

PROCESS FOR PREPARING THE ANTIVIRAL AGENT

[1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-
2-methylenecyclopentyl]-6H-purin-6-one

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RELATED APPLICATIONS

This application claims the priority benefit of U.S. Provisional Application No. 60/432,549 filed December 11, 2002, the disclosure of which is incorporated herein by reference in its entirety.

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BACKGROUND OF THE INVENTION

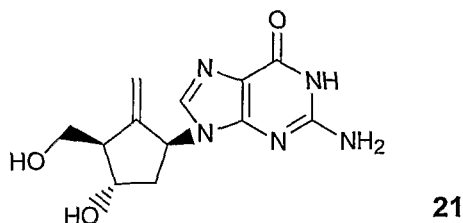
Entecavir, [1S-(1 α , 3 α , 4 β)]-2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one, is currently being evaluated as a drug for use in treating hepatitis B viral infections.

Entecavir and its use as an antiviral agent are described in U.S. Patent 15 5,206,244 to Zahler *et al.*, assigned to the present assignee. Improved processes of preparing entecavir are described by Bisacchi *et al.*, in WO 98/09964, also to the present assignee.

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- 20 infections.

SUMMARY OF THE INVENTION

This invention is directed to various methods for preparing entecavir as recited in the claims appended hereto. Entecavir (the compound of formula 21) has the 25 structural formula shown below:



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

This invention is also directed to a resin adsorption process for isolation and purification of entecavir and intermediates thereof.

DETAILED DESCRIPTION OF THE INVENTION

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ABBREVIATIONS

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

	Ac	=	acyl;
	AP	=	HPLC area percent;
10	Bn	=	benzyl;
	BHT	=	2,6-di-tert-butyl-4-methylphenol;
	CHP	=	cumene hydroperoxide, or α,α -dimethylbenzylhydroperoxide;
	DCM	=	dichloromethane;
	de	=	diastereometric excess;
15	DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene;
	DEAD	=	diethylazodicarboxylate;
	DEMA	=	diethoxymethyl acetate;
	DIPT	=	(-)-diisopropyl tartrate;
	DMAP	=	4- <i>N,N</i> -dimethylaminopyridine;
20	DMF	=	<i>N,N</i> -dimethylformamide;
	DiPMA	=	di-isopropyloxymethyl acetate; [(iPr-O) ₂ CHOAc];
	DMSO	=	dimethyl sulfoxide;
	ee	=	enantiomeric excess;
	Et	=	ethyl;
25	EtOAc	=	ethyl acetate;
	Et ₃ N	=	triethylamine;
	FMSA	=	fluoromethane sulfonic acid;
	HCl	=	hydrochloric acid
	IPA	=	isopropanol;
30	K ₂ CO ₃	=	potassium carbonate;
	KF	=	potassium fluoride;

	KHCO_3	=	potassium bicarbonate;
	KHMDS	=	potassium hexamethyldisilazide or potassium bis(trimethylsilyl)amide;
	KOH	=	potassium hydroxide;
5	KOtBu	=	potassium <i>tert</i> -butoxide;
	LAH	=	lithium aluminum hydride;
	LiOH	=	lithium hydroxide;
	<i>m</i> -CPBA	=	meta-chloroperbenzoic acid;
	MeOH	=	methanol
10	MOP	=	2-methoxy-2-propoxy-acetal;
	MSA	=	methanesulfonic acid;
	MTBE	=	methyl <i>tert</i> -butyl ether;
	NaBH_4	=	sodium borohydride;
	Na_2CO_3	=	sodium carbonate;
15	NaHCO_3	=	sodium bicarbonate;
	NaH	=	sodium hydride;
	NaOH	=	sodium hydroxide;
	NaOtBu	=	sodium <i>tert</i> -butoxide;
	NMP	=	N-methyl-2-pyrrolidinone;
20	TMS	=	trimethylsilyl;
	PPTS	=	pyridinium 4-toluenesulfonate or pyridinium <i>p</i> -toluenesulfonate;
	PTSA	=	para-toluene sulfonic acid;
	Red-Al® or RED-AL®	=	sodium bis(2-methoxyethoxy)aluminum hydride;
	TBAH	=	n-tetrabutyl ammonium hydroxide;
25	TBHP	=	<i>tert</i> -butylhydroperoxide;
	TEOF	=	tri-ethylorthoformate;
	TFA	=	trifluoroacetic acid;
	THF	=	tetrahydrofuran;
	$\text{Ti}(\text{O}-i\text{Pr})_4$	=	titanium (IV) isopropoxide;
30	TiPOF	=	trisopropylorthoformate;
	TMOF	=	trimethylorthoformate.

DEFINITIONS

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.

“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.

“Acid” refers to any compound that contains hydrogen and dissociates in water or solvent to produce positive hydrogen ions, as well as 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, etc.; and so forth.

“Activated methyl carbonic acid reagent” means a reagent effective to prepare a methyl carbonate ester from an alcohol. Non-limiting examples include methyl chloroformate, dimethyl pyrocarbonate, and the like.

“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 "C₁₋₄alkyl" refers to alkyl groups of 1 to 4 carbon atoms. 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.

"Alkoxy" as used herein includes alkyl groups as defined above, bonded through an oxygen atom, *i.e.*, -O-alkyl.

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

"Allyl" refers to the group -CH₂-CH=CH₂, as well as such groups optionally having one or more (preferably 0 to 1) non-interfering substituents as defined below.

"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, ZrO₂, ascorbic acid, aromatic amines, phenols, quinones including BHT, citric acid, ascorbic acid, vitamin E, benzoic acid, phosphoric acid, and so forth.

"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, benzoxazolyl, 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.

"Base" when used herein includes hydroxides or alkoxides, hydrides, or compounds such as ammonia, 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 C₁₋₅ 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 (K₂CO₃), sodium carbonate (Na₂CO₃), potassium bicarbonate (KHCO₃), and sodium bicarbonate (NaHCO₃), alkyl ammonium hydroxides such as n-tetrabutyl ammonium hydroxide (TBAH); and so forth.

"Benzyl" includes the group -CH₂-phenyl, as well as such groups optionally containing non-interfering substituents on the methyl or phenyl portions of the benzyl, unless otherwise indicated.

"Benzyl halide" refers to a benzyl group having a halide substituent on the alkyl portion of the benzyl group, *i.e.*, Ph-CH₂-X, wherein X is halide, and Ph denotes a phenyl ring as defined below.

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

"Brominated styrene-based resin" refers to one or more styrene-based resins having one or more bromine substituents, and includes without limitation, SP207 Sepabeads, SP700 Sepabeads, Diaion HP20, Diaion SP70, Diaion SP825, Diaion

SP850, Diaion HP2MG methacrylate, AMBERLITE XAD4, AMBERLITE XAD7HP, AMBERLITE XAD16, and AMBERLITE XAD1600.

“Chiral amine” or “CA” as used herein refers to an amine or mixture of amines that is optically active including dextrorotatory or laevorotatory forms of amines. Preferably, the chiral amine comprises a pure or substantially pure form of one optical isomer, but optically active mixtures (*i.e.*, mixtures that are not equimolar) are also contemplated. If reference is made herein to a “homochiral amine,” it is intended to encompass the broader concept of “chiral amine” as well. For example, these amines include, without limitation, (1R,2R)-(+)-1,2-diphenylethylenediamine, (R)-(-)-1-cyclohexylethylamine, D-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1S,2S)-(+)-1,2-diaminocyclohexane, dehydroabietylamine, (1R,2R)-1,2-diaminomethylcyclohexane, cinchonidine and cinchonine

“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.

“Halide” or “halo” refers to F, Cl, Br, or I, preferably Cl or I.

“Hydride reagent” refers to reagents that are capable of delivering H⁻ ions. Exemplary hydride reagents include, but are not limited to, lithium aluminum hydride (LiAlH₄), sodium borohydride (NaBH₄), 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.

“Hydroperoxide” means a compound or complex comprising the hydroperoxide moiety HO₂-, such as compounds having the formula (R^POOH),
5 wherein R^P can be hydrogen (*e.g.*, hydrogen peroxide H₂O₂), 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.

10 “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
15 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).

“Homochiral diester of tartaric acid” as used herein includes single diastereomers of alkyl tartrates including diethyl tartrate and diisopropyl tartrate.

20 “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,
25 Rh₆(CO)₁₆, and so forth.

“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
30 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, -CO₂R, aryl, alkylaryl, C₃₋₇cycloalkyl, -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, -CO₂R, aryl, alkylaryl, C₃₋₇cycloalkyl, -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.

"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-isopropylloxymethylacetate.

"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, KHCO₃, NEt₃, 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.

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

"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.

“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

5 Synthesis, incorporated herein by reference.

“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, NaBH₄, LAH, lithium borohydride, diisobutylaluminum hydride, sodium
10 bis(2-methoxyethoxyaluminum) hydride, and the like. The term “reducing reagent” will include “hydride reagents” as recited above.

“Strong non-nucleophilic base” means a non-aqueous base that does not act as a nucleophile, such as sodium or potassium bistrimethylsilylamide, lithium diisopropylamide, sodium bistrimethylsilylamide, potassium, lithium, or sodium
15 hydride.

“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.

20 “Trimethylsilylating reagent” means a reagent effective to prepare a trimethylsilyl ether from an alcohol. Non-limiting examples include chlorotrimethylsilane, trimethylsilyl trifluoromethanesulfonate, and the like.

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 as “a base”, “a metal
25 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,”
30 encompasses use of potassium hydroxide as a base, or, where appropriate, mixtures of

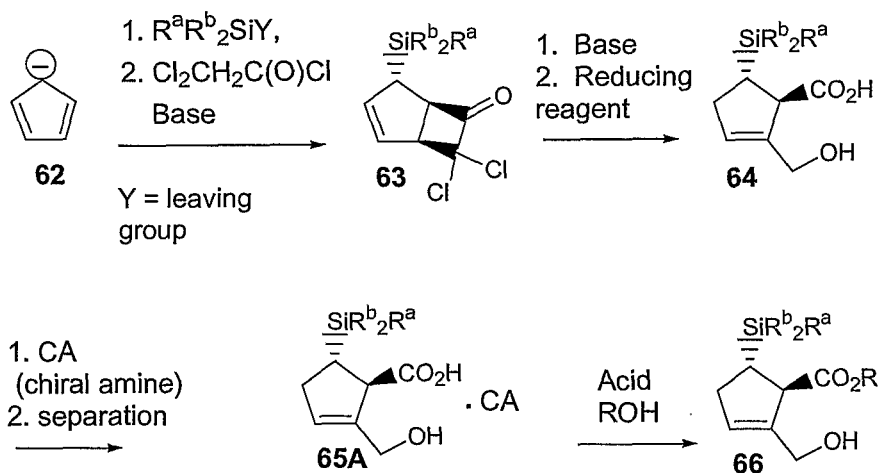
potassium hydroxide plus one or more additional bases set forth in the group from which a selection may be made. One skilled in the field may make appropriate selections given the reactions steps and conditions and result to be achieved.

Methods of Preparation

5 The compound entecavir and novel intermediates therefor 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 are commercially available or can be readily prepared by one of ordinary skill in the art. Solvents, temperatures, pressures, starting materials having
10 the desired groups, and other reaction conditions, may be readily selected as appropriate by one of ordinary skill in the art.

PROCESS A

SCHEME 1



15

Process A of the invention comprises preparation of the ester of formula **66**, a preferred intermediate or starting material for preparing entecavir **21**. In the ester of formula **66**, R is a C_1 to C_4 alkyl or benzyl, preferably methyl; R^a is allyl, phenyl, C_1 to C_6 alkylphenyl or C_1 to C_6 alkoxyphenyl, more preferably R^a is selected from phenyl, C_1 to C_3 alkylphenyl, and C_1 to C_3 alkoxyphenyl; and R^b is C_1 to C_6 alkyl, preferably methyl. The ester can be prepared by any method that provides the ester in
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high diastereomeric and enantiomeric purity. A preferred procedure is shown in **Scheme 1**, wherein sodium cyclopentadienide **62** is treated with a silylating reagent, *e.g.*, $R^a(R^b)_2SiY$, wherein *Y* is a leaving group, *e.g.*, phenyldimethylchlorosilane wherein R^a is phenyl, R^b is methyl, and *Y* is Cl. The reaction may be carried out in a solvent such as MTBE and/or THF. The resulting silane moiety serves as a masked hydroxy group that can be unveiled later in the synthetic process. The product of the silylation reaction can then be elaborated using a 2+2 cycloaddition reaction with ketene, *e.g.*, generated from dichloroacetyl chloride and an appropriate base (*e.g.*, Et_3N , NaOH, KOH, $NaHCO_3$, $KHCO_3$, Na_2CO_3 , K_2CO_3 , TBAH, etc.), to give the cyclobutanone of formula **63**. The cyclobutanone can then be opened with a suitable base (*e.g.*, Et_3N , NaOH, KOH, $NaHCO_3$, $KHCO_3$, Na_2CO_3 , K_2CO_3 , TBAH, etc.), and the resulting intermediate reduced with a suitable reducing agent, *e.g.*, $NaBH_4$, to provide the carboxylic acid of formula **64**.

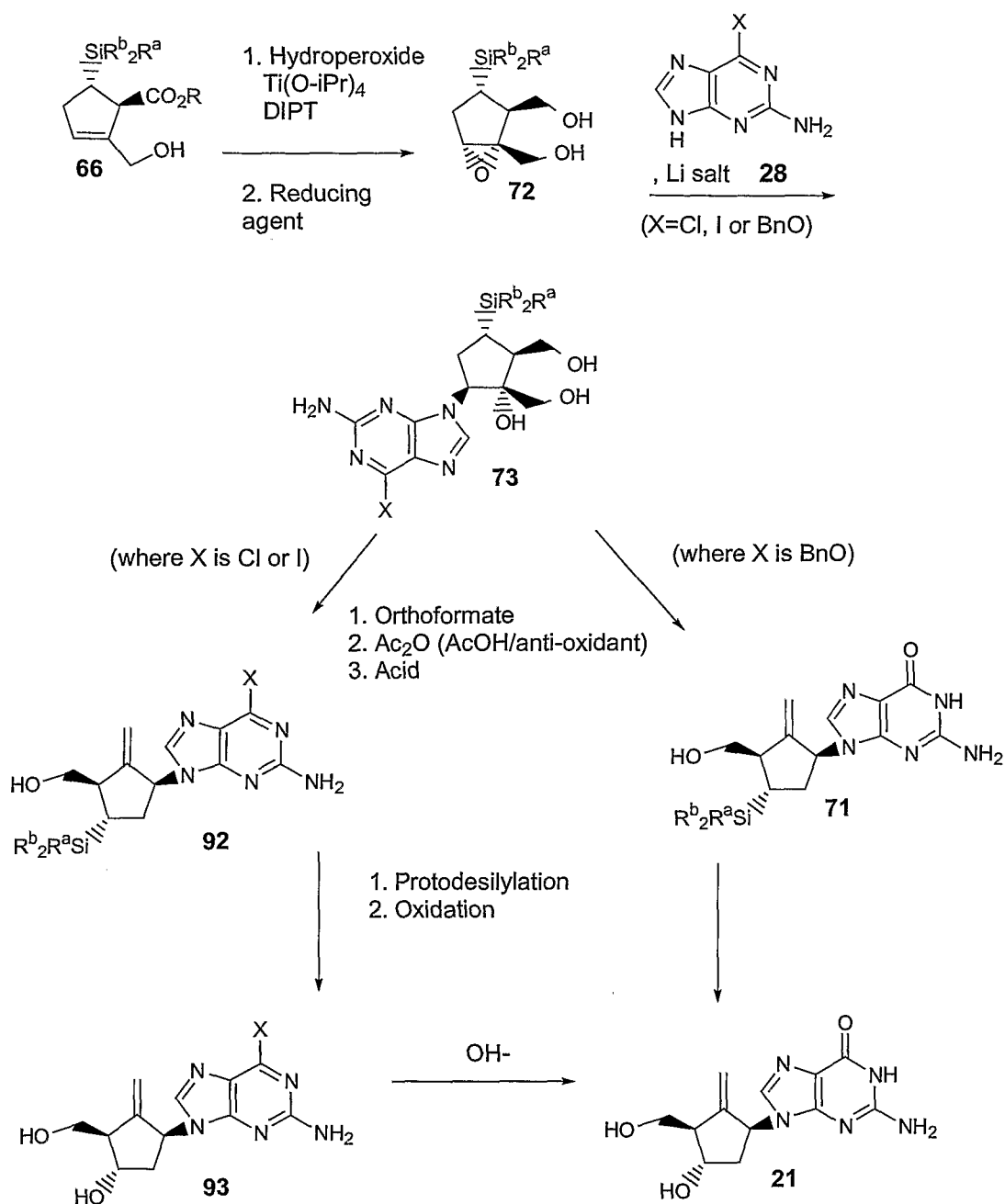
Resolution of the enantiomers of the carboxylic acid **64** can be accomplished by salt formation with chiral amines (CAs) and separation of the resulting diastereomeric salts. A diastereomeric mixture of ammonium salts of the carboxylic acid of formula **64** is preferably prepared using *R,R*-(-)-2-amino-1-(4-nitrophenyl)-1,3-propanediol. Those of ordinary skill in the art will appreciate that other chiral amines can be used to achieve the resolution of the enantiomers of the carboxylic acid of formula **64**. These amines include, for example, (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine, (i>R)-(-)-1-cyclohexylethylamine, D-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1*S*,2*S*)-(+)-1,2-diaminocyclohexane, dehydroabietylamine, (1*R*,2*R*)-1,2-diaminomethylcyclohexane, cinchonidine and cinchonine.

Separation of the resulting diastereomeric salts can be accomplished by any separation procedure known to those of ordinary skill in the art, such as chromatography or crystallization. Separation of the diastereomeric salts is preferably effected by crystallization. For example, the diastereomerically enriched ammonium salt of formula **65A** (where the chiral amine used is *R,R*-(-)-2-amino-1-(4-nitrophenyl)-1,3-propanediol) can be isolated by crystallization from EtOH. The ammonium salt of formula **65A** isolated by this procedure can have a chemical purity

of 98% and 98% de Conversion of the ammonium salt of formula **65A** to the ester of formula **66** (R is alkyl) can be accomplished by heating in an acidic solution, *e.g.*, MeOH and an appropriate acid, such as sulfuric acid or p-toluenesulfonic acid, or HCl in methylene chloride. Alternatively, compound **65A** can be converted into a free acid
5 which is subjected to esterification with alcohol, *e.g.*, MeOH, in the presence of PTSA, at refluxing conditions, to provide compound **66**.

PROCESS B

SCHEME 2



Process B of the invention comprises preparing entecavir **21**, via coupling an epoxide of formula **72**, with a substituted guanine derivative to prepare a carbocyclic nucleoside, the compound of formula **73**, which is then elaborated to the compound **21**. One embodiment of Process B is depicted in **Scheme 2**. In this process, a preferred starting material for the epoxide of formula **72** is an ester of formula **66** (which can be prepared as described in **Scheme 1**). The compound of formula **66** can be epoxidized and the ester group can be reduced to furnish the cyclopentane epoxide

of formula **72** in high diastereomeric purity. For example, the compound of formula **66** can serve as starting material for a diastereoselective epoxidation reaction. In one embodiment, the cyclopentane epoxide of formula **72** is formed after the epoxidation and reduction steps in at least 96% de. The diastereoselective epoxidation is effected with a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst, such as a transition metal catalyst. Preferably, the homochiral ester is 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 dry DCM or toluene. Methods suitable for effecting the catalytic epoxidation reactions are described in United States Patent Nos. 4,471,130; 4,594,439; and 4,900,847, incorporated herein by reference. After workup, the crude product can be carried on in the synthesis without further purification.

The crude product from the epoxidation reaction is treated with a reducing reagent that selectively reduces the ester group to an alcohol, such as, *e.g.*, NaBH₄, LAH, lithium borohydride, diisobutylaluminum hydride, sodium bis(2-methoxyethoxyaluminum) hydride, and the like. In one embodiment, the reducing agent used in the reaction is NaBH₄ in IPA. The reduction provides the cyclopentane epoxide having the formula **72**.

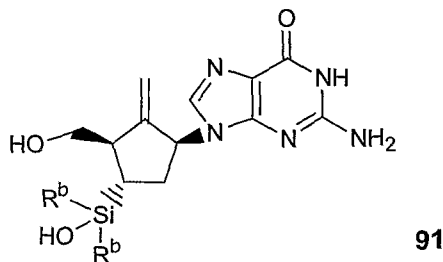
The cyclopentane epoxide of formula **72** can then be heated, for example, to about 80°C with an alkali metal salt, *e.g.*, a lithium salt, of the purine compound of formula **28**, wherein X is Cl, I, or benzyloxy (BnO) in a dipolar aprotic solvent such as DMF to prepare the compound of formula **73**. For example, the lithium salt of 2-amino-6-O-benzyloxypurine is prepared by treatment with base such as LiOH or LiH. This coupling reaction to prepare the carbocyclic nucleoside is advantageous in that it provides a high N-9 to N-7 ratio (*e.g.*, N-9:N-7 >20:1), allows convenient workup and purification procedures, and provides useful yields of the compound of formula **73**. For example, after water workup, the crude product of the coupling reaction of the purine compound of formula **28** wherein X is BnO, and the cyclopentane epoxide of formula **72**, can be purified by simple recrystallization from a solution of EtOAc-hexanes to provide the compound of formula **73** in 65% yield.

The compound of formula **73**, wherein X is BnO, can then be converted to the compound of formula **71** by converting the vicinal diol moiety to an alkene.

Analogously, the compound of formula **73**, wherein X is Cl or I, can be converted to compound **92** by converting the vicinal diol moiety to an alkene. In one embodiment, the vicinal diol of the compound of formula **73** is converted to an alkene as in compounds **71** and **92**, by a two-step procedure. In the first step, the compound of formula **73** is treated with an orthoformate derivative, such as DEMA, DiPMA, TiPOF, TEOF, or TMOF, in the presence of an acid such as PPTS or TFA. The reaction is preferably carried out in an inert solvent such as DCM, toluene, or *tert*-butyl methyl ether, at room temperature for a sufficient amount of time to form a product comprising a diastereomeric mixture of dioxolanes. In the second step, the diastereomeric mixture of dioxolanes is heated with acetic anhydride, preferably in the presence of acetic acid and an antioxidant, *e.g.*, BHT, to form the alkene. In embodiments wherein X is BnO, the crude product from the acetic anhydride treatment can then be heated with acid such as aqueous mineral acid or aqueous organic acid, *e.g.*, HCl or MSA, to hydrolyze the 6-benzyloxy group (as well as an 2-N-acetyl group formed in the acetic anhydride treatment) to provide the methylene compound of formula **71**, or its salts (*e.g.*, MSA or HCl salts). The intermediates of formulas **71** and **92** can be isolated in the form of a salt by treatment with an acid such as HCl, MSA, (1S)-(+)-10-camphorsulfonic acid, (R)-chloropropionic acid, N-[(R)-1-(1-naphthyl) ethyl] phthalamic acid, L-tartaric acid, dibenzyl-L-tartaric acid, L-lactic acid, (1R, 3S)-camphoric acid, L-aspartic acid, (S)-citronellic acid, etc.

Preparation of the final compound **21** from compound **71** can then be accomplished by converting the silane moiety to a hydroxy moiety. This conversion can be achieved via protodesilylation of the silane moiety followed by oxidation with an oxidizing source, such as, for example, hydrogen peroxide. 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 or acid as described below in **Scheme 6**. Upon debenzylation (which may, in some

embodiments, be achieved in the protodesilylation step (e.g., when MSA or FMSA are used), there is provided the protodesilylated intermediate of formula **91**

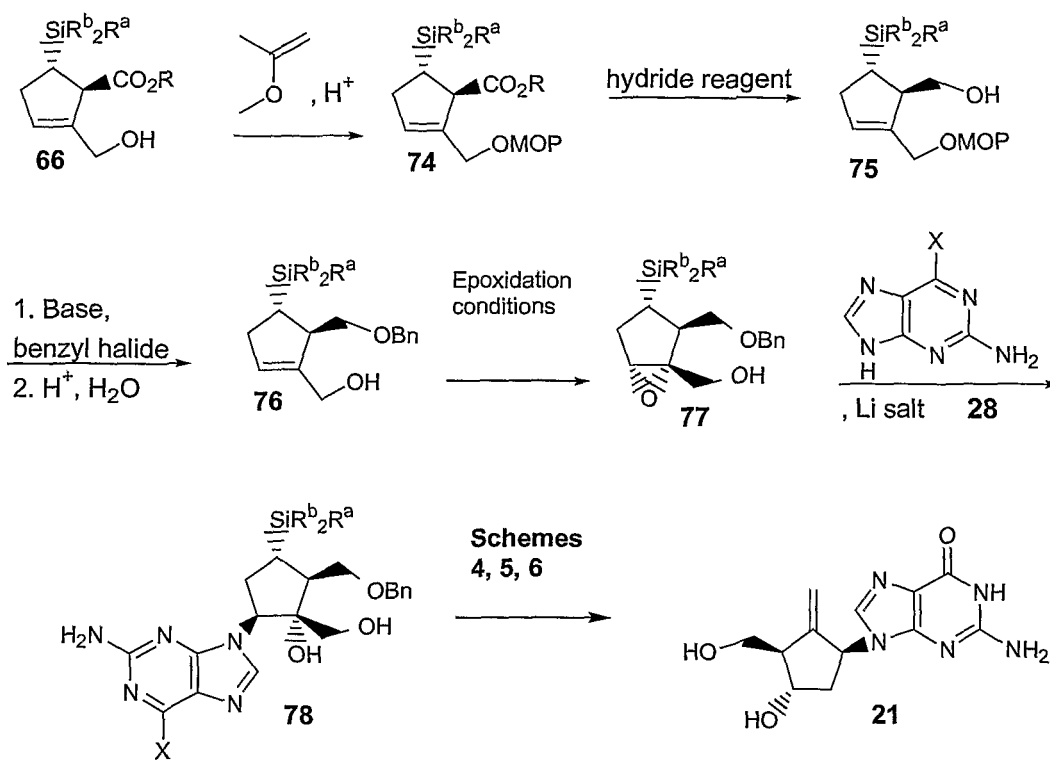


The protodesilylated intermediate **91** can then be oxidized. The oxidizing agent(s) can be selected in view of the reagent used to achieve protodesilylation. For example, when boron trifluoride-acetic acid complex is used, the compound can be oxidized with hydrogen peroxide and KHCO_3 , to provide the target compound of formula **21**, and when a Bronsted acid is used, compound **91** may be oxidized with hydrogen peroxide, KHCO_3 , and KF . Other acids and oxidizing agents that may be useful may be recited above. Alternatively, conversion of the silyl moiety to a hydroxy group may be achieved as described in Scheme 6, below, and additional methods that may be useful for the transformation of the silyl group to the hydroxy group are described in 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. The compound of formula **21** can be further purified, for example, by recrystallization from water, and/or via resin purification as described below in Process K.

In alternate embodiments of Process B, the purine **28**, coupled with cyclopentane epoxide **72** to give compound **73**, is other than 2-amino-6-benzyloxypurine, such as 2-amino-6-chloropurine or 2-amino-6-iodopurine. In this embodiment, compound **73** is upon treatment with the orthoformate, acid, etc., converted to compound **92**, which upon protodesilylation and oxidation is converted to compound **93**. In this instance, wherein 2-amino-6-chloropurine or 2-amino-6-iodopurine is used, an additional treatment with aqueous base or acid (preferably aqueous base) may be utilized to convert the halo group of compound **93** into the 6-oxo moiety. For example, aqueous NaOH solution may be used to convert the compound of formula **93** to the compound of formula **21**.

PROCESS C

SCHEME 3



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The ester of formula **66** can also be converted to the compound of formula **21** by the methods of Process C. One embodiment of Process is depicted in **Scheme 3**. In contrast to Process B, the epoxidation reaction of the cyclopentane in Process C is performed after the ester moiety has been reduced. In Process C, the primary alcohol moiety of the ester of formula **66** (R= alkyl) is protected with a protecting group such as a MOP by treatment with 2-methoxypropene and a catalytic amount of an acid, such as PPTS, in an inert solvent such as toluene, to yield the compound of formula **74**. The carboxylic ester moiety of **74** can be reduced with a hydride reagent, preferably Red-Al® or LAH. In one embodiment, the ester moiety of **74** is reduced, preferably after the addition of a suitable base, such as with a tertiary amine base, *e.g.*, Et₃N, in the same reaction vessel to give the compound of formula **75**. In another embodiment, the ester moiety of **74** is reduced with a hydride reagent after workup, to give compound **75**. The resultant alcohol moiety of the compound of formula **75** is first protected with a protecting group that is resistant to hydrolysis conditions that are

then used to remove the MOP group. For example, the alcohol moiety of the compound of formula **74** can be treated with a base (*e.g.*, KOtBu, KHMDS, NaH, phase-transfer catalyst conditions using 50% NaOH), and a benzyl halide, *e.g.*, benzyl bromide or benzyl chloride, preferably in solvent such as toluene or THF, to protect the alcohol moiety as a benzyl ether. The MOP acetal can then be hydrolyzed by addition of aqueous acid, such as 1 N HCl, to give the allylic alcohol of formula **76**. Other protecting groups known in the field may be found in the literature, such as Greene and Wuts, cited above in the general definitions herein.

The allylic alcohol of formula **76** serves as starting material for a diastereoselective epoxidation reaction, wherein the product, the cyclopentane epoxide of formula **77**, is formed in high diastereomeric purity. For example, the epoxidation can be effected using a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst, such as a transition metal catalyst. Alternately, the diastereoselective epoxidation may be performed with a peracid, such as MPPA, as described in Scheme 14 and Example 12. Preferably, diastereoepoxidation is performed with the homochiral ester DIPT, the hydroperoxide TBHP or CHP, and the metal catalyst Ti(O-*i*Pr)₄. Preferably, the reaction is carried out in an inert solvent such as toluene, methylene chloride, etc. In one embodiment, the cyclopentane epoxide of formula **77** is formed in at least 96% de

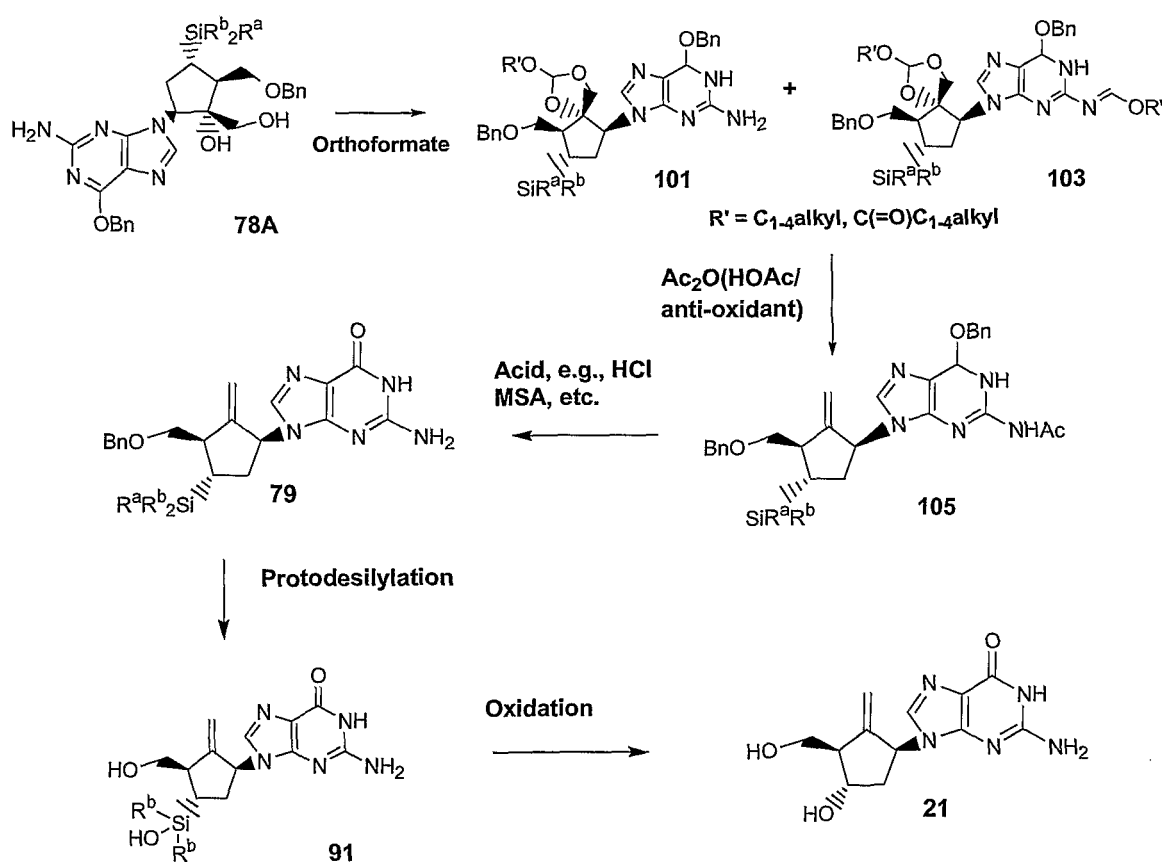
The cyclopentane epoxide of formula **77** can then be reacted (*e.g.*, at elevated temperature, *e.g.*, preferably at about 80°C) with an alkali metal salt of purine compound of formula **28**, wherein X is Cl, I or BnO, in a dipolar aprotic solvent such as DMF to prepare the compound of formula **78**. Preferably, the purine compound of formula **28** is 2-amino-6-benzyloxypurine. The 2-amino-6-benzyloxypurine is commercially available or can be prepared from 6-chloroguanine and the sodium salt of benzyl alcohol (*e.g.*, upon treatment with NaOH in benzyl alcohol, toluene, and MeOH, or upon treatment with the sodium salt of benzyl alcohol, benzyl alcohol, in EtOH/water.). The alkali metal salt can be generated in situ by reaction of 2-amino-6-O-benzyloxypurine with, for example, LiH or LiOH. The crude compound of formula **78**, wherein X is benzyloxy, can be isolated and purified. For example, the crude

compound **78** can be isolated upon addition of IPA and water, then purified by recrystallization with solvents or solvent mixtures known in the field.

