., $Na_2CO_3 \cdot 1.5\, H_2O_2$), urea peroxohydrate ($CO(NH_2)_2 \cdot H_2O_2$), the peroxohydrate of melamine, ($C_3H_6N_6 \cdot H_2O_2$), sodium pyrophosphate peroxohydrate ($Na_4P_2O_7 \cdot 2\, H_2O_2$), sodium sulfate peroxohydrate hydrate ($2\, Na_2SO_4 \cdot H_2O_2 \cdot 2\, H_2O$), potassium carbonate peroxohydrates, rubidium carbonate peroxohydrates, and cesium carbonate peroxohydrates (the last three have the general formula $M_2CO_3 \cdot 3H_2O_2$). The preferred peroxohydrate for this oxidization step is sodium carbonate peroxohydrate.

Scheme 8



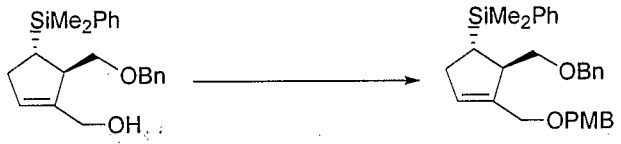
[0057] Alternatively, compound **7a** can be treated with at least one acid selected from: (i) halogenated methanesulfonic acids; and (ii) optionally methanesulfonic acid as discussed above, followed by treatment with at least one non-aqueous base (e.g., $NR^eR^fR^g$, wherein R^e, R^f and R^g are independently hydrogen, alkyl, cycloalkyl, aryl, or said R^g and R^f together with the N to which they are bonded optionally form a

heterocycle), to give the compound of formula **7c** as the major product (typically about 80% to about 95% yield). Illustrative bases include tertiary amine bases such as triethylamine, *N,N*-dimethylethylamine, diisopropylethylamine (Hunig's base) or tetramethylenediamine (TMEDA), or a nitrogen containing heterocycle, such as pyridine. The compound of formula **8a** may also be formed with up to 20% yield (for example, 5%, 10% or 15%). Further, oxidation of compound **7c** or a mixture of compound **7c** and **8a** affords the compound of formula I. The oxidation step may be achieved using at least one oxidizing agent such as peroxohydrates (e.g., sodium carbonate peroxohydrate) as discussed above.

[0058] The following examples further illustrate the present invention, but should not be construed in any way to limit its scope.

Example 1

Preparation of compound 1b':



1a' **1b'**

[0059] Compound **1a'** (6.02 g, 17.1 mmol, 1.00 equiv) was dissolved in toluene (6.70 mL). PMB-Cl (para-methoxybenzyl chloride) (7.00 mL, 51.2 mmol, 3.00 equiv) was added followed by TBAHS (tetrabutylammonium hydrogen sulfate) (0.577 g, 1.71 mmol, 0.0100 equiv) and 50% NaOH (6.70 mL). The reaction was stirred for four hours at room temperature. The reaction mixture was combined with water (23 mL) and toluene (50 mL) and the phases were split. The organic layer was washed again with water (23 mL) and the phases were split. The combined aqueous layers were extracted with toluene (50 mL) and the combined organic layers were concentrated by rotary evaporation. Column chromatography of the crude material was done using a 120 gram silica column and a mobile phase gradient of 2-15% ethyl acetate in hexanes. The desired fractions were combined and concentrated to give the compound of formula **1b'**(6.17 g) as yellow oil in 76% yield. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2 H) 7.35-7.22 (m, 9 H), 6.92-6.87 (m, 3 H), 5.71 (s, 1 H),

4.49-4.35 (m, 4 H), 4.06-4.04 (m, 2 H), 3.84 (s, 3 H), 3.41-3.37 (m, 1 H), 3.30-3.28 (m, 1 H), 2.92 (s, 1 H), 2.57-2.56 (m, 1 H), 2.33-2.31 (m, 1 H), 1.64-1.59 (m, 1 H), 0.27 (s, 6 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.5, 142.8, 139.0, 138.9, 134.3, 131.0, 129.8, 129.7, 129.3, 129.0, 128.7, 128.7, 128.2, 128.1, 114.2, 114.1, 77.6, 73.4, 72.1, 68.1, 55.7, 48.4, 33.8, 25.6, -4.2, -4.2; MS (infusion) = 473 ($M+H^+$); HRMS m/e calc'd for $C_{30}H_{37}O_3Si$ ($M+H^+$): 473.2512, found 473.2501.

Example 2

Preparation of compound 1c':

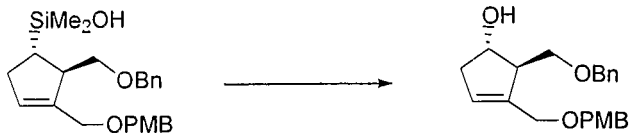


1b' **1c'**

[0060] Compound **1b'** (6.17 g, 13.1 mmol, 1.00 equiv) was dissolved in DMSO (62 mL) and potassium t-butoxide (5.00 g, 44.0 mmol, 3.37 equiv) was added forming thick slurry. The reaction was stirred at room temperature overnight after which the starting material was not detected by HPLC. The reaction mixture was transferred to a separatory funnel and ethyl acetate (124 mL) and water (124 mL) were charged. The phases were split and the aqueous layer was extracted twice with ethyl acetate (2 x 124 mL). The combined organic layer was concentrated to a residue and purified by column chromatography using a 120 gram silica column and a mobile phase gradient of 10-50% ethyl acetate in hexanes. The desired fractions were combined and concentrated to give the compound of formula **1c'** (3.50 g) as yellow oil in 65% yield. ^1H NMR (360 MHz, $CDCl_3$) δ 7.25-7.15 (m, 5 H) 7.10 (d, J = 8.6 Hz, 2 H), 6.75 (d, J = 8.6 Hz, 2 H), 5.63 (s, 1 H), 4.40 (q, J = 11.9 Hz, 2 H), 4.26 (q, J= 11.3 Hz, 2 H), 3.85 (s, 2 H), 3.72-3.70 (m, 1 H), 3.68 (s, 3 H), 3.42 (bs, 1 H), 3.15-3.10 (m, 1 H), 2.93 (s, 1 H), 2.36-2.33 (m, 1 H), 2.09-2.05 (m, 1 H), 1.21 (q, J= 9.3 Hz, 1 H), 0.00 (s, 3 H), -0.05 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.4, 142.0, 138.7, 131.9, 131.5, 130.6, 129.7, 129.2, 129.1, 114.9, 76.1, 74.8, 73.0, 68.5, 56.5, 49.5, 34.3, 32.2, 0.0, -1.6; MS (infusion) = 413 ($M+H^+$); HRMS m/e calc'd for $C_{24}H_{33}O_4Si$ ($M+H^+$): 413.2148, found 413.2163.

Example 3

Preparation of compound 1d:

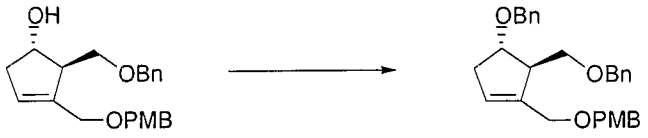


1c' 1d

[0061] The compound of formula **1c'** (1.00 g, 2.42 mmol, 1.00 equiv) was dissolved in methanol (25 mL) and was heated to 65 °C. $KHCO_3$ (0.726 g, 7.26 mmol, 3.00 equiv) was dissolved in water (3.4 mL) and added to the reaction. KF (0.281 g, 4.84 mmol, 2.00 equiv) was dissolved in water (0.8 mL) and added to the reaction. A 30% weight solution of H_2O_2 (0.840 mL, 7.26 mmol, 3.00 equiv) was added portion-wise over 30 minutes. The reaction was stirred at 68 °C for 4.5 hours at which point the starting material was not detected by HPLC. The reaction was cooled to 10 °C. $NaHSO_3$ (1.10 g) was dissolved in water (2 mL) and added to the reaction mixture which was warmed to room temperature and stirred until peroxide was no longer evident by peroxide strip testing. The mixture was passed through a Celite pad which was washed with ethyl acetate (2 x 25 mL). The organic layer was washed with water (20 mL) and 10% brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated. The compound of formula **1d** as crude yellow oil (0.860 grams, quantitative yield) was carried forward to the next reaction without further purification. ^1H NMR (360 MHz, $CDCl_3$) δ 7.29-7.20 (m, 5 H) 7.15 (d, J = 8.7 Hz, 2 H), 6.79 (d, J = 8.9 Hz, 2 H), 5.59 (s, 1 H), 4.41 (q, J = 12.1 Hz, 2 H), 4.32 (q, J = 11.4 Hz, 2 H), 3.89 (s, 2 H), 3.73 (s, 3 H), 3.63 (dd, J = 9.1, 4.6 Hz, 1 H), 3.30 (t, J = 8.8 Hz, 1 H), 2.79-2.77 (m, 1 H), 2.69 (dd, J = 22.8, 10.8 Hz, 1 H), 2.22 (dd, J = 19.2, 4.3 Hz, 1 H), 2.05 (bs, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.6, 139.5, 138.9, 130.7, 129.8, 128.8, 128.1, 128.0, 127.5, 114.2, 77.6, 73.7, 72.2, 71.5, 67.9, 55.7, 55.2, 40.2; MS (infusion) = 355 ($M+H^+$); HRMS m/e calc'd for $C_{22}H_{27}O_4(M+H^+)$: 355.1909, found 355.1917.