The compound of formula **78** can then be converted to the compound of formula **21** using various reaction sequences analogous to those used to convert the compound of formula **73** to the compound of formula **21** in Process B, which are further described in Schemes 4, 5 and 6, below.

PROCESS C(a)

SCHEME 4



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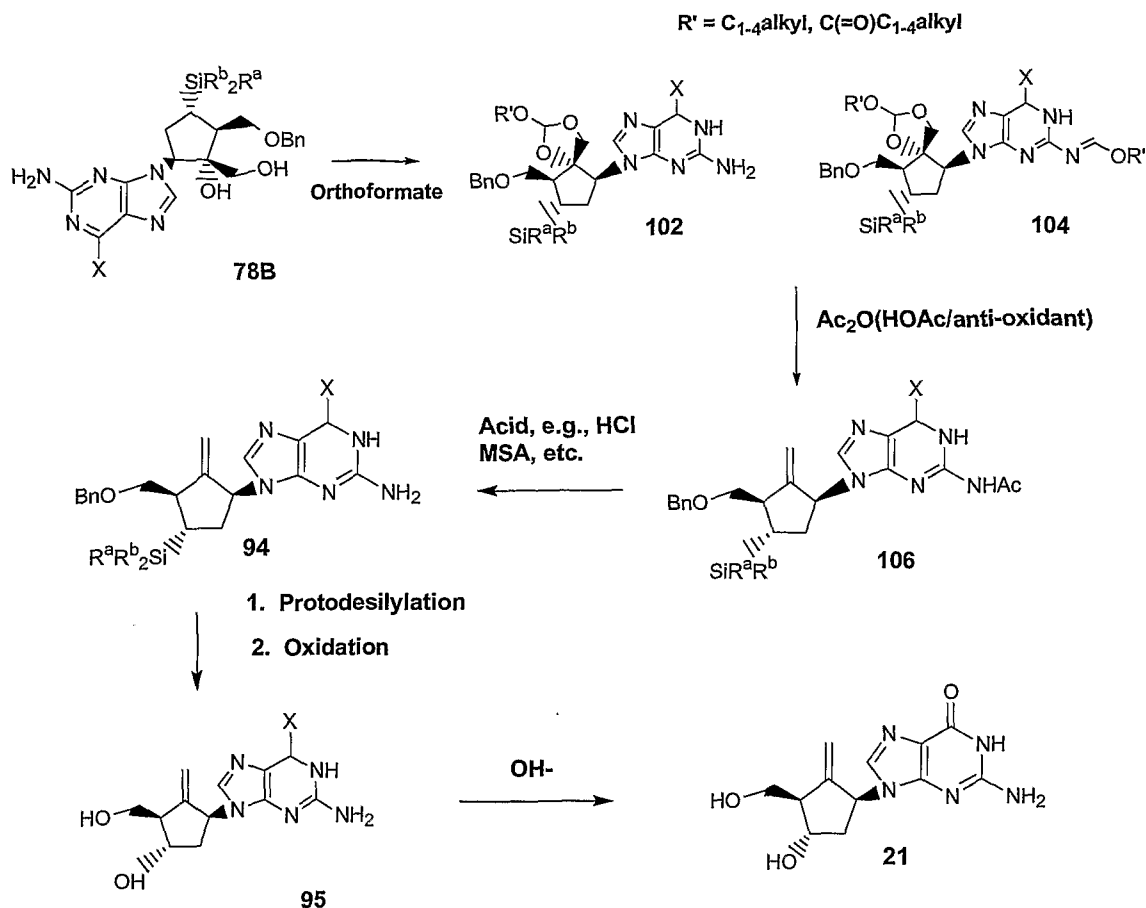
Scheme 4 describes a process for converting compound **78A** (compound **78** wherein X is OBn), to the compound of formula **21**. Compound **78A** can be treated with an orthoformate derivative, such as DEMA, DiPMA, TMOF, TiPOF, TEOF, etc., preferably in an inert solvent such as toluene, DCM, MTBE etc., as described in **Scheme 2**, in the presence of a catalytic amount of an acid such as TFA or PTSA, or an acid catalyst such as PPTS, etc., to form a product comprising a diastereomeric

mixture of dioxolanes, *e.g.*, compounds **101** and **103**. The diastereomeric mixture of dioxolanes **101** and **103** can be heated with acetic anhydride preferably in the presence of acetic acid and an anti-oxidant, such as BHT, to form alkene having the formula **105**. The crude product **105** can then be heated with acid, such as with aqueous HCl or MSA, in an appropriate solvent such as MeOH and water, to hydrolyze the 6-benzyloxy and N-acetyl groups and provide the methylene compound of formula **79**. The intermediate **79** can be isolated in the form of a salt by treatment with an acid such as HCl, MSA, (1S)-(+)-10-camphorsulfonic acid, (R)-chloropropionic acid, N-[(R)-1-(1-naphthyl) ethyl] phthalamic acid, L-tartaric acid, dibenzyl-L-tartaric acid, L-lactic acid, (1R, 3S)-camphoric acid, L-aspartic acid, (S)-citronellic acid, etc. In one embodiment, intermediate **79** or salts thereof are further purified by recrystallization, *e.g.*, intermediate **79** salts thereof are treated with NaOH in an organic solvent and crystallized before proceeding to the next step.

Preparation of the final compound of formula **21** from compound **79**, or salts thereof, can then be accomplished by converting the silane moiety to a hydroxy moiety. This conversion can be achieved via protodesilylation of the silane moiety with reagent(s) selected to provide the intermediate compound **91**, followed by oxidation. Protodesilylation may be achieved with boron trifluoride-acetic acid complex or a Bronsted acid in inert solvent, *e.g.*, MSA in methylene chloride. Oxidation may be carried out as described in **Scheme 2**, using oxidizing agents and additives appropriately selected, *i.e.*, depending on the reagent used for protodesilylation and the oxidizing agent, *e.g.*, in the case of a Bronsted acid, hydrogen peroxide in the presence of KHCO₃ and KF may be used, to provide compound **21**. Compound **21** can be further purified, for example, by recrystallization from water, and/or via resin purification as described below in Process K.

PROCESS C(b)

SCHEME 5



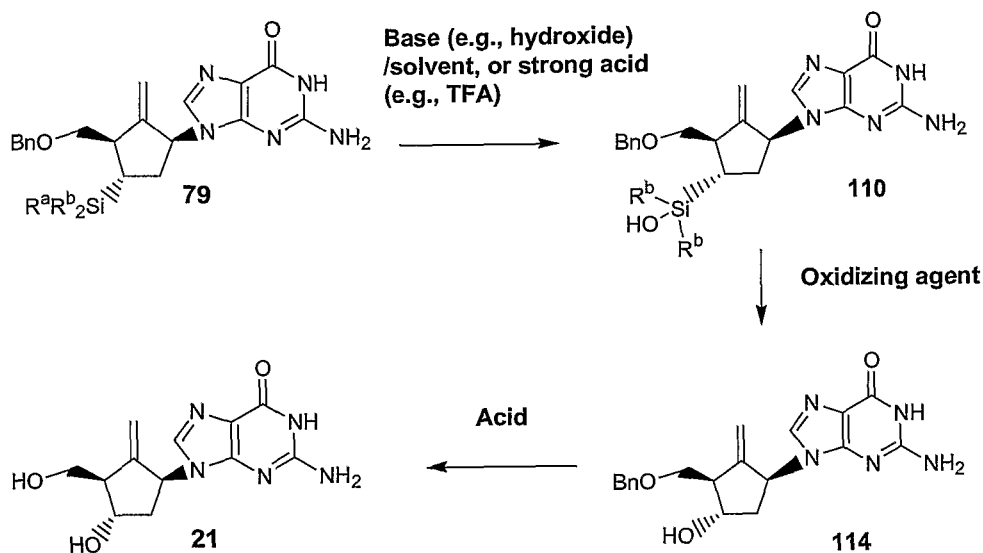
Scheme 5 describes an alternate process for making compound **21**, wherein the purine **28** of **Scheme 3** is 2-amino-6-chloropurine or 2-amino-6-iodopurine, such that coupling with cyclopentane epoxide **77**, yields compound **78B** (compound **78** wherein X is Cl or I). As in **Scheme 4**, compound **78B** can be treated with an orthoformate derivative to form a product comprising a diastereomeric mixture of dioxolanes **102** and **104**, which can be heated with acetic anhydride, preferably in the presence of acetic acid and an anti-oxidant, *e.g.*, BHT, to form alkene **106**. The product **106** can then be heated with acid, such as HCl or MSA, as described in **Scheme 4**, to hydrolyze the acyl group and provide compound **94**, or salts thereof, which retain the 6-position X group. Protodesilylation, debenzylolation, and oxidation as described in **Scheme 4**, provides the intermediate compound **95**. Compounds **94** and **95** can be isolated in the form of their salts by treatment with acid(s) as previously described for compound **79**. Compound **95** can then be treated with aqueous base or acid (preferably, an aqueous base) to convert the halo group of compound **95** into the

6-oxo moiety of compound **21**. As may be appreciated, with Process C(b) an additional step may be used for the conversion of compound **78** to **21**, as compared with Process C(a).

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PROCESS C(c)

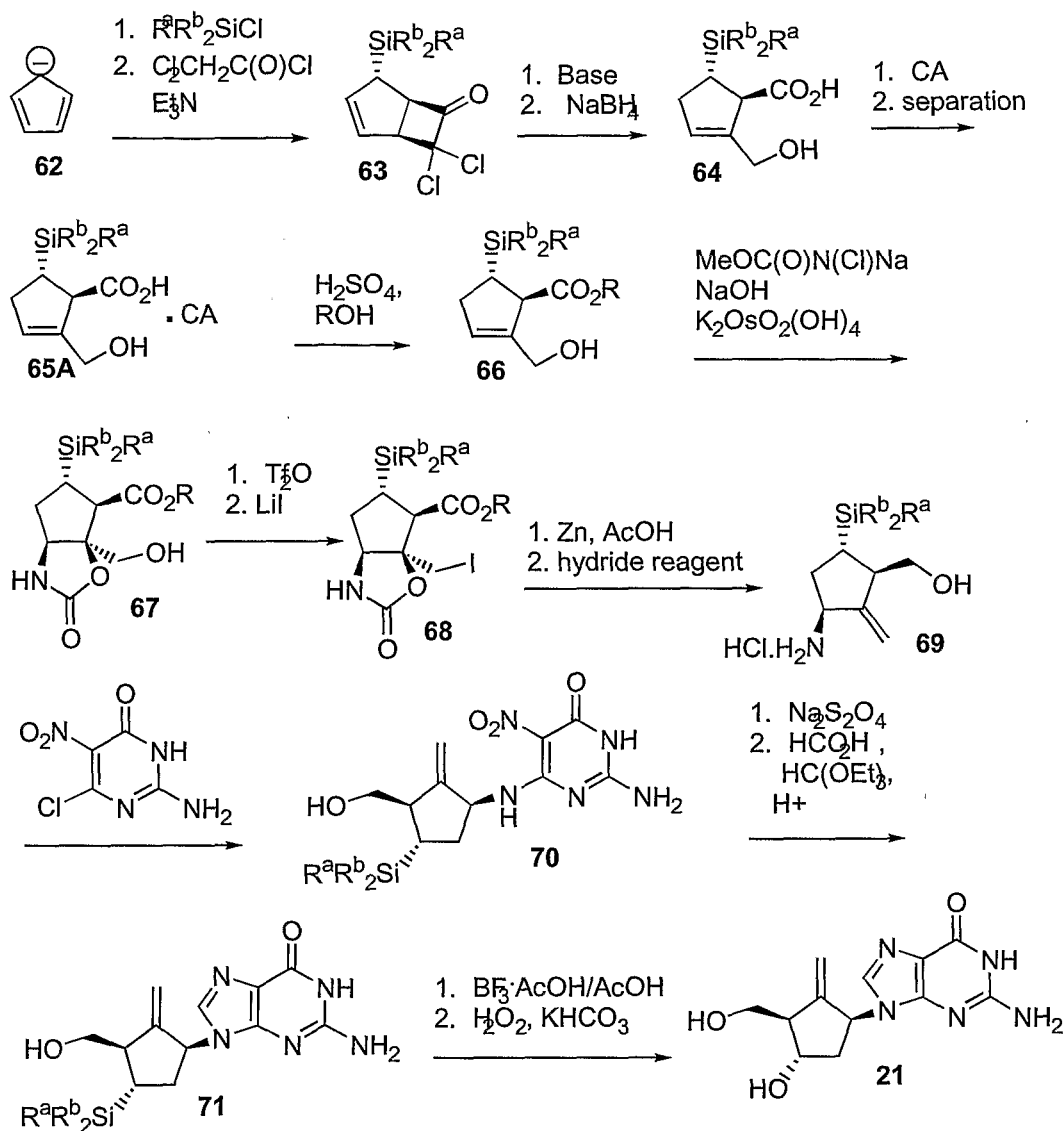
SCHEME 6



Scheme 6 shows an alternate process for preparing compound **21** from compound of formula **79**, which is shown in **Scheme 4**. As compared with **Scheme 4**, in this scheme a different base or acid is used to achieve the protodesilylation, followed by oxidation and debenzylation to convert compound **79** to compound **21**. Compound **79** is treated with a base such as a hydroxide, *e.g.*, NaOH or KOH, or alkoxide such as KOtBu, in a polar aprotic solvent such as DMF, DMSO, or NMP, or with a strong acid such as TFA, and heated at a time and temperature sufficient to achieve the conversion to intermediate **110**. Compound **110** can then be oxidized with hydrogen peroxide in the presence of KHCO₃ and KF in a solvent such as MeOH, to provide intermediate **114**. Intermediate **114** can be debenzylated upon treatment with a Lewis acid such as BCl₃, BBr₃, etc., or a Bronsted acid such as MSA, TFMSA, etc., in solvent such as DCM, and the reaction mixture can be neutralized with base such as NaOH, to provide compound **21**. Compound **21** can be further purified by recrystallization from water and/or resin purification as described below.

PROCESS D

SCHEME 7



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In Process D of the invention, the ester of the formula **66** (Scheme 1) can be converted to the compound of formula **21** using different synthetic methods. In Process D, the ester of formula **66** is aminohydroxylated to provide a chiral oxazolidinone of the formula **67**. After a series of synthetic steps, a pyrimidine carbocyclic nucleoside, the compound of formula **70** is prepared. The pyrimidine carbocyclic nucleoside can be elaborated to a purine containing compound, the methylene compound of formula **71** which is subsequently converted to the compound

of formula **21** by, for example, the oxidation procedure described in the final steps of Processes B and C. One embodiment of Process D is depicted in **Scheme 7**.

Aminohydroxylation conditions are used to convert the ester of formula **66** to the oxazolidinone of formula **67**. Amino hydroxylation procedures are analogous to those described in Li, G.; Angert, H.; Sharpless, K.B. *Angew. Chem. Int. Ed.*, (1996), at 2813. Preferably, the aminohydroxylation conditions comprise treatment with: the reagent prepared from the treatment of methyl carbamate with *tert*-butyl hypochlorite and sodium hydroxide [*i.e.*, MeOC(O)N(Cl)Na]; and potassium osmate in an inert solvent such as DCM. Alternative reagents include EtOC(O)N(Cl)Na and BnOC(O)N(Cl)Na. Preferably, the chiral oxazolidinone of formula **67** is formed in at least 96% de

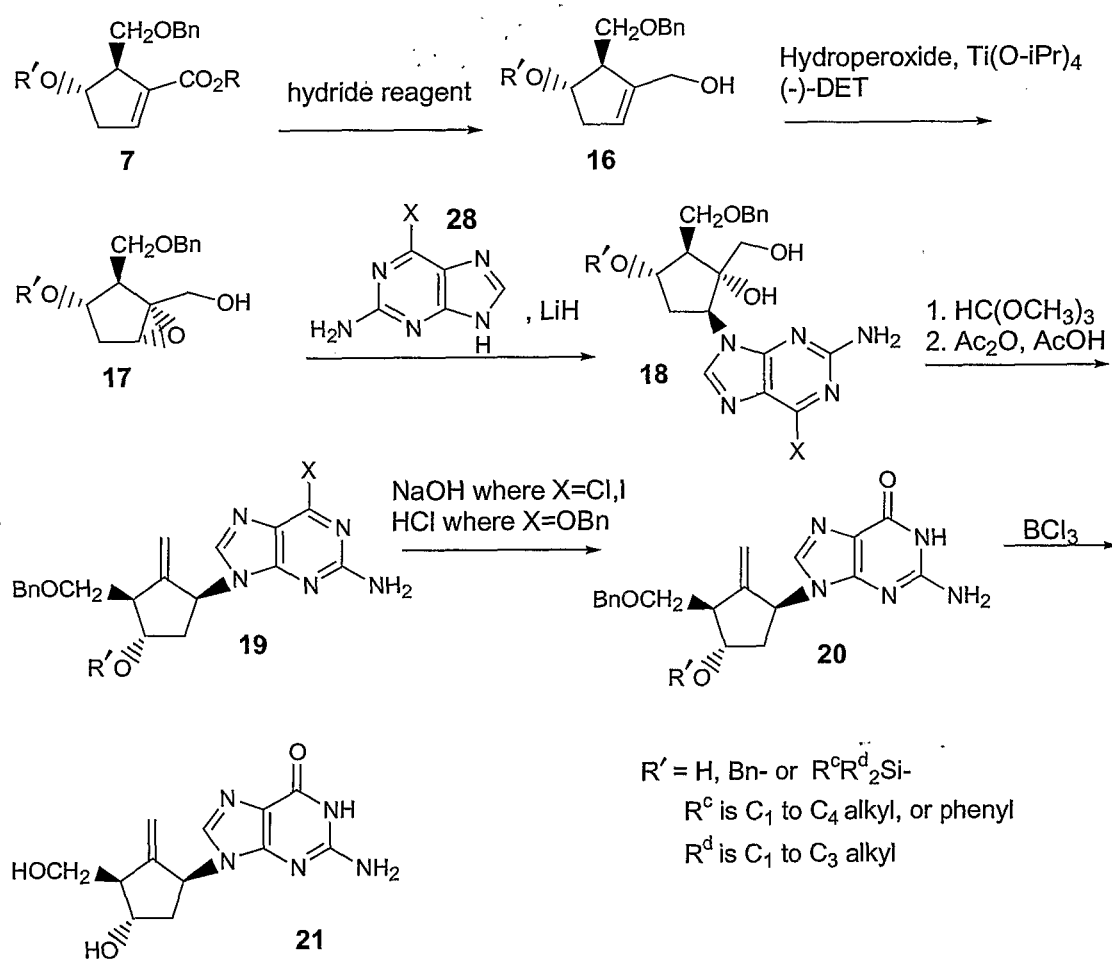
The primary alcohol moiety of the oxazolidinone of formula **67** can then be converted to an iodide. For instance, in one preferred procedure, the compound of formula **67** is treated with trifluoromethanesulfonic anhydride (Tf₂O) in the presence a tertiary amine base such as pyridine, and subsequently treated with an iodide salt, e.g., lithium iodide. The resulting iodide of the formula **68** can then be converted to a methylene compound of formula **69** by a two step procedure. In the first step the iodide of formula **68** is treated with zinc powder and acetic acid. The ester moiety of the resulting intermediate can then be reduced to a primary alcohol in the second step by a hydride reagent such as sodium bis[2-methoxyethoxyaluminum] hydride to give the amine of the formula **69**.

The amine of the formula **69** is subsequently reacted with a substituted chloropyrimidine. The amine can be condensed, for example, with 2-amino-6-chloro-5-nitro-4-(3H)-pyrimidinone in the presence of a tertiary amine base, preferably triethylamine, in refluxing n-butanol to give a pyrimidine compound of formula **70**. The pyrimidine compound of formula **70** can then be converted to a purine derivative by a two step procedure. In the first step, the nitro moiety of the pyrimidine is reduced with, for example, sodium dithionite, to give a triaminopyrimidine intermediate. Alternative reducing agents and conditions that can also successfully reduce the nitro group include NaBH₄/THF, NaBH₄-BiCl₃, Sn/HCl, SnCl₂, Mg/(NH₄)₂SO₄/MeOH, CuBr·SMe₂, TiCl₂(Cp)₂/Sm, iron and nickel catalyzed

procedures. In the second step, treatment of the triaminopyrimidine intermediate with formic acid, hydrochloric acid, and an orthoformate derivative, *e.g.*, triethylorthoformate, effects cyclization and provides the methylene compound of formula **71**. The methylene compound of formula **71** can be converted to the compound of formula **21** by the oxidation procedure described in the final steps of Processes B and C.

PROCESS E

SCHEME 8



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Process E of the invention comprises using an alternative carbocyclic sugar precursor, an allylic alcohol of the formula **16**, to prepare the compound of formula **21**. Process E is similar to Processes B and C as all three processes use cyclopentane epoxide intermediates to accomplish a coupling reaction with a guanine precursor. In a first embodiment of Process E, the protecting group that serves to protect the

secondary alcohol of the cyclopentane ring of **16** is a benzyl/substituted benzyl ether, while in a second embodiment a silyl ether protecting group (R^cR^dSi) protects the same secondary alcohol. (In this instance, R^c is linear or branched C_1 to C_4 alkyl, or phenyl, and R^d is linear or branched C_1 to C_3 alkyl.) A preferred benzyl ether
5 protecting group is benzyl ether, per se, while a preferred silyl ether is *tert*-butyldimethyl silyl ether. The difference in these protecting groups changes the identity of the intermediates for the different embodiments of Process E. Certain embodiments of Process E are depicted in **Scheme 8**.

In one embodiment of Process E, the allylic alcohol of formula **16** is obtained
10 through a reduction of the ester of the formula **7**. The ester of the formula **7**, wherein R and R' are as defined above, can be obtained by Processes E(a)-E(d) that are described below. The ester of formula **7** can be reduced with hydride reagents that selectively effect 1,2-reduction of the ester. For example, in one embodiment, diisobutylaluminum hydride reduces the ester group and provides the allylic alcohol
15 of the formula **16**.

The allylic alcohol of formula **16** 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 the formula **17**. In one embodiment, the
20 homochiral diester is (-)-diethyl tartrate [(-)-DET], 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.

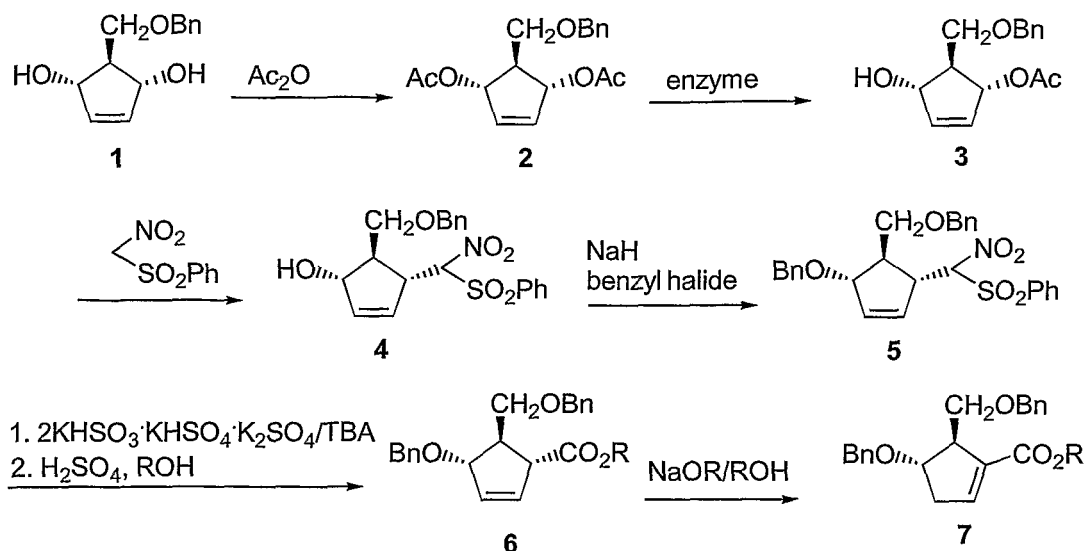
The epoxide of formula **17** can be subsequently coupled to an alkali metal salt (e.g., lithium) of a purine compound of formula **28**, wherein X is Cl, I or BnO, in a
25 dipolar aprotic solvent such as DMF to afford the compound of formula **18**. Preferably the coupling of the cyclopentane epoxide of the formula **17** is conducted with the lithium salt of 2-amino-6-benzyloxypurine. The compound of formula **18**, wherein X is benzyloxy, can be purified by crystallization from solvents such as ethyl acetate and hexanes. Typically the yield of the coupling step after purification is at
30 least 75%.

The vicinal diol moiety of the compound of formula **18** can then be converted to an alkene moiety. For example, the diol moiety can be converted to an alkene by procedures that are analogous to those used in Processes B and C. Accordingly, in one embodiment, the compound of formula **18** 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 the methylene compound of formula **19**. Alternatively, this reaction can be performed in the presence of antioxidant such as BHT as described previously. In the instance of the second embodiment of Process E (where the secondary alcohol of **18** is protected by a silyl ether group), the silyl ether protecting group is simultaneously hydrolyzed during the acetic anhydride/ acetic acid treatment step (*i.e.*, R' is H in the methylene compound of formula **19**).

In embodiments of the Process E, wherein X 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 **19** with aqueous mineral acid, such as 2 N HCl to give the methylene compound of formula **20**. In embodiments of Process E, wherein X is Cl or I, the 6-halo group can be hydrolyzed by treatment with aqueous acid or base (e.g., aqueous hydroxide solution). Removal of the remaining benzyl ether protecting group(s) on the cyclopentane ring, such as by boron trichloride treatment in an inert solvent, *e.g.*, DCM, provides the compound of formula **21**.

PROCESS E(a)

SCHEME 9



The ester of formula 7 can be prepared by methods that yield scaleable quantities of enantiomerically pure ester. In Process E(a) the ester of formula 7 can be prepared from a diol of the formula 1, which is prepared according to procedures described in *J. Am. Chem. Soc.* **1989**, 3456 and *J. Am. Chem. Soc.* **1996**, 9526. One embodiment of Process E(a) is depicted in **Scheme 9**.

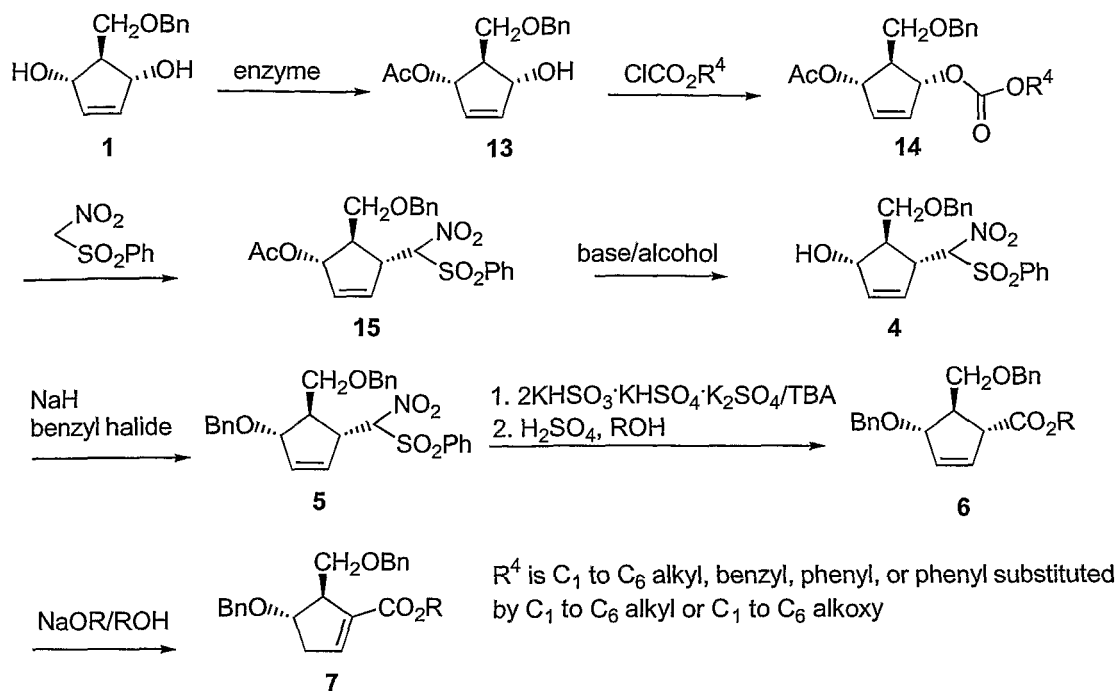
The diol of formula 1 can be acetylated with, for example, acetic anhydride and pyridine to provide a diacetate of the formula 2. Selective enzymatic hydrolysis of one of the prochiral acetate functions of the diacetate provides enantiomerically pure monoacetate of the formula 3. Preferably the enzyme used is a hydrolase such as Lipase PS-30 from *Pseudomonas cepacia* or Pancreatin. Preferably the enantiomeric excess of the product monoacetate of formula 3 is at least 96% ee, more preferably at least 98% ee. In some embodiments the enzyme is immobilized on a support, *e.g.*, polypropylene, to aid in recovery of the enzyme and facilitate reaction workup. The reaction is typically carried out in a mixture of a buffer and an organic solvent, preferably having a buffer/organic solvent ratio of about 3/1 to about 20/1, preferably about 9:1. The buffer is selected to have a buffering range effective to maintain the pH of the reaction mixture in a range effective to support enzyme catalysis, such as at about pH=7. For example, 25 mM potassium phosphate buffer can be used. In one embodiment the organic solvent is toluene.

The monoacetate of formula 3 can be coupled to phenylsulfonylnitromethane to provide a compound of formula 4. The coupling is preferably catalyzed by a palladium (0) catalyst such as tetrakis(triphenylphosphine)palladium in THF with a tertiary amine base, such as triethylamine. The secondary hydroxyl group of the compound of formula 4 is protected using a benzyl halide and a non-nucleophilic strong base such as sodium hydride to give the dibenzyl compound of formula 5. The dibenzyl compound of formula 5 can be oxidized, such as with potassium peroxymonosulfate: tetrabutyl ammonium, preferably in a solvent mixture of DCM and MeOH. The intermediate carboxylic acid can be esterified, for example, by directly heating with an alcohol (ROH), preferably MeOH, and sulfuric acid in the same reaction vessel to afford the ester of formula 6.