Example 4

Preparation of compound 1e:

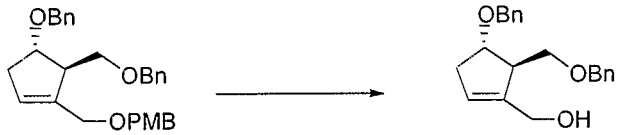


1d **1e**

[0062] The compound of formula **1d** (0.880 g, 2.50 mmol, 1.00 equiv) was dissolved in toluene (4.4 mL) and cooled to 6 °C. A solution of KHMDS (potassium bis(trimethylsilyl)amide) in toluene (0.75 M, 6.70 mL, 5.00 mmol, 2.00 equiv) was added drop wise followed by benzyl bromide (0.330 mL, 2.75 mmol, 1.10 equiv). The reaction was warmed to room temperature. The reaction was then cooled to 10°C and KHMDS (2.00 mL) was charged three times (every two hours) as the reaction appeared to stall. The reaction was stirred overnight, cooled to 10 °C, and additional toluene (4.4 mL), KHMDS (2.00 mL), and BnBr (0.0300 mL) were charged. The reaction was stirred an additional 42 hours after which time 3.6 RAP compound **1d** remained. The reaction was quenched with 1 M HCl until the apparent pH was 7. The reaction mixture was transferred to a separatory funnel with toluene (20 mL) and water (10 mL). The phases were split and the aqueous was back-extracted with toluene (20 mL). The combined organic was concentrated to a residue. Column chromatography of the crude material was done using a 120 gram silica column and a mobile phase gradient of 1-75% ethyl acetate in hexanes. The desired fractions were combined and concentrated to give the compound of formula **1e** (0.600 g) as a yellow oil in 55% yield for two steps. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24-7.15 (m, 10 H) 7.13 (d, J = 8.7 Hz, 2 H), 6.75 (d, J = 8.6 Hz, 2 H), 5.60 (s, 1 H), 4.43 (s, 2 H), 4.37 (q, J = 6.7 Hz, 2 H), 4.33-4.24 (m, 2 H), 4.12-4.09 (m, 1 H), 3.93 (s, 2 H), 3.69 (s, 3 H), 3.48 (dd, J = 9.5, 4.5 Hz, 1 H), 3.30 (dd, J = 9.5, 6.7 Hz, 1 H), 2.93 (s, 1 H), 2.60 (dd, J = 17.2, 10.6 Hz, 1 H), 2.30 (d, J = 17.0, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.5, 140.0, 139.2, 138.9, 130.9, 129.8, 128.7, 128.7, 128.1, 128.0, 127.9, 127.8, 127.5, 114.1, 82.4, 73.5, 72.0, 71.1, 70.2, 68.0, 55.7, 53.2, 38.5; MS (infusion) = 445 (M+ H^+); HRMS m/e calc'd for $C_{29}H_{33}O_4$ (M+ H^+): 445.2379, found 445.2389.

Example 5

Preparation of compound 1f:

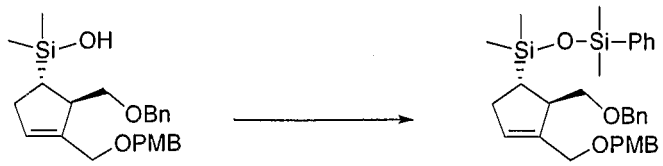


1e **1f**

[0063] The compound of formula **1e** (0.500 g, 1.13 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (11.7 mL) and water (0.93 mL) was added. The reaction mixture was cooled to 2 °C and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (0.383 g, 1.69 mmol, 1.50 equiv) was added. The solution turned black. The mixture was stirred at 0-2 °C for two hours at which time 1.3 RAP of the starting material remained by HPLC. 5% aqueous $NaHCO_3$ (10 mL) was added followed by water (10 mL). The phases were split. The aqueous layer was extracted three times with CH_2Cl_2 (3 x 25 mL). The combined organic phase was washed with water (20 mL) and concentrated to a residue. Column chromatography of the crude material was done using a 120 gram silica column and a mobile phase gradient of 10-100% ethyl acetate in hexanes. The desired fractions were combined and concentrated to give the compound of formula **1f** (0.250 g) as a yellow oil in 69% yield. ^1H NMR (360 MHz, $CDCl_3$) δ 7.37-7.25 (m, 10 H) 5.62 (s, 1 H), 4.53 (s, 2 H), 4.22 (q, J = 11.8 Hz, 2 H), 4.14 (s, 2 H), 4.02-3.97 (m, 1 H), 3.61 (dd, J = 9.0, 5.0 Hz, 1 H), 3.46 (dd, J = 16.8, 8.4 Hz, 1 H), 3.06 (s, 1 H), 2.64 (dd, J = 16.8, 7.0 Hz, 1 H), 2.45 (bs, 1 H); 2.37 (dd, J = 17.1, 1.9 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.6, 138.8, 137.9, 128.9, 128.8, 128.3, 128.3, 128.1, 128.0, 126.1, 82.3, 73.9, 71.6, 71.4, 61.5, 52.9, 38.0; MS (infusion) = 325 (M+ H^+); HRMS m/e calc'd for $C_{21}H_{25}O_3$ (M+H^+): 325.1804, found 325.1808.

Example 6

Preparation of compound 2a':



1c' **2a'**

[0064] The compound of formula **1c'** (2.00 g, 4.80 mmol, 1.00 equiv) was dissolved in DMF (74 mL) and imidazole (1.97 g, 29.0 mmol, 6.00 equiv) was added. The mixture was cooled to 0-5 °C followed by drop wise addition of $Ph(CH_3)_2SiCl$ (3.40 mL, 20.2 mmol, 4.20 equiv) while maintaining temperature 0-5 °C. The reaction mixture was stirred at 25 °C for 42 hours. The reaction mixture was diluted with water (50 mL) and diethyl ether (50 mL). Phases were separated and the aqueous phase was back-extracted with diethyl ether (50 mL). The combined organic phase was concentrated on a rotavap to a light yellow oil and purified by column chromatography (0-75% EtOAc in hexanes) to give 1.95 grams (74% yield) of compound **2a'** as a light yellow oil (AP=93.7%). ^1H NMR (360 MHz, CD_2Cl_2) δ 7.19 (d, 2 H), 6.98-6.91 (m, 8 H), 6.86 (d, 2 H), 6.52 (d, 2 H), 5.32 (s, 1 H), 4.04 (s, 2 H), 4.02 (q, 2 H), 3.67 (q, 2 H), 3.42 (s, 3 H), 3.08-3.03 (m, 2 H), 2.99 (s, 1 H), 2.57 (s, 1 H), 2.14-2.12 (m, 1 H), 1.90-1.87 (m, 1 H); 0.99-0.96 (m, 2 H), -0.04 (s, 6 H), -0.29 (s, 6 H); ^{13}C NMR (90 MHz, CD_2Cl_2) δ 165.5, 148.5, 145.7, 144.6, 138.8, 135.3, 135.2, 134.8, 134.2, 133.6, 133.2, 119.5, 79.2, 78.8, 77.6, 73.4, 60.5, 38.2, 37.5, 33.5, 28.5, 19.3, 5.9, 3.9.

Example 7

Preparation of compound 2b':



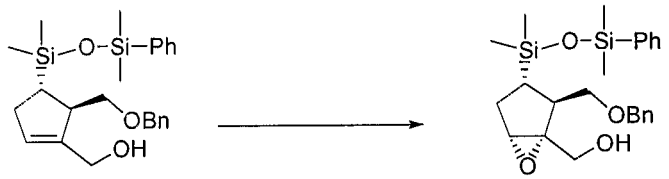
2a' **2b'**

[0065] The compound of formula **2a'** (4.8 g) was dissolved in CH_2Cl_2 (110 mL) and water (8.9 mL) and the solution was cooled to 0-5 °C. DDQ (30.3 g, 1.50 equiv) was added in one portion. The reaction mixture turned into a blue solution. The reaction was stirred at 0-5 °C until deemed to be complete by HPLC, typically 2 hours. The reaction mixture, a yellow suspension, was diluted with 5% aqueous $NaHCO_3$ (80 mL) and water (90 mL). The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phase was washed with water (50 mL) and evaporated to a residue which was applied to a silica gel

column (150 g) that was eluted with 10% EtOAc in hexanes to give the compound of formula **2b'** as a colorless oil (2.6 g, 69% yield, 96.8% AP).

Example 8

Preparation of compound 2c':



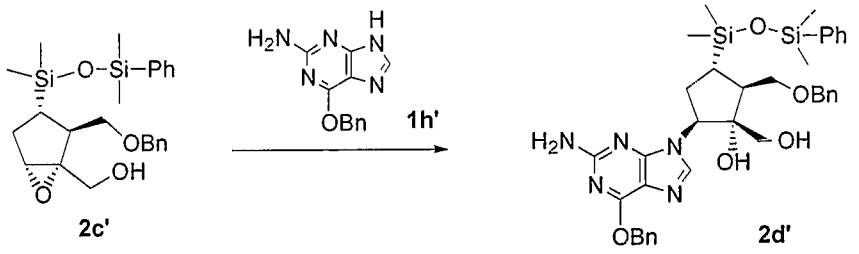
2b' **2c'**

[0066] To a dry vessel, 4A° Molecular Sieves (13.0 g) and toluene (13 mL) were charged, the slurry was cooled to -35 to -40 °C under N_2. A solution of (-)-DIPT (0.40 g, 0.28 equiv) in toluene (2 mL) was added at -35 to -40 °C. The slurry was stirred at -35 to -45 °C for 30 minutes. Titanium (IV) isoproxide (0.43 mL, 0.24 equiv) was added to the tartrate solution and stirred at -35 to -45 °C for 30 min. Then a solution of compound **2b'** (2.6 g, 1.0 equiv) in 13 mL of toluene was added over 5 minutes while maintaining the temperature at -35 to -40 °C. The resulting brown slurry was stirred at -35 to -40 °C for 1-1.5 h. tert-Butyl hydroperoxide (5.5M in decane, 2.2 mL, 2.0 equiv) was added to reaction mixture over 10 min. at -35 to -45 °C. The reaction was stirred at -35 to –45 °C until the epoxidation was deemed complete by HPLC, typically 3-5 h. Upon completion of the reaction, 30% NaOH saturated with sodium chloride (0.9 mL) was added to quench the titanium-tartrate catalyst and to hydrolyze (-)-DIPT. A solution of sodium bisulfite (1.4 g) in water (3.2 mL) was added over 10 min while maintaining the temperature between 10-30 °C. This was stirred for 1-3 h until a peroxide test strip tested negative for peroxides. Celite (3.2 g) was charged, and the reaction mixture was filtered. The filter cake was washed with toluene (2 x 20 mL). The filtrate was washed with 5% $NaHCO_3$ (20 mL), and 10% NaCl (20 mL). The resulting solution is evaporated to give the compound of formula **2c'** as a yellow oil (2.1g, 78% yield, 89% AP). ^{1}H NMR (360 MHz, CD_2Cl_2) δ 7.25-7.21 (m, 2 H), 7.04-6.98 (m, 8 H), 5.32 (s, 1 H), 4.13 (s, 2 H), 3.83 (q, 2 H), 3.18-3.04 (m, 2 H), 2.59 (s, 1 H), 2.20-2.16 (m, 1 H), 1.95-1.91 (m, 1 H); 0.95-0.92 (m, 2 H), -0.01 (s, 6 H),

-0.25 (s, 6 H); ^{13}C NMR (90 MHz, CD_2Cl_2) δ 151.8, 145.7, 144.4, 138.8, 135.2, 134.2, 133.7, 133.5, 132.2, 79.8, 78.9, 66.2, 53.8, 38.1, 37.5, 33.7, 28.5, 19.3, 5.8, 3.8.