Isomerization of the double bond provides the desired ester of formula 7. The isomerization can be accomplished by heating the crude ester of formula 6 under basic conditions. Preferably the basic conditions comprise heating the ester with a sodium alkoxide/alcohol mixture. As will be apparent to those of ordinary skill in the art, the alkoxide and alcohol mixture are preferably selected so that transesterification of the ester moiety during the isomerization is minimized or eliminated. By way of example, if a methyl ester is desired for the compound of formula 7 (*i.e.*, R=methyl) then the basic conditions chosen for the isomerization are preferably sodium methoxide/MeOH. The ester of formula 7 can be purified by recrystallization from a mixture of solvents such as hexanes and *tert*-butyl methyl ether.

PROCESS E(b)

SCHEME 10



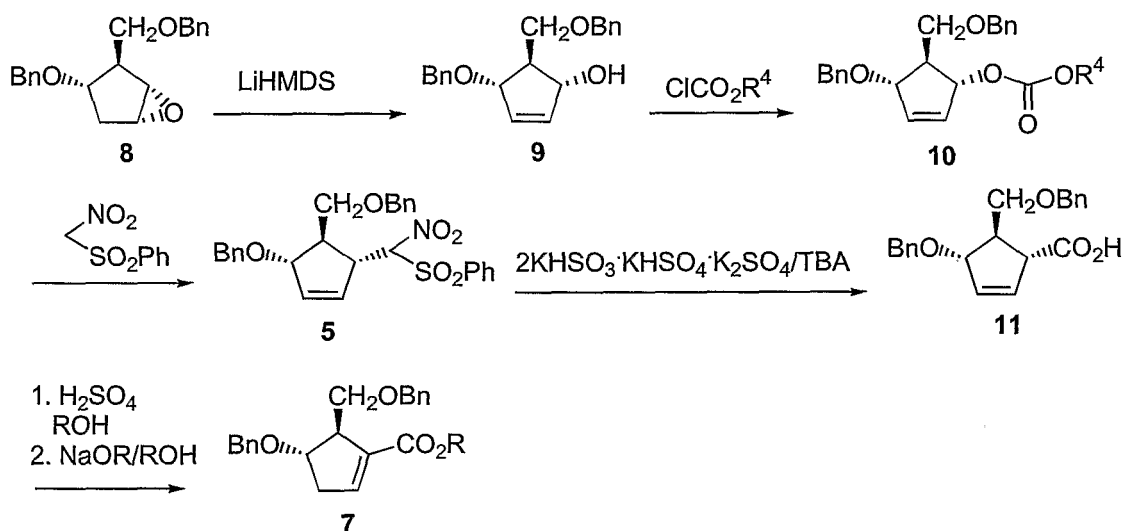
In Process E(b), the ester of formula 7 is prepared using alternative synthetic methods. One embodiment of Process E(b) is depicted in **Scheme 10**. The diol of formula 1 is selectively acetylated using a hydrolase enzyme, such as Lipase PS-30 or Pancreatin to generate enantiomerically enriched monoacetate compound of formula 13. Here again, the enzyme can be immobilized on a support. The acetylation reaction can be carried out in an organic solvent such as mixture of heptane: methyl *tert*-butyl ether. Preferably, the enantiomeric excess of the product, the monoacetate of formula 13, is at least 96% ee, more preferably at least 98% ee.

The monoacetate of formula 13 can be converted to the alkyl carbonate of the formula 14, wherein R⁴ is preferably C₁ to C₆ alkyl, benzyl, phenyl, or phenyl substituted by C₁ to C₆ alkyl, for example, by treatment with an activated alkyl carbonic acid derivative, such as methyl chloroformate, dimethyl carbonate, etc. Preferably, the conversion is accomplished with methyl chloroformate and a tertiary amine base, *e.g.*, pyridine, in an inert solvent, preferably DCM.

The alkyl carbonate of formula 14 can then be coupled with phenylsulfonylnitromethane to provide a compound of formula 15. The coupling is preferably catalyzed by a Pd(0) catalyst, *e.g.*, tetrakis(triphenylphosphine)palladium, tris(dibenzylideneacetone)dipalladium(0), bis(dibenzylideneacetone)-

palladium(0)-CHCl₃, in a solvent, *e.g.*, THF, with a tertiary amine base, such as triethylamine. The compound of formula **15** is treated with a base, *e.g.*, potassium carbonate in MeOH, to remove the acetate group and provide the compound of formula **4**. The secondary alcohol moiety can be protected as a benzyl ether group by reacting the compound of formula **4** with a benzyl halide, *e.g.*, benzyl bromide, preferably in the presence of a strong non-nucleophilic base, *e.g.*, sodium hydride, to give the compound of formula **5**. The compound of formula **5** can be converted to the ester of formula **7** by the methods already described in Process E(a).

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PROCESS E(c)SCHEME 11

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Alternatively, Process E(c) can be used to prepare the ester of formula **7** (where R'' is benzyl). One embodiment of Process E(c) is depicted in **Scheme 11**. A cyclopentane epoxide of the formula **8** serves as the chiral starting material. The cyclopentane epoxide of formula **8** can be prepared according to the procedure described in United States Patent No. 5,206,244, the disclosure of which is incorporated by reference as if fully set forth herein. An allylic alcohol of formula **9** is prepared by heating the epoxide of formula **8** with a strong non-nucleophilic base, *e.g.*, lithium hexamethyldisilazide in THF. After aqueous workup, the allylic alcohol of formula **9** can be used without further purification. Here again, the allylic alcohol

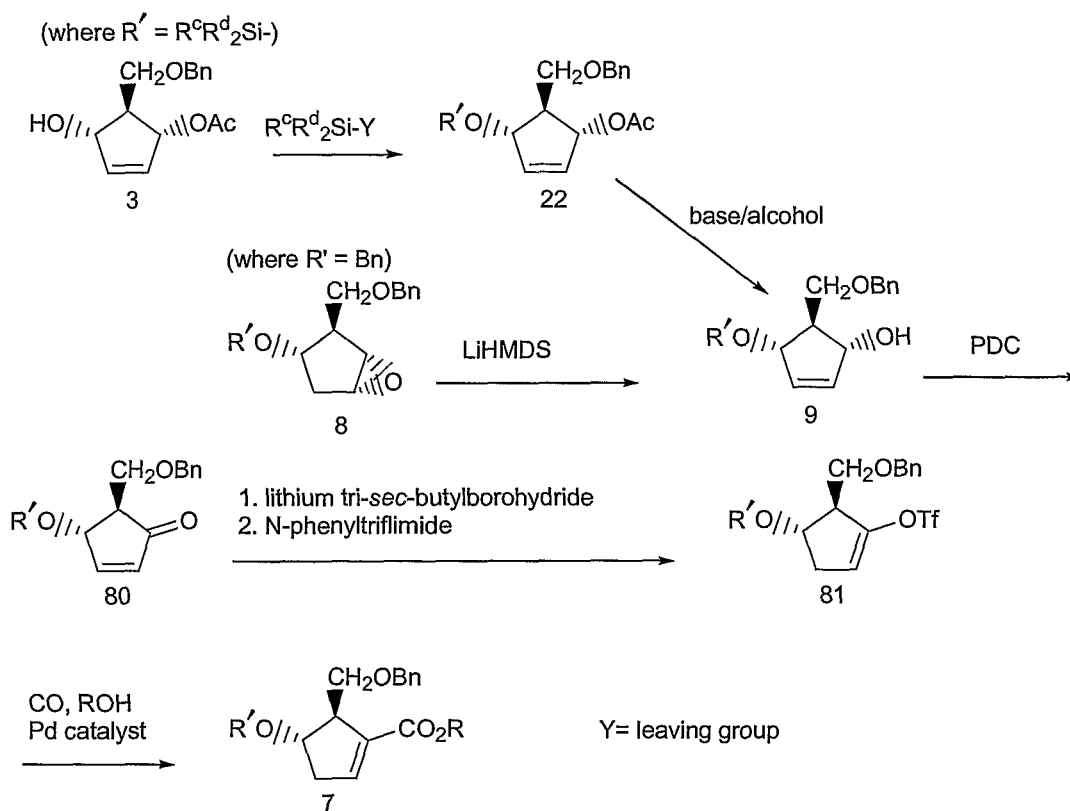
moiety can be converted to the alkyl carbonate group, wherein R^4 is preferably C_1 to C_6 alkyl, benzyl, phenyl, or phenyl substituted by C_1 to C_6 alkyl, for example, by treatment with an activated alkyl carbonic acid derivative, such as methyl chloroformate, dimethyl carbonate, etc to give the alkyl carbonate of the formula 10.

- 5 In one embodiment, the allylic alcohol of formula 9 is stirred with methyl chloroformate and a tertiary amine base, preferably pyridine, in an inert solvent, e.g., DCM, to give a methyl carbonate. The crude alkyl carbonate can be directly coupled to phenylsulfonylnitromethane in THF to provide a compound of formula 5. The coupling of the alkyl carbonate compound is preferably catalyzed by a palladium (0) catalyst such as tetrakis(triphenylphosphine)palladium in THF with a tertiary amine base, e.g. triethylamine. The compound of formula 5 can be converted to the ester of formula 7 by the methods described in Process E(a).

PROCESS E(d)

SCHEME 12

15

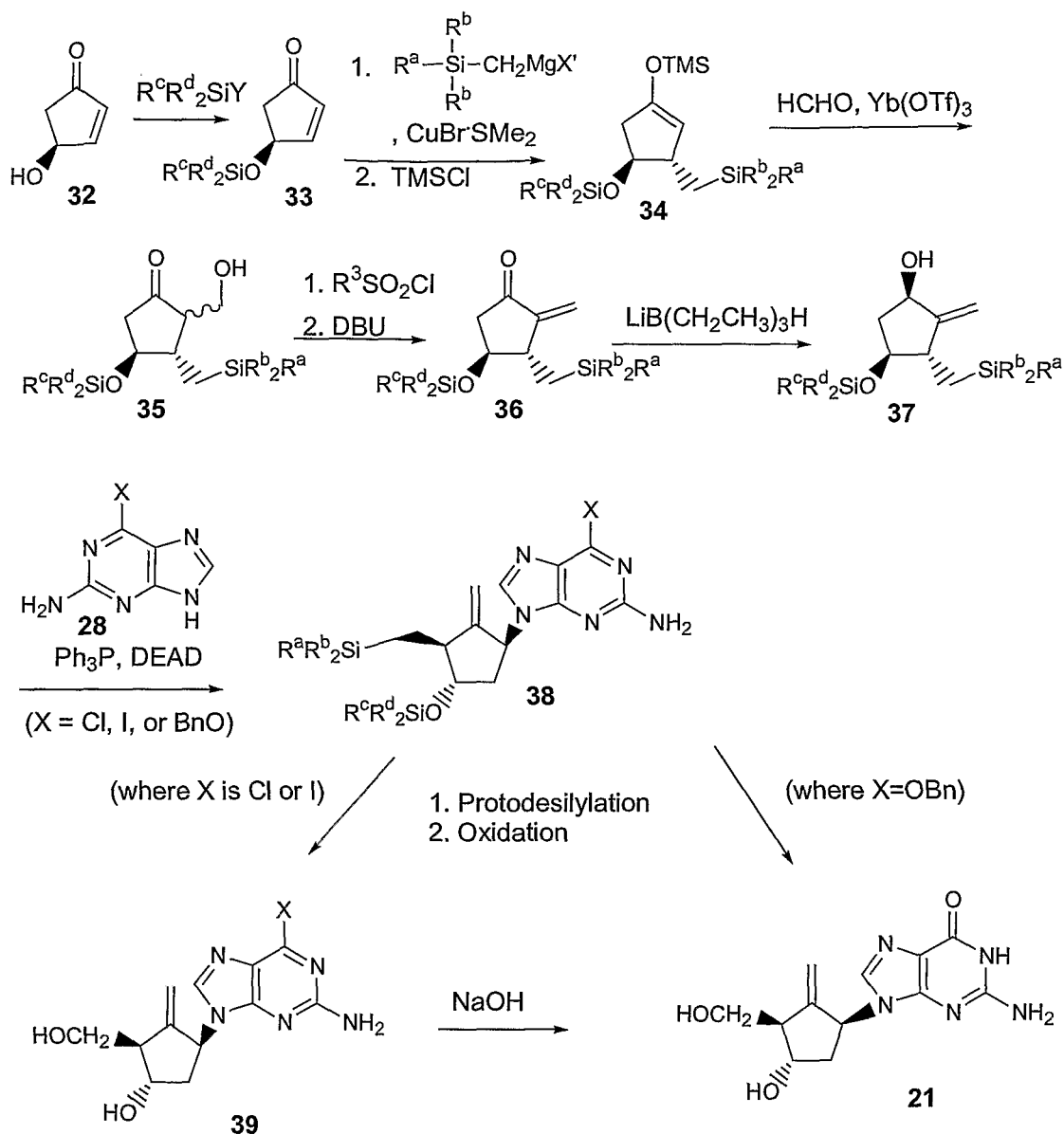


Process E(d) can also be used to prepare the ester of formula 7, wherein R' is benzyl or silyl. Embodiments of Process E(d) are depicted in **Scheme 12**. In the process, the allylic alcohol of formula 9 is oxidized with an oxidizing reagent such as pyridinium dichromate (PDC), pyridinium chlorochromate, manganese dioxide, and the like, in an inert solvent, preferably DCM, to afford the cyclopentenone of formula 80. The cyclopentenone is reduced with hydride reagents that selectively effect a 1,4-hydride addition. Suitable reducing conditions include, for example, treatment with lithium tri-*sec*-butylborohydride in THF. The intermediate from the reduction is trapped with an activated trifluoromethanesulfonic acid derivative such as N-phenyltriflimide to provide the triflate of the formula 81. An alkyloxycarbonyl group is then inserted onto the ring using, for example, a palladium catalyzed carbonyl insertion reaction to prepare the ester of formula 7. Preferably the insertion reaction is performed in a mixture of DMF and an alcohol, preferably MeOH, with an excess amount of a tertiary amine base, such as triethylamine. A preferred catalyst for the reaction is a palladium (0) catalyst, *e.g.*, tetrakis(triphenylphosphine)palladium.

In embodiments of Process E(d) wherein R' is a benzyl or substituted benzyl group, the allylic alcohol 9 can be prepared as described in Process E(c) from the cyclopentane epoxide of formula 8. In embodiments of Process E(d) wherein R' is a silyl ether protecting group, the allylic alcohol can be prepared in a two-step procedure from the monoacetate of formula 3 (which can be prepared as described in Process E(a)). The secondary alcohol moiety of the monoacetate of formula 3 is reacted with a silylating reagent $R^cR^d_2SiY$, wherein Y is a suitable leaving group, *e.g.*, chloride, triflate, and the like. In one embodiment, the secondary alcohol is protected as a *tert*-butyldimethylsilyl ether using *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of pyridine in an inert solvent such as DCM to give a compound of formula 22. The acetyl group of the compound of formula 22 is hydrolyzed by using a base *e.g.*, potassium carbonate in an alcohol solvent, to give the allylic alcohol of formula 9.

PROCESS F

SCHEME 13



Process F of the invention includes preparation of a suitably substituted cyclopentanol of formula 37, and coupling of the cyclopentanol with a guanine precursor, such as 2-amino-6-iodopurine under Mitsunobu conditions to give a carbocyclic nucleoside, the methylene compound of formula 38. The methylene compound of formula 38 can then be elaborated to the compound of formula 21. One embodiment of Process F is depicted in **Scheme 13**.

The cyclopentenone of formula 32 (also known as 4-(S)-hydroxy-2-cyclopenten-1-one) serves as starting material for Process F. The cyclopentenone can be obtained according to procedures described in Khanapure, S.; Najafi, N.;

Manna, S.; Yang, J.; Rokash, J. *J. Org. Chem.*, **1995**, 60, 7448. The alcohol moiety of the cyclopentenone of formula **32** can be protected as a silyl ether using the silylating reagent of the formula R^cR^dSiY (wherein R^c , R^d and Y are as defined in Process E and E(d)). For example, the alcohol moiety of the cyclopentenone of formula **32** can be protected as a *tert*-butyldimethylsilyl ether using *tert*-butyldimethylsilyl chloride (TBSCl), a tertiary amine base such as N,N-dimethylethylamine, and a catalytic amount of 4-N,N-dimethylaminopyridine in an inert solvent such as DCM to give the cyclopentenone of formula **33**. The cyclopentenone of formula **33** can then be treated with a Grignard reagent prepared from a (halomethyl)dialkylphenylsilane of the formula $R^aR^bSiCH_2X'$ (wherein R^a and R^b are as described above for Process A, and X' is Cl, Br, or I) and magnesium, in the presence of copper (I) salt such as Cu (I) bromide dimethylsulfide complex. In one embodiment, (chloromethyl)-dimethylphenylsilane is used to prepare the Grignard reagent. A trimethylsilylating reagent such as chlorotrimethylsilane (TMSCl) can be used to treat the intermediate enolate to form the silyl enol ether of formula **34**. The resulting silyl enol ether is hydroxymethylated, for example by using aqueous formaldehyde in the presence of a Lewis acid, *e.g.*, Yb(OTf)₃, La(OTf)₃, Pr(OTf)₃, Nd(OTf)₃, Sm(OTf)₃, Eu(OTf)₃, Eu(OTf)₃, Gd(OTf)₃, Dy(OTf)₃, Ho(OTf)₃, or Er(OTf)₃ in THF to give the compound of formula **35**.

The compound of formula **35** can be dehydrated by reacting the compound with a sulfonylating agent of the formula R^3SO_2Cl , wherein R^3 is C₁ to C₆ alkyl, trifluoromethyl, phenyl, or substituted phenyl (substituted by C₁ to C₆ alkyl and/or C₁ to C₆ alkoxy) in the presence of a tertiary amine base, *e.g.*, triethylamine, and then eliminating the intermediate sulfonate by addition of a strong base, preferably DBU, to give the methylene compound of formula **36**. Preferably the sulfonylating agent used is methanesulfonyl chloride. The carbonyl moiety of the methylene compound of formula **36** can be reduced by hydride reagents that selectively effect 1,2-reduction of the carbonyl group and provides the allylic alcohol with high diastereoselectivity. These hydride reagents include sodium borohydride, zinc borohydride, lithium aluminum hydride, diisobutylaluminum hydride, sodium borohydride-cerium chloride, lithium triethylborohydride, lithium

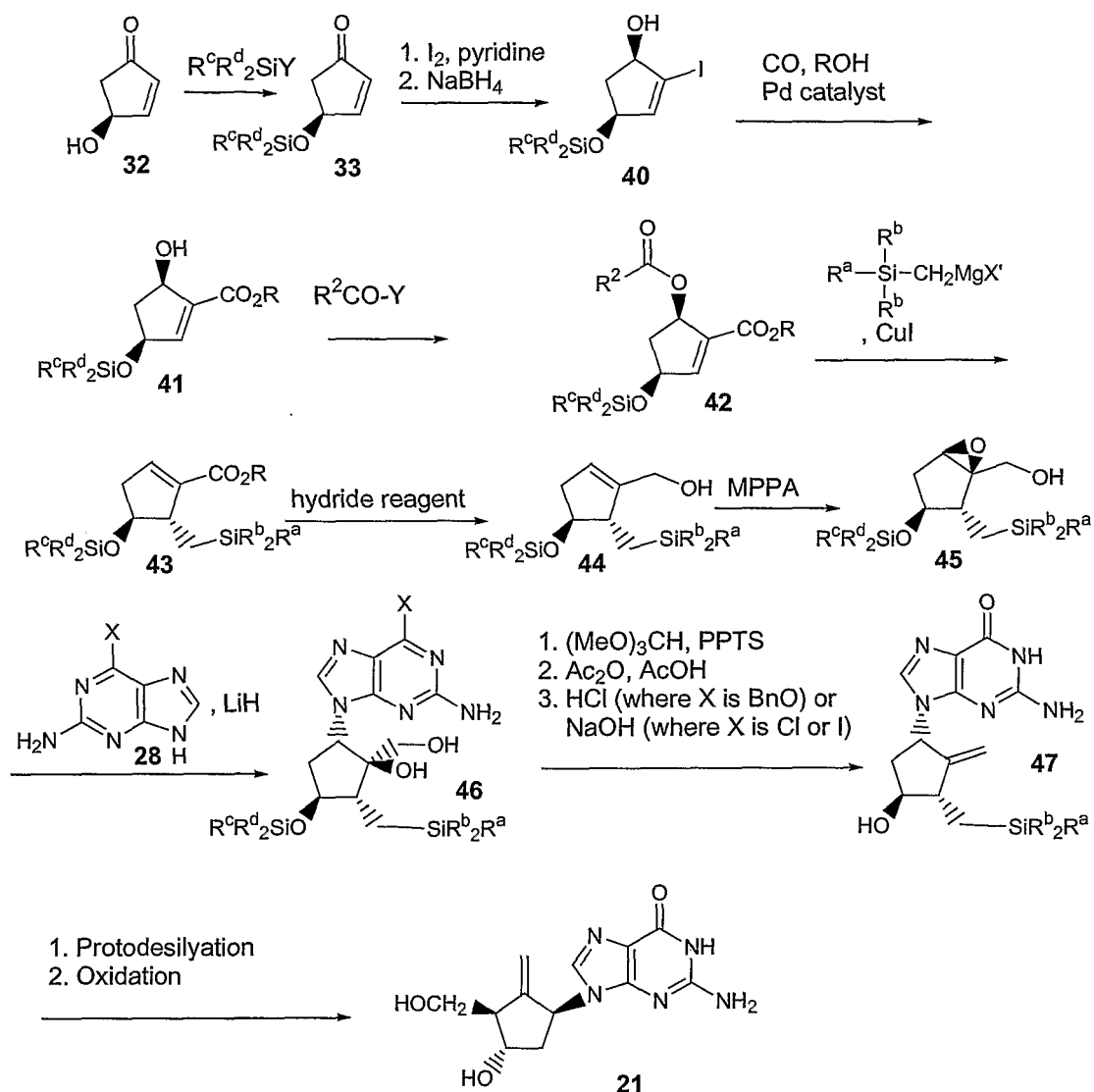
9-BBN hydride, 9-BBN pyridine, borane-sulfide complex, 5,5-diphenyl-2-methyl-3,4-propan-1,3,2-oxazaborolidine (Corey Reagent), lithium tri-*tert*-butoxyaluminum hydride, sodium cyanoborohydride, lithium tri-*sec*-butyl borohydride (L-Selectride®), sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®), diisobutylaluminum chloride and borane-tetrahydrofuran complex. The carbonyl group can be reduced, for example, with lithium triethylborohydride in THF to give the crude allylic alcohol of formula **37** in 95% yield in an 8:1 diastereomeric ratio. The crude product is purified, for example, using silica gel chromatography to isolate the desired diastereomer of the allylic alcohol of the formula **37**.

10 The allylic alcohol of formula **37** is condensed with 2-amino-6-iodopurine (purine compound of formula **28**, wherein X is I) under Mitsunobu conditions. Alternatively, other guanine precursors, such as 2-amino-6-chloropurine and 2-amino-6-O-benzoyloxypurine can be used in the condensation. Preferred Mitsunobu conditions include treatment of the allylic alcohol with about 1.3 molar equivalents each of triphenylphosphine, DEAD, and 2-amino-6-iodopurine in THF. The product of the Mitsunobu reaction, the methylene compound of formula **38**, can be further purified by, for example, silica gel chromatography.

 The methylene compound of formula **38** can be converted to the compound of formula **21**. In one conversion method, the dialkylphenylsilane moiety of the methylene compound of formula **38** can be converted to a hydroxy moiety by oxidation procedures analogous to those used in Processes B and C. The silyl ether protecting group is simultaneously hydrolyzed during these procedures. For example, the methylene compound of formula **38** can be treated with tetrafluoroboric acid-dimethyl ether complex in DCM. After addition of potassium bicarbonate and potassium fluoride, the intermediate silanol from this reaction is oxidized with hydrogen peroxide to provide the compound of formula **39**. The two reactions can be conveniently performed using a one-pot procedure. The 6-iodo group can be hydrolyzed by heating the compound of formula **39** with aqueous base such as a 2 N sodium hydroxide solution. After neutralization the aqueous solution can be heated with decolorizing carbon and allowed to crystallize to furnish the purified compound of formula **21**.

PROCESS G

SCHEME 14



5

Process G includes preparation of a cyclopentane epoxide of the formula **45**, and coupling of the cyclopentane epoxide with a guanine precursor to give a carbocyclic nucleoside, the compound of formula **46**. The compound of formula **46** can then be converted by a series of synthetic steps to the compound of formula **21**.

10 One embodiment of Process G is depicted in **Scheme 14**.

In Process G, the cyclopentenone of formula **33** (prepared as described in Process F) can be iodinated, for example, by treatment with iodine solution. Preferably, the reaction solvent is a mixture of DCM and pyridine. The resulting iodo

cyclopentenone intermediate is reduced, with a hydride reagent, for example, sodium borohydride in MeOH, to form the iodo compound of formula **40** in >98% de. The iodo compound of formula **40** can then be subjected to a carbonyl insertion reaction. For example, the allylic alcohol of formula **40** is reacted with carbon monoxide and an alcohol ROH wherein R is C₁ to C₄ alkyl or benzyl to form the ester of formula **41**. Preferably, the insertion reaction is conducted with carbon monoxide and MeOH in the presence of a tertiary amine base, *e.g.*, triethylamine, in a pressurized sealed reaction vessel. The reaction is preferably catalyzed by a palladium catalyst, *e.g.*, dichloro bis(triphenylphosphine)palladium. The crude product from the insertion reaction can be purified by column chromatography to provide pure compound of formula **41**.

The secondary alcohol of the compound of formula **41** is acylated by treatment with an activated acid derivative of the formula R²C(O)-Y, and a base, preferably lithium hexamethyldisilazide. While other activated acid derivatives can be used (including alkyl and aryl acid derivatives) to form the acyl intermediate **42**, adamantane carbonyl chloride is preferably used (*i.e.*, R²=adamantane). With this preferred reagent, a more crystalline intermediate is obtained that is more easily purified and handled. The intermediate of formula **42** is subjected to allylic displacement by treatment with the Grignard reagent prepared from a (halomethyl)dialkylphenylsilane of the formula R^aR^b₂SiCH₂X' (wherein R^a and R^b are as described above for Process A, and X' is Cl, Br, or I) and magnesium, in the presence of copper (I) salt such as Cu (I) iodide. In one embodiment, (chloromethyl)-dimethylphenylsilane is used to prepare the Grignard reagent. The reaction product, the compound of formula **43**, can be used in the next synthetic step without further purification.

The compound of formula **43** can be reduced with a hydride reagent, such as diisobutylaluminum hydride in toluene, to provide the allylic alcohol of formula **44**. Epoxidation of the crude allylic alcohol of the formula **44** provides the cyclopentane epoxide having the formula **45**. For example, in one epoxidation method, the allylic alcohol is treated with a peracid, *e.g.*, magnesium monoperoxyphthalate (MPPA) in MeOH, to prepare the cyclopentane epoxide. Using this method, the cyclopentane

epoxide of formula **45** is of sufficient diastereomeric purity to be used in the next synthetic step without further purification.

In the next step of Process G, the cyclopentane epoxide of formula **45** is converted to the compound of formula **46** by condensation with an alkali metal salt, *e.g.* lithium salt, of 2-amino-6-O-benzyloxypurine in a dipolar aprotic solvent, *e.g.*, DMF. The lithium salt, for example, can be generated by reaction of 2-amino-6-benzyloxypurine with lithium hydride. The crude product from the condensation reaction can be purified by recrystallization from a suitable solvent, *e.g.*, MeOH, to provide the pure compound of formula **46**. Here again similar to Processes B and C, alkali metal salts of other guanine precursors, *e.g.*, 2-amino-6-chloropurine, 2-amino-6-iodopurine, can be used in place of 2-amino-6-benzyloxypurine to couple with the cyclopentane epoxide of the formula **45**.

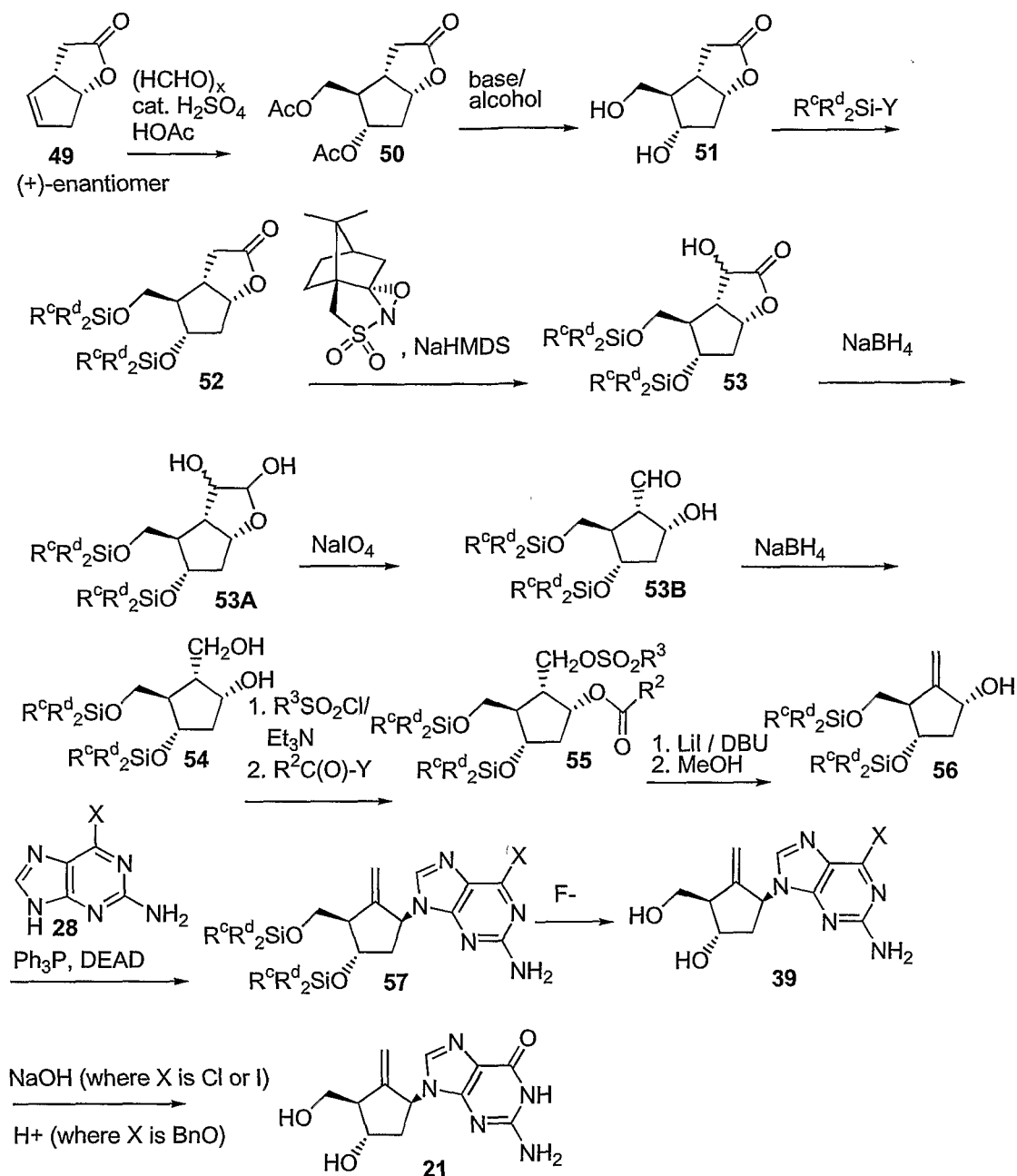
The diol moiety of the compound of formula **46** is then converted to an alkene. For example, the conversion to the methylene compound of formula **47** can be performed using a two step procedure. The compound of formula **46** is treated with an orthoformate derivative, preferably trimethylorthoformate, and a catalytic amount of an acid such as TFA or PTSA, or acid catalyst such as PPTS. The excess orthoformate reagent is evaporated, and the resulting mixture of dioxolanes is heated with acetic anhydride. The methylene compound of formula **47** is obtained after evaporation of the acetic anhydride and acid workup, which treatment also hydrolyzes the 6-O-benzyloxy group. In embodiments of Process G, wherein X is Cl or I, the 6-halo group on the purine can be hydrolyzed using hydroxide solution, *e.g.*, NaOH.

The phenyldimethylsilylmethyl group of the methylene compound of formula **47** can be converted to a hydroxymethyl moiety, for example, by the procedures described in Processes B, C, and F. For example, in one embodiment, the methylene compound of formula **47** can be treated with tetrafluoroboric acid-dimethyl ether complex in DCM to provide the silanol intermediate. Treatment of the silanol intermediate with potassium bicarbonate, potassium fluoride, and hydrogen peroxide provides the compound of formula **21**.

30

PROCESS H

SCHEME 15



- 5 In Process H of the invention, a bicyclic lactone, the compound of formula **52**, is converted to a methylene compound of formula **56**. The methylene compound of formula **56** is coupled with a guanine precursor such as 2-amino-6-chloropurine (purine compound of formula **28**, X=Cl) to give a carbocyclic nucleoside, the methylene compound of formula **57**. The methylene compound of

formula **57** is subsequently converted to the compound of formula **21** by deprotection and hydrolysis steps. Embodiments of Process H are depicted in **Scheme 15**.

The compound of formula **52** can be treated with the oxaziridine reagent, *e.g.*, (1*S*)-(+)-(10-Camphorsulfonyl)oxaziridine, and a strong non-nucleophilic base, preferably sodium bis[trimethylsilyl]amide (NaHMDS) in THF, to generate a compound of formula **53**. After quenching the reaction with, for example, MeOH, the compound of formula **53** can be directly reduced by treatment with a suitable hydride reagent such as sodium borohydride in MeOH, to reduce the lactone moiety and provide the compound of formula **53A**. The vicinal diol of the compound of formula **53A** can be oxidatively cleaved by treatment with an oxidizing agent such as sodium periodate, potassium permanganate, or ruthenium oxide. The resulting aldehyde containing intermediate **53B** can then be reduced with a suitable hydride reagent, *e.g.*, sodium borohydride, to generate the diol of the formula **54**.

The primary alcohol moiety of the diol of formula **54** can be selectively converted to a suitable leaving group, preferably using a sulfonylating reagent having the formula R^3SO_2Cl , wherein R^3 is C_1 to C_6 alkyl, trifluoromethyl, phenyl, or substituted phenyl (substituted by C_1 to C_6 alkyl or C_1 to C_6 alkoxy). For example, the diol of formula **54** is treated with *p*-toluenesulfonyl chloride (TsCl), a tertiary amine base such as pyridine, and a catalytic amount of 4-*N,N*-dimethylaminopyridine to convert the primary alcohol to a tosylate group. The secondary alcohol is protected as an ester by acylation with an acylating agent to provide the compound of formula **55**. Preferably the secondary alcohol is protected by an acyl group of the formula $R^2C(=O)-$, wherein R^2 is alkyl, aryl, arylalkyl, any of which can be substituted. Most preferably, R^2 is methyl so that the acyl protecting group in the compound of formula **55** is acetyl. A preferred acylating agent is an acylating agent of the formula $R^2C(O)Y$, wherein *Y* is a leaving group. For example, the acylating agent can be an anhydride, acid chloride, and the like.

The compound of formula **55** is treated with an iodide salt, *e.g.*, lithium iodide, and a strong base such as DBU to effect elimination of the intermediate iodide. Hydrolysis of the acyl ester is carried out by direct addition of MeOH to the basic reaction mixture, providing the methylene compound of formula **56**. The methylene

compound of formula **56** can be further purified by, for example, silica gel chromatography.

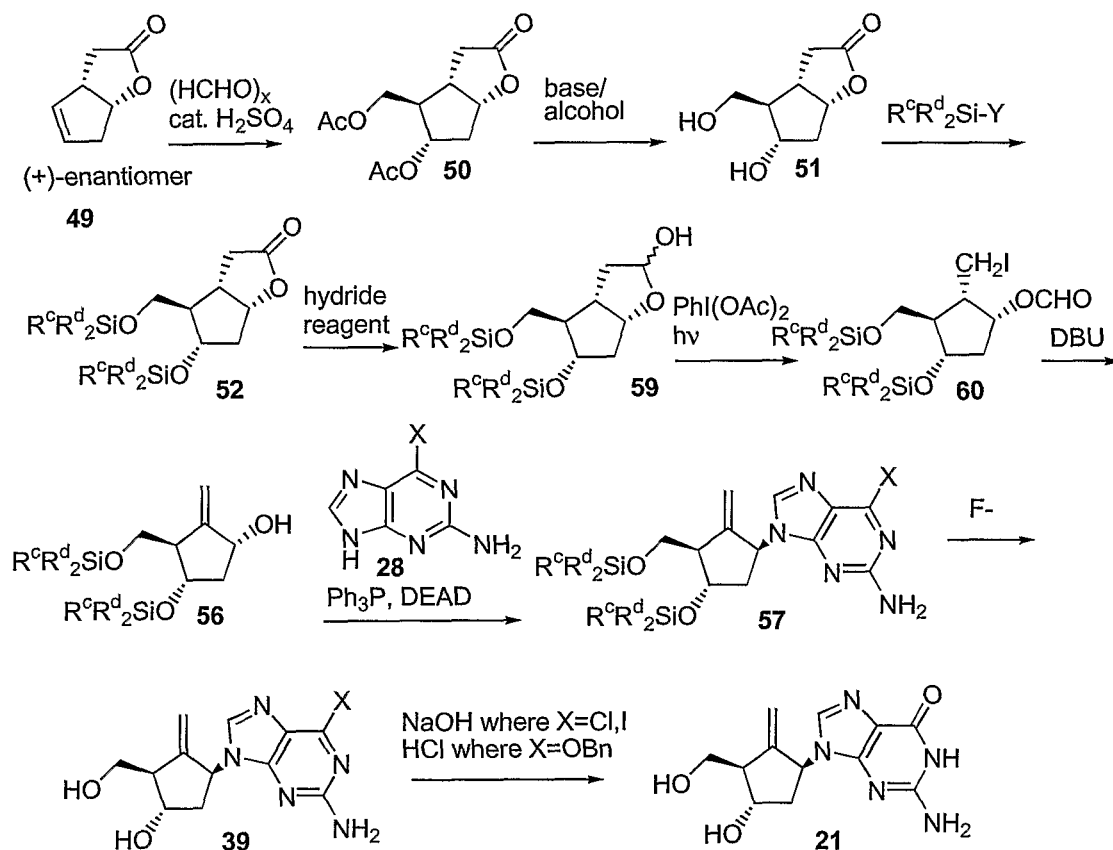
The methylene compound of formula **56** serves as a suitable compound for coupling with a guanine precursor (purine compound of formula **28**, wherein X is Cl, Br or benzyloxy). For instance, the methylene compound of formula **56** is treated under Mitsunobu conditions with 2-amino-6-chloropurine to give the methylene compound of formula **57**. Preferably the Mitsunobu conditions comprise treatment with DEAD and triphenylphosphine. The methylene compound of formula **57** can be further purified by, for example, silica gel chromatography.

The conversion of the methylene compound of formula **57** to the compound of formula **21** can be completed by deprotection of the silyl ether moieties and hydrolysis of the 6-X group on the purine moiety. The two silyl ether moieties are cleaved by treatment with fluoride ion (*e.g.*, tetralkylammonium fluoride reagent such as tetrabutylammonium fluoride in THF) to give the compound of formula **39**. In embodiments of the process wherein the purine moiety has a 6-chloro or iodo group, the 6-halo group is hydrolyzed by heating the compound of formula **39** with aqueous base or acid, preferably aqueous base, *e.g.*, 2 N sodium hydroxide solution, to give the compound of formula **21**. In embodiments of the process where X is a 6-O-benzyloxy group, conversion to the 6-oxo group can be performed using acidic conditions, *e.g.* 2 N HCl. The compound of formula **21** can be further purified by, for example, silica gel chromatography.

In Process H, the homochiral bicyclic lactone of formula **49** can be used as starting material for the preparation of the compound of formula **52**, and can be prepared as described in Corey *et al. J. Med. Chem.* **1993**, 36, 243. The bicyclic lactone of formula **49** can be treated with paraformaldehyde in a mixture of glacial acetic acid and sulfuric acid to add formaldehyde across the double bond. This treatment yields a diacetate of formula **50**. The diacetate of formula **50** is subsequently stirred with a base such as potassium carbonate in an alcohol solvent, *e.g.*, MeOH, to hydrolyze the acetate moieties and provide the diol of the formula **51**. The alcohol moieties of the diol of formula **51** can be protected as silyl ether groups by treating the diol with a silylating reagent of the formula $R^cR^d_2SiY$ (wherein R^c , R^d ,

and Y are as described above in the description of Process E) to provide the compound of formula **52**. In one embodiment of Process H, the silylating reagent is *tert*-butyldimethyl chloride (TBSCl).

5

PROCESS ISCHEME 16

10 Similar to Process H of the invention, Process I of the invention comprises preparation of a methylene compound of formula **56** from the homochiral bicyclic lactone intermediate, the compound of formula **52**. The coupling of the methylene compound of formula **56** to a guanine precursor (purine compound of formula **28**), and subsequent conversion of the resultant carbocyclic nucleoside to the compound of

15 formula **21** are analogous to the methods used in Process H as well. The preparation of the methylene compound of formula **56** from the compound of formula **52**,

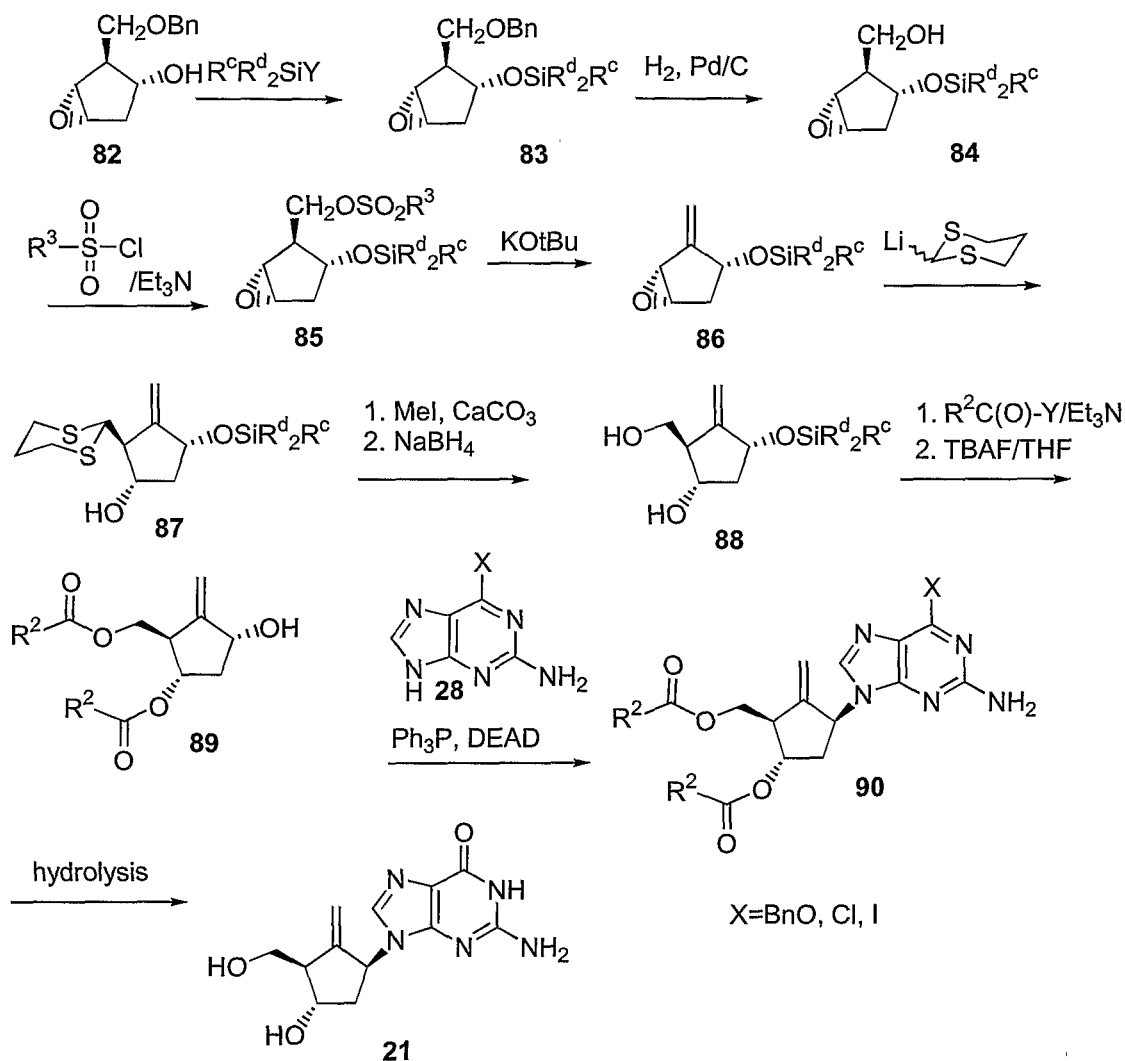
however, is achieved by different synthetic methods than those used in Process H. One embodiment of Process I is depicted in **Scheme 16**.

In Process I, the lactone moiety of the compound of formula **52** is reduced under controlled reaction conditions to provide the lactol of formula **59**. For instance, the compound of formula **52** can be treated with a hydride reagent, *e.g.*, diisobutylaluminum hydride in toluene at 25°C to achieve reduction to the lactol oxidation state. The reduction product, the lactol of formula **59**, is subsequently cleaved using an oxidizing agent, such as iodobenzene diacetate under UV irradiation (sun lamp) in DCM to give the iodide compound of formula **60**. The iodide compound of formula **60** can be treated with a strong base such as DBU to effect elimination of the iodide moiety with removal of the formate ester upon water workup to yield the methylene compound of formula **56**.

The methylene compound of formula **56** can be coupled to a guanine precursor, such as 2-amino-6-iodopurine (purine compound of formula **28** wherein X is I), under reaction conditions such as those described for the conversion of the methylene compound of formula **56** to the compound of formula **57** described above in Process H. The resulting carbocyclic nucleoside, the compound of formula **39**, can be converted to the compound of formula **21** by methods such as those used in the Process H.

PROCESS J

SCHEME 17



5

Process J of the invention depicts another approach for the preparation of the compound of formula **21** (Scheme 17). Process J includes formation of a methylene compound of formula **89**, and subsequent coupling of the methylene compound with a guanine precursor, e.g., 2-amino-6-iodopurine, using Mitsunobu conditions to yield a carbocyclic nucleoside intermediate, the methylene compound of formula **90**. The protecting groups of **90** are removed and the X group is hydrolyzed to provide the compound of formula **21**.

The methylene compound of formula **89** is prepared from the cyclopentane epoxide of formula **82**, prepared as described in Example 1 of United States Patent No. 5,206,244. The secondary alcohol moiety of **82** is protected as a silyl ether having the formula $R^cR^d_2SiO-$ wherein R^c and R^d are as described above in the description of Process E. In one embodiment, the secondary alcohol of **82** is protected as a *tert*-butyl dimethylsilyl ether. The primary alcohol is unmasked by catalytic reduction of the benzyl group of **83** with, for example, palladium on carbon to give the compound of formula **84**. The compound of formula **86** is prepared by a base catalyzed elimination procedure. In the first step of the procedure, the primary alcohol of **84** is converted into a suitable leaving group, preferably using a sulfonating reagent having the formula R^3SO_2Cl , wherein R^3 is as described above in Process F, to give the compound having the formula **85**. A strong base, *e.g.*, potassium *t*-butoxide, in a suitable solvent, *e.g.* THF, is then used to effect the elimination of alkyl or (substituted) phenylsulfonic acid to provide the exocyclic methylene moiety in the compound of formula **86**.

A hydroxymethyl moiety is then installed on the cyclopentane ring adjacent to the exocyclic methylene moiety in the compound of formula **86** to give the compound of formula **87**. To efficiently effect this transformation, a regioselective 1,2-addition of a carbon nucleophile to the epoxide of the compound of formula **86** is preferably conducted. Preferably, the carbon nucleophile is a carbanion of 1,3-dithiane, *e.g.*, lithium salt of 1,3-dithiane, that adds to the allylic position to provide the compound of formula **87**. The lithium salt of 1,3-dithiane can be generated with a strong non-nucleophilic base, *e.g.*, *n*-butyl lithium, lithium diisopropylamide, lithium hexamethylsilazide, and the like in an ethereal solvent, *e.g.*, THF. A chelating agent such as 1,4-diazabicyclo[2.2.2]octane (DABCO) is preferably added to enhance the efficiency of the process. The reaction is preferably carried out below 25°C, more preferably below about -15°C to ensure high regioselectivity. Preferably, the regioselectivity of the addition is >10:1, more preferably >15:1.

The dithianylmethyl group of the compound of formula **87** is readily converted to an alcohol by a hydrolysis reaction followed by a reduction reaction. The hydrolysis to an intermediate aldehyde is carried out, for example, by stirring a

mixture of compound of formula **87** with calcium carbonate and iodomethane in aqueous acetonitrile. Other methods for hydrolyzing dithioacetals are well known in the art and include methods recited in Greene, T.W.; Wuts, P.G.M. *Protecting Groups in Organic Synthesis 2nd Edition*; Wiley and Sons: New York, 1991, pp. 199-201.

- 5 The intermediate aldehyde can be reduced with a suitable hydride reagent, *e.g.*, sodium borohydride, to provide the compound of formula **88**.

The compound of formula **88** is converted to a compound suitable for coupling with a protected guanine derivative, by acylation of the alcohol groups. Acyl groups of the formula $R^2C(=O)-$ wherein R^2 is as described above for Process H can serve as
10 protecting groups. Preferably, R^2 is methyl so that the acyl group is acetyl. The silyl ether group is then cleaved using fluoride ion, *e.g.*, tetrabutylammonium fluoride, to give the methylene compound of formula **89**.

The compound of formula **89** is coupled to a suitable guanine precursor, *e.g.*, 2-amino-6-iodopurine, to provide a carbocyclic nucleoside intermediate, the
15 methylene compound of formula **90**. In alternative embodiments, 2-amino-6-chloropurine or 2-amino-6-benzyloxypurine can be used as the guanine precursor. The methylene compound of formula **90**, can be converted to the compound of formula **21** by suitable hydrolysis methods. For example, the ester groups can be cleaved by treatment with an alkali metal alkoxide, *e.g.* sodium methoxide, and the
20 6-halo group can be hydrolyzed by heating in aqueous base. In embodiments of the process wherein 2-amino-benzyloxypurine is used as a guanine precursor, the 6-benzyloxy group is hydrolyzed using acid, *e.g.*, HCl.

PROCESS K

RESIN PURIFICATION

25 Another aspect of this invention is the use of a resin adsorption process for isolation and purification of the compound of formula **21** or intermediates therefor. This process employs a crude mixture comprising compound **21** or a mixture comprising entacavir intermediate(s) and other reagents, such as, for example, an oxidative mixture resulting from the treatment of an intermediate for compound **21**
30 with hydrogen peroxide in an oxidative desilylation reaction in the presence of KF and $KHCO_3$. Compound **21** is soluble in water at 2.2 mg/mL and more preferably

below 1.5 mg/mL. Compound **21** and related compounds are adsorbed on the resin specifically while inorganic salts pass through. The resin bed is then washed with water to remove any additional salts and compound **21** or a compound related thereto (*e.g.*, such as an intermediate or precursor) is eluted from the resin via washing with
5 an organic solvent. In one embodiment, the organic solvent comprises a mixture of MeOH and water, preferably 40-60% MeOH:40-60%water, more preferably 45-55% MeOH:45-55%water, even more preferably 50:50 MeOH and water, as 50% MeOH provides optimal separation of compound **21** or compound related thereto which is then concentrated and crystallized to obtain a pure compound. As use herein, by
10 "pure" it is meant a compound having greater than or equal to 97%, or more preferably 99%, purity. Most preferred is a compound wherein all impurity peaks are less than 0.1 area percent as determined by high performance liquid chromatography (HPLC).

Resins suitable for use in this adsorption process are hydrophobic resins with
15 selectivity for non-polar molecules. In one embodiment, the resin is styrene-based. More preferably, the styrene-based resins are brominated to provide for greater strength and abrasion resistance. Exemplary resins with such properties include, but are not limited to, SP207 Sepabeads, SP700 Sepabeads, Diaion HP20, Diaion SP70, Diaion SP825, Diaion SP850, Diaion HP2MG methacrylate, AMBERLITE XAD4,
20 AMBERLITE XAD7HP, AMBERLITE XAD16, and AMBERLITE XAD1600. In a preferred embodiment, SP207 is used as the resin as this resin exhibits abrasion resistance, long-term recycling utilization, and the ability to withstand extremes of organic solvent conditions, temperatures, and pH, to be particularly useful in purification of compound **21** and compounds related thereto.

25 The following examples further illustrate the present invention, but of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

PROCESS FOR THE PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-
1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-
6H-purin-6-one (21)

5 PREPARATION OF (1 α , 4 α , 5 α)-7,7-Dichloro-4-(dimethylphenylsilyl)-
 bicyclo[3.2.0]hept-2-en-6-one (63)

A 3-L three necked flask equipped with a mechanical stirrer, a 500-mL addition funnel, a thermometer and an argon inlet was charged with
10 phenyldimethylchlorosilane (153.6 g, 0.90 moles) and anhydrous THF (320 mL). The flask was then cooled to -78°C. To this stirring solution, was added sodium cyclopentadienide (441 mL, 2.04 M in THF, 0.90 moles) over a period of one hour. The reaction mixture was stirred for about two hours and then it was allowed to warm to about 0°C over a period of two hours. At this time the reaction was assumed to be
15 complete. The reaction was quenched by addition of cold water (~150 mL) and allowed to warm to ~15°C. The mixture was diluted with hexanes (~100 mL) and transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted with hexanes (200 mL). The combined organic layer was washed with brine (200 mL), dried over anhydrous magnesium sulfate, filtered, and
20 concentrated *in vacuo* to give the crude diene as dark brown oil (177 g, ~98% yield). The crude diene was used without further purification in the next reaction.

A 3-L three necked flask equipped with a mechanical stirrer, 500-mL addition funnel, thermometer, and argon inlet was charged with diene of the above reaction (176.5 g, 0.88 moles) and hexanes (600 mL). The mixture was cooled to about -10°C
25 and dichloroacetyl chloride (173 mL, 1.80 moles) was added over the course of five minutes. To this stirred mixture a solution of Et₃N (251 mL, 1.80 moles) in hexanes (400 mL) was added over a period of one hour. The resulting mixture was stirred for about three hours at 0-4°C and then at ambient temperature for about ten hours to complete the reaction. The reaction was quenched by addition of water (400 mL).
30 After stirring for about 30 minutes at room temperature, the solution was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was

extracted with hexanes (300 mL). The combined organic layer was washed with water (250 mL), sodium bicarbonate (5%, 250 mL) and water (500 mL). The combined filtrate was concentrated *in vacuo*. The resulting dark oil was further dried under high vacuum to give 307 g of the crude title compound.

5

PREPARATION OF trans-5-(Dimethylphenylsilyl)-2-(hydroxymethyl)-
2-cyclopentene-1-carboxylic acid (64)

A 3-L three necked flask equipped with a mechanical stirrer, a 500-mL addition funnel, a thermometer and an argon inlet was charged with the above obtained **63** (211 g, 0.68 moles), *tert*-butanol (348 g), water (710 mL), and Et₃N (343 g, 3.39 moles). The reaction mixture was heated to reflux for 3 hours. The reaction mixture was cooled to ~10°C and potassium carbonate (300 g, 2.17 moles) was added over 30 minutes. After 30 minutes, sodium borohydride (13.6 g, 0.359 moles) was added in portion-wise. After 1 hour the cooling bath was removed and the reaction mixture was allowed to warm slowly. The reaction mixture was carefully quenched with water (800 mL). The pH was adjusted to ~3.0 and the resulting mixture extracted with EtOAc (800 mL). The organic extract was concentrated *in vacuo*. The resulting dark oil was further dried under high vacuum give 185 g of the racemic title compound.

20

PREPARATION OF (1R, 5S)-5-(Dimethylphenylsilyl)-2-(hydroxymethyl)-
2-cyclopentene-1-carboxylic acid, (1R, 2S)-2-amino-1-(4-nitrophenyl)-
1,3-propanediol (1:1) salt (65A)

25

A 3-L three necked flask equipped with a mechanical stirrer, addition funnel, thermometer and argon inlet was charged with **64** (185 g, 0.67 moles), absolute ethanol (925 g) and R,R-(-)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (102 g, 0.483 moles), and heated to 50°C. The solution was seeded with the salt **65A** and left at 40°C for 5 hours. The resulting crystals were filtered on a Buchner funnel and washed with ethanol. The solid was dried to give the title compound in ~28.3% yield

30

(94 g) from sodium cyclopentadienide. The product has a purity of 98 AP and 99% ee.

PREPARATION OF (1R, 5S)-5-(Dimethylphenylsilyl)-2-(hydroxymethyl)-2-
5 cyclopentene-1-carboxylic acid methyl ester (66)

To a 2-L 3-necked round bottomed flask equipped with a mechanical stirrer, an addition funnel and a thermometer, was charged **65A** (390 g, 0.8 mole) and MeOH (800 mL). The reaction mixture was cooled to about 0°C. Concentrated sulfuric acid
10 (123 g, 1.2 moles) was slowly added to the reaction flask with stirring. After addition of the acid, the reaction mixture was stirred for about 12 hours at room temperature to complete the reaction. After completion of the reaction, the reaction mixture was concentrated *in vacuo* to remove about 500 mL of MeOH. The residue was diluted with EtOAc (600 mL) and water (1000 mL). The mixture was transferred to a
15 separatory funnel and the organic layer was separated. The aqueous layer was extracted with EtOAc (600 mL). The combined organic layer was washed with saturated sodium bicarbonate (500 mL), water (500 mL), brine (500 mL) and concentrated *in vacuo* to afford the crude title compound (224 g) as a brown oil.

20 PREPARATION OF [1R-(1 α , 2 α , 3 β , 5 α)]-3-(Dimethylphenylsilyl)-6-
oxabicyclo[3.1.0]hexane-1,2-dimethanol (72)

To a 5-L 3-necked round bottomed flask equipped with a mechanical stirrer, an addition funnel and a thermometer, was charged activated molecular sieves (224 g)
25 and DCM (1000 mL) under an atmosphere of argon. The solution was cooled to about -30°C. DIPT (18 g, 0.08 moles) was added to the solution and the mixture stirred at -30°C for about 20 minutes. Titanium (IV) isopropoxide (18.2 mL, 0.064 moles) was then added to the reaction mixture. The reaction mixture was stirred at -30°C for about 20 minutes.

30 Compound **66** (224 g, 0.8 moles) in DCM (500 mL) was charged to the reaction mixture via syringe at -30°C. The reaction mixture was stirred at -30°C for

about 20 minutes. TBHP (308 mL, 5 M/decane, 1.6 moles) was added to the reaction mixture using an addition funnel, keeping the reaction temperature between -20°C to -30°C. After complete addition of TBHP, the reaction mixture was stirred between -20°C to -30°C for about 2 hours. After the reaction was complete, the excess peroxide was quenched by addition of aqueous sodium bisulfite (250 g of sodium bisulfite in 500 mL of water). After the addition of sodium bisulfite, the mixture was stirred for about 30 minutes and filtered through a pad of diatomaceous earth (CeliteHyflo®). The filtrate was transferred to a separatory funnel and the aqueous layer was separated. The organic layer was washed with saturated sodium bicarbonate solution (1000 mL) and then water (500 mL). The organic layer was concentrated *in vacuo* to give the crude epoxide (276 g) as an oil.

To a 3-L 3-necked round bottomed flask equipped with a mechanical stirrer and a thermometer was charged the above obtained epoxide (276 g, 0.8 moles) and IPA (800 mL) under an atmosphere of argon. The resulting solution was cooled to about 0°C in an ice bath and to it was added solid sodium borohydride (68 g, 1.6 moles) in portions. After the addition was complete, the cooling bath was removed and the reaction mixture was stirred for about 16 hours to complete the reaction. After completion of the reaction, the excess borohydride was quenched by adding the reaction mixture to a solution of saturated ammonium chloride (2000 mL). After the borohydride was completely quenched, the reaction mixture was extracted with EtOAc (1200 mL). The organic layer was washed with water (500 mL), brine (500 mL), and concentrated *in vacuo* to afford the title compound (251 g) as light yellow oil.

25 PREPARATION OF [1S-(1 α , 2 β , 3 α , 4 β)]-1-[2-Amino-6-(phenylmethoxy)-9H-purin-9-yl]-4-(dimethylphenylsilyl)-2-hydroxy-2,3-cyclopentanedimethanol (73, X=BnO)

To a 3-L 3-necked round bottomed flask equipped with a mechanical stirrer and a thermometer, was charged 2-amino-6-benzoyloxypurine (193 g, 0.8 moles), lithium hydroxide monohydrate (33.6 g, 0.64 moles) and 72 (251 g, 0.8 moles) in

DMF (800 mL). The mixture was heated to 80°C and stirred for about 20 hours. After completion of the reaction, the reaction mixture was cooled to room temperature and extracted with EtOAc (3000 mL). The organic layer was washed with brine (1500 mL). The organic layer was washed with citric acid (1000 mL), brine (1000 mL) and concentrated *in vacuo* to furnish crude triol (330 g) as a thick brown oil. The product was crystallized from EtOAc-hexanes to give the title compound (~225 g) as a solid crystalline material.

10 PREPARATION OF [1S- (1 α , 3 α , 4 β)]-2-Amino-9-[4-(dimethylphenylsilyl)-3-(hydroxymethyl)-2-methylenecyclopentyl]-1,9-dihydro-6H-purin-6-one (71)

A 2.0-L 3-necked round bottomed flask, oven dried and equipped with a mechanical stirrer, an addition funnel, a temperature probe, and argon inlet, was charged with 73 (77.5 g, 0.1493 moles), pyridinium p-toluenesulfonate (1.875 g, 0.007465 mole), and DCM (371 mL) under an argon atmosphere. The resulting slurry was stirred and cooled to 0°C. Diethoxymethyl acetate (122 mL, 0.7465 moles) was added slowly over a period of about 15 minutes. The reaction mixture was warmed to room temperature over a period of one hour. After the complete consumption of the starting material, the resulting brown reaction mixture was slowly added to a stirring saturated solution of sodium bicarbonate (775 mL). The resulting mixture was extracted with EtOAc (1000 mL). The organic layer was concentrated *in vacuo* to afford a mixture of dioxolanes as a viscous brown oil (~125 g) which was transferred to a 2-L 3-necked round bottomed flask. The flask was additionally charged with acetic anhydride (279 mL, 2.96 moles) and heated at about 120°C for 30 hours. After the complete consumption of the starting material, the reaction mixture was cooled ~65°C, and MeOH (745 mL) was added. The reaction mixture was stirred while maintaining the temperature at 65°C for 40 minutes. Water (5-10 mL) was added to the reaction mixture, and the reaction mixture was cooled to about 45°C. Concentrated HCl (220 mL) was added and the mixture was reheated at 65°C for 4 hours. The mixture was cooled to ~20°C, and extracted with a hexane-*tert*-butyl methyl ether (9:1) mixture (1500 mL). The organic extract was concentrated *in*

vacuo. The residue was transferred to a 3-L 3-necked flask and heated to 55°C and at this temperature, 10 N NaOH (413 mL) was added to adjust the pH of the solution to about 12.8. The reaction mixture was heated to 75°C and stirred at that temperature for ~4 hours. Concentrated HCl (30 mL) was slowly added to the reaction mixture to adjust the pH to 7 and the reaction mixture was allowed to cool to 20°C over a 4 hour period. The slurry was filtered and the cake washed with a mixture of cold MeOH-water (3:7) (200 mL), followed by water (800 mL), and *tert*-butyl methyl ether (150 mL). The light brown colored crude product was dried to afford the title compound (37.7 g, 64%).