Example 9

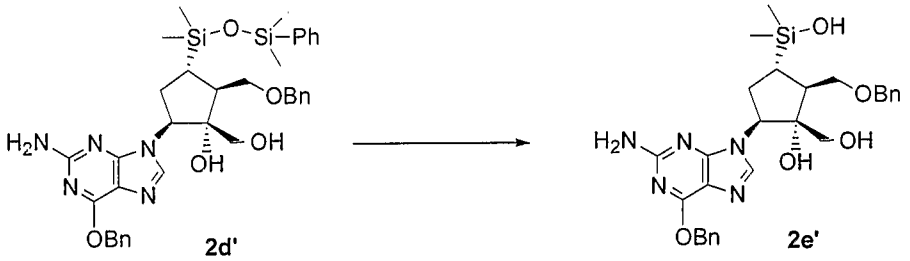
Preparation of compound 2d':



[0067] To a mixture of compound **2c'** (2.1 g) and compound **1h'** (1.30 g, 1.15 equiv) in DMF (10 mL), LiOH (0.10 g, 0.87 equiv) was charged. The resulting solution was heated at 90 °C until deemed to be complete by HPLC, typically 4 h. The reaction was cooled to room temperature and was diluted with EtOAc (30 mL) and water (30 mL). The pH was adjusted from 12.0 to 5.1 by addition of 1M HCl (2.4 mL). The reaction mixture was then extracted with EtOAc (2 x 35 mL). The combined organic phase was washed with brine (2 x 30 mL) and evaporated to a residue. The crude oil was purified using column chromatography and was eluted with 20 to 50% EtOAc in hexanes to give the compound of formula **2d'** as a white solid (0.74 g, 23.8 % yield, 96.9% AP). ^1H NMR (360 MHz, $CDCl_3$) δ 7.55-7.50 (m, 4 H), 7.36-7.22 (m, 11 H), 5.57 (q, 2 H), 4.90 (s, 2 H), 4.41 (s 2 H), 4.40-4.36 (m, 1 H), 3.55 (dd, 2 H), 3.38 (dd, 2 H), 2.70 (q, 1 H), 2.38-2.36 (m, 1 H), 2.14-2.10 (m, 1 H), 1.52-1.48 (m, 1 H), 0.36 (s, 3 H), 0.35 (s, 1 H), 0.12 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.4, 158.1, 154.0, 139.5, 137.3, 136.2, 132.9, 129.5, 128.5, 128.3, 127.9, 127.8, 116.0, 82.3, 73.5, 69.3, 68.3, 65.1, 62.7, 48.4, 27.1, 23.7, 0.7, 0.6, -1.2, -1.2; HRMS m/e calc'd for $C_{36}H_{45}N_5O_5Si_2$ ($M+H^+$): 684.3038, found 684.3031.

Example 10

Preparation of compound 2e':



[0068] Condition (1): the compound of formula **2d'** (20 mg, 0.029 mmol, 1.0 equiv) was dissolved in THF (0.200 mL) and was cooled to 0 °C. Tetrabutylammonium fluoride (TBAF) (0.030 mL, 0.029 mmol, 1.0 M in THF, 1.0 equiv) was added and the reaction was warmed to room temperature. The reaction appeared to stall after two hours, the reaction was then cooled to 0 °C and additional TBAF (0.030 mL, 0.029 mmol, 1.0 M in THF, 1.0 equiv) was added. This was repeated three times until a 95% conversion was achieved. The material was transferred to a pipet column and eluted using a gradient of 25% ethyl acetate in hexanes to 100% ethyl acetate, and 10-30% methanol in ethyl acetate. The product of formula **2e'** was contaminated with its dimer.

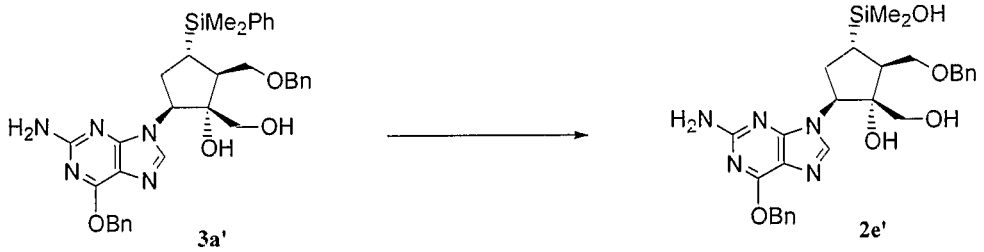
[0069] Condition (2): the reaction was repeated using CSA in CH_2Cl_2 and CH_3OH, and the product of formula **2e'** contained 3% of its dimer.

[0070] Condition (3): the reaction was repeated using basic conditions with 10 N NaOH in THF, and the product **2e'** contained only 0.65% dimer, but the reaction stalled at 91% conversion. After purification, the product was isolated in 71 AP.

[0071] Condition (4): the reaction was repeated using potassium t-butoxide (22 mg, 0.18 mmol, 8.0 equiv) and DMSO (0.15 mL) and after one hour no starting material was evident. Water (0.4 mL) was added along with ~ 1 mg seed and the reaction mixture was cooled to 0 °C and stirred 30 minutes. The slurry was filtered and washed with water (2 mL) and dried at 40 °C to give the compound of formula **2e'** as an orange solid in 58% yield.

Example 11

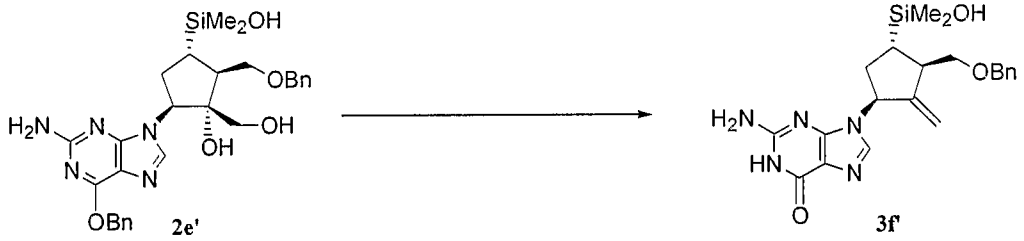
Alternative preparation of compound 2e':



[0072] The compound of formula **3a'** (disclosed in PCT patent application PCT/US03/39554 and US patent application Ser. No. 10/734012, as the compound of formula **78A**) (10.0 g, 16.4 mmol, 1.00 equiv) was dissolved in DMSO (100 mL) to give a light brown solution which was cooled to 13 °C using an ice bath. Potassium tert-butoxide (14.4 g, 131 mmol, 8.00 equiv) was added to give thick light brown slurry which was warmed to room temperature. After two hours 0.1 RAP of the starting material remained by HPLC. The reaction mixture was added portion wise to water (600 mL) at 13-15 °C. The pH was adjusted to 8.2 with 6 M HCl and the slurry was filtered and washed with water (2 x 100 mL). The material was dried at 40 °C for 60 hours. Several small scale purifications were attempted. The best results were obtained by slurrying the light brown solid (3.90 g) in ethyl acetate (20 mL), filtering and washing the cake with ethyl acetate (2 x 20 mL). After combining the different batches, the compound of formula **2e'** (6.48 g total) was isolated as an off-white solid with impurity profiles ranging from 91.6-96.0 AP (72% yield). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.50 (s, 1 H), 7.32 (d, J = 8.2 Hz, 2 H), 7.21-7.07 (m, 8 H), 5.39 (q, 2 H), 4.93 (s, 1 H), 4.39 (m, 1 H), 4.28 (q, 2 H), 3.41 (dd, J = 9.3, 5.7 Hz, 1 H), 3.33-3.31 (m, 1 H), 3.18 (q, 2 H), 2.43-2.40 (m, 1 H), 2.33-2.28 (m, 1 H); 2.17-2.11 (m, 1 H) 1.37-1.31 (m, 1 H), 0.00 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 162.9, 159.0, 139.8, 138.4, 137.1, 129.8, 129.7, 129.7, 129.5, 129.3, 129.3, 116.9, 84.1, 74.9, 71.5, 69.9, 65.5, 63.1, 49.9, 28.9, 27.0, -0.0, -1.2; HRMS m/e calc'd for $C_{28}H_{36}N_5O_5Si$ ($M+H^+$): 550.2486, found 550.2477; mp = 163.2.

Example 12

Preparation of compound 3f':



[0073] The compound of formula **2e'** (1.00 g, 1.80 mmol, 1.00 equiv) was slurried in toluene (6 mL). TFA (trifluoroacetic acid) (0.110 mL, 1.40 mmol, 0.750 equiv) was added followed by TIOF (triisopropylorthoformate) (1.22 mL, 5.40 mmol, 3.00 equiv). The resulting brown solution was stirred at room temperature for one hour at which point 0.54 AP of compound **2e'** was remaining by HPLC. BHT (2,6-Di-tert-butyl-4-methylphenol) (1.00 g) was added followed by acetic anhydride (2.00 mL) and acetic acid (0.210 mL, 3.60 mmol, 2.00 equiv). The reaction mixture was warmed to 116 °C and the distillate (4 mL) was collected. Toluene (2 mL) was charged and the reaction was continued for 14 hours and cooled to room temperature. Methanol (6.0 mL) was charged to a separate round bottom flask and was cooled to 14 °C. 6 M HCl (2.7 mL) was added to the methanol. The reaction mixture was added drop wise followed by a methanol rinse (2.0 mL) of the reaction flask. The reaction mixture was warmed to 25 °C and then heated to 68 °C. After five hours no change was detected by HPLC. The reaction was cooled to 25 °C and transferred to a separatory funnel using methanol (2 mL). The reaction mixture was washed a total of six times with heptane (4 x 6 mL, 2 x 10 mL) which lowered the BHT to 0.33 AP. After two extractions of the mixture with ethyl acetate (2 x 20 mL) the combined organic phase was dried over Na_2SO_4 and concentrated. Column chromatography of the crude material was done on a 120 gram silica column and a mobile phase gradient of 40-100% ethyl acetate in hexanes followed by 10% methanol in ethyl acetate. The desired fractions were combined and concentrated to give the compound of formula **3f'** (0.160 g, 20% yield) but an impurity identified as the dimer of compound **3f'** by LC-MS was present. The material was re-slurried in 25:75 hexane:ethyl acetate and filtered to give a white solid with only trace dimer present by HPLC. ^1H NMR (360 MHz, CD_3OD) δ 7.80 (s, 1 H), 7.34-7.27 (m, 5 H), 5.31-5.27 (m, 1 H), 5.30 (s, 1 H),

5.02 (s, 1 H), 4.57 (s, 2 H), 3.78 (dd, J = 9.3, 4.8 Hz, 2 H), 3.71 (dd, J = 9.3, 4.8 Hz, 1 H), 2.84 (s, 1 H), 2.17-2.13 (m, 2 H); 1.39-1.37 (m, 1 H), -0.00 (s, 6 H); ^{13}C NMR (90 MHz, CD_3OD) δ 159.4, 155.2, 153.9, 153.1, 139.6, 138.6, 129.5, 129.0, 128.8, 117.4, 112.1, 74.3, 73.6, 59.7, 45.8, 34.9, 28.3, -1.31; MS (LC-MS) = 426 (M+ H^+); HRMS m/e calc'd for $C_{21}H_{28}N_5O_3Si$ (M+ H^+): 426.1961, found 426.1963; mp = 193.3 °C.

Example 13

Preparation of compound 5a':

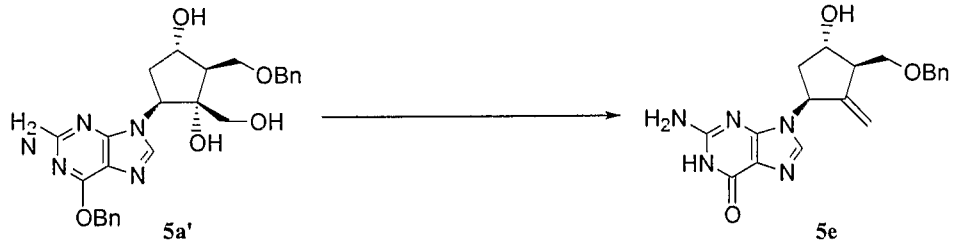


[0074] The compound of formula **2e'** (2.00 g, 3.64 mmol, 1.00 equiv) was dissolved in methanol (50 mL) and warmed to 65 °C. $KHCO_3$ (1.09 g, 10.9 mmol, 3.00 equiv) was dissolved in water (5.0 mL) and added to the reaction. KF (0.423 g, 7.28 mmol, 2.00 equiv) was dissolved in water (1.2 mL) and added to the reaction. A 30% weight solution of H_2O_2 (1.20 mL, 10.9 mmol, 3.00 equiv) was added portion wise over 30 minutes. The reaction was stirred at 68 °C for 3 hours at which point additional H_2O_2 (1.20 mL, 10.9 mmol, 3.00 equiv) was added. After 4 hours H_2O_2 (0.600 mL, 5.45 mmol, 1.50 equiv) was added. The reaction was cooled to 25 °C and the pH was adjusted to 7 with 6M HCl. $NaHSO_3$ (2.80 g) was dissolved in water (6 mL) and added to the reaction mixture at 10 °C which was then warmed to room temperature and stirred until peroxide was no longer evident by peroxide strip testing. The mixture was concentrated to remove methanol. Water (20 mL) and ethyl acetate (100 mL) were charged and the phases were split. The aqueous layer was extracted twice with ethyl acetate (2 x 100 mL) and the combined organic was concentrated. The resulting solid was slurried in ethyl acetate (20 mL) and filtered. The cake was washed with ethyl acetate (50 mL) and water (30 mL). The cake was dried at 40 °C giving the compound of formula **5a'** as a white solid (1.78 grams, quantitative yield) which was carried forward to the next reaction without further purification. ^1H NMR (360 MHz, DMSO-d_6) δ 7.62 (s, 1 H), 7.27 (d, J = 7 Hz, 2 H), 7.18-7.02 (m, 8 H),

6.33 (s, 2 H), 5.26 (t, J = 12.7 Hz, 2 H), 4.87 (s, 1 H), 4.77-4.67 (m, 2 H), 4.59 (d, J = 5.2 Hz, 1 H), 4.28 (s, 2 H), 3.88 (q, J = 5.9 Hz, 1 H), 3.59-3.46 (m, 2 H), 3.08-3.06 (m, 1 H), 2.81 (dd, J = 11.5, 4.9 Hz, 1 H), 2.64 (q, J = 8.9 Hz, 1 H), 2.07 (q, J = 6.6 Hz, 1 H), 1.66 (t, J = 11.6 Hz, 1 H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 160.5, 159.5, 155.3, 140.1, 139.0, 137.0, 128.9, 128.8, 128.6, 128.4, 127.9, 127.7, 114.1, 81.3, 72.4, 69.9, 68.9, 67.2, 62.5, 61.8, 56.5, 37.5; MS (infusion) = 492 (M+ H^+); HRMS m/e calc'd for $C_{26}H_{30}N_5O_5$ (M+ H^+): 492.2247, found 492.2262.

Example 14

Preparation of compound 5e:

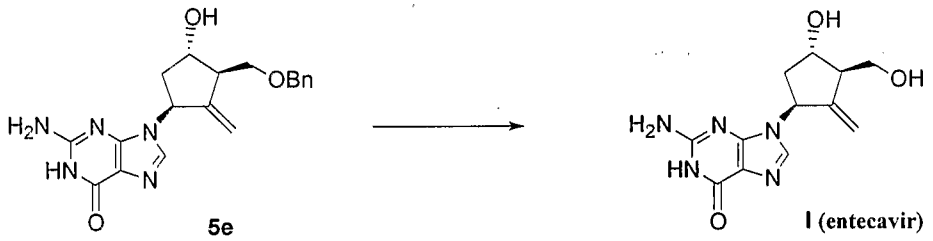


[0075] The compound of formula **5a'** (1.00 g, 2.04 mmol, 1.00 equiv) was slurried in toluene (6 mL) and CH_2Cl_2 (2 mL). TFA (trifluoroacetic acid) (0.120 mL, 1.50 mmol, 0.750 equiv) was added followed by TIOF (triisopropylorthoformate) (1.36 mL, 6.12 mmol, 3.00 equiv). The resulting brown solution was stirred at room temperature for one hour at which point 0.22 AP of compound 5a' remained by HPLC. BHT (2,6-Di-tert-butyl-4-methylphenol) (1.00 g) was added followed by acetic anhydride (2.00 mL) and acetic acid (0.230 mL, 3.60 mmol, 2.00 equiv). The reaction mixture was warmed to 116 °C and the distillate (4 mL) was collected. The reaction was continued for 14 hours and cooled to room temperature. Methanol (6.0 mL) was charged to a separate round bottom flask and was cooled to 14 °C. 6 M HCl (2.7 mL) was added to the methanol. The reaction mixture was added drop wise followed by a methanol rinse (2.0 mL) of the reaction flask. The reaction mixture was warmed to 25 °C and then heated to 68 °C. After five hours the reaction was cooled to 25 °C and transferred to a separatory funnel using methanol (2 mL). The reaction mixture was washed twice with 90% ethyl acetate in heptanes (2 x 30 mL) and concentrated to a residue. Methanol (9 mL) was added followed by 4 N NaOH to adjust the pH to 8. Brown slurry formed immediately, and it was cooled to 0 °C for

30 minutes and filtered. The cake was washed with water (3 x 3 mL), and heptane (2 x 10 mL). Re-slurry of the crude cake in heptanes/ethyl acetate (75:25) did not improve the impurity profile. Solids crashed out of the mother liquor from the previous crystallization and were subjected to column chromatography on silica gel using a gradient of 50-100% ethyl acetate in hexanes followed by 10-30% ethyl acetate in methanol giving 0.210 g of the compound of formula **5e**. Column chromatography was repeated on the solids isolated from the re-slurry giving an additional 0.120 g of the compound of formula **5e** (44% yield). ^{1}H NMR (360 MHz, CD_3OD) δ 7.56 (s, 1 H), 7.27-7.18 (m, 5 H), 5.44-5.39 (m, 1 H), 5.14 (s, 1 H), 4.70 (s, 1 H), 4.48 (q, 2 H), 4.30-4.28 (m, 1 H) 3.62 (d, J = 5.5 Hz, 2 H), 2.69 (s, 1 H), 2.31-2.24 (m, 1 H); 2.14-2.08 (m, 1 H); ^{13}C NMR (90 MHz, CD_3OD) δ 159.8, 155.6, 153.8, 152.2, 140.0, 138.8, 129.9, 129.3, 129.2, 117.7, 112.0, 74.7, 73.8, 73.1, 57.4, 53.6, 41.3; MS (infusion) = 368 (M+ H^+); HRMS m/e calc'd for $C_{19}H_{23}N_5O_3$ (M+ H^+): 368.1723, found 368.1722; mp = 134.3 °C.

Example 15

Preparation of compound I (entecavir):

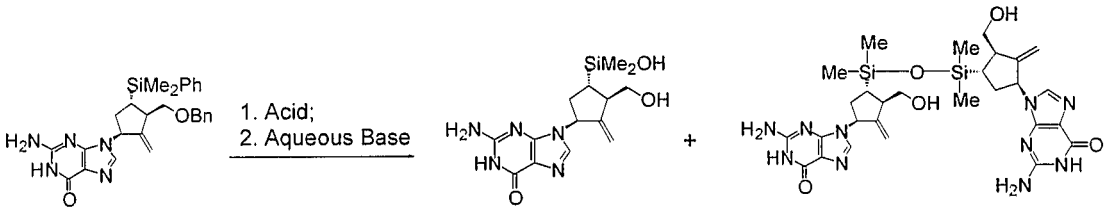


[0076] To a solution of **5e** (2.0 g, 5.44 mmoles) in methylene chloride (20 mL), cooled to -20°C, was added a methylene chloride solution of boron trichloride (1M, solution, 22 mL. 22 mmoles, 4.04 equivalents) over a period of ~30 minutes. During addition, the temperature was maintained at -19° to -23°C. After stirring for an additional 3 hours at -20°C, methanol (14 mL) was added to quench the reaction. The reaction mixture was stirred until HPLC showed no borane ester (~4 hours). MTBE (30 mL) was added, and the reaction mixture was stirred overnight at room temperature. The solid obtained was filtered, washed with MTBE (~5 mL), and dried under vacuum at room temperature to obtain 1.66 g of the hydrochloride salt of entecavir. The HCl salt (0.72 g, 2.29 mmoles) was taken in ~13 mL of water and

heated to ~40°C. The pH was adjusted to ~7 with 2N NaOH. The thin slurry obtained was heated to 80 - 85°C and treated with activated carbon (0.12 g). After 30 minutes at reflux, the hot mixture was filtered on a Celite pad. The filtrate was cooled to room temperature over 3 hours and further stirred at 0°C for 2 hours. The crystals obtained were filtered, washed with water, and dried under vacuum to obtain the compound of formula I (entecavir) (0.32g, 44% overall yield from **5e**).