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

A 2-L 3-necked round bottomed flask, oven dried and equipped with a mechanical stirrer, an addition funnel, temperature probe, and argon inlet, was charged with compound **71** (34.1 g, 86.2 moles), acetic acid (40.4 mL, 8 eq) and acetic acid-boron trifluoride complex (38 mL). The reaction mixture was heated to 95°C, stirred for 4 hours and then cooled to room temperature. The reaction mixture was diluted with MeOH (200 mL) and quenched with aqueous KOH (10 N, ~220 mL) to adjust the pH to about 9.5. Potassium bicarbonate (17.9 g) followed by aqueous hydrogen peroxide (30 wt. %, 39 g) was added to the solution. The resulting solution was warmed to 70°C and stirred for 10 hours. The reaction was cooled to 5-10°C. Sodium bisulfite (16.2 g) was added portion-wise over 30 minutes. The reaction mixture was concentrated *in vacuo* to remove most of the MeOH. The resulting yellow semi-solid was cooled to -5°C and concentrated HCl (~55 mL) added to adjust the pH to 0.15. The resulting solution was extracted with EtOAc (500 mL) and aqueous KOH (10 N, ~48 mL) added to adjust the pH to ~11. The solution was stirred for 1 hour and then the pH was adjusted to ~7 with HCl (4 mL). The reaction mixture was stirred at room temperature for 1 hour and at ~5°C for 3 hours. The solid was collected by filtration and dried under high vacuum for 16 hours. The solid was redissolved in water (600 mL) at 90°C. The clear solution was cooled to ~60-55°C

and seeded with **21**. The solution was allowed to cool to room temperature for 5 hours. The resulting white crystalline solid was collected by filtration and dried under vacuum at 50°C for 16 hours to afford the title compound (12.9 g).

5

EXAMPLE 2

PROCESS FOR THE PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (**21**)

10

PREPARATION OF (1R, 5S)-5-(Dimethylphenylsilyl)-2-[(1-methoxy-1-methylethoxy)methyl]-2-cyclopentene-1-methanol (**75**)

- To a 1-L 3-necked round bottomed flask equipped with a mechanical stirrer and a thermometer was charged **66** (29.6 g, 0.1 moles, obtained as described in
- 15 Example 1) and toluene (50 mL) under an atmosphere of argon. The resulting solution was cooled to ~0°C in an ice bath and 2-methoxypropene (95 mL, 1.0 mole) was added. Pyridinium p-toluenesulfonate (0.5 g, 0.002 moles) was added at 0°C and the resulting mixture was stirred at 0°C for 10 minutes. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1.5 hours.
- 20 After completion of the reaction, the reaction mixture was cooled to -78°C. Triethylamine (27 mL, 0.2 moles) was added to keep the reaction mixture in a basic environment. LAH (1 M in THF, 0.1 moles) was added at -78°C. The cooling bath was removed after 30 minutes and the reaction was allowed to warm to ambient temperature. The reaction mixture was stirred at room temperature for 1-2 hours.
- 25 The reaction mixture was cooled to 0°C and 2 N NaOH (20 mL) was added. After this addition, the reaction mixture was stirred for 30 min and filtered. The pad was washed with DCM (400 mL). The organic filtrate was washed with brine (100 mL) and concentrated *in vacuo* to afford the title compound (35 g) as a light yellow oil.

PREPARATION OF (4S, 5R)-4-(Dimethylphenylsilyl)-
5-[(phenylmethoxy)methyl]-1-cyclopentene-1-methanol (76)

To a 250-mL 3-necked round bottomed flask equipped with a mechanical
5 stirrer and a thermometer was charged **75** (35 g, 0.1 moles) and THF (60 mL) under
an atmosphere of argon. NaH (6 g, 60%, mineral oil suspension, 0.15 moles) was
added to the solution. The mixture was heated at 60°C for 1 hour and then cooled to
room temperature. Benzyl bromide (23.8 mL, 0.2 moles) and tetrabutylammonium
bromide (10 g, 0.03 moles) were added to the suspension. The reaction mixture was
10 heated at 70°C for 6 hours and then the reaction mixture was cooled to room
temperature. 1,9-diazabicyclo[5.4.0]undecen-7-ene (45 mL, 0.2 moles) was added
and heated at 50°C for 45 min. The reaction mixture was cooled to room temperature,
quenched with 1N HCl to pH ~1 and extracted with a mixture of EtOAc-hexane (250
mL). The organic layer was washed with water (500 mL), brine (100 mL) and
15 concentrated *in vacuo* to afford the title compound (42 g) as a brown oil.

PREPARATION OF [1R-(1 α , 2 α , 3 β , 5 α)]-3-(Dimethylphenylsilyl)-2-
((phenylmethoxy)methyl)-6-oxabicyclo[3.1.0]hexane-1-methanol (77)

20 To an oven dried, 1-L 3-necked round bottomed flask equipped with a
mechanical stirrer, a temperature probe, and an argon line was charged activated
molecular sieves (35 g) and DCM (160 mL) under an atmosphere of argon. The
solution was cooled to about -30°C. DIPT (2.34 g, 0.01 moles) followed by titanium
(IV) isopropoxide (2.36 mL, 0.008 moles) was added to the reaction mixture. The
25 reaction mixture was stirred at -30°C for about 20 minutes. Crude **76** (42 g, ~0.1
moles) in DCM (40 mL) was added to the reaction mixture and stirred for about 30
minutes. TBHP (40 mL, 0.2 moles) was added to the reaction mixture at -30°C.
After complete addition of TBHP, the reaction mixture was stirred at -30°C for about
5 hours to complete the reaction. The excess peroxide was quenched with aqueous
30 sodium bisulfite (20 g). The mixture was filtered through a Buchner Funnel with a
pad of diatomaceous earth (Hyflo Celite®). The filtrate was washed with saturated

NaHCO₃ solution (100 mL) and brine (100 mL). The organic layer was concentrated *in vacuo* to give the crude title compound (60 g, >100% material balance) as an oil.

5 PREPARATION OF [1R-(1 α , 2 α , 3 β , 5 α)]-5-[2-Amino-6-(phenylmethoxy)-9H-purin-9-yl]-3-(dimethylphenylsilyl)-1-hydroxy-2-[(phenylmethoxy)methyl]cyclopentanemethanol (78A, X=BnO)

To a 1-L 3-necked round bottomed flask equipped with a mechanical stirrer and a thermometer, was charged 2-amino-6-benzyloxypurine (24 g, 0.1 moles),
10 lithium hydride (0.48 g, 0.06 moles) and DMF (40 mL). The mixture was heated at 60°C for about 1 hour under an atmosphere of argon. 77 (60 g, 0.1 moles) in 20 mL DMF was added. The reaction temperature was heated at 105°C for 5 hours, cooled to room temperature and diluted with EtOAc (600 mL). The organic layer was washed with brine (300 mL), 1 M citric acid (150 mL), and NaHCO₃ solution (100
15 mL). The organic layer was concentrated *in vacuo* to furnish crude title product (60 g) as an oil. It was crystallized from EtOAc and hexane to give 23 g of the title compound as a crystalline solid.

20 PREPARATION OF [1S-(1 α , 3 α , 5 β)]-2-Amino-9-[4-(dimethylphenylsilyl)-2-methylene-3-[(phenylmethoxy)methyl]cyclopentyl]-1,9-dihydro-6H-purin-6-one (79)

A 100-mL 3-necked round bottomed flask, oven dried and equipped with a mechanical stirrer, an addition funnel, a temperature probe, and an argon inlet was
25 charged with 78A (12.2 g, 0.02 moles), pyridinium p-toluenesulfonate (0.25 g, 0.001 moles) and DCM (20 mL) under argon atmosphere. The resulting solution was stirred at room temperature and DEMA (16 mL, 0.1 moles) was added. The reaction mixture was stirred at room temperature for one hour. After the complete consumption of the starting material, the resulting reaction mixture was quenched with a saturated
30 solution of NaHCO₃ (100 mL) and extracted with EtOAc (100 mL). The organic layer was washed with brine (2 x 50 mL) and concentrated *in vacuo* to afford the

mixture of dioxalanes as a viscous oil which was transferred to a 250-mL 3-necked round bottomed flask, equipped with a mechanical stirrer, a condenser, a temperature probe, and an oil bath. Acetic anhydride (20 mL, 0.2 moles) was added to this flask and the resulting mixture was heated at 120°C for 15 hours. After the complete
5 consumption of the starting material, the reaction mixture was cooled ~60°C and MeOH (50 mL) was added. An HCl solution (50 mL, 6 N) was added to the reaction mixture and the temperature was raised to 70°C and stirred for a total of 6 hours. During this period, a 50% MeOH/water solution was added (50 mL). The reaction mixture was concentrated to remove the excess MeOH (150 mL MeOH) on a rotary
10 evaporator. The resulting mixture was warmed to ~50-55°C. NaOH (10 N) was added to adjust the pH of the solution to ~6.5. The resulting suspension was stirred at ~50°C for 1 hour, and then cooled to 28°C over the course of 2 hours. The solid was filtered, washed with 1:2 MeOH/water (80 mL), water (100 mL), and dried to afford the title compound (7.65 g).

15

ALTERNATIVE CONVERSION OF 78A TO 79

78A (5 kg) was dissolved in toluene (17 L) and treated with pyridium-p-toluenesulfonate (110 g, 0.05 mole) and DEMA (5.33 kg, 4 moles) at ambient
20 temperature, affording a diastereomeric mixture of orthoesters. The reaction was quenched with aqueous NaOH while maintaining the pH above 7.5. *Tert*-butyl methyl ether (70 L) was added and the layers were separated. The product rich organic layer was dried by azetropic distillation to a moisture content of less than 0.1%. Butylated hydroxytoluene (10 kg) and glacial acetic acid (0.99 kg, 2 equiv) and acetic anhydride
25 (10.9 kg, 13.2 equiv) were added to the toluene reaction mixture, and the mixture was heated to 120 to 125°C for several hours.

At the end of the olefination reaction, the reaction mixture was added to MeOH (80 L) and aqueous HCl (6 N, 21.6 L) while maintaining the temperature at less than 35°C. The reaction mixture was heated to 60 to 65°C to effect
30 debenzylation/deacetylation. The reaction mixture was cooled to ambient temperature and washed with heptane (2 x 35 L) to remove butylated hydroxytoluene. The layers

were separated and the product rich aqueous methanolic layer was heated to 55 to 65°C. Water (14.2 L) was added, followed by cooling to ambient temperature over 2 to 5 hours to effect crystallization of the hydrochloride salt of **79**. The crystal slurry was filtered and washed with water (2 x 20.2 L) and heptane (2 x 30 L). The filter
5 cake was dried to 60 to 65°C to a moisture content of less than 3.5% (3.64 kg, 85.6% yield).

The above hydrochloride salt of **79** (1.26 kg) was suspended in MeOH (13 L) and heated to 55 to 65°C to achieve complete dissolution. The apparent pH of the solution was adjusted to 5.4 to 6.4 with 1 N NaOH (about 1.5 L) while maintaining
10 the temperature at 50 to 65°C. The free base slurry was held at 50 to 65°C for an additional 60 to 90 minutes then slowly cooled to ambient temperature over 90 to 120 minutes. More water (about 1.5 L) was added over 45 to 60 minutes, and the pH was readjusted to 5.5 to 6.4 with 1 N HCl or NaOH. The crystal slurry was filtered and washed with 1:1 MeOH:water (2.6 L), followed by water (2.8 L) and finally heptane
15 (4 L). The cake was dried in a vacuum oven at 60-65°C to a moisture content of less than 1% (1.03 kg, 85%).

The free base can be reprecipitated from toluene/heptane to afford highly purified **79** in 90-93% yield, 99% AP, 99.0 + % potency.

20 ALTERNATIVE CONVERSION OF **78A** TO
METHANESULFONATE SALT OF **79**

Under nitrogen, a solution of **78A** (50.0 g, 82.06 mmol), triisopropyl orthoformate (46.85 g, 246.2 mmol) and TFA (7.02 g, 61.57 mmol) in toluene (300 ml) was stirred for one hour at room temperature. To this solution were added
25 butylated hydroxytoluene (50 g), acetic anhydride (100 ml) and glacial acetic acid (4.93 g, 82.10 mmol) and the solution was heated to 120°C. After holding the reaction solution at 120°C for 12.5 hours, the dark solution was cooled to room temperature and added to a cold (4°C) solution of methanesulfonic acid (63.40 g, 659.70 mmol) in water (300 ml) at a rate to keep the temperature at 5-10°C. The
30 reaction mixture was stirred for 15 minutes at 5-10°C and MeOH (600 ml) was added at a rate to keep the temperature at 5-10°C. After stirring at 5-10°C for 15 minutes,

the reaction mixture was heated to 65°C and held for 12 hours. After cooling to room temperature, the crude reaction mixture was washed with heptane (300 ml) and the layers separated. Additional MeOH (200 ml) was added to the product rich aqueous layer, and it was again extracted with heptane (300 ml). The reaction mixture was heated to 65°C and water (500 ml) was added so as to keep the temperature at 65-55°C to initiate crystallization of the methanesulfonate salt. The reaction solution was cooled to 10°C and the solids were filtered, washed with water (200 ml), and dried at 50°C under vacuum to afford 39.5 g of the methanesulfonate salt of **79** with AP of 99.6 and purity of 86.4%.

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (**21**)

To a 500-mL round bottomed flask, equipped with a magnetic stirrer, a nitrogen inlet, an oil bath, and a temperature probe was charged **79** (7.2 g, 4.7 mmols) and boron trifluoride-acetic acid complex (12.3 mL, 88.2 mmols). The reaction mixture was heated at ~70°C for 3.5 hours, cooled to room temperature, and diluted with MeOH (80 mL)/H₂O (4 mL). The mixture was neutralized with KOH (10 N, ~40 mL) to pH ~9.6. Potassium bicarbonate (4.45 g, 44.1 mmols) was added to the solution and the resulting suspension was warmed up to ~60°C. Hydrogen peroxide (30 wt. % in water, 7.49 g, 73 mmols) was added, and then the reaction mixture was heated at 65°C for 11 hours. The resulting mixture was cooled to 0°C and sodium bisulfite (4.42 g) was added. MeOH was removed from the reaction mixture. The resulting mixture was diluted with water (50 mL) and acidified with HCl to pH ~0.5. The mixture was washed with methyl *tert*-butyl ether (100 mL) and neutralized with NaOH (10 N) to pH ~6.7. The resulting solution was cooled to room temperature and stirred for 6 hours to crystallize the product. The white crystalline solid was collected by filtration to afford 2.05 g of the title compound.

ALTERNATE CONVERSION OF **79** TO **21**
WITH METHANESULFONIC SALT

A solution of **79** (30 g, 61.77 mmol) in methylene chloride (90 mL) was cooled and treated with methanesulfonic acid (90 mL). The resulting dark solution was stirred at 18-25°C until the reaction was considered complete by an HPLC analysis. The reaction mixture was then quenched into a mixture of 45% aqueous KOH (155 mL) and MeOH (1.8 L) at 10 to 15°C. The resulting potassium methanesulfonate salt that formed was removed by filtration. The filtrate was concentrated, pH adjusted to 7.5 to 8.8 with glacial acetic acid (17 mL) and then treated with aqueous KHCO₃ (18.6 g in 82 mL of water, 3 equiv), aqueous KF (9.1 g in 25 mL of water, 2.5 equiv), and 30% aqueous hydrogen peroxide (19.8 mL, 3.1 equiv). The reaction mixture was then held at 60-70°C until the formation of **21** was complete as determined by HPLC analysis.

ALTERNATE CONVERSION OF **79** TO **21**
VIA COMPOUNDS **110** AND **114**

15

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-(dimethylhydroxysilyl)-2-methylene-3-[(phenylmethoxymethyl]cyclopentyl]-6H-purin-6-one (**110**)

An aqueous solution of KOH (45 wt.%, 5.1 mL) was charged to a solution of compound **79** (4.85 g, 10 mmol) in NMP (49 mL). The mixture was heated at 50 °C for 12 hours. The reaction was cooled to room temperature. Water (75 mL) was charged while maintaining the reaction temperature below 35 °C. The reaction mixture was cooled to 5 –10 °C, neutralized with aqueous HCl (6 N, ~ 10 mL) to pH~7, and then stirred at 0 – 5 °C for 0.5 hour. The solid was collected by filtration, and the wet cake washed with water (3 x 50 mL). The solid was dried under vacuum at (50 °C) for 24 hours to afford the title compound **110** (3.66 g in 87% yield).

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-2-methylene-3-[(phenylmethoxymethyl]cyclopentyl]-6H-purin-6-one (**114**)

30

A solution of KF (0.14 g, 0.23 mmol) in MeOH (1.4 mL) was added to a suspension of compound **110** (1.0 g, 2.3 mmol) in MeOH (8.4 mL) at room

temperature. Potassium bicarbonate (0.47 g, 2.3 mmol) was charged to the resulting suspension. The mixture was stirred at 45 °C for 0.5 hour to form a clear solution and aqueous hydrogen peroxide (30 wt.%, 1.6 mL) was added. The reaction was heated at 45 °C for 3 hours, then cooled to 0 – 5 °C. An aqueous solution of sodium bisulfite (10 wt.%, 5.0 mL) was added portion-wise in 0.5 hour. The mixture was slowly acidified with aqueous HCl (6 N, ~ 8 mL) to pH=0.45. The resulting solid was filtered off and the filtrate neutralized with aqueous NaOH (4 N, ~ 10 mL) to pH~8. The mixture was stirred at 0 – 5 °C for 1 hour. The solid was collected by filtration and dried under vacuum at 40 °C for 24 hours to afford the title compound **114** (0.66 g in 77% yield).

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (**21**)

To a solution of **114** (2.0 g, 5.44 mmol) in methylene chloride (20 mL), cooled to -20°C, was added a methylene chloride solution of boron trichloride (1M, solution, 22 mL, 22 mmol, 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 **21**. The HCl salt (0.72 g, 2.29 mmol) 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 small Hyflo 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 **21** (0.32g, 44% overall yield from **114**).

ISOLATION AND PURIFICATION OF COMPOUND **21**

Isolation of **21** was achieved by a resin adsorption procedure in which the oxidation mixture was diluted about 20 fold with water (about 1 mg of **21** per mL of diluted stream) and loaded onto SP207 resin (1 kg). The resin bed was first washed with water to remove salt, and compound **21** was eluted off the resin using 50:50 MeOH:water solution (about 20 L). The eluent, after a polish filter, was concentrated by distillation under vacuum at a temperature less than or equal to 55°C to a batch volume of about 25 mL/g of **21**. The resulting slurry was heated to 90°C to form a clear solution. The clear solution was then slowly brought to ambient temperature to crystallize **21**. After stirring the slurry for several hours at ambient temperature, **21** was filtered and dried under vacuum at ambient temperature until the moisture content of the product was between 6 and 7 wt. %. This procedure gave **21** in an average yield of 75 % from compound **79** and an HPLC area % of greater than 99.9.

EXAMPLE 3

PROCESS FOR THE PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (**21**)

PREPARATION OF [3aS-(3a α , 5 α , 6 β , 6a α)]-5-(Dimethylphenylsilyl)hexahydro-6a-(hydroxymethyl)-2-oxo-2H-cyclopentoxazole-6-carboxylic acid methyl ester (**67**)

To a 500-mL round bottomed flask equipped with a magnetic stirrer and a thermometer was charged methyl carbamate (4.5 g, 60 mmol) and MeOH (40 mL) under an atmosphere of argon. The resulting solution was cooled to ~0°C in an ice bath. *Tert*-butyl hypochlorite (6.52 g, 60 mmol) was added and the resulting mixture was stirred at 0°C for 15 minutes. A methanolic solution of sodium hydroxide (2.44 g of sodium hydroxide (60 mmol in 40 mL MeOH) was added to this solution and the resulting mixture was stirred at room temperature for 1 hour. The mixture was directly concentrated *in vacuo* to give a white powdery reagent. To this reagent, isopropanol (53 mL), and water (26 mL) were added. The resulting mixture was stirred at room temperature until the mixture became a clear solution. This mixture was cooled to ~0°C and then **66** (5.8 g, 20 mmol, obtained as described in Example 1)

was added. The mixture was stirred for 10 minutes and then potassium osmate hydrate (280 mg) was added. The mixture was stirred at 0°C for 1.5 hours followed by 12 hours at room temperature to complete the reaction. The reaction was quenched by addition of sodium thiosulfate (4 g) and stirred for 1 hour at room temperature.

- 5 The mixture was filtered through a bed of diatomaceous earth (Celite®), and the filtrate diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with water (3 x 50 mL), brine (50 mL) and dried over magnesium sulfate. The organic layer was concentrated *in vacuo* to afford the title compound (5.9 g in 85% yield).

10

PREPARATION OF [3aS-(3a α , 5 α , 6 β , 6a α)]-5-(Dimethylphenylsilyl)hexahydro-6a-(iodomethyl)-2-oxo-2H-cyclopentoxazole-6-carboxylic acid methyl ester (68)

- To a 500-mL 3-necked round bottomed flask equipped with a magnetic stirrer and a thermometer was charged **67** (33.75 g, 96.7 mmol), DCM (100 mL) followed by
15 pyridine (9.4 mL, 116 mmol) under an atmosphere of argon. The resulting mixture was cooled to 0°C. To this stirring mixture, trifluoromethanesulfonic anhydride (19.5 mL, 116 mmol) was slowly added over a period of 10 minutes keeping the temperature below 5°C. The mixture was stirred at the same temperature for 2 hours to complete the reaction. The mixture was washed with HCl (1 N, 2 x 50 mL), water
20 (3 x 50 mL), dried over magnesium sulfate, and concentrated *in vacuo* to afford the triflate which was used without further purification in the next step.

- The above triflate was taken in a 500-mL round bottomed flask which was charged with acetone (100 mL) and then cooled to 0°C. To this solution, lithium iodide (25 g, 193 mmol) was added in portion-wise over a period of 30 minutes. The
25 mixture was stirred at room temperature for 3 hours to complete the reaction. The mixture was directly concentrated *in vacuo* to remove the acetone. The resulting residue was dissolved in DCM (100 mL). The solution was washed with aqueous sodium thiosulfate solution (2 x 100 mL), water (2x 100 mL), and dried over magnesium sulfate. The organic layer was concentrated *in vacuo* to give the title
30 compound (51.5 g) as an oil.

PREPARATION OF [1R-(1 α , 3 α , 5 β)]-3-Amino-3-(dimethylphenylsilyl)-
2-methylene-1-cyclopentanemethanol hydrochloride (2:1) (69)

To a round bottomed flask was mixed crude **68** (10.9 g, 20.5 mmol) zinc solid (2.68 g, 2 eq, 41 mmol) in acetic acid (20 mL). The reaction mixture was heated at 100°C for 1 h and then cooled to room temperature. The crude mixture was mixed with *tert*-butyl methyl ether (30 mL) and filtered and the cake was rinsed with *tert*-butyl methyl ether (70 mL) at room temperature. The combined filtrate was neutralized to pH 7 with NaOH solution (1 N). The organic layer was washed with brine (30 mL), dried (MgSO₄) and concentrated *in vacuo* to afford a light yellow crude oil. This crude oil was used for the next step without further purification. The crude oil was dissolved in toluene (20 mL) and cooled to -65°C. Sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®, 65 wt. % in toluene, d=1.036, 12.3 mL) was added into the solution over ~20 min. The reaction mixture was allowed to warm up to -20°C and stirred at -20°C for 1 h. The reaction was quenched with NaOH (1 N, 20 mL) at 0°C and warmed to room temperature. After stirring at room temperature for 1.5 h, the mixture was filtered through a pad of diatomaceous earth (Celite®) and the cake was rinsed with *tert*-butyl methyl ether (100 mL). The filtrate was dried (MgSO₄) and a solution of HCl in ether (1 N, 22 mL) was added at room temperature to precipitate out of the HCl salt. After stirring for 1 h at room temperature, the HCl salt was collected by filtration and dried under vacuum to afford **69** (HCl salt, 4.4 g, 72% over 3 steps) as a beige-colored solid.

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-6-[[4-(dimethylphenylsilyl)-3-(hydroxymethyl)-2-methylenecyclopentyl]amino]-5-nitro-4(3H)-pyrimidinone (70)

A 3-necked 500 mL round bottomed flask equipped with stirrer, temperature probe and reflux condenser was charged with the amine **69** (1.49 g, 5 mmol), 2,4-diamino-5-nitropyrimidin-6-one (1.56 g, 5.35 mmol) and n-butanol (20 mL). The resultant thin slurry was subjected to heating at 40-45°C over 15 minutes. Triethylamine (0.71 mL, 5.1 mmol) was added slowly over a period of 2 minutes. The reaction mixture was stirred at about 70°C for 1 h. HPLC data showed that the reaction was almost complete. At this point, five washes of 25 mL of water was given

to the reaction mixture at 70°C. The last wash was almost colorless. The crude product, **70**, in n-butanol was used without further purification in the next reaction.

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-9-[4-(dimethylphenylsilyl)-3-(hydroxymethyl)-2-methylenecyclopentyl]-1,9-dihydro-6H-purin-6-one (**71**)

Solid Na₂S₂O₄ (2 g, 12 mmol) was charged into the flask containing crude **70** and the resulting slurry was heated to ~60°C, over 20 minutes. Formic acid (9.5 mL, 250 mmol) was added slowly over the course of 10 minutes at 65°C. The resulting mixture was stirred for 5 min and heated to ~70°C for 1 hour. The mixture was cooled to 25°C and neutralized with 6 N NaOH solution to effect a pH=7.04. The aqueous layer was separated and extracted with n-BuOH (5 mL). The combined organic layer was filtered through a pad of diatomaceous earth and transferred into 3-neck 50 mL reaction flask equipped with overhead stirrer, temperature probe and distillation head. The resultant solution was distilled under *in vacuo* to remove water and excess n-butanol to afford the pyrimidine intermediate

The resultant slurry containing the intermediate was heated to 40-50°C and triethylorthoformate (8 mL, 48 mmol) was added over 3 minutes, followed by conc. HCl (0.2 mL) over 1 min. The reaction mixture was heated at ~85°C for 3 h. The reaction mixture was cooled to room temperature and stirred at room temperature for 12 h. The reaction mixture was neutralized to a pH of ~7.2 with aqueous NaOH solution. The resulting crude product over an ion exchange column to give the product **71** (1.25 g) in ~65% yield.

The compound of formula **70** could then be converted to the compound of formula **21** as described in the Example 1.

EXAMPLE 4

PROCESS FOR THE PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (**21**)

PREPARATION OF (4S, 5R)-4-(Phenylmethoxy)-5-[(phenylmethoxy)methyl]-
1-cyclopentene-1-methanol (16)

To a round bottomed flask equipped with an argon inlet, magnetic stirrer and cooling bath was dissolved (4S, 5R)-4-(Phenylmethoxy)-5-[(phenylmethoxy)methyl]-
5 1-cyclopentene-1-carboxylic acid methyl ester **7** (3.62 g, 10.2 mmol) in DCM (40 mL). The solution was cooled to -78°C and diisobutylaluminum hydride (1 M in toluene, 22.4 mL, 22.4 mmol) was added into the solution over the course of 10 minutes. After stirring at -78°C for 1 hour the reaction mixture was quenched with a saturated solution of potassium sodium tartrate (Rochelle salt, 50 mL) and stirred at
10 room temperature overnight. The organic layer was diluted with ethyl acetate, separated, dried (sodium sulfate) and concentrated *in vacuo* to afford the crude allylic alcohol as colorless oil (3.06 g, 90%). After standing at room temperature the title compound crystallized out as a white solid.

15 PREPARATION OF [1R-(1 α , 2 α , 3 β , 5 α)]-3-(Phenylmethoxy)-
2-[(phenylmethoxy)methyl]-6-oxabicyclo[3.1.0]hexane-1-methanol (17)

To a flame dried round bottomed flask equipped with an argon inlet, magnetic stirrer and cooling bath was added (-)-(D)-diethyltartrate (188 mg, 0.91 mmol) and 4A molecular sieves (flame dried, 1.45 g) in DCM (10 mL). The reaction suspension was
20 cooled to -25°C and titanium (IV) isopropoxide (0.20 mL, 0.69 mmol) was added into the suspension. The reaction mixture was stirred at -25°C for 1 hour and then *tert*-butyl hydroperoxide (3 M in octane, 1.52 mL, 4.5 mmol) was added. After stirring the mixture for about 1.5 hours at -25°C, **16** (0.73 g, 2.28 mmol in 4 mL DCM) was added into the solution over the course of 10 minutes. The reaction mixture was
25 stirred at -25°C for 3-4 hours and quenched with sodium hydroxide (5 N, 2 mL). The mixture was stirred for 1 hour at room temperature and filtered through a bed of diatomaceous earth (Celite®). The bed was rinsed with DCM (2 x 10 mL). The combined organic layer was washed with brine (20 mL), dried (sodium sulfate) and concentrated *in vacuo* to afford (0.76 g, ~100%) a colorless oil. Flash column
30 chromatography (2:1 to 1:1 hexane/ethyl acetate) gave 0.55 g of the title compound (73%) as a light yellow solid (mp 60-62°C).

PREPARATION OF [1S-(1 α , 2 β , 3 α , 5 β)]-5-[2-Amino-6-(phenylmethoxy)-
9H-purin-9-yl]-1-hydroxy-3-(phenylmethoxy)-2-
(phenylmethoxy)methyl]cyclopentanemethanol (18, X=BnO)

5 To a round bottomed flask equipped with an argon inlet, a magnetic stirrer and a reflux condensor were charged 2-amino-6-O-benzyloxypurine (1.66 g, 6.87 mmol) with dimethylformamide (20 mL). Lithium hydride (32.7 mg, 4.13 mmol) was added into the suspension, and the resulting mixture was stirred for 1 hour. A solution of **17** (2.13 g in 2 mL dimethylformamide, 6.25 mmol) was added into the solution. The
10 solution was heated to 120-130°C for 1 hour. The resulting solution was worked up by quenching with sodium hydroxide (1 N, 20 mL), and extracting with ethyl acetate (2 x 150 mL). The combined organic layer was washed with saturated ammonium chloride solution (200 mL) and brine (100 mL), dried (sodium sulfate), and concentrated *in vacuo* to afford a light brown solid. This solid was dissolved in ethyl
15 acetate/DCM and passed through a pad of flash silica gel (eluted with ethyl acetate) to afford 3.1 g of the title compound (85%) as light yellow solid. Recrystallization (ethyl acetate/hexanes) gave 2.81 g of the title compound in ~78% yield as an off white solid.

20 PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[2-methylene-
4-(phenylmethoxy)-3-[(phenylmethoxy)methyl]cyclopentyl]-6H-purin-6-one (20)

A 1-L round bottomed flask equipped with an argon inlet, and a magnetic stirrer was charged with **18** (2.6 g, 4.4 mmol), trimethyl orthoformate (2.38 mL, 21.8 mmol), pyridinium p-toluenesulfonate (0.56 g, 2.22 mmol), and DCM (20 mL). The
25 reaction mixture was stirred for about 16 hours at room temperature. After the completion of the reaction, the reaction mixture was quenched with sodium bicarbonate solution (50 mL). The resulting mixture was extracted with ethyl acetate (2 x 50 mL) and the combined organic layer was washed with brine (50 mL), dried (sodium sulfate), and concentrated *in vacuo* to afford the orthoformate intermediate.
30 The crude product was dissolved with acetic acid/acetic anhydride (1.5 mL/30 mL) in a round bottomed flask. The solution was heated to reflux for about 5 hours and then

cooled to room temperature. The acetic acid/acetic anhydride was removed by vacuum distillation to afford an intermediate mixture (2.34 g). The above intermediate mixture (2.2 g, 3.7 mmol) was dissolved in acetonitrile (60 mL) and 2 N HCl (30 mL), and then heated to reflux to complete the reaction. The mixture was cooled to room temperature and neutralized by addition of triethylamine. The mixture was directly concentrated *in vacuo* to remove most of acetonitrile. Ethanol was added to the resulting solid residue and the suspension was stirred for 1 hour. The solid was collected by filtration, rinsed with ethanol, and dried under high vacuum to afford 1.57 g of the title compound in 93% yield.