Example 16

Preparation of compound 7b':



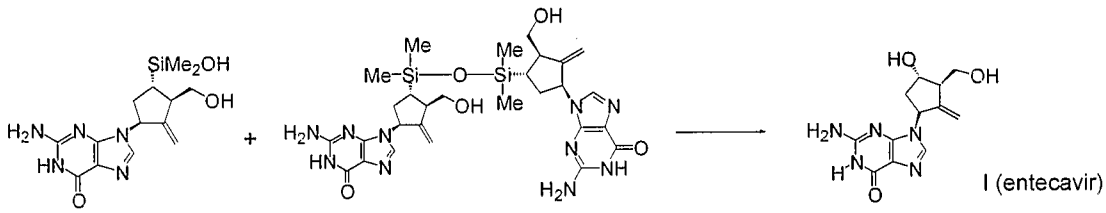
7a' 7b' 7c'

[0077] A 1000 mL jacketed vessel equipped with overhead stirrer, thermometer, an addition funnel and a nitrogen inlet was charged with compound **7a'** (40 g), DCM (180 mL), and sulfolane (20 mL), and the reaction mixture was cooled to 10 to 15°C. MSA (14.48 g, 2 eq.) was added drop-wise to the vessel while maintaining the temperature of the reaction mixture below 15°C. The reaction mixture was further cooled to between about 5 to 10°C. TFMSA (22 mL, 3.2 eq.) was added slowly to the vessel while maintaining the reaction temperature below about 10°C. The reaction mixture warmed to ambient temperature and stirred overnight. After the reaction was complete as determined by HPLC, the reaction mixture was cooled to 0 – 10°C, and 2N NaOH (360 mL) was added slowly while maintaining the vessel temperature below 15°C. The resulting slurry was warmed to ambient temperature and allowed to stir for about 1.5 hours. Toluene (600 mL) was added and the mixture stirred for 30 minutes. The rich aqueous solution was washed with toluene (2 x 600 mL), diluted with water (370–375 mL) and quenched with glacial acetic acid at 80 to 85°C to bring the pH of the solution to 6.8 to 7.2. After holding the slurry for about 2 h at 80 to 85°C and at room temperature for 4 h, the slurry was further cooled to 0 to 10°C and stirred for 1–1.5 h. The slurry was then filtered, washed with water (2 x 80 mL),

heptane (2 x 80 mL) and dried under vacuum at 55^{0}C to afford 23.26 g of compound **7b'** (84.6% yield) (may contain about 5 to about 15% of compound **7c'**). LC/MS for **7c'**: retention time = 5.95 min.; (M+H) = 653. (HPLC condition: Solvent A: 5% CH_3CN, 95% H_2O, 10 mM NH_4OAc; Solvent B: 95% CH3CN, 5% H2O, 10 nM NH_4OAc; Gradient Time: 15 min.; Start % B = 0' Final % B = 100; Flow rate 2.2 ml/min.; column = Luna C18, 50 x 4.6 mm; wavelength = 210 nM)

Example 17

Preparation of compound I (entecavir):



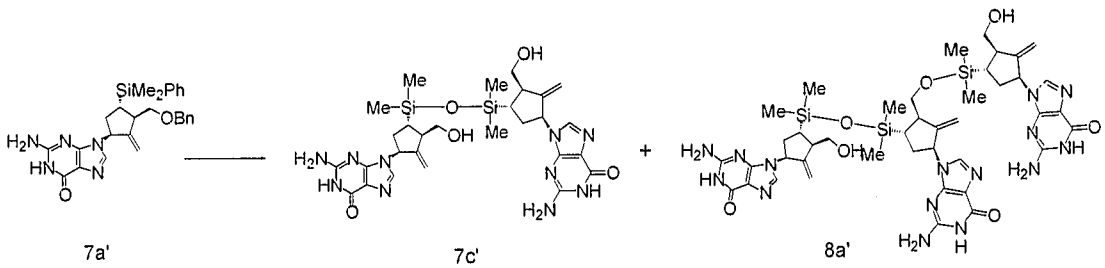
7b' 7c'

[0078] A 500 mL 3-necked round bottom flask equipped with overhead stirrer, a condenser and a thermometer was charged with compound **7b'** (10 g) (may contain up to to15% of compound **7c'**), sodium carbonate peroxohydrate (14 g), and methanol (250 mL). The reaction mixture was heated to reflux with agitation until the reaction was complete as determined by HPLC. The reaction mixture was then cooled down to room temperature, filtered through a filter paper to give a filter cake, which was rinsed with methanol (5 x 50 mL). The filtrate was transferred to a 500 mL equipped with a magnetic stirrer and a thermometer, and aqueous sodium thiosulfate (5 x 50 mL, 0.4 M) was added with agitation until the residual peroxide was quenched. The resulting cloudy solution was filtered through a filter paper while maintaining the temperature of the solution at about 55°C, and the filter cake was rinsed with warm water (45 mL, at 50°C to 60°C). To the resulting clear filtrate was added glacial acid while maintaining the temperature of the solution at 70 to 75°C until the pH of the solution was 6 to 7. The resulting mixture was heated to 90 to 95°C for about 30 minutes, and then cooled to room temperature slowly with agitation. The resulting slurry was filter collected and washed with cold water (2 x 50 mL), and dried under vacuum to give the compound of formula I (typical yield: 79 to 85%). Compound I

may be further purified through decolorization upon treating with carbon and recrystallization from methanol, water, or a mixture thereof.

Example 18

Preparation of compound 7c' and 8a':



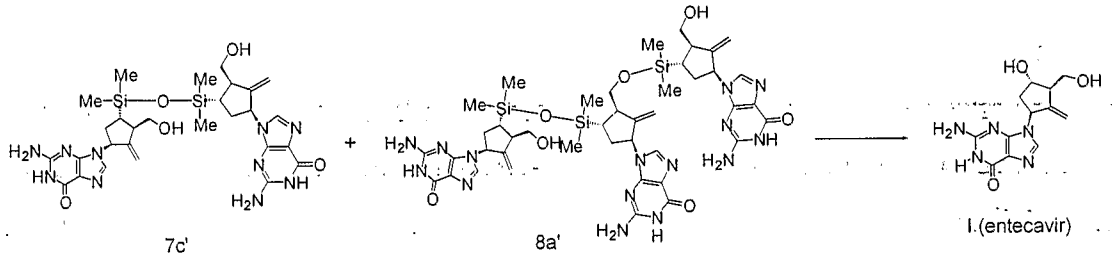
[0079] A dry 1-L 4-neck jacketed reactor with an overhead stirrer, a thermometer, an addition funnel and a N_2 inlet/outlet was charged with compound **7a'** (30 g, 56.2 mmol) and DCM (100 mL) with agitation, and the reaction mixture was cooled to below 5°C. MSA (36.2g, 376.6 mmol, 6.7 eq.) was slowly added to the reactor while maintaining the reactor temperature less than 15°C. CF_3SO_3H (TFMSA, 16.5 mL, 182.7 mmol, 3.25 eq.) was then added slowly via the addition funnel while maintaining the reactor temperature below 5°C. The reaction mixture was allowed to warm to ambient temperature (21-25 °C) and continued to stir until reaction was complete as determined by HPLC. Triethylamine (87 mL, 623.9mmol) was added to the reaction mixture slowly while maintaining the reactor temperature below 15°C. The resulting cloudy suspension was continued to stir at room temperature for about 5 hours. The suspension was cooled to 10 °C -15 °C and pre-mixed water (240mL) and MeOH (480 mL) was added to the suspension while maintaining the temperature below 15°C. The resulting slurry was heated to about 28-30°C and agitated for about 2-3 hours. The pH of the slurry was adjusted to 6.5 to 7.5 using glacial AcOH or TEA as required. The resulting mixture was heated to about 70 °C for about 1 hour and the distillate was removed. MeOH (100mL) was charged to the reactor and distillation was resumed at about 80°C until a final volume of 17-20g/mL was reached. The resulting slurry was cooled to about 20 to 25 °C slowly and held at 17 to 22°C for about 4 hours. The slurry was filtered collected, washed with DCM (2 x 100 mL), premixed MeOH (315mL) and DI water (135mL), MeOH (900mL), and dried at 55 to 60°C in a vacuum oven to give compound **7c'** (17.88 g, 93.5%, may contain about 1%

to about 20% of compound **8a'**). LC/MS for 8a': retention time = 20.1 min.; (M+H) = 971. HPLC condition: run time = 36 min.; flow rate = 1 mL/min.; column temp. = 25 deg. C; column = Inertsil ODS-2, 150 x 4.6 mm, 5 μm; wavelength = 254 nm; Solvent A = H_2O; Solvent B = CH_3CN;

Gradient:time (min.)	% A	%B
0	96	4
4	96	4
15	72	28
20	40	60
30	40	60
30.5	96	4
36	96	4

Example 19

Preparation of compound I (entecavir):



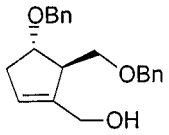
[0080] A 500 mL 3-necked round-bottom flask equipped with mechanical agitation, a condenser and a thermometer was charged with compound **7c'** (15 g) (may contain about 1% to about 20% of compound **8a'**), sodium carbonate peroxohydrate (13.2 g) and methanol (225 mL, 15 volumes) with agitation. The resulting mixture was heated to reflux and agitated until reaction was complete as determined by HPLC. The reaction mixture was then cooled to 20 to 25°C and the resulting slurry was filtered through a filter paper and rinsed with methanol (5 x 50 mL). The filtrate was transferred to a 500 mL round-bottom flask equipped with a thermometer and a magnetic stirrer. Aqueous sodium thiosulfate was added (5 x 75 mL, 0.4M) and agitated until residual peroxide was quenched. The resulting slurry was concentrated under reduced pressure while maintaining the flask temperature at about 55°C until a final volume of about 135 mL was achieved. The resulting mixture

was heated to 70 to 75°C to form a hazy solution/slurry, and 2N NaOH was added to adjust the pH of the solution to 10 to 11. The hazy solution/slurry was filtered through a filter paper while maintaining the temperature at about 55°C, and the filter cake was rinsed with warm water (3 x 45 mL, at 50 to 60°C). The pH of the clear filtrate was adjusted to 6 to 7 at 70 to 75°C using glacial acetic acid. The resulting mixture was heated to 90 to 95°C for about 30 minutes and then cooled to room temperature slowly with agitation. The resulting slurry was filtered collected and washed with 2 x 50mL cold water (5-10°C), and dried under vacuum to give compound I (typical yield: 75 to 80%). Compound I may be further purified through decolorization upon treating with carbon and recrystallization from methanol, water, or a mixture thereof.

[0081] It is to be understood that the invention, as defined in the following claims, should not be restricted solely to the embodiments itemized herein.