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

To a round bottomed flask equipped with magnetic stirrer and nitrogen inlet-outlet were mixed **20** (2.7 g, 5.9 mmol) with CH₂Cl₂ (10 mL). The mixture was cooled to -78°C and BCl₃ (1 M, 35.4 mL, 35.4 mmol) was added into the reaction suspension at a rate so that the reaction temperature did not exceed -65°C. The reaction mixture was stirred at -78°C for 0.5 h and then it was warmed up to -20°C. After stirring at -20°C for 1 h, the reaction mixture was re-cooled to -78°C and MeOH (30 mL) was added into the reaction mixture and warmed to room temperature. The reaction mixture was concentrated *in vacuo* to remove MeOH to afford a light yellow oil. This oil was re dissolved in MeOH (30 mL); Decolorizing carbon (2.7 g) was added into the solution and stirred at room temperature for 0.5 h. The suspension was filtered through diatomaceous earth and the cake was rinsed with MeOH (10 mL). The combined filtrate was concentrated *in vacuo* to afford a clear oil. This oil was dissolved in water (20 mL) and extracted with ethyl acetate (2 x 30 mL). The aqueous layer was neutralized by addition of NaOH to effect a pH ~7.2. The solid from the suspension was collected by filtration and recrystallized with water (30 mL) to afford 1.36 g of **21**.

EXAMPLE 5

PROCESS FOR THE PREPARATION OF [1S-(1 α , 3' α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

5 PREPARATION OF COMPOUND (1 α , 2 β , 3 α)-2-[(Phenylmethoxy)methyl]-4-cyclopentene-1,3-diol diacetate ester (2)

To a round bottomed flask equipped with magnetic stirrer was dissolved 1 (2.2 g, 10 mmol) in acetic anhydride (4 mL) and pyridine (2.5 mL). After stirring at room temperature overnight, the excess acetic anhydride and pyridine was removed by vacuum distillation, the crude oil was chromatographed (silica, 2:1 Hexane/EtOAc) to afford 2.8 g (92%) of 2 as light yellow oil.

PREPARATION OF (+)-(1 α , 2 β , 3 α)-2-[(Phenylmethoxy)methyl]-4-cyclopentene-1,3-diol monoacetate ester (3) (without immobilization of the enzyme)

15 Enantioselective asymmetric hydrolysis of the diacetate 2 was carried out using the enzyme Pancreatin or Lipase PS-30 from *Pseudomonas cepacia*. The reaction mixture contained 25 mM potassium phosphate buffer (36 mL, pH 7.0), toluene (4 mL) and the diacetate 2 (2 mg/mL) and Lipase PS-30 or Pancreatin (50 mg/mL). The reaction was carried out at 25°C, maintaining the pH at 7.0 by addition of 1 N NaOH as required. The progress of the reaction was monitored by high pressure liquid chromatography. The reaction was terminated when the concentration of the remaining substrate 2 dropped below 0.05 mg/mL. The reaction mixture was concentrated under reduced pressure to obtain (+)-monoacetate 3. After 16 h of reaction time, a reaction yield of 80 M% and an ee of 98% was obtained using Lipase PS-30. A reaction yield of 75% and an ee of 98.5% was obtained using Pancreatin.

PREPARATION OF (+)-(1 α , 2 β , 3 α)-2-[(Phenylmethoxy)methyl]-4-cyclopentene-1,3-diol monoacetate ester (3) (using immobilized Lipase PS-30)

30 Enantioselective asymmetric hydrolysis of diacetate 2 was carried out using immobilized Lipase PS-30. Crude Lipase PS-30 from *Pseudomonas cepacia* was immobilized on polypropylene (Accurel Systems International Corp.) and

immobilized enzyme was used. The reaction contained 25 mM potassium phosphate buffer (1.8 L, pH 7.0), toluene (200 mL), diacetate **2** (52 g), and immobilized Lipase PS-30 (180 g). After 18 h reaction time, a reaction of 80 M% (32.5 g) and ee of 98% were obtained for the (+)-monoacetate **3**. At the end of the reaction, the immobilized
5 enzyme was filtered and the clear supernatant obtained was extracted with two volumes of ethyl acetate. The separated organic phase was concentrated under reduced pressure to obtain the desired product **3**.

10 PREPARATION OF [1S-(1 α , 4 α , 5 β)]1-4-[Nitro(phenylsulfonyl)methyl]-
5-[(phenylmethoxy)methyl]-2-cyclopenten-1-ol (**4**)

To a round bottomed flask equipped with an argon inlet, magnetic stirrer, addition funnel and reflux condensor was added compound **3** (0.98 g, 3.74 mmol), phenylsulfonylnitromethane (0.91 g, 4.5 mmol) and tetrakis[triphenylphosphine]-palladium (43 mg, 0.037 mmol) in THF (7 mL) at 0°C. The reaction mixture was
15 degassed using argon for a few minutes. Triethylamine (1.1 g, 1.6 mL, 11.4 mmol) was added into the reaction mixture over the course of 2 minutes at 0°C. The reaction mixture was stirred at 0°C for 1 hour and allowed to warm up to room temperature. The reaction mixture was then stirred at room temperature for 3 hours. The reaction mixture was quenched with 1 N HCl at 0°C (15 mL) and extracted with hexane/ethyl
20 acetate (1:1; 2 x 20 mL). The combined organic layer was washed with brine (30 mL), dried (sodium sulfate) and concentrated *in vacuo* to afford a red-colored oily residue (2.2 g). Silica pad filtration was performed to remove the baseline materials to give the title compound (1.36 g).

25 PREPARATION OF [1R-(1 α , 4 α , 5 β)]-[[Nitro[4-(phenylmethoxy)-
5-[(phenylmethoxy)methyl-2-cyclopenten-1-yl]methyl]sulfonyl]benzene (**5**)

To a round bottomed flask with an argon inlet, a magnetic stirrer and a cooling bath was charged **4** (3.0 g, 7.43 mmol) in THF at 0°C. Sodium hydride (60% suspension in mineral oil, 0.68 g, 17 mmol) was added into the reaction mixture
30 portion-wise over the course of 10 minutes with stirring. The resulting suspension was stirred at 0° for 30 minutes, warmed to room temperature, and stirred for 1 hour

at room temperature. Benzyl bromide (1.52 g, 1.06 mL, 8.91 mmol) was added and the reaction mixture was heated at 45°C for 3 hours to complete the reaction. The reaction was quenched with cold HCl (1 N, 30 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layer was washed with brine (30 mL), dried (sodium sulfate), and concentrated *in vacuo* to afford the title compound as a light brown oil (3.98 g). The crude product was used without further purification in the next step.

10 PREPARATION OF (4S, 5R)-4-(Phenylmethoxy)-5-[(phenylmethoxy)methyl]-
 1-cyclopentene-1-carboxylic acid methyl ester (7)

To a round bottomed flask equipped with an argon inlet, a magnetic stirrer, an addition funnel and a reflux condensor was added **5** (2.7 g, 5.47 mmol) and sodium carbonate (2.58 g, 46 mmol) in a mixture of DCM/MeOH (3:1, 10 mL) at room temperature. The reaction mixture was heated to reflux and a solution of potassium peroxymonosulfate:tetrabutyl ammonium salt (2.3% active oxygen, 11 g in 15 mL of DCM, 7.9 mmol) in DCM was added into the reaction suspension dropwise over a period of 10 hours. After refluxing for about 14 hours, the reaction mixture was cooled to room temperature and diluted with MeOH (50 mL). The resulting mixture was cooled to -40°C. Concentrated sulfuric acid was added to neutralize the reaction medium to acidic pH (1.2 mL was used). The reaction mixture was warmed up to room temperature and stirred at room temperature for 3 hours. The reaction mixture was quenched with water/brine (1:1; 40 mL) and extracted with hexane/ethyl acetate (2:1, 2 x 200 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (100 mL) and brine (100 mL), dried (sodium sulfate) and concentrated *in vacuo* to afford crude intermediate (1.88 g, >100% material balance) which was used in the next step without any further purification.

To a round bottomed flask equipped with an argon inlet and a magnetic stirrer was dissolved the above obtained intermediate (2.95 g, 8.1 mmol) in dry MeOH (10 mL). A sodium methoxide solution in MeOH solution (25 wt. %, 0.34 g, 1.6 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 2 hours. After completion, the reaction mixture was neutralized with

HCl (10 mL) at 0°C, and extracted with ethyl acetate/hexane (1:1; 2 x 100 mL). The combined organic layer was washed with brine, dried (sodium sulfate), and concentrated *in vacuo* to afford a solid. Recrystallization with hexane/*tert*-butyl methyl ether (10:1) at -20 to -30°C gave 1.83 g of the title compound in 64% yield as a light yellow solid.

EXAMPLE 6

PROCESS FOR THE PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

10

PREPARATION OF (-)-(1 α , 2 β , 3 α)-2-[(Phenylmethoxy)methyl]-4-cyclopentene-1,3-diol monoacetate ester (13) (without immobilization of the enzyme)

Enantioselective acetylation of the diol **1** was carried out using immobilized Lipase PS-30 from *Pseudomonas cepacia*. The reaction mixture contained heptane/*t*-butyl methyl ether (10/1 v/v, 1 L), diol **1** (5 g), immobilized Lipase PS-30 (25 g), and isopropenyl acetate (2 eq) as the acylating agent. The reaction was carried out at 33°C. The progress of the reaction was monitored by high pressure liquid chromatography. The reaction was terminated when the concentration of the remaining substrate **1** dropped below 0.1 mg/mL. After 4 h, a reaction yield of 80% and an ee of 98% was obtained for the (-)-monoacetate **13**.

20

PREPARATION OF [1R-(1 α , 4 α , 5 β)]-Carbonic acid, methyl 4-(acetoxo)-5-[(phenylmethoxy)methyl]-2-cyclopenten-1-yl ester (10)

To a round bottomed flask equipped with magnetic stirrer and N₂ inlet-outlet were mixed **13** (2.62 g, 10 mmol), pyridine (1.18 g, 12 mmol) with CH₂Cl₂ (5 mL). The mixture was cooled to -5°C and methyl chloroformate (1.134 g, 12 mmol) was added into the reaction suspension at a rate so that the reaction temperature did not exceed 0°C. The reaction mixture was stirred at 0°C for 1 h and warmed up to room temperature for 1 h. The resulting mixture was quenched with saturated ammonium chloride solution at 0°C. The quenched solution was extracted with 1:2 EtOAc/hexane (30 mL x 2). The combined organic layer was washed with brine

30

(30 mL); dried (Na₂SO₄); concentrated *in vacuo*, and dried under high vacuum to afford crude **14** (3.32 g, 100%) as light brown oil. It was used in the next reaction without further purification.

5 PREPARATION OF [1R-(1 α , 4 α , 5 β)]-[[Nitro[4-(acetoxymethyl)-2-cyclopenten-1-yl]methyl]sulfonyl]benzene (**15**)

To a round-bottomed flask equipped with magnetic stirrer was dissolved phenylsulfonylnitromethane (2.41 g, 12 mmol) in dry THF (25 mL). At 0°C, sodium hydride (0.46 g, 60% mineral oil dispersion, 12 mmol) was added over 5 min. After
10 warming up to room temperature and stirred at room temperature for 1 h, crude **14** (3.3 g, 10 mmol in 5 mL of THF) was added over ~10 min. The reaction was stirred at room temperature for 30 min and at 50°C for 1 h. The reaction mixture was worked up by the addition of saturated ammonium chloride solution (30 mL) followed by extraction with ethyl acetate (2 x 40 mL). The combined organic phase was
15 washed with brine (30 mL); dried (Na₂SO₄) and concentrated *in vacuo* to afford **15** as a crude brown oil (5.12 g, >100%) which was used in the next step without purification.

20 PREPARATION OF [1R-(1 α , 4 α , 5 β)]-[[Nitro[4-(hydroxymethyl)-5-[(phenylmethoxymethyl)-2-cyclopenten-1-yl]methyl]sulfonyl]benzene (**4**)

To a round bottomed flask equipped with magnetic stirrer was dissolved crude **15** (5.12 g, 10 mmol) in 25 mL MeOH. Potassium carbonate (140 mg, 1 mmol) was added into the flask at room temperature and the resulting mixture was stirred overnight. The reaction mixture was concentrated *in vacuo* to remove MeOH. The
25 concentrate was extracted with ethyl acetate (2 x 30 mL) and saturated ammonium chloride solution (30 mL). The combined organic layer was washed with brine (20 mL); dried (Na₂SO₄) and concentrated *in vacuo* to afford a light brown oil. Flash column chromatography (1:2 to 1:1 EtOAc/hexane) afford 2.92 g of **4** (73%) as a colorless oil.

30 EXAMPLE 7

PROCESS FOR THE PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

5 PREPARATION OF [1R-(1 α , 4 α , 5 β)]-4-(Phenylmethoxy)-5-[(phenylmethoxy)methyl]-2-cyclopenten-1-ol (9) (R'=Bn)

To a round bottomed flask equipped with an argon inlet, a magnetic stirrer, a cooling condensor, and an oil bath was charged [1S-(1 α , 2 α , 3 β , 5 α)]1-3-(Phenylmethoxy)-2-[(phenylmethoxy)methyl]-6-oxabicyclo[3.1.0]hexane **8** (20.19 g, 65 mmol, as prepared in United States Patent No. 5,206,244, herein incorporated by reference) in THF (150 mL). Lithium hexamethyldisilazide (1 M in hexane, 190 mL, 190 mmol) was added into the solution at room temperature. The reaction mixture was heated at 60°C for 1.5 hours. The resulting solution was cooled to room temperature and diluted with MeOH (200 mL). After stirring for 20 minutes at room temperature, the reaction mixture was quenched with HCl (1 N, 300 mL), and extracted with ethyl acetate (3 x 300 mL). The combined organic layer was washed with brine (2 x 200 mL), dried (sodium sulfate), and concentrated *in vacuo* to afford 22.7 g of the title compound (>100% material balance) which was used in the next step without any further purification.

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PREPARATION OF [1R-(1 α , 4 α , 5 β)]-Carbonic acid, methyl 4-(phenylmethoxy)-5-[(phenylmethoxy)methyl]-2-cyclopenten-1-yl ester (10)

To a round bottomed flask equipped with an argon inlet, a magnetic stirrer and a cooling bath was charged crude **9** (12.3 g, 39.6 mmol) and pyridine (9.7 mL, 120 mmol) in DCM (100 mL). The solution was cooled to -20 to -15°C and methyl chloroformate (4.2 g, 3.41 mL, 44 mmol) was added into the solution over the course of 20 minutes. The reaction mixture was stirred at -15°C for 0.5 hour and then slowly warmed to room temperature to complete the reaction. The resulting mixture was quenched with HCl (2 N, 120 mL) at 0°C and extracted with ethyl acetate (2 x 300 mL). The combined organic layer was washed with brine (200 mL), dried (sodium sulfate), concentrated *in vacuo*, and dried under high vacuum to afford the crude title

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compound as a brown oil which was used in the next step without any further purification.

PREPARATION OF [1R-(1 α , 4 α , 5 β)]-[[Nitro[4-(phenylmethoxy)-

5 5-[(phenylmethoxy)methyl]-2-cyclopenten-1-yl]methyl]sulfonyl]benzene (5)

To a round bottomed flask equipped with an argon inlet, a magnetic stirrer and a cooling bath was dissolved crude **10** (9.8 g, 26.5 mmol), phenylsulfonylnitromethane (5.4 g, 26.8 mmol) and tetrakis(triphenylphosphine)palladium (0.6 g, 0.52 mmol) in THF (80 mL) at 0°C. The reaction mixture was degassed using argon for a few minutes. Triethylamine (8.4 g, 11.1 mL, 79.5 mmol) was added to the reaction mixture over the course of 10 minutes at 0°C. The reaction mixture was stirred at 0°C for 1 hour and allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was then quenched with 2 N HCl at 0°C (100 mL) and extracted with hexane/ethyl acetate (1:1; 2 x 30 mL). The combined organic layer was washed with brine (100 mL), dried (sodium sulfate), and concentrated *in vacuo* to afford a red-colored oily residue. Silica pad filtration was conducted using ethyl acetate to remove the baseline materials and give the title compound (14.2 g crude, >100%) as a light brown oil which was used in the next step without any further purification.

The conversion of compound of formula **5** to the ester of formula **7** is described in Example 5.

EXAMPLE 8

25 PROCESS FOR THE PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

PREPARATION OF (4S, 5R)-4-(Phenylmethoxy)-5-[(phenylmethoxy)methyl]-
30 2-cyclopenten-1-one (80)

To a round bottomed flask equipped with an argon inlet, magnetic stirrer were mixed with molecular sieves (4 g); pyridinium dichromate (4.16 g, 20 mmol) and HOAc (0.60 g, 10 mmol) with CH₂Cl₂ (25 mL) at 0°C and stirred for 1 h. Allylic alcohol **9** (3.11 g, 10 mmol, prepared according to Example 7) in CH₂Cl₂ (5 mL) was added into the flask over ~5 min. After stirring for 2.5 h at 0°C, the reaction mixture was filtered through a pad of silica gel and the cake was rinsed with 1:3 CH₂Cl₂/EtOAc. The resulting filtrate was extracted with HCl (1 N, 40 mL)/ EtOAc (50 mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to afford a brown oil. This brown oil was chromatographed with 1:2 EtOAc/Hexane to afford **80** (2.85 g, 92%) of light yellow oil

PREPARATION OF (4S, 5R)-Trifluoromethanesulfonic acid 4-(phenylmethoxy)-5-[(phenylmethoxy)methyl]-1-cyclopenten-1-yl ester (**81**)

To a round bottomed flask equipped with an argon inlet, magnetic stirrer were mixed with **80** (1.7 g, 5.5 mmol) with THF (15 mL) and cooled to -78°C. Lithium tri-*sec*-butylborohydride (L-Selectride®) (1 M in THF, 5.5 mL, 5.5 mmol) was added over ~20 min. at -78°C. The reaction mixture was stirred at -78°C for 1.5 h and N-phenyltrifluoromethanesulfonimide (1.98 g, 5.5 mmol) was added at -78°C. After stirring at -78°C for 1 h, the reaction mixture was allowed to slowly warm up to room temperature and stirred at room temperature overnight. The resulting mixture was worked up with saturated NH₄Cl solution (30 mL) and extracted with EtOAc (52 mL). The emulsion was filtered through a pad of diatomaceous earth and washed with EtOAc (20 mL) the combined organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to afford a brown oil (3.2 g, 100%). This brown oil was used in the next reaction without further purification.

PREPARATION OF (4S, 5R)-4-(Phenylmethoxy)-5-[(phenylmethoxy)methyl]-1-cyclopentene-1-carboxylic acid methyl ester (**7**)

To a round bottomed flask equipped with an argon inlet, magnetic stirrer were mixed crude **81** (3.2 g, 5.5 mmol) DMF (25 mL); MeOH (10 mL) and triethylamine (1.54 mL, 11 mmol). Pd(Ph₃)₄ (635 mg, 0.55 mmol) was added into the solution and

the resulting mixture degassed 3 times with CO gas. The reaction was stirred at 1 atmosphere of CO gas at room temperature for 2 h. TLC showed no the absence of starting material. The reaction was worked up with NaOH (0.5 N, 100 mL) at room temperature and extracted with EtOAc (2 x 50 mL). The combined EtOAc layer was washed with brine (50 mL); dried (Na₂SO₄) and concentrated *in vacuo* to afford a light yellow oil. Flash column chromatography (1:2 hexane/EtOAc) gave **7** (1.36 g, 70% over 4 steps).

EXAMPLE 9

10 PROCESS FOR THE PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (**21**)

15 PREPARATION OF [1R-(1 α , 4 α , 5 β)]-4-[[1,1-Dimethylethyl)dimethylsilyl]oxy]-5-[(phenylmethoxy)methyl]-2-cyclopenten-1-ol acetate ester (**22**)

To a round bottomed flask equipped with a nitrogen inlet was dissolved compound **3** (1.85 g, 7.05 mmol) in CH₂Cl₂ (10 mL), and the resulting solution was cooled to 0°C. To the reaction mixture was added triethylamine (1.43 g, 2 mL, 14.1 mmol), 4-N,N-dimethylaminopyridine (DMAP, ~100 mg) and *tert*-butyldimethyl chlorosilane (1.17 g, 7.75 mmol) at 0°C. The resulting mixture was warmed to room temperature and stirred overnight. The resulting mixture was worked up by addition of NaOH solution (0.5 N, 20 mL) at 10°C and extracted with a solution of ethyl acetate/hexanes (1:2 v/v, 2 x 30 mL). The combined organic layer was washed with brine (30 mL), dried (Na₂SO₄), and concentrated *in vacuo* to compound **22** as a crude light oil.

PREPARATION OF [1R-(1 α , 4 α , 5 β)]-4-[[1,1-Dimethylethyl)dimethylsilyl]oxy]-5-[(phenylmethoxy)methyl]-2-cyclopenten-1-ol (**9**)

The above obtained compound **22** was dissolved in MeOH (30 mL), and potassium carbonate (150 mg) was added at room temperature. After stirring at room temperature for 5 h, the MeOH was removed by concentrating the reaction mixture *in*

vacuo. The resulting mixture was extracted with ethyl acetate/hexanes (1:2 v/v, 2 x 30 mL) and saturated NH₄Cl solution (20 mL). The combined organic layer was washed with brine (30 mL), dried (Na₂SO₄), and concentrated *in vacuo* to afford a light yellow oil. The oil was further purified by flash column chromatography (hexanes/ethyl acetate 8:1 to 3:1) to afford compound **9** (2.28 g, 97% overall from compound **3**).

PREPARATION OF (4S, 5R)-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-
[(phenylmethoxy)methyl]-2-cyclopenten-1-one (**80**)

To a 250-mL 3-necked flask, oven dried and equipped with a mechanical stirrer was charged with pyridinium dichromate (20.24 g, 53.80 mmol), molecular sieves (oven dried) and DCM (40 mL). The resulting slurry was cooled to 0°C and to this slurry, acetic acid (which had been dried over molecular sieves, 1.61 g, 26.90 mmol) was charged. The resulting mixture was stirred for 30 minutes at 0°C. **9** (10 g, 29.89 mmol) in DCM (10 mL) was added to the reaction mixture over a period of 10 minutes. The resulting reddish colored reaction mixture was stirred for 2 hours at 0°C. After the reaction was completed, ethyl acetate (100 mL), acetonitrile (5 mL), and diatomaceous earth (Celite®, 5 g) were added sequentially, and the resulting mixture was stirred for 10 minutes. The slurry was filtered on a bed of diatomaceous earth (Celite®) to give a dark colored filtrate. The filtrate was washed with 5% aqueous NaHSO₃ (2 x 250 mL) followed by water (100 mL). The organic layer was dried over magnesium sulfate and the solvent was concentrated *in vacuo* to give 9.5 g of the title compound as a dark transparent, brown oil.

PREPARATION OF (4S, 5R)-Trifluoromethanesulfonic acid 4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[(phenylmethoxy)methyl]-
1-cyclopenten-1-yl ester (**81**)

An oven dried 250-mL 3-necked round bottomed flask, equipped with a mechanical stirrer and an argon inlet, was charged with **80** (9.5 g, 29.89 mmol) and THF (10 mL). The resulting mixture was cooled to -78°C. Lithium tri-*sec*-butylborohydride (L-Selectride®) (1 M, 6.25g, 32.88mmol) in THF (20 mL) was

added over a 20 minute period. To this reaction mixture, N-phenyltriflimide (10.46 g, 29.29 mmol) in THF (20 mL) was added over a period of 5 minutes, keeping the reaction temperature below -78°C. The reaction mixture was stirred overnight while allowing it to warm to room temperature. *Tert*-butyl methyl ether (100 mL) was added to the reaction mixture and the resulting organic layer was washed with saturated aqueous sodium bicarbonate solution (2 x 75 mL) followed by brine (5 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give the title compound (27 g) as yellow oil.

10 PREPARATION OF (4S, 5R)-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-[(phenylmethoxy)methyl]-1-cyclopentene-1-carboxylic acid methyl ester (7)

A 250-mL 3-necked round bottomed flask equipped with a mechanical stirrer was charged with **81** (27.0 g, 29.89 mmol), dimethylformamide (20 mL), MeOH (20 mL) and triethylamine (20.74 mL, 149.45 mmol). The reaction mixture was flushed three times with argon. To this mixture was added tetrakis(triphenylphosphine) (1.762 g, 1.49 mmol). The reaction mixture was flushed three times with carbon monoxide. The reaction mixture was stirred at room temperature for 18 hours under an atmosphere of carbon monoxide. The reaction mixture was extracted with *tert*-butyl methyl ether (200 mL) and the reddish mixture was filtered on a bed of diatomaceous earth (Celite®). The filtrate was concentrated *in vacuo* to give 30 g of a blackish colored oil which upon column chromatography purification gave the title compound as an oil (4.5 g, 40% yield overall yield from **23**).

EXAMPLE 10

25 PROCESS FOR THE PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

30 PREPARATION OF COMPOUND (4S, 5R)-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-[(phenylmethoxy)methyl]-1-cyclopentene-1-methanol (16)

A 500-mL 3-necked round bottomed flask, equipped with an argon inlet, a temperature probe, and a mechanical stirrer, was charged with (4S, R)-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-[(phenylmethoxy)methyl]-1-cyclopentene-1-carboxylic acid methyl ester (**7**) (10 g, 26.55 mmol, as prepared in Example 9) in DCM (200 mL). The solution was cooled to -78°C and to this solution diisobutylaluminum hydride (1 M, 66.39 mL, 66.375 mmol in toluene) was added slowly. The reaction mixture was stirred at -78°C for 2 hours to complete the reaction. The reaction mixture was poured into saturated solution of potassium sodium tartrate (400 mL). The mixture was stirred for 2 hours. The organic layer was separated and the aqueous layer was extracted with n-hexane (200 mL). The combined organic layer was washed with water (50 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give the title compound (9.3 g) as a yellowish oil.

PREPARATION OF [1R-(1 α , 2 α , 3 β , 5 α)]-3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-[(phenylmethoxy)methyl]-6-oxabicyclo[3.1.0]hexane-1-methanol (**17**)

A 250-mL oven dried three necked round bottomed flask was equipped with a magnetic stir bar, argon inlet, and temperature probe charged with oven dried powdered molecular sieves 4A° (9.0 g). DCM (30 mL) was added to the flask and the resulting suspension was stirred room temperature for 5 minutes. Diethyl D-tartrate (2.13 g, 10.32 mmol) in DCM (18 mL) was added at room temperature and the mixture was cooled to -30°C. Keeping the temperature at ~-30°C, titanium (IV) isopropoxide (2.665 mL, 9.03 mmol) was added. The reaction mixture was stirred at -30°C for 30 minutes followed by 15 minutes at -15°C. The mixture was cooled to -30°C. To this mixture, a solution of compound **16** (4.5 g, 12.9 mmol) in DCM (18 mL) was added. The mixture was stirred for 30 minutes at -30°C followed by addition of a solution of *tert*-butyl hydroperoxide (5.0-6.0 M; 9.40 mL, 5.176 mmol). The reaction mixture was stirred between -30°C to -20°C for 3 hours to complete the reaction. The reaction was quenched by addition of water (45 mL). The reaction mixture was stirred with vigorous mixing and allowed to warm up to room temperature (15 to 20°C). When the temperature reached ~15°C, 30% sodium

hydroxide solution (10 mL) was added slowly to give a milky white slurry. This slurry was added into a 3.0-L Erlenmeyer flask containing *tert*-butyl methyl ether (1100 mL). The mixture was stirred for 30 minutes and then filtered on a bed of diatomaceous earth (Celite®). The aqueous layer was separated from the filtrate and discarded. The organic layer was washed with 10% aqueous sodium thiosulfate (100 mL) and water (2 x 160 mL). The combined organic layer was washed with water (100 mL), brine (50 mL), and dried over magnesium sulfate. The organic layer was concentrated *in vacuo* to give the title compound in quantitative yield (5.47 g) as an oil.

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PREPARATION OF COMPOUND [1S-(1 α , 2 α , 4 β , 5 α)]-5-[2-Amino-6-(phenylmethoxy)-9H-purin-9-yl]-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-hydroxy-2-[(phenylmethoxy)methyl]cyclopentanemethanol (18)

To a round bottomed flask equipped with an argon inlet, magnetic stirrer and refluxing condenser were charged O-benzyloxy guanine (1.66 g, 6.87 mmol) with DMF (20 mL). LiH (32.7 mg, 4.13 mmol) was added into the suspension and stirred for 1 h. A solution of **17** (2.13 g in 2 mL DMF, 6.25 mmol) was added into the solution and heated to 120-130°C for 1 h. The resulting solution was worked up by quenching with NaOH (1 N, 20 mL) and extracted with EtOAc (2 x 150 mL). The combined organic layer was washed with saturated NH₄Cl (200 mL), brine (100 mL), dried (Na₂SO₄) and concentrated in vacuum to afford a light brown solid. This solid was dissolved in EtOAc/CH₂Cl₂ and passed through a pad of flash silica gel (eluted with EtOAc) to afford 3.102 g of **18** (85%) as light yellow solid. Recrystallization (EtOAc/Hex.) gave 2.6 g (1st crop, 72%) and 0.21 g (2nd crop, 5.8%) of **18** as an off white solid.

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PREPARATION OF [1S-(1 α , 2 β , 4 β)]-4-[2-Amino-6-(phenylmethoxy)-9H-purin-9-yl]-3-methylene-2-[(phenylmethoxy)methyl]cyclopentanol (19)

A round bottomed flask equipped with an argon inlet, magnetic stirrer was charged **18** (2.6 g, 4.4 mmol), trimethylorthoformate (2.38 mL, 21.8 mmol), pyridinium p-toluenesulfonate (0.56 g, 2.22 mmol) and CH₂Cl₂ (20 mL). The

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reaction mixture was stirred for about 16 h at room temperature. After the completion of the reaction, the reaction mixture was quenched with NaHCO₃ (50 mL). The resulting mixture was extracted with EtOAc (2 x 50 mL) and the combined organic layer was washed with brine (50 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford the orthoformate. The crude product was dissolved with HOAc/Ac₂O (1.5 mL/30 mL) in a round bottomed flask and heated to reflux for about 5 h. The mixture was then cooled to room temperature. The HOAc/Ac₂O was removed by vacuum distillation to afford a light brown oil. The crude product was purified by a silica pad filtration to afford 2.34 g of a mixture.

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PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-2-methylene-3-[(phenylmethoxy)methyl]cyclopentyl]-6H-purin-6-one (20)

The above mixture (2.2 g, 3.7 mmol) was dissolved in CH₃CN (60 mL) and 2 N HCl (30 mL) and the resulting solution was heated to reflux. The reaction mixture was monitored by HPLC. After the completion of the reaction, the mixture was cooled to room temperature and neutralized by addition of triethylamine. The mixture was directly concentrated *in vacuo* to remove most of CH₃CN. Ethanol was added to the resulting solid residue, and the suspension was stirred for 1 h. The resulting solid was collected by filtration. The solid was rinsed with EtOH and dried under high vacuum to afford 1.57 g of **20**.

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The compound of formula **20** was then converted to the compound of formula **21** according to the procedure described in Example 4.

EXAMPLE 11

25 PROCESS FOR THE PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

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PREPARATION OF (4S)-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-cyclopenten-1-one (33)

To a 1-L round bottomed flask was charged (4S)-4-Hydroxy-2-cyclopenten-1-one (**32**) (20 g, 204 mmol, prepared described in Khanapure, S.; Najafi, N.; Manna, S.; Yang, J.; Rokash. *J. Org. Chem.*, **1995**, *60*, 7448) in DCM (200 mL) followed by N,N-dimethylethylamine (47.7 g, 653 mmol), *tert*-butyldimethylsilyl chloride (46.1 g, 306 mmol) and a catalytic amount of 4-N,N-dimethylaminopyridine (1 g). The mixture was stirred at room temperature for 24 hours. The reaction mixture was poured into ethyl acetate (200 mL) and the organic layer washed with water (200 mL), aqueous HCl (1 N, 2 x 100 mL), brine (100 mL) and saturated sodium bicarbonate solution (100 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford the title compound as a crude product (42 g, ~98% yield).

PREPARATION OF (3S, 4S)-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[(dimethylphenylsilyl)methyl]-1-[(trimethylsilyl)oxy]cyclopentane (**34**)

To a suspension of magnesium (1.18 g, 48.5 mmol) in THF (15 mL) at room temperature in 100 mL round bottomed flask was added (chloromethyl)-dimethylphenylsilane (8.86 g, 48.5 mmol). The resulting mixture was stirred for ~1 hour to form the Grignard reagent. To this solution, copper (I) bromide-dimethylsulfide complex (2.13 g, 10.4 mmol) was added, and the mixture was stirred at room temperature for 30 minutes. The resulting solution was cooled to -78°C, and to it was added slowly chlorotrimethylsilane (1.2 g, 11.3 mmol), followed by a solution of **33** (2 g, 9.4 mmol) in THF (2 mL). The reaction mixture was stirred at -78°C for 1 hour and at 0°C for 3 hours to complete the reaction. The reaction mixture was poured into a flask containing hexanes (200 mL) and stirred for 10 minutes. The mixture was filtered through a bed of diatomaceous earth (Celite®) and the resulting filtrate was concentrated *in vacuo* to dryness to afford the crude title compound.

PREPARATION OF [3S-(3 α , 4 β)]-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[(dimethylphenylsilyl)methyl]-2-(hydroxymethyl)cyclopentanone (**35**)

The residue containing **34** was dissolved in THF (80 mL) and transferred to a 500-mL round bottomed flask. To this solution was added yttrium

trifluoromethanesulfonate (5.84 g) and aqueous formaldehyde (18.5 mL, 37 wt. % solution). The resulting mixture was stirred at room temperature for 12 hours to complete the reaction. The reaction was quenched by slow addition of water (30 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with brine (200 mL), dried over magnesium sulfate, and concentrated *in vacuo* to dryness to give the crude title compound (2.12 g, 57% yield).

PREPARATION OF (3S, 4S)-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[(dimethylphenylsilyl)methyl]-2-methylenecyclopentanone (36)

To a solution of **35** (1.2 g, 3.06 mmol) in DCM (20 mL) was added triethylamine (0.554 mL, 3.97 mmol) at -0°C slowly followed by methanesulfonyl chloride (0.284 mL, 3.67 mmol). The resulting mixture was stirred for 2 hours at room temperature to complete the reaction and form the mesylate. 1,8-diazabicyclo[5.4.0]undec-7-ene (0.685 mL, 4.58 mmol) was added to the reaction mixture and the reaction mixture was stirred for 3 hours at room temperature to complete the reaction. The reaction mixture was poured into a stirring mixture containing aqueous ammonium chloride solution (10%, 25 mL) and DCM (25 mL). The organic layer was separated and washed with water, brine, and dried over magnesium sulfate. Concentration of the organic layer *in vacuo* gave the crude title compound, 1.1 g in 96% yield.

PREPARATION OF [1R-(1 α , 3 β , 4 α)]-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[(dimethylphenylsilyl)methyl]-2-methylenecyclopentanol (37)

To a cooled (-78°C), stirred solution of **36** (4.8 g, 12.81 mmol) in THF (25 mL) in a 100-mL round bottomed flask equipped with an argon inlet was added lithium triethylborohydride (super hydride®, 24.4 mL, 24.4 mmol, 1.0 M THF solution) over a period of 15 minutes. The reaction mixture was stirred at the same temperature for 1 hour and slowly warmed to room temperature to complete the reaction. The reaction mixture was quenched with sodium hydroxide solution (10%, 25 mL) and extracted with ethyl acetate (2 x 25 mL). The organic layer was separated, washed with brine (50 mL), and dried over magnesium sulfate.

Concentration of the organic layer *in vacuo* gave the crude title compound, 4.58 g in 95% yield in a 8:1 diastereomeric ratio. The title compound was purified by using silica gel flash chromatography ethyl acetate/hexanes (1:4 v/v) to afford the desired diastereomer, 4 g in 83% yield.

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PREPARATION OF [1S-(1 α , 3 α , 4 β)]-9-[4-[(1,1-Dimethylethyl)dimethylsilyl]oxy]-
3-[(dimethylphenylsilyl)methyl]-2-methylenecyclopentyl]-
6-iodo-9H-purin-2-amine (38, X=I)

To a solution of **37** (1.6 g, 4.24 mmol) in THF (20 mL) in a 100-mL round
10 bottomed flask was added sequentially triphenylphosphine (1.49 g, 5.7 mmol), iodo
guanine (1.49 g, 5.7 mmol) and diethylazodicarboxylate (0.91 mL, 5.7 mmol) at -
78°C. The reaction mixture was stirred at -78°C for 2 hours, then warmed slowly to
room temperature over a period of 1 hour, and stirred at room temperature for 12
hours to complete the reaction. The reaction was quenched by addition of saturated
15 ammonium chloride solution (50 mL) and the resulting mixture extracted with a
mixture of *tert*-butyl methyl ether and heptane (1:4; 2 x 25 mL). The organic layer
was dried over magnesium sulfate and concentrated *in vacuo* to give crude product
which was purified by silica gel chromatography to afford the title compound in 71%
yield (1.87 g).

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PREPARATION OF [1R-(1 α , 3 α , 5 β)]-3-(2-Amino-6-iodo-9H-purin-9-yl)-
5-hydroxy-2-methylenecyclopentanemethanol (39)

To a solution of **38** (1.8 g, 2.9 mmol) in DCM (25 mL) was added
tetrafluoroboric acid-dimethyl ether complex (3.53 mL, 29 mmol) at room
25 temperature. The resulting mixture was stirred for 4 hours. MeOH (25 mL) was
added to the reaction mixture to make it homogenous. Solid potassium bicarbonate
(4.35 g, 43.5 mmol) was slowly added and the resulting mixture stirred at room
temperature for 1.5 hours. Potassium fluoride (0.85 g, 14.6 mmol) was added,
followed by aqueous hydrogen peroxide (30 wt. % solution, 3 mL). The reaction
30 mixture was stirred at room temperature for 4 hours. The reaction mixture was
concentrated *in vacuo* to dryness to give a residue. The residue was triturated with

DCM (3 x 25 mL). The combined organic layer was concentrated *in vacuo* to give the title compound as a solid (0.96 g, 85% yield).

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-1,9-Dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

A mixture of **39** (0.5 g, 1.29 mmol) in sodium hydroxide (2 N, 10 mL) was heated at 70°C under an atmosphere of argon for 1 hour to complete the reaction. The reaction mixture was cooled to 0°C and neutralized slowly by addition of 3 N HCl. Decolorizing carbon (0.5 g) was added. This mixture was heated at ~90°C for 1 hour. The hot mixture was filtered through a bed of diatomaceous earth (Celite®). The resulting clear filtrate was cooled and seeded with **21** to effect crystallization. The product was collected by filtration and dried under vacuum to afford the title compound as a white crystalline solid (0.21 g, 60% yield).

EXAMPLE 12

PROCESS FOR THE PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

PREPARATION OF (1R, 4S)-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-iodo-2-cyclopenten-1-ol (40)

To a solution of **33** (40 g, 188 mmol, as prepared in Example 11) in THF (100 mL) in 1-L round bottomed flask was added a solution of iodine (105 g, 414 mmol) in DCM (100 mL). The resulting solution was stirred at 0°C. To this solution, pyridine (36 mL) was slowly added through a dropping funnel over a period of 20 minutes. The mixture was then stirred at the same temperature for 3 hours to complete the reaction. The reaction mixture was diluted with *tert*-butyl methyl ether (300 mL) and washed with sodium bisulfite solution (600 mL), HCl (0.5 N, 500 mL), brine (200 mL) and dried over magnesium sulfate. The organic layer was concentrated *in vacuo* to dryness to give the intermediate iodo-ketone as a yellow oil (56 g) in 89% yield.

To a round bottomed flask equipped with an argon inlet, magnetic stirrer was charged cerium chloride heptahydrate (30.8 g, 82.75 mmol) and MeOH (150 mL) and stirred at room temperature for 30 minutes. To this stirred solution, the iodo-ketone (56 g, 165.5 mmol) in MeOH (60 mL) was added and cooled to -60°C. To this cooled solution, sodium borohydride (6.25 g, 165.5 mmol) was added in portion-wise. After stirring the reaction mixture at -50°C for 20 minutes, the reaction was warmed to -30°C and stirred for another 30 minutes to complete the reaction as judged by TLC. The reaction mixture was diluted with *tert*-butyl methyl ether (400 mL) and washed with saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate and filtered on a sintered funnel. The filtrate was concentrated on a rotary evaporator to afford the desired product **40** as yellow oil (51 g, 91% yield).

PREPARATION OF (3S, 5R)-3-[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-hydroxy-1-cyclopentene-1-carboxylic acid methyl ester (**41**)

To a solution of **40** (18 g, 52.89 mmol) in MeOH (100 mL) in a sealed reactor (Parr reactor) was added triethylamine (36 mL, 264.5 mmol) and dichlorobis(triphenylphosphine)palladium II [$\text{PdCl}_2(\text{Ph}_3\text{P})_2$] (2 mole %). The reactor was flushed with nitrogen for about 5 minutes. The reactor was heated to about 50°C and pressurized to about 15 psi. The reaction was continued while stirring at the same pressure and temperature for 5 hours to complete the reaction. The reaction mixture was concentrated, diluted with ethyl acetate (50 mL) and filtered. The organic layer was washed with water, brine and dried over magnesium sulfate. The organic layer was concentrated *in vacuo* to dryness to give crude product which was purified by column chromatography to give the title compound (11.6 g) in ~81 % yield.

PREPARATION OF (3S, 5R)-5-(Benzoyloxy)-4-[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-cyclopentene-1-carboxylic acid methyl ester (**42**)

To a solution of **41** (0.55 g, 2 mmol) in THF (2 mL) at -78°C was added lithium hexamethyldisilazide (3 mL, 1 M, 3 mmol) and the resulting solution was stirred for 1 hour. To this solution, 1-adamantanecarbonyl chloride (596 mg, 3 mmol) was added and the resulting mixture was stirred for 15 min at -78°C followed by 30

minutes at room temperature to complete the reaction. The reaction mixture was diluted with ethyl acetate (25 mL) and washed with sodium bicarbonate solution, water, and brine. The organic layer was concentrated *in vacuo* to dryness to give the crude product. The crude product was crystallized from MeOH-water to give the title compound (0.57 g) in ~75% yield.

PREPARATION OF (4S, 5S)-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-[(dimethylphenylsilyl)methyl]-1-cyclopentene-1-carboxylic acid methyl ester (43)

To a suspension of magnesium (1.18 g, 48.5 mmol) in THF (15 mL) at room temperature was added phenyldimethylchlorosilane (8.86 g, 48.5 mmol). The resulting mixture was stirred for ~1 hour to form the Grignard reagent. To this solution, copper (I) iodide (0.3 g, 5%) was added and the resulting solution stirred at room temperature for 30 minutes. The resulting solution was cooled to -78°C and to it was added slowly a solution of **42** (14 g, 32.33 mmol) in THF (20 mL). The reaction mixture was stirred at -78°C for 7 hours to complete the reaction. The reaction was quenched by slow addition of MeOH (10 mL) and warming to room temperature. The mixture was diluted with ethyl acetate (300 mL) and washed with saturated ammonium chloride (200 mL), sodium hydroxide (1 N, 2 x 150 mL), water (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give the crude title compound, 13 g in 100% yield.

PREPARATION OF (4S, 5S)-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-[(dimethylphenylsilyl)methyl]-1-cyclopentene-1-methanol (44)

To a solution of **43** (15 g, 37.13 mmol) in hexanes (100 mL) was added diisobutylaluminum hydride (113 mL, 113.4 mmol, 1 N in hexanes) at -78°C slowly over a period of 30 minutes keeping the temperature below -60°C. The resulting mixture was stirred for 2 hours at the same temperature to complete the reaction. The reaction mixture was quenched by addition of sodium hydroxide (2 N, 200 mL). The organic layer was separated and washed with water, brine, and dried over magnesium sulfate. The organic layer was concentrated *in vacuo* to dryness to give the crude title compound (13 g, 100% yield).

PREPARATION OF (1R, 2R, 3S, 5R)-3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-[(dimethylphenylsilyl)methyl]-6-oxabicyclo[3.1.0]hexane-1-methanol (45)

To a cooled (0°C), stirred solution of **44** (14 g, 37.23 mmol) in MeOH (50 mL) was added magnesium monoperoxyphthalate (MPPA, 80% pure, 27.62 g, 44.68 mmol) in six portions over a period of 1 hour, keeping the temperature <0°C. The reaction mixture was stirred at the same temperature for 4 hours to complete the reaction. The reaction mixture was diluted with ethyl acetate (300 mL) and washed with saturated sodium bisulfite (200 mL), sodium hydroxide (0.5 N, 2 x 150 mL), brine (150 mL) and dried over magnesium sulfate. The organic layer was concentrated *in vacuo* to dryness to give the crude title compound (13.5 g, 92%)

PREPARATION OF [1S-(1 α , 2 β , 3 α , 5 β)]-5-[2-Amino-6-(benzyloxy)-9H-purin-9-yl]-3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-[(dimethylphenylsilyl)methyl]-

1-hydroxycyclopentanemethanol (46, X=BnO)

To a solution of 2-amino-6-O-benzyloxypurine (20 g, 84 mmol) in dimethylformamide (50 mL) at room temperature was added lithium hydride (0.4 g, 50.4 mmol) as a solid in one portion. The suspension was stirred at room temperature for 4 hours at which point a clear solution was observed. To this solution was added a solution of **45** (13.2 g, 33.6 mmol) in dimethylformamide (20 mL). The reaction mixture was heated at 80°C for 4 hours to complete the reaction. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with sodium hydroxide (1 N, 200 mL), water (100 mL) and brine (100 mL). The organic layer was stirred with charcoal (20 g) for 1 hour and filtered. The filtrate was concentrated *in vacuo* to dryness to give crude product (20.4 g). The crude product was crystallized from MeOH to give the title compound as white solid (8.8 g, 41% yield).

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-amino-9-[4-[[1,1-dimethylethyl]dimethylsilyl]oxy]-3-[(dimethylphenylsilyl)methyl]-2-methylenecyclopentyl]-9H-purin-6-one (47)

To a round bottomed flask equipped with a magnetic stirrer and nitrogen inlet/outlet was charged compound **46** (1.27 g, 2 mmol), trimethylorthoformate (2.12 g, 20 mmol) and CH₂Cl₂ at room temperature. The reaction mixture was cooled to 0°C and pyridinium p-toluenesulfonate (5 mg) was added to the solution. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was concentrated *in vacuo* to dryness, and the resulting concentrate extracted with ethyl acetate (100 mL) and saturated NaHCO₃ solution (50 mL). The organic layer was separated, dried (Na₂SO₄), and concentrated *in vacuo* to afford thick light yellow oil. The oil was mixed with excess acetic anhydride (25 mL) and a catalytic amount of acetic acid (2 drops), and the resulting mixture was heated to reflux for 10 h. After cooling to room temperature, the excess acetic anhydride was removed by vacuum distillation, and the resulting brown oil was mixed with MeOH (30 mL) and 4 N HCl solution (10 mL). The solution was heated to reflux under a nitrogen atmosphere overnight. The MeOH was removed by distillation and the solution was neutralized to a pH of ~7.2 with NaOH (10 N, ~4.5 mL). The resulting suspension was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to afford a thick semi-solid oil (compound **47**). The crude compound **47** could be used in the next reaction without further purification.

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

To a solution of compound **47** (1 g, 1.67 mmol) in DCM (10 mL) was added tetrafluoroboric acid-dimethyl ether complex (0.45 g, 3.34 mmol) at 0°C. The solution was stirred for 2 hours at 0°C followed by 14 hours at room temperature. To this solution was added sequentially, potassium bicarbonate (10 g, 10 mmol), potassium fluoride (0.58 g, 10 mmol), and aqueous hydrogen peroxide (30 wt. % solution, 1.2 mL, 10.6 mmol). The reaction mixture was stirred at room temperature

for 14 hours. The reaction mixture was concentrated *in vacuo*. The residue was recrystallized from water to afford the title compound (180 mg, 39% yield).

EXAMPLE 13

5 PROCESS FOR THE PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

10 PREPARATION OF [3aS-(3a α , 4 α , 5 β , 6a α)]-5-(Acetyloxy)-4-[(acetyloxy)methyl]hexahydro-2H-cyclopenta[b]furan-2-one (50)

To a 100 mL round bottomed flask was charged (3aS, 6aR)-3, 3a, 6, 6a-tetrahydro-2H-cyclopenta[b]furan-2-one **49** (3.85 g, 31 mmol, prepared as described in Corey *et al. J. Med Chem.* **1993**, 36, 243), paraformaldehyde (3.0 g), glacial acetic acid (30 mL), and concentrated sulfuric acid (1 mL). The mixture was heated to 74°C
15 for 24 hours. To the solution was added sodium acetate (4 g). The solution was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (200 mL). The solution was washed with saturated sodium bicarbonate solution until no gas evolution was observed. The organic phase was dried over sodium sulfate and concentrated *in vacuo* to give the crude product (4.1 g). The crude product was
20 purified by silica gel column chromatography to provide the title compound (3.1 g, 39%).

PREPARATION OF [3aS-(3a α , 4 α , 5 β , 6a α)]-Hexahydro-5-hydroxy-4-(hydroxymethyl)-2H-cyclopenta[b]furan-2-one (51)

25 To a solution of **50** (10.0 g, 39 mmol) in MeOH (100 mL) was added potassium carbonate (15 g). The suspension was stirred at room temperature for 3 hours. To the suspension was added ethyl acetate (60 mL). The resulting suspension was filtered through a pad of diatomaceous earth (Celite®). The filtrate was concentrated *in vacuo* to give crude product. The crude product was dissolved in
30 MeOH (15 mL) and to it was added diethyl ether (100 mL). The resulting suspension

was stirred for 2 hours at room temperature. The solid was filtered to give the title compound (3.62 g, 54%).

5 PREPARATION OF (3aS-(3a α , 4 α , 5 β , 6a α)]-5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]hexahydro-2H-cyclopenta[b]furan-2-one (52)

10 To a suspension of **51** (4.1 g, 23.8 mmol) in DCM (40 mL) was added N,N-diisopropylethylamine (9.44 g, 71.4 mmol), 4-N,N-dimethylaminopyridine (0.41 g), and *tert*-butyldimethylsilyl chloride (10.8 g, 71.4 mmol). The reaction mixture was stirred at room temperature for 14 hours. The reaction was worked up by washing with 1.0 N HCl, 1.0 N sodium hydroxide, and brine. The organic solution was concentrated *in vacuo* to give the crude product. Column chromatography on silica gel using ethyl acetate/hexanes (1/2 v/v) to give the title compound (7.8 g, 82%).

15 PREPARATION OF [1R-(1 α , 2 β , 3 α , 5 α)]-3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-5-hydroxycyclopentanemethanol (54)

20 To a suspension of **52** (1.0 g, 2.5 mmol) and (1S)-(+)-(10-camphorsulfonyl)oxaziridine (0.86 g, 7.75 mmol) in THF (10 mL) was added sodium hexamethyldisilazide (5 mL of 1 M solution in THF) at -78°C. The reaction mixture was stirred for 1.5 hours. It was then quenched with MeOH (15 mL) at -78°C and to the mixture was added sodium borohydride, (0.34 g, 9.0 mmol). The reaction mixture was warmed to room temperature and stirred for 1 hour. It was poured into ethyl acetate (100 mL), washed with 1.0 N sodium hydroxide (3 x 50 mL), dried over sodium sulfate, and concentrated *in vacuo* to give the crude triol intermediate **53A** (1.1 g). The intermediate **53A** was dissolved in MeOH (10 mL) and water (5 mL). To the resulting solution was added sodium periodate (2.14 g, 10.0 mmol) and the resulting mixture was stirred for 1 hour at room temperature. The mixture was poured into ethyl acetate (100 mL), washed with water (50 mL), dried over sodium sulfate, and concentrated *in vacuo* to give the crude aldehyde intermediate **53B**. The residue was dissolved in MeOH (10 mL), and to it was added sodium borohydride (0.227 g,

25

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6.0 mmol) at 0°C. The reaction mixture was stirred for 1 hour. Column purification of the crude product on silica gel using ethyl acetate/hexanes (1/2 v/v) gave the title compound (0.68 g, 70%).

5 PREPARATION OF [1R-(1 α , 2 α , 3 β , 4 α)]-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-2-[[[(4-methylphenyl)sulfonyl]oxy]methyl]-cyclopentanol acetate ester (55)

To a solution of **54** (0.7 g, 1.79 mmol) in DCM (3 mL) was added pyridine (1 mL), and p-toluenesulfonyl chloride (0.34 g, 1.79 mmol) at 0°C. The reaction
10 mixture was warmed to room temperature and stirred for 20 hours. To the reaction mixture was added pyridine (1 mL), and acetic anhydride (1 mL) at room temperature. The reaction mixture was stirred for 18 hours. It was poured into ethyl acetate (50 mL), washed with 1.0 N sodium hydroxide (2 x 20 mL), brine (20 mL), dried over sodium sulfate, and concentrated *in vacuo* to afford the title compound (0.86 g, 77%).

15 PREPARATION OF [1R-(1 α , 3 β , 4 α)]-4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-2-methylenecyclopentanol (56)

To a solution of **55** (0.585 g, 0.88 mmol) in dimethylformamide (4 mL) was added lithium iodide (0.236 g, 1.76 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene
20 (10 eq). The resulting mixture was heated to 100°C for 2 hours. The mixture was cooled to room temperature and to it was added MeOH (4 mL). The mixture was stirred for 14 hours at room temperature. It was poured into ethyl acetate (100 mL), washed with 1.0 N HCl (3 x 20 mL), brine (20 mL), dried over sodium sulfate, and concentrated *in vacuo*. Purification via silica gel chromatography using ethyl
25 acetate/hexanes (1:2, v/v) gave the title compound (0.18 g, 52%).

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-6-Chloro-9-[4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-2-methylenecyclopentyl]-9H-purin-2-amine (57)

30 To a suspension of **56** (120 mg, 0.32 mmol), triphenylphosphine (84.5 mg, 0.64 mmol), and 2-amino-6-chloropurine (108 mg, 0.64 mmol) in THF (10 mL) was

added diethyl azodicarboxylate (111 mg, 0.64 mmol) at -20°C. The reaction mixture was stirred at -20°C for 1 hour. It was poured into DCM (50 mL), washed with 0.5 N sodium hydroxide (3 x 10 mL), dried over sodium sulfate, and concentrated *in vacuo*. Purification via silica gel chromatography gave the title compound (0.11 g, 63%).

5

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-6-Chloro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-9H-purin-2-amine (39)

To a solution of **57** (180 mg, 0.344 mmol) in THF (2 mL) was added tetrabutylammonium fluoride (2 mL of 1 M solution in THF). The reaction mixture was stirred at room temperature for 1 hour. It was poured into DCM (50 mL), washed with water (3 x 10 mL), dried over sodium sulfate, and concentrated *in vacuo* to give the title compound (55 mg, 54%).

10

PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

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39 was converted to **21** by the procedure described in Example 11.

EXAMPLE 14

PROCESS FOR THE PREPARATION OF [1S-(1 α , 3 α , 4 β)]-2-Amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one (21)

20

PREPARATION OF (2-Benzyloxymethyl-6-oxa-bicyclo[3.1.0]hex-3-yloxy)-tert-butyl-dimethylsilane (83) (R^c=tert-butyl, R^d=CH₃)

25

A solution of t-butyl dimethyl chlorosilane (3.58 g, 23.8 mmol) in DMF (10 mL) was slowly added to a solution of DMAP (0.25 g, 2.0 mmol), imidazole (3.24 g, 48 mmol), and 2-benzyloxy-6-oxa-bicyclo[3.1.0]hexan-3-ol **82** (3.5 g, 15.9 mmol) in DMF (20 mL) at room temperature. The mixture was stirred at room temperature for 16 h. The reaction was quenched with water (50 mL) and extracted with ethyl acetate-hexane (1:1, 180 mL). The organic layer was separated, washed with water (80 mL) and half saturated brine (80 mL), and dried (Na₂SO₄).

30

Concentration followed by purification with silica gel chromatography gave 4.85 g (91%) of desired product **83** as an oil.

PREPARATION OF [3-(*tert*-Butyl-dimethyl-silanyloxy)-6-oxa-bicyclo[3.1.0]hex-2-yl]-methanol (**84**) ($R^c = \textit{tert}$ -butyl, $R^d = \text{CH}_3$)

5

A mixture of ether **83** (2.0 g), and 10% Pd/C (0.5 g) in MeOH (45 mL) was stirred at room temperature under hydrogen (1 atm) for 3.5 h. The mixture was treated with ethyl acetate (60 mL) for 10 min. The catalyst was removed by filtration on diatomaceous earth (Celite®) and washed with ethyl acetate (40 mL).

10 Concentration of the filtrate under vacuum followed by purification of the product on a silica gel pad provided 1.39 g (95%) of alcohol **84** as an oil.

PREPARATION OF Toluene-4-sulfonic acid 3-(*tert*-butyl-dimethyl-silanyloxy)-6-oxa-bicyclo[3.1.0]hex-2-ylmethyl ester (**85**)

15

($R^c = \textit{tert}$ -butyl, $R^d = \text{CH}_3$, $R^3 = \textit{p}$ -methylphenyl)

A solution of *p*-toluenesulfonyl chloride (1.12 g, 5.9 mmol) in DCM (10 mL) was slowly added to a solution of alcohol **84**, triethylamine (2.1 g, 21 mmol), and DMAP (0.12 g, 1.0 mmol) in DCM (25 mL) at room temperature. The mixture was stirred at room temperature for 16 h, treated with hexane (60 mL), washed with water (25 mL x 3) and brine (20 mL), and dried (Na_2SO_4). Concentration of the solution followed by purification with silica gel chromatography gave 1.91 g (96%) of tosylate **85** as a white solid.

20

PREPARATION OF *tert*-Butyl-dimethyl-(2-methylen-6-oxa-bicyclo[3.1.0]hex-3-yloxy)-silane (**86**) ($R^c = \textit{tert}$ -butyl, $R^d = \text{CH}_3$)

25

Potassium *t*-butoxide (1.9 g, 15.6 mmol) was added to a solution of tosylate **85** (5.2 g, 13.0 mmol) in THF (100 mL) at 0°C. After stirring at 0°C for 1.5 h, the mixture was treated with hexane (200 mL), washed with water (100 mL x 2) and brine (80 mL x 2), dried (Na_2SO_4). Concentration of the solution gave 2.75 g (93%) of alkene **86** as an oil.

30

PREPARATION OF 4-(*tert*-Butyl-dimethyl-silanyloxy)-2-[1,3]dithian-
2-yl-3-methylene-cyclopentanol (87) ($R^c=tert\text{-butyl}$, $R^d=CH_3$)

A butyllithium solution (2.5 M in hexane, 4.8 mL, 12 mmol) was added to a solution of 1,3-dithiane (1.5 g, 12 mmol) in THF (22 mL) at 0°C under nitrogen. The mixture was stirred at room temperature for 1 h and then cooled to 0°C. The above solution was slowly added to a solution of vinyl epoxide **86** (2.3 g, 10 mmol) in THF (40 mL) at -30°C. The mixture was stirred at -30°C for 3 h and then warmed up to room temperature. The reaction was quenched by addition of hexane (80 mL) and 5% aqueous KH_2PO_4 solution (70 mL). The organic layer was separated, washed with brine (60 mL x 2), and dried (Na_2SO_4). Concentration of the solution followed by purification with silica gel chromatography gave 3.06 g (88%) of dithiane **87** as a white solid.

PREPARATION OF 4-(*tert*-Butyl-dimethyl-silanyloxy)-2-hydroxymethyl-
3-methylene-cyclopentanol (88) ($R^c=tert\text{-butyl}$, $R^d=CH_3$)

A mixture of dithiane **87** (0.60 g, 1.7 mmol), calcium carbonate (1.3 g, 13 mmol), and iodomethane (2.4 g, 16.4 mmol) in acetonitrile-water (94:6, 8 mL) was stirred at room temperature for 16 h. Ethyl acetate (10 mL) and hexane (10 mL) were added to the reaction mixture which was then dried over sodium sulfate. The solid was removed by filtration. Concentration of the filtrate provided a crude aldehyde which was then dissolved in ethanol and cooled to 0°C. Sodium borohydride (120 mg, 3.2 mmol) was added at 0°C. The mixture was stirred at 0°C for 1 h. The reaction was quenched with a saturated aqueous KH_2PO_4 solution (5 mL) and water (5 mL). Ethanol was removed by evaporation under vacuum. The aqueous layer was extracted with ethyl acetate (15 mL x 2). The combined organic layers were dried (Na_2SO_4). Concentration of the solution followed by purification with silica gel chromatography gave 301 mg (67%) of the diol **88**.

PREPARATION OF Acetic acid 2-acetoxymethyl-4-hydroxy-
3-methylene-cyclopentyl ester (89) ($R^2=CH_3$)

Acetic anhydride (250 mg, 2.5 mmol) was added to a mixture of diol **88**, DMAP (10 mg, 0.08 mmol), and triethylamine (360 mg, 3.6 mmol) in DCM (5 mL) under nitrogen at room temperature. After 3 h at room temperature, the reaction mixture was treated with hexane (10 mL), ethyl acetate (5 mL), and half saturated brine (10 mL). The organic layer was separated, washed with half saturated brine (10 mL), and dried (Na₂SO₄). Concentration of the solution gave a crude bis-acetate which was dissolved in THF (10 mL). Tetrabutylammonium fluoride (TBAF·3H₂O, 400 mg, 1.3 mmol) was added to the solution at room temperature. After 1 h, the reaction mixture was treated with ethyl acetate (20 mL) and then washed with brine (15 mL x 2). The aqueous layers were back-extracted with ethyl acetate (15 mL). The combined organic layers were dried (Na₂SO₄). Concentration of the solution followed by purification with silica gel chromatography gave 255 mg (96%) of the desired alcohol **89** as an oil.

15 PREPARATION OF Acetic acid 2-acetoxymethyl-4-(2-amino-6-iodopurin-9-yl)-3-methylene-cyclopentyl ester (**90**) (R²=CH₃, X=I)

A mixture of alcohol **89** (100 mg, 0.44 mmol), triphenylphosphine (137 mg, 0.52 mmol), and 6-iodo-2-aminopurine (115 mg, 0.44 mmol) in THF was cooled to 0°C. DEAD (87 mg, 0.50 mmol) was slowly added to the mixture which was stirred at 0°C for 3 h and then warmed up to room temperature for 16 h. The mixture was treated with ethyl acetate (9 mL) and filtered on diatomaceous earth (Celite®). Concentration of the filtrate provided a residue which was treated with ethyl acetate (3 mL), 2 N HCl (4 mL), and hexane (6 mL). The aqueous layer was separated. The organic layer was extracted with 2 N HCl (4 mL x 3). The combined aqueous layers was neutralized with K₂HPO₄ to pH ~7 and extracted with ethyl acetate (25 mL, 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated to give a crude product which was purified by silica gel chromatography to provide 175 mg (85%) of **90** containing some triphenylphosphine oxide. Crystallization of the crude product from ethanol gave 132 mg (64%) of desired **90**.

30 The compound of formula **90** can be converted to the compound of formula **21** by hydrolysis of the ester group using, for example, by treatment with an alkali metal

alkoxide. The 6-iodo group can be hydrolyzed to provide the compound of formula 21, according to the procedure described for the preparation of compound of formula 21 in Example 11.