WE CLAIM:

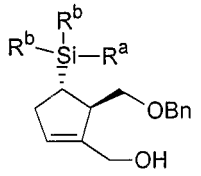
1. A process for the preparation of a compound of formula **1f**,



1f

comprising:

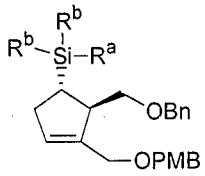
(a) reacting a compound of formula **1a**,



1a

wherein R^a is allyl, phenyl, or phenyl substituted with one, two or three C_1-C_4 alkyl or C_1-C_4 alkoxy; and each R^b is independently C_1-C_4 alkyl,

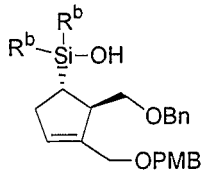
with PMB-halide in the presence of a base to give a compound of formula **1b**,



1b

wherein R^a and R^b are defined as hereinabove;

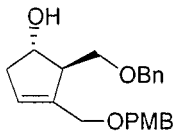
(b) converting the compound of formula **1b** to a compound of **1c** via protodesilylation,



1c

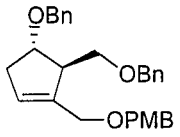
wherein R^b is defined as hereinabove;

(c) contacting the compound of formula **1c** with an oxidizing agent to give a compound of formula **1d**,



1d ;

(d) treating the compound of formula **1d** with benzyl halide in the presence of a base to give a compound of formula **1e**,

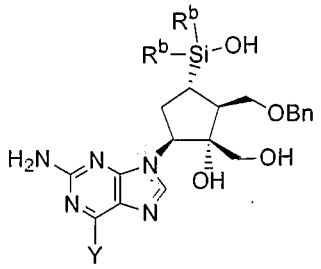


1e ; and

(e) deprotecting the PMB group in the compound of formula of **1e** to provide the compound of formula **1f**.

2. The process of claim 1, wherein R^a is phenyl and each R^b is methyl.

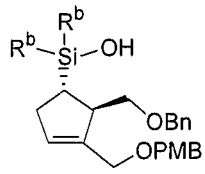
3. A process for the preparation of a compound of formula **2e**,



2e

wherein each R^b is independently C_1-C_4 alkyl, and Y is OBn, Cl, Br, or I; comprising:

(a) reacting a compound of formula **1c**,

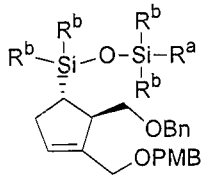


1c

wherein each R^b is defined as hereinabove,

with $R^aSi(R^b)_2$-halide, wherein R^a is allyl, phenyl, or phenyl substituted with one, two or three C_1-C_4 alkyl or C_1-C_4 alkoxy; and each R^b is defined as hereinabove;

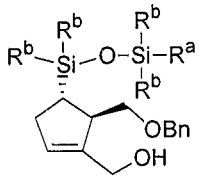
in the presence of a base to give a compound of formula **2a**,



2a

wherein R^a and each R^b are defined as hereinabove;

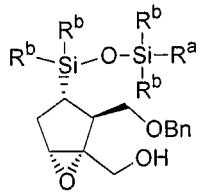
(b) deprotecting the PMB group in the compound of formula **2a** to give a compound of formula **2b**,



2b

wherein R^a and each R^b are defined as hereinabove;

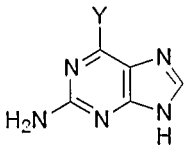
(c) converting the compound of formula **2b** to a compound of formula **2c** via a diastereoselective epoxidation,



2c

wherein R^a and each R^b are as defined hereinabove;

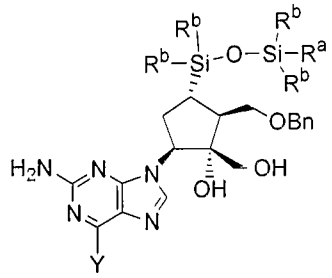
(d) reacting a compound of formula **2c** with a compound of formula **1h**,



1h,

wherein Y is OBn, Cl, Br, or I, in the presence of an alkali metal base,

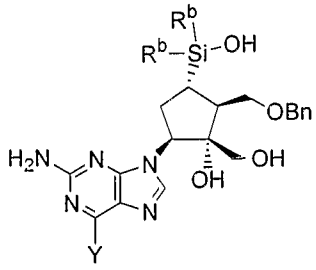
to give a compound of formula **2d**,



2d

wherein R^a, each R^b and Y are defined as hereinabove; and

(e) converting the compound of formula **2d** to give a compound of formula **2e** via desilylation,

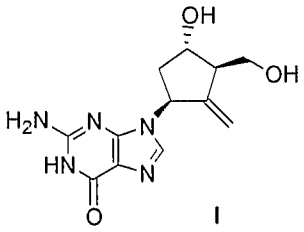


2e

wherein each R^b and Y are defined as hereinabove.

4. The process of claim 3, wherein R^a is phenyl; each R^b is methyl; and Y is OBn.

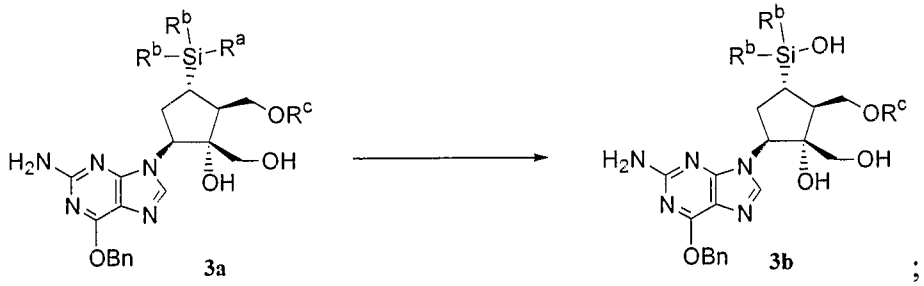
5. A process for the preparation of a compound of formula I,



I

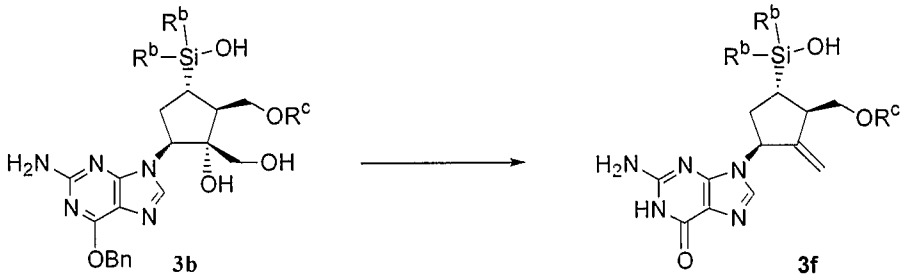
comprising:

(a) converting the compound of formula **3a** to a compound of formula **3b** via protodesilylation, wherein R^a is allyl, phenyl, or phenyl substituted with one, two or three C_1-C_4 alkyl or C_1-C_4 alkoxy; each R^b is independently C_1-C_4 alkyl; and R^c is H or Bn,



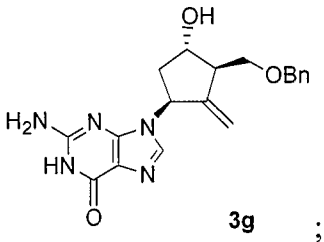
;

(b) further converting the compound of formula **3b** to a compound of formula **3f,**



wherein each R^b and R^c are defined as hereinabove;

(c) oxidizing the compound of formula **3f** to give the compound of formula I when R^c is H; or a compound of formula **3g** when R^c is Bn,



; and

(d) deprotecting the benzyl group in the compound of formula **3g** wherein R^c is Bn to give a compound of I.

6. The process of claim 5, wherein step (b) comprises:

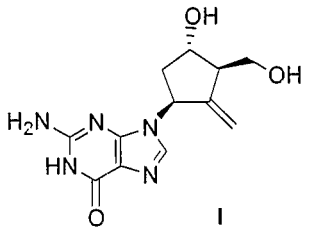
(i) reacting the compound of formula **3b** with an orthoformate derivative, in the presence of a catalytic amount of an acid, or acid catalyst;

(ii) further reacting the resulting mixture from step (i) with an acid anhydride of formula R^d-C(=O)-O-C(=O)-R^d, wherein R^d is C_1-C_4 alkyl; and optionally an acid of formula of R^d-C(=O)OH, wherein R^d is C_1-C_4 alkyl; and further optionally in the presence of an antioxidant; and

(iii) hydrolyzing the resulting compound from step (ii), with an aqueous mineral acid.

7. The process of claim 6, wherein R^a is phenyl; each R^b is methyl; and R^d is methyl.

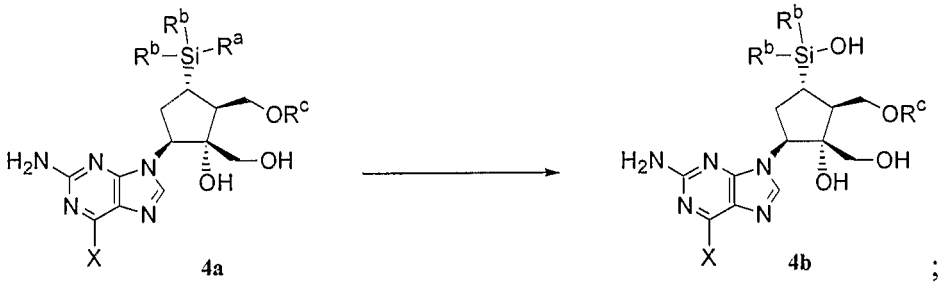
8. A process for the preparation of a compound of formula I,



I

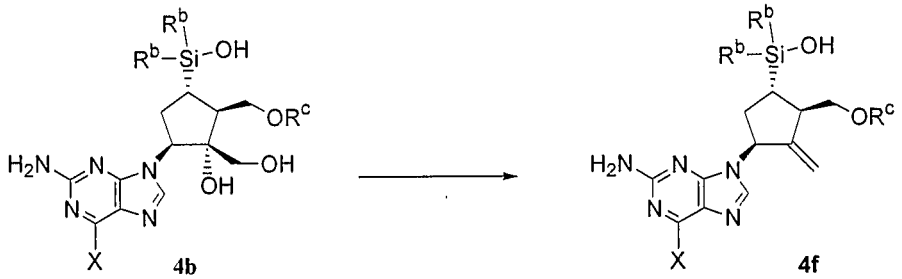
comprising:

(a) converting the compound of formula **4a** to a compound of formula **4b** via protodesilylation, wherein R^a is allyl, phenyl, or phenyl substituted with one, two or three C_1-C_4 alkyl or C_1-C_4 alkoxy; each R^b is independently C_1-C_4 alkyl; R^c is H or Bn; and X is Cl, Br, or I,



4a **4b** ;

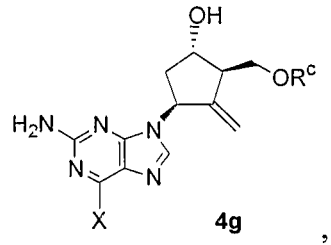
(b) further converting the compound of formula **4b** to a compound of formula **4f,**



4b **4f**

wherein each R^b, R^c and X are defined as hereinabove;

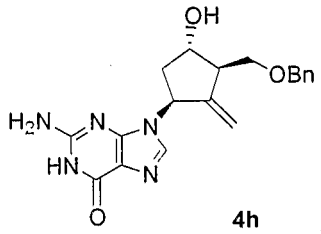
(c) oxidizing the compound of formula **4f** to give a compound of formula **4g,**



4g ,

wherein R^c is defined as hereinabove;

(d) reacting the compound of formula **4g** with an aqueous base to provide the compound of formula I when R^c is H; or a compound of formula **4h** when R^c is Bn,



4h ; and

(e) deprotecting the benzyl group in the compound of formula **4h** to give a compound of I.

9. The process of claim 8, wherein step (b) comprises:

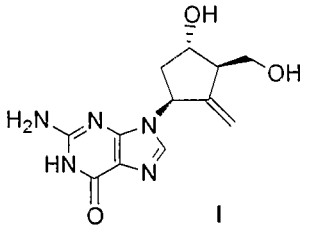
(i) reacting the compound of formula **4b** with an orthoformate derivative, in the presence of a catalytic amount of an acid, or acid catalyst;

(ii) further reacting the resulting mixture from step (i) with an acid anhydride of formula R^d-C(=O)-O-C(=O)-R^d, wherein R^d is C_1-C_4 alkyl; and optionally an acid of formula of R^d-C(=O)OH, wherein R^d is C_1-C_4 alkyl; and further optionally in the presence of an antioxidant; and

(iii) hydrolyzing the resulting compound from step (ii), with an aqueous mineral acid.

10. The process of claim 9, wherein R^a is phenyl; each R^b is methyl; and R^d is methyl.

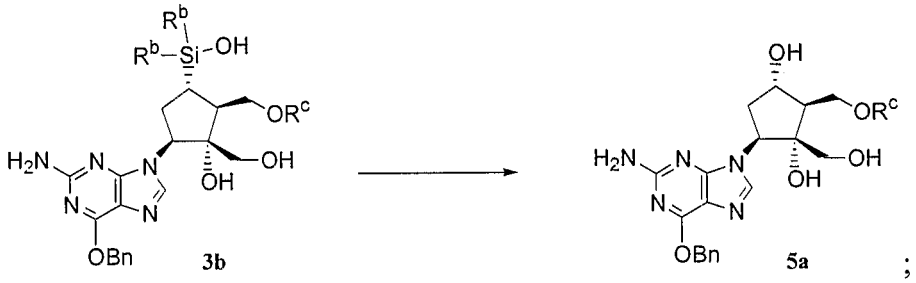
11. A process for the preparation of a compound of formula I,



I

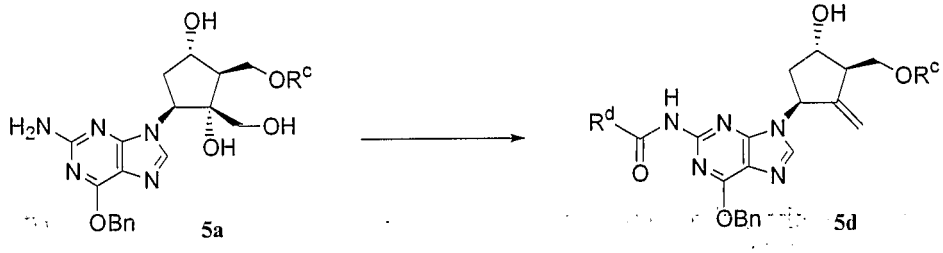
comprising:

(a) oxidizing the compound of formula **3b** to a compound of formula **5a**, wherein each R^b is independently C_1-C_4 alkyl; and R^c is H or Bn,



3b **5a** ;

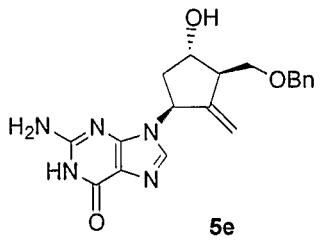
(b) converting the compound of formula **5a** to a compound of formula **5d,**



5a **5d**

wherein R^c is defined as hereinabove; and R^d is C_1-C_4 alkyl;

(c) hydrolyzing the compound of formula **5d** to provide the compound of formula I when R^c is H; or a compound of formula **5e** when R^c is Bn,



5e ; and

(d) deprotecting the benzyl group in the compound of formula **5e** to give a compound of I.

12. The process of claim 11, wherein step (b) comprises:

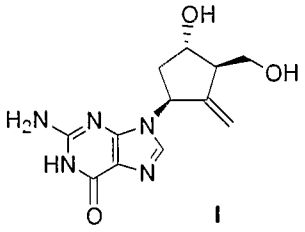
(i) reacting the compound of formula **5a** with an orthoformate derivative, in the presence of a catalytic amount of an acid, or acid catalyst;

(ii) further reacting the resulting mixture from step (i) with an acid anhydride of formula R^d-C(=O)-O-C(=O)-R^d, wherein R^d is C_1-C_4 alkyl; and optionally an acid of formula of R^d-C(=O)OH, wherein R^d is C_1-C_4 alkyl; and further optionally in the presence of an antioxidant; and

(iii) hydrolyzing the resulting compound from step (ii), with an aqueous mineral acid.

13. The process of claim 12, wherein each R^b is methyl; and R^d is methyl.

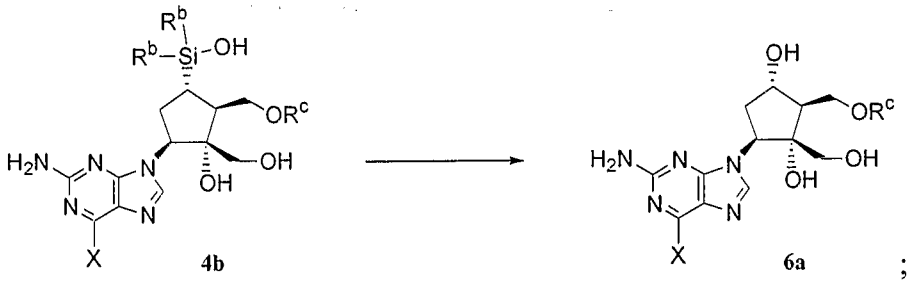
14. A process for the preparation of a compound of formula I,



I

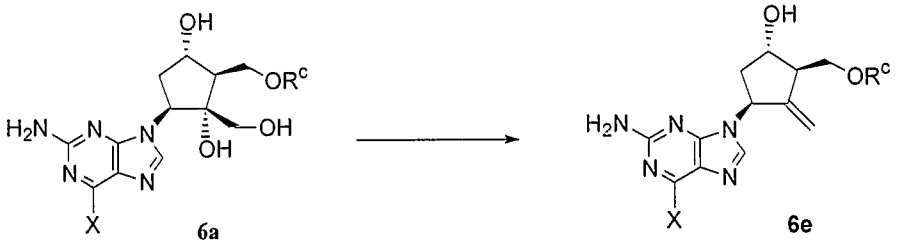
comprising:

(a) oxidizing the compound of formula **4b** to a compound of formula **6a**, wherein each R^b is C_1-C_4 alkyl; R^c is H or Bn; and X is Cl, Br, or I;



4b 6a ;

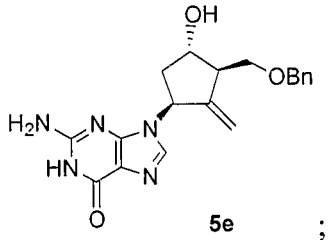
(b) converting the compound of formula **6a** to a compound of formula **6e,**



6a 6e

wherein R^c and X are defined as hereinabove;

(c) hydrolyzing the compound of formula **6e** with an aqueous base to provide the compound of formula I (entecavir) when R^c is H; or a compound of formula **5e** when R^c is Bn,



5e ; and

(d) deprotecting the benzyl group in the compound of formula **5e** to give a compound of I.

15. The process of claim 14, wherein step (b) comprises:

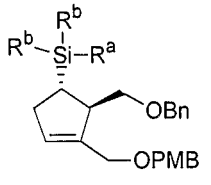
(i) reacting the compound of formula **6a** with an orthoformate derivative, in the presence of a catalytic amount of an acid, or acid catalyst;

(ii) further reacting the resulting mixture from step (i) with an acid anhydride of formula R^d-C(=O)-O-C(=O)-R^d, wherein R^d is C_1-C_4 alkyl; and optionally an acid of formula of R^d-C(=O)OH, wherein R^d is C_1-C_4 alkyl; and further optionally in the presence of an antioxidant; and

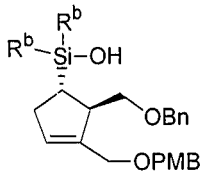
(iii) hydrolyzing the resulting compound from step (ii), with an aqueous mineral acid.

16. The process of claim 15, wherein each R^b is methyl; and R^d is methyl.

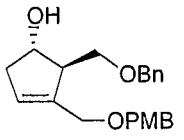
17. A compound selected from the group consisting of:



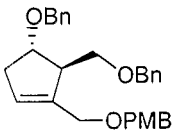
1b ;



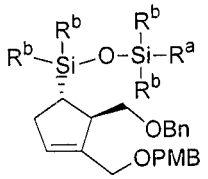
1c ;



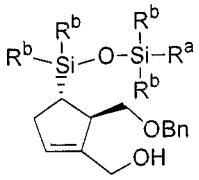
1d ;



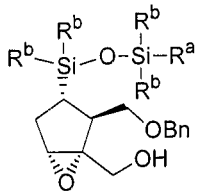
1e ;



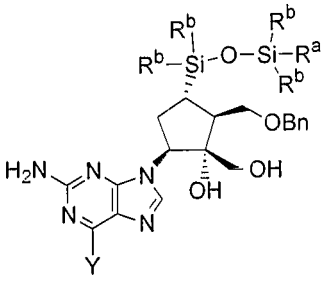
2a ;



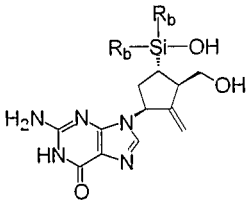
2b ;



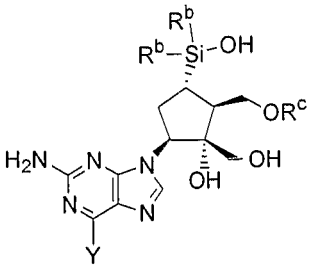
2c ;



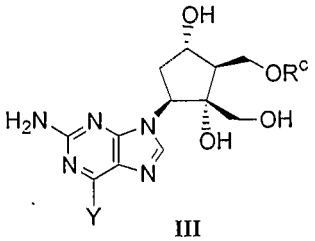
2d ;



7b ;



II ; and

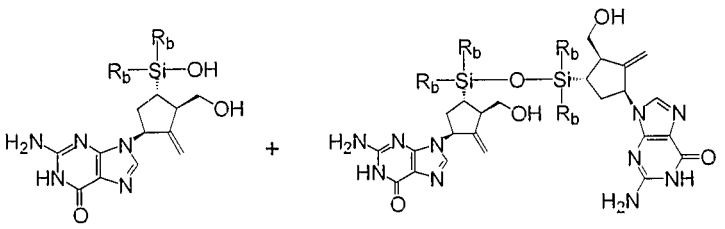


III ,

wherein each R^a at each occurrence is independently allyl, phenyl, or phenyl substituted with one, two or three C_1-C_4 alkyl or C_1-C_4 alkoxy; and each R^b at each occurrence is independently C_1-C_4 alkyl; each R^c at each occurrence is independently H or Bn; and each Y at each occurrence is independently OBn, Cl, Br, or I.