Where noted above, publications and references, including but not limited to
5 patents and patent applications, cited in this specification are herein incorporated by reference in their entirety in the entire portion cited as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth.

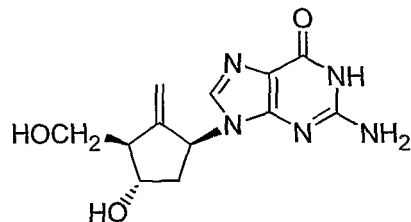
While this invention has been described with an emphasis upon preferred
10 embodiments, it will be obvious to those of ordinary skill in the art that variations in the preferred devices and methods may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein.

Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the claims that follow. For example, it should
15 be understood that the reaction steps set forth in the appended claims need not necessarily be performed in the order in which they appear, and one skilled in the field may be able to vary the order of reaction steps. Additionally, certain reaction sequences may be performed simultaneously, such as, for example, protodesilylation and debenzylation, or these reactions can be performed in separate steps, without
20 departing from the spirit and scope of the invention. It is intended that all such modifications are encompassed within the scope of the appended claims.

CLAIMS

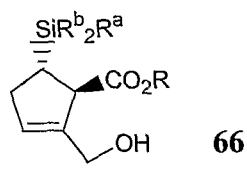
The invention claimed is:

1. A process for the preparation of entecavir having the formula



21, comprising:

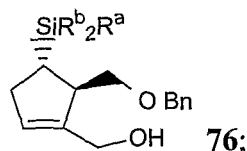
- 5 (a) treating an ester of the formula



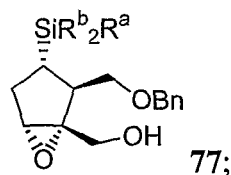
wherein R^a is allyl, phenyl, C_1 to C_6 alkylphenyl, or C_1 to C_6 alkoxyphenyl; R^b is C_1 to C_6 alkyl; and R is C_1 to C_4 alkyl or benzyl;

with an enol ether of acetone and an acid to protect the hydroxy group,

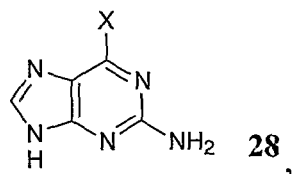
- 10 followed by treatment with a hydride reagent to reduce the carboxylic acid ester moiety, and then alkylating the resulting alcohol with a benzyl halide and removing the enol ether hydroxy protecting group to give an allylic alcohol of the formula



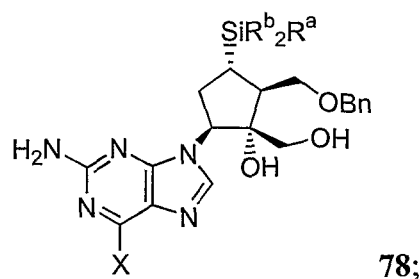
- (b) epoxidizing the product from step (a) with a diastereoselective
15 epoxidation to give a cyclopentane epoxide having the formula



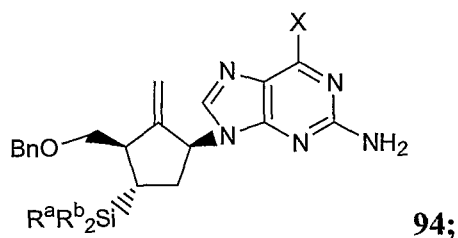
- (c) treating the cyclopentane epoxide from step (b) with an alkali metal salt of a purine compound of formula



wherein X is Cl, I, or benzyloxy, to give a compound of formula

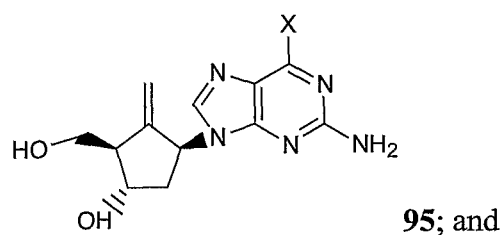


(d) when X is Cl or I, converting the vicinal diol of formula **78** to the methylene compound of formula,



5

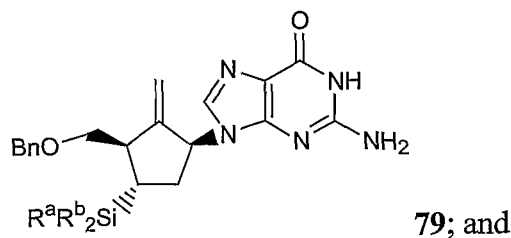
(e) hydrolyzing the benzyl ether moiety on the primary alcohol of compound **94** and converting the silane moiety of compound **95** to a hydroxy moiety to give a compound of formula,



10

(f) hydrolyzing the chloro or iodo moiety X to provide the compound of formula **21**; or

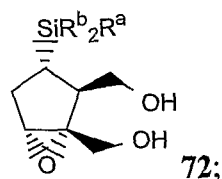
(d') when X is benzyloxy, converting the vicinal diol of formula **78** to the methylene compound of formula



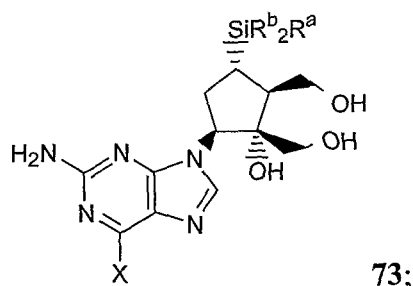
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(e') hydrolyzing the benzyl ether moiety on the primary alcohol of compound **79** and converting the silane moiety to a hydroxy moiety to provide the compound of formula **21**; or

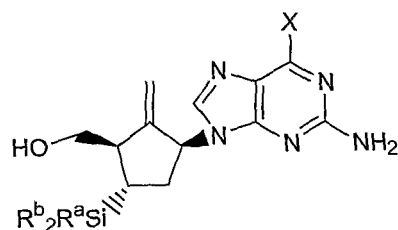
(a'') epoxidizing the ester of formula **66** with a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst, and reduction of the ester group, to give a cyclopentane epoxide having the formula



- 5 (b'') treating the cyclopentane epoxide from step (a'') with an alkali metal salt of the purine compound of formula **28** to give a compound of formula



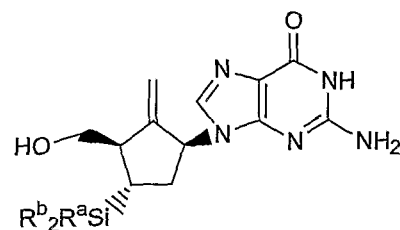
(c'') when X is Cl or I, converting the vicinal diol of formula **73** to the methylene compound of formula



10

(d'') converting the silane moiety of compound **92** to a hydroxy moiety and hydrolyzing the chloro or iodo moiety X to provide the compound of formula **21**; or

(c''') when X is benzyloxy, converting the vicinal diol of formula **73** to the methylene compound of formula



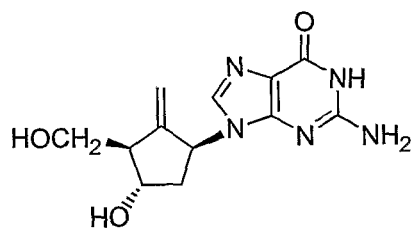
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(d''') converting the silane moiety of compound **71** to a hydroxy moiety to provide the compound of formula **21**.

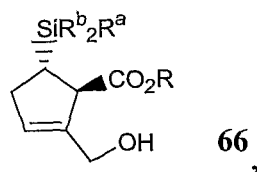
2. The process of Claim 1, in which, in step (b) the diastereoselective epoxidation is performed with a peracid or with a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst.

5

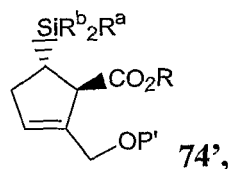
3. A process for the preparation of entecavir having the formula



- (a) protecting the hydroxy moiety of an ester of the formula

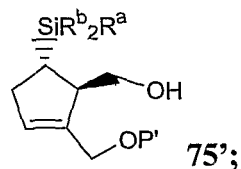


- 10 wherein R^a is allyl, phenyl, C_1 to C_6 alkylphenyl, or C_1 to C_6 alkoxyphenyl; R^b is C_1 to C_6 alkyl; and R is C_1 to C_4 alkyl or benzyl, to provide a compound of formula



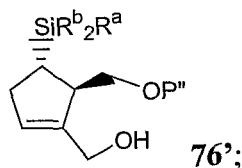
wherein P' is a protecting group;

- 15 (b) reducing the carboxylic ester moiety of the compound **74'** with at least one reducing reagent to provide a compound of formula,

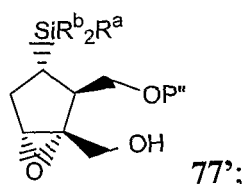


- (c) protecting the unprotected hydroxy moiety of compound **75'**, with a protecting group P'' that is resistant to conditions used to remove P' , then removing

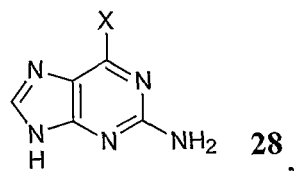
the protecting group P' of the compound of **75'**, to provide the compound having the formula,



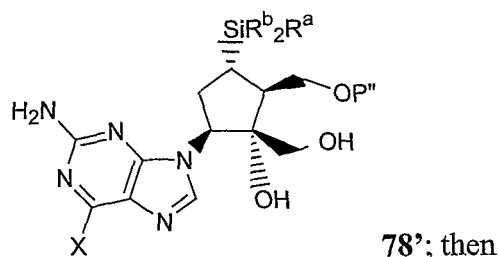
- (d) epoxidizing the product from step (c) with a diastereoselective epoxidation
5 to give a cyclopentane epoxide having the formula



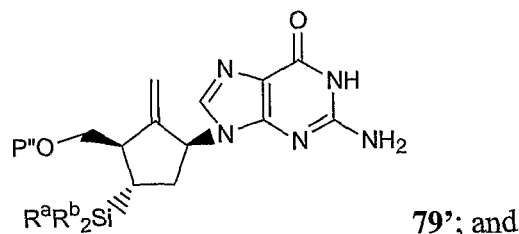
- (e) treating the cyclopentane epoxide from step (d) with an alkali metal salt
of a purine compound of formula



- 10 wherein X is Cl, I, or benzyloxy; to give a compound of formula

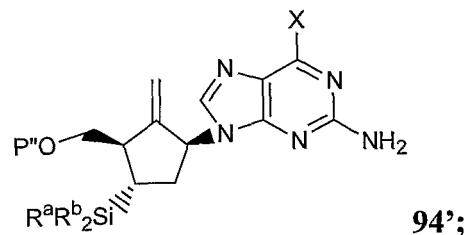


- (f) when X is benzyloxy, converting the vicinal diol of formula **78'** to
provide the methylene compound of formula

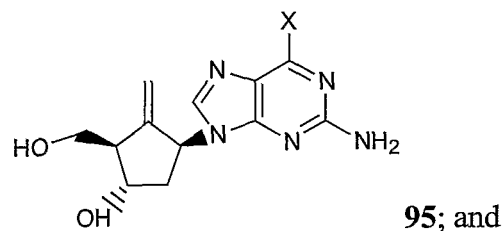


- 15 (g) removing the protecting group P'' on the primary alcohol of compound **79**
and converting the silane moiety to a hydroxy moiety to provide the compound of
formula **21**; or

(f') when X is Cl or I, converting the vicinal diol of formula **78'** to provide the methylene compound of formula,



5 (g') removing the protecting group P'' on the primary alcohol of compound **94'** and converting the silane moiety to a hydroxy group to give a compound of formula,



(h') hydrolyzing the chloro or iodo moiety X to provide the compound of
10 formula **21**.

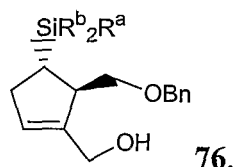
4. The process of Claim 3, wherein, in step (g), the protecting group P'' on the primary alcohol of compound **79'** is benzyl, said step of converting the silane
15 moiety of compound **79** to a hydroxy group is achieved with protodesilylation and oxidation, and said benzyl protecting group is removed upon protodesilylation.

5. The process of Claim 3, wherein the protecting group P'' on the primary alcohol of compound **79'** is removed after the silane moiety is converted to a hydroxy
20 moiety.

6. The process of Claim 3, wherein in step (a), the hydroxy moiety is protected as a MOP by treatment with 2-methoxypropene and a catalytic amount of a weak acid.

7. The process of Claim 3, wherein in step (b), the carboxylic ester moiety of the compound **74'** is reduced with a hydride reagent selected from at least one of sodium bis(2-methoxyethoxy)aluminum hydride and lithium aluminum hydride in the presence of a base.

8. The process of Claim 3, wherein in step (c), the unprotected hydroxy moiety is protected as a benzyl ether upon treatment with a base and a benzyl halide, wherein, removal of the protecting group P' of the compound of **75'** provides the allylic alcohol having the formula,



9. The process of Claim 8, wherein the base is selected from at least one of potassium *tert*-butoxide, sodium hydride, KHMDS, aqueous NaOH, and the benzyl halide is benzyl bromide or benzyl chloride.

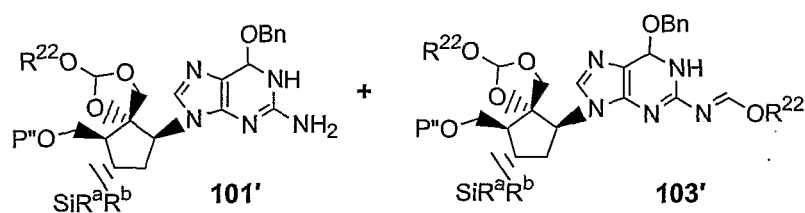
10. The process of Claim 3, in which in step (d), the diastereoselective epoxidation is performed by treatment with a peracid.

11. The process of Claim 3, in which in step (d), the diastereoselective epoxidation is performed by treatment with a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst

12. The process of Claim 11, wherein the homochiral diester of tartaric acid is (-)-diisopropyl tartrate, the hydroperoxide is *tert*-butylhydroperoxide or α,α -dimethylbenzylhydroperoxide, and the metal catalyst is titanium (IV) isopropoxide.

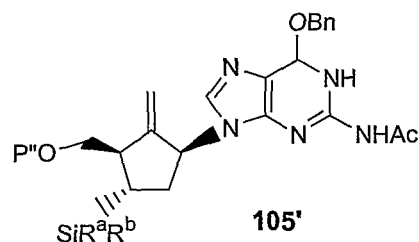
13. The process of Claim 3, wherein in step (e), the cyclopentane epoxide from step (d) is treated with 2-amino-6-benzyloxypurine in dichloromethane.

14. The process of Claim 3, wherein X is benzyloxy and in step (f), the compound **78'** is converted to the methylene compound of formula **79'** by (f)(i) treating compound **78'** with an orthoformate derivative in an inert solvent to produce a diastereomixture of dioxolanes having the formulae **101'** and **103'**,



wherein R²² is C₁₋₄alkyl or -C(=O)C₁₋₄alkyl;

(f)(ii) treating the product from step (f)(i) with an acetic anhydride in the presence of at least one antioxidant to produce an alkene compound having the formula **105'**;



(f) (iii) treating the product from step (f)(ii) with an acid to hydrolyze the 6-benzyloxy and N-acetyl groups to provide the compound of formula **79'**.

15. The process of Claim 14, wherein in step (f)(i), the orthoformate derivative is selected from at least one of diethoxymethyl acetate, diisopropoxyxymethyl acetate, TMOF, TEOF, and TiPOF.

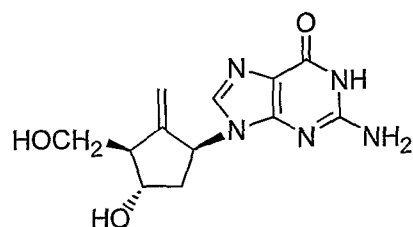
16. The process of Claim 14, wherein in step (f)(ii), the at least one antioxidant is selected from BHT and benzoic acid.

17. The process of Claim 3, in which the step of converting the compound 79' to compound 21 is achieved with protodesilylation and oxidation, wherein the protodesilylation is performed with KOH or NaOH, in solvent, or with TFA, and the
 5 primary alcohol moiety is deprotected after the silane moiety is converted to a hydroxy group, to provide the compound of formula 21.

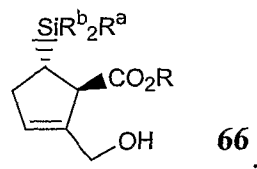
18. The process of Claim 3, in which the step of converting the compound 79' to compound 21 is achieved with protodesilylation and oxidation, wherein the step
 10 of protodesilylation is achieved with at least one acid selected from boron trifluoride-acetic acid complex and a Bronsted acid.

19. The process of Claim 3, in which the step of converting the compound 79' to compound 21 is achieved with protodesilylation and oxidation, and the
 15 oxidation is achieved with hydrogen peroxide in the presence of potassium bicarbonate and potassium fluoride.

20. A process for the preparation of entecavir having the formula

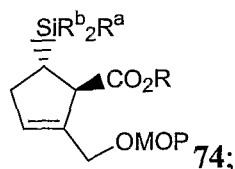


20 (a) treating an ester of the formula

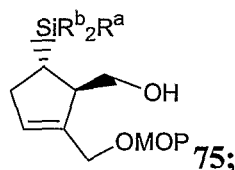


wherein R^a is allyl, phenyl, C₁ to C₆ alkylphenyl, or C₁ to C₆ alkoxyphenyl; R^b is C₁ to C₆ alkyl; and R is C₁ to C₄ alkyl or benzyl; with 2-methoxypropene and a catalytic amount of a weak acid to provide a compound of formula

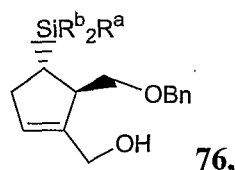
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- (b) reducing the carboxylic ester moiety of the compound **74** with a hydride reagent selected from at least one of sodium bis(2-methoxyethoxy)aluminum hydride and lithium aluminum hydride, in the presence of a base to provide a compound of formula,

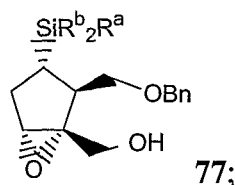


- (c) protecting the unprotected hydroxy moiety of compound **75**, as a benzyl ether upon treatment of compound **75** with a base and a benzyl halide, then removing the MOP group of the compound **75**, to provide the allylic alcohol having the formula,



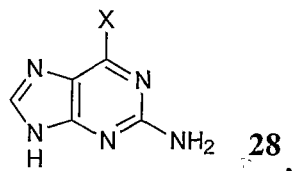
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- (d) epoxidizing the product from step (c) with (-)-diisopropyl tartrate, *tert*-butylhydroperoxide or cumene hydroperoxide, and titanium (IV) isopropoxide, to give a cyclopentane epoxide having the formula

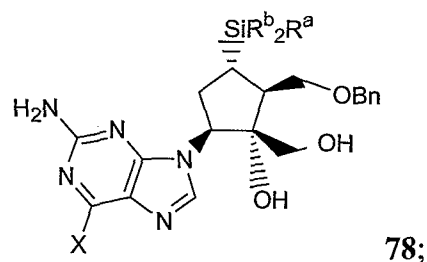


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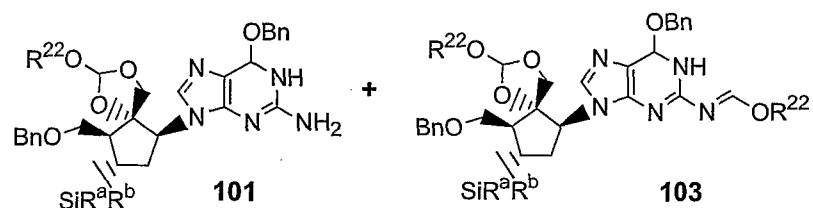
- (e) treating the cyclopentane epoxide from step (d) with an alkali metal salt of a purine compound of formula



wherein X is benzyloxy; to give a compound of formula

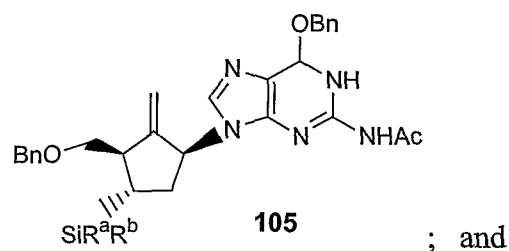


(f)(i) treating compound **78** with an orthoformate derivative selected from diethoxymethyl acetate and diisopropylloxymethyl acetate in an inert solvent to produce a diastereomixture of dioxolanes having the formulae **101** and **103**,

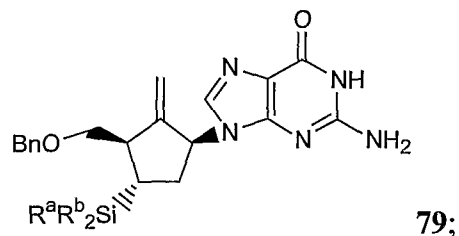


wherein R^{22} is ethyl, $-C(=O)$ ethyl, isopropyl, or $-C(=O)$ isopropyl;

(f)(ii) treating the product from step (f)(i) with an acetic anhydride in the presence of BHT to produce an alkene compound having the formula **105**;



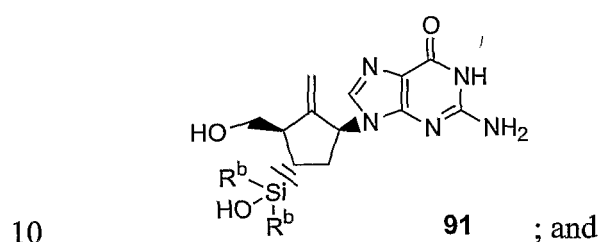
(f) (iii) treating the product from step (f)(ii) with an acid to hydrolyze the 6-benzyloxy and N-acetyl groups and provide the compound of formula **79**,



(g) converting the silane moiety to a hydroxy moiety by protodesilylating the silane moiety of compound **79** upon treatment with at least one reagent effective to

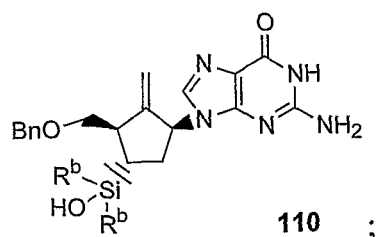
achieve protodesilylation, followed by oxidation with a peroxide, and debenzylating compound **79**, wherein debenzylation may be achieved upon protodesilylation, to provide the compound of formula **21**.

- 5 21. The process of Claim 20, in which step (g) comprises treating compound **79** with an acid selected from boron trifluoride-acetic acid complex and a Bronsted acid, wherein said step of protodesilylation removes the benzyl protecting group of compound **79** to provide the compound of formula **91**,

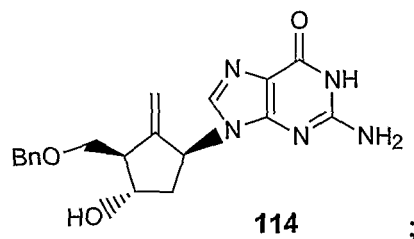


oxidizing the compound **91** with hydrogen peroxide in the presence of potassium bicarbonate and potassium fluoride to provide the compound **21**.

- 15 22. The process of Claim 20, in which step (g) comprises treating compound **79** with potassium hydroxide or sodium hydroxide in solvent, or TFA to provide the compound of formula **110**,



- 20 oxidizing compound **110** with hydrogen peroxide in the presence of potassium bicarbonate and potassium fluoride to provide the compound **114**;



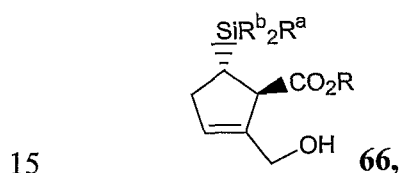
and debenzylating compound **114** to provide compound **21**.

23. A method for isolating entecavir or an entecavir intermediate from a diluted mixture, the diluted mixture comprising entecavir and water or a mixture comprising an entecavir intermediate and other process reagents comprising:
- adsorbing the diluted mixture onto a hydrophobic resin bed;
 - washing the resin bed with water to remove salt; and
 - eluting the entecavir or entecavir intermediate from the resin bed with an organic solvent.

10

24. The method of Claim 23 wherein the hydrophobic resin is a brominated styrene based resin.

25. A process for the preparation of an ester of the formula



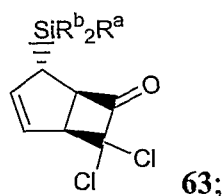
wherein R^a is alkyl, phenyl, C_1 to C_6 alkylphenyl, or C_1 to C_6 alkoxyphenyl; R^b is C_1 to C_6 alkyl; and R is C_1 to C_4 alkyl or benzyl comprising:

- (a) reacting a cyclopentadienide ion



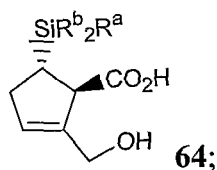
20 with a silylating reagent having the formula $R^a(R^b)_2Si-Y$, wherein Y is a leaving group; and

(b) reacting the product of step (a) with a ketene to give a cyclobutanone of the formula

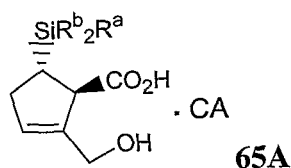


25 (c) treating the product from step (b) with a base effective for opening the cyclobutanone ring;

(d) reducing the product from step (c) with a reducing agent to give a racemic carboxylic acid of the formula



(e) resolving the product from step (d) by treatment with a chiral amine and
5 separation of the resulting diastereomeric salts to give a compound of formula



wherein CA represents a chiral amine; and

(f) heating the product from step (e) in a solution of an acidic solution to
give the ester product of formula **66**.

10

26. The process of Claim 25, in which, in step (b), the ketene is formed from dichloroacetyl chloride and a base.

27. The process of Claim 25, in which, in step (c), the base is potassium
15 carbonate in *t*-butanol.

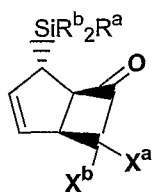
28. The process of Claim 25, in which, in step (d), the reducing reagent is NaBH₄.

20 29. The process of Claim 25, in which, in step (e), the chiral amine is selected from the group consisting of R,R-(-)-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1R,2R)-(+)-1,2-diphenylethylenediamine, (R)-(-)-1-cyclohexylethylamine, D-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1S,2S)-(+)-1,2-diaminocyclohexane, dehydroabietylamine, (1R,2R)-1,2-
25 diaminomethylcyclohexane, cichonidine, and cinchonine.

30. The process of Claim 25, in which, in step (f), the acidic solution comprises a solution of an alcohol, R-OH, wherein R is C₁ to C₄ alkyl or benzyl, and an acid.

- 5 31. The process of Claim 25, in which,
 in step (b), the ketene is formed from dichloroacetyl chloride and a base;
 in step (c), the base is potassium carbonate in *t*-butanol;
 in step (d), the reducing reagent is NaBH₄;
 in step (e), the chiral amine is R,R-(-)-2-amino-1-(4-nitrophenyl)-1,3-
 10 propanediol; and
 in step (f), the acidic solution comprises a solution of an alcohol, R-OH,
 wherein R is C₁ to C₄ alkyl or benzyl, and an acid.

32. A compound of formula



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wherein:

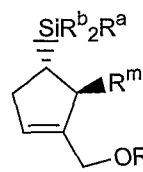
R^a is allyl, phenyl, C₁ to C₆ alkylphenyl or C₁ to C₆ alkoxyphenyl;

R^b is C₁ to C₆ alkyl; and

X^a and X^b are halide.

20

33. A compound of formula



or a salt thereof wherein:

R^a is allyl, phenyl, C₁ to C₆ alkylphenyl or C₁ to C₆ alkoxyphenyl;

R^b is C₁ to C₆ alkyl;

R^m is -CO₂R⁶ or -CH₂OR⁶;

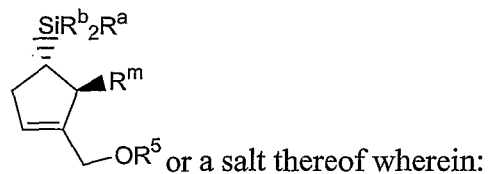
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R⁵ is hydrogen or a hydroxy protecting group; and

R⁶ is hydrogen, C₁ to C₄ alkyl, or benzyl.

34. A compound of Claim 33 wherein:
R^m is -CO₂R⁶; and
R⁵ and R⁶ are both hydrogen.
- 5
35. The compound of Claim 34 wherein:
R^a is phenyl; and
R^b is methyl.
- 10
36. A compound of Claim 33 as a salt with a chiral amine selected from the group consisting of R,R-(-)-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1R,2R)-(+)-1,2-diphenylethylenediamine, (R)-(-)-1-cyclohexylethylamine; D-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1S,2S)-(+)-1, 2-diaminocyclohexane, dehydroabietylamine, (1R,2R)-1, 2-diaminomethylcyclohexane, cinchonidine, and
- 15 cinchonine.
37. The compound of Claim 36 wherein:
R^m is -CO₂R⁶;
R⁵ and R⁶ are both hydrogen;
R^a is phenyl;
R^b is methyl; and
the chiral amine is R,R-(-)-2-amino-1-(4-nitrophenyl)-1,3-propanediol.
- 20
38. The compound of Claim 33 wherein:
R^m is -CH₂OR⁶;
R⁵ is hydrogen; and
R⁶ is benzyl.
- 25
39. The compound of Claim 38 wherein:
R^a is phenyl; and
R^b is methyl.
- 30

40. A compound having the formula



R^a is phenyl;

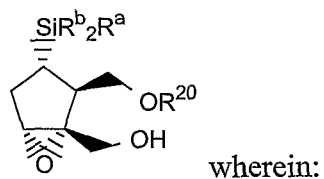
R^b is C_1 to C_6 alkyl;

R^m is $-CO_2R^6$ or $-CH_2OR^6$;

R^5 is hydrogen or a hydroxy protecting group; and

R^6 is hydrogen, C_1 to C_4 alkyl, or benzyl, said compound produced according to the process of claim 22.

41. A compound of formula



R^a is alkyl, phenyl, C_1 to C_6 alkylphenyl, or C_1 to C_6 alkoxyphenyl;

R^b is C_1 to C_6 alkyl; and

R^{20} is hydrogen or benzyl.

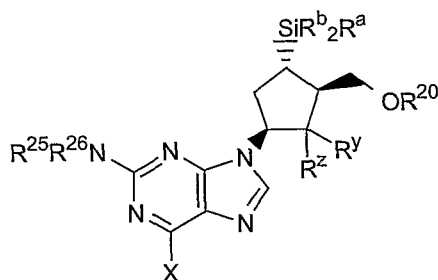
42. The compound of Claim 41 wherein:

R^a is phenyl;

R^b is methyl; and

R^{20} is benzyl.

43. A compound of formula



or a salt thereof wherein:

R^a is alkyl, phenyl, C_1 to C_6 alkylphenyl, or C_1 to C_6 alkoxyphenyl;

R^b is C_1 to C_6 alkyl;

R^{20} is hydrogen or benzyl;

5 X is Cl, I, or benzyloxy;

R^y and R^z are taken together to form methylene ($=CH_2$), or R^y is OR^{23} , and R^z is $-CH_2OR^{24}$, wherein R^{23} and R^{24} are each hydrogen or are taken together to form a ring to define a dioxolane, said dioxolane being optionally substituted with $-O(C_{1-4}alkyl)$ or $-O(C=O)(C_{1-4}alkyl)$; and

10 R^{25} and R^{26} are both hydrogen, or one of R^{25} and R^{26} is hydrogen and the other is acyl; or R^{25} and R^{26} are taken together to form $=CH(OC_{1-4}alkyl)$ or $=CH(OC(=O)C_{1-4}alkyl)$.

44. The compound of Claim 43 wherein:

15 R^a is phenyl;

R^b is methyl; and

X is benzyloxy.

45. The compound of claim 44 in which

20 R^{20} is benzyl;

R^y is OH, and R^z is $-CH_2OH$, and

R^{25} and R^{26} are both hydrogen.

25 46. The compound of Claim 43 wherein:

R^a is phenyl;

R^b is methyl;

X is benzyloxy;

R^y is OR^{23} , and R^z is $-CH_2OR^{24}$, wherein