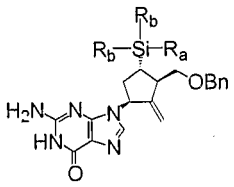
18. The compound of claim 17, wherein each R^a at each occurrence is independently phenyl; each R^b at each occurrence is independently methyl; each R^c at each occurrence is independently Bn; and each Y at each occurrence is independently OBn, Cl, or I.

19. A process for the preparation of a mixture of a compound of formula **7b** and a compound of formula **7c**, wherein each R^b is independently C_1-C_4 alkyl,



7b 7c

comprising contacting a compound of formula **7a**,



7a

wherein R^a is allyl, phenyl, or phenyl substituted with one, two or three C_1-C_4 alkyl or C_1-C_4 alkoxy, and each R^b is as defined as hereinabove,

with at least one acid selected from:

(i) halogenated methanesulfonic acids; and

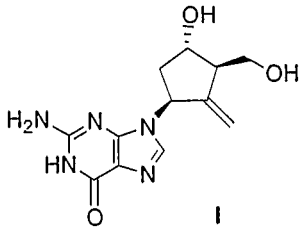
(ii) optionally methanesulfonic acid,

followed by treatment with at least one aqueous base.

20. The process of claim 19, wherein said optionally methanesulfonic acid is present.

21. The process of claim 19, wherein said at least one acid is a mixture of trifluromethanesulfonic acid and methanesulfonic acid.

22. The process of claim 19, further comprising oxidizing the compound of **7b** or a mixture of the compound of formula **7b** and the compound of formula **7c** using at least one peroxohydrate to give the compound of formula I



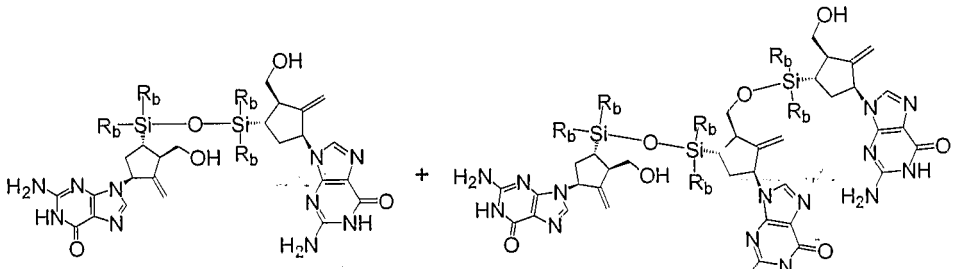
I

23. The process of claim 22, wherein said peroxohydrate is sodium carbonate peroxohydrate, urea peroxohydrate, peroxohydrate of melamine, sodium pyrophosphate peroxohydrate, sodium sulfate peroxohydrate hydrate, potassium carbonate peroxohydrates, rubidium carbonate peroxohydrates, or cesium carbonate peroxohydrate.

24. The process of claim 22, wherein said peroxohydrate is sodium carbonate peroxohydrate.

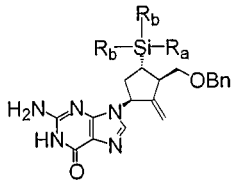
25. The process of claim 24, wherein R^a is phenyl and each R^b is methyl.

26. A process for the preparation of a compound of formula **7c**, and optionally a compound of formula **8a**, wherein each R^b is independently C_1-C_4 alkyl,



7c optionally 8a

comprising contacting a compound of formula **7a**,



7a

wherein R^a is allyl, phenyl, or phenyl substituted with one, two or three C_1-C_4 alkyl or C_1-C_4 alkoxy, and each R^b is as defined as hereinabove,

with at least one acid selected from:

(i) halogenated methanesulfonic acids; and

(ii) optionally methanesulfonic acid,

followed by treatment with at least one non-aqueous base.

27. The process of claim 26, wherein said optionally methanesulfonic acid is present and said optionally compound of formula **8a** is present.

28. The process of claim 26, wherein said at least one acid is a mixture of trifluromethanesulfonic acid and methanesulfonic acid.

29. The process of claim 26, wherein said non-aqueous base is $NR^eR^fR^g$, wherein R^e, R^f and R^g are independently hydrogen, alkyl, cycloalkyl, aryl, or said R^g and R^f together with the N to which they are bonded optionally form a heterocycle.

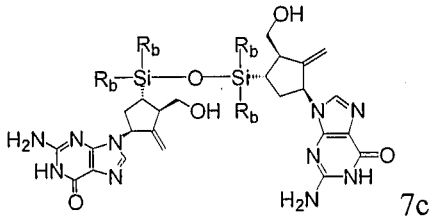
30. The process of claim 26, wherein non-aqueous base is tertiary amine base.

31. The process of claim 26, wherein R^a is phenyl and each R^b is methyl.

32. The process of claim 27, wherein R^a is phenyl and each R^b is methyl.

33. The process of claim 30, wherein R^a is phenyl and each R^b is methyl.

34. A compound of formula **7c**,

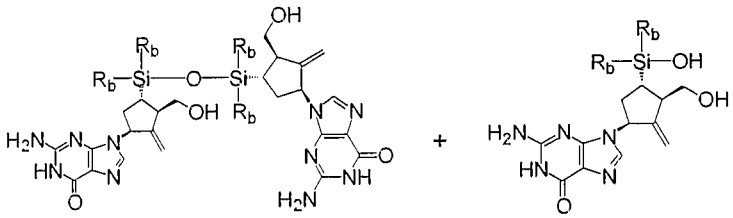


7c

wherein each R^b is independently C_1-C_4 alkyl.

35. The compound of claim 34 which is more than about 80% pure.

36. A chemical composition comprising a compound of formula **7c**, and optionally a compound of formula **7b**,

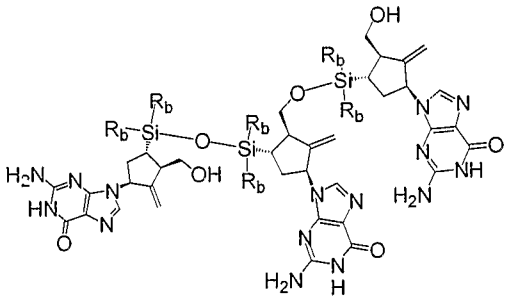


7c optionally 7b

wherein each R^b is independently C_1-C_4 alkyl; and when said compound of formula **7b** is present, the ratio of compound **7c** to **7b** is greater than 10:90.

37. The composition of claim 36, wherein each R^b is Me.

38. A compound of formula **8a**,

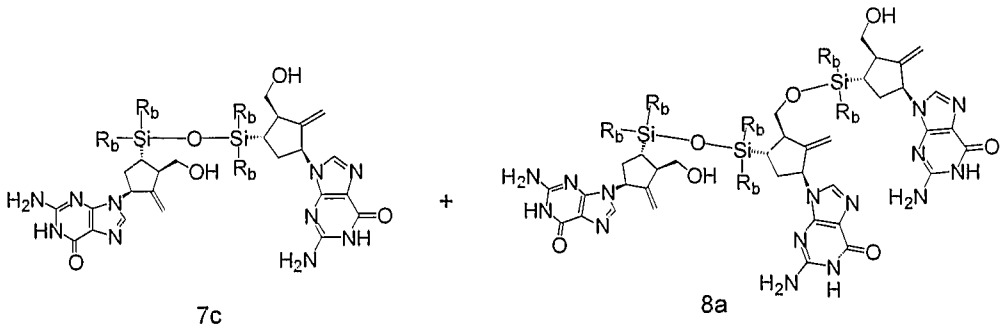


8a

wherein each R^b is independently C_1-C_4 alkyl.

39. The compound of claim 38, wherein each R^b is Me.

40. A chemical composition comprising a compound of formula **7c** and a compound of formula **8a**,

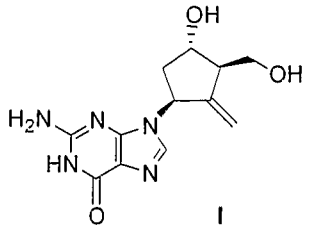


7c 8a

wherein each R^b is independently C_1-C_4 alkyl.

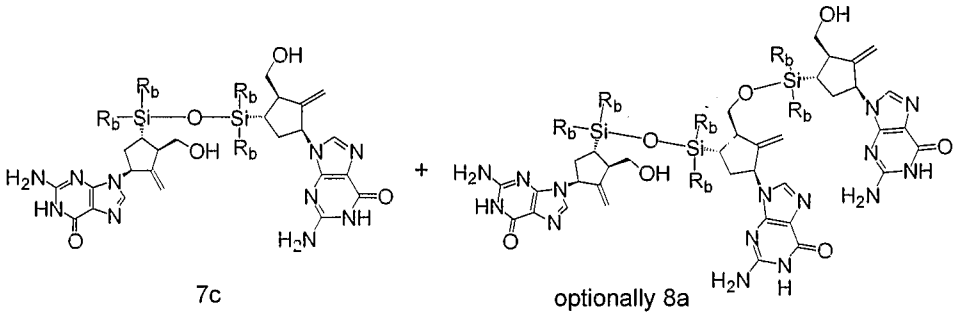
41. The composition of claim 40, wherein each R^b is Me.

42. A process for the preparation of a compound of formula I,



I

comprising oxidizing a compound of formula **7c**, or a mixture of a compound of formula **7c** and a compound of formula **8a**,



7c optionally 8a

wherein each R^b is independently C_1-C_4 alkyl.

43. The process of claim 42, wherein the oxidation is achieved by using at least one peroxohydrate.

44. The process of claim 42, wherein each R^b is Me.

45. The process of claim 43, wherein said peroxohydrate is sodium carbonate peroxohydrate, urea peroxohydrate, peroxohydrate of melamine, sodium pyrophosphate peroxohydrate, sodium sulfate peroxohydrate hydrate, potassium carbonate peroxohydrates, rubidium carbonate peroxohydrates, or cesium carbonate peroxohydrate.

46. The process of claim 43, wherein said peroxohydrate is sodium carbonate peroxohydrate.

47. The process of claim 46, wherein each R^b is Me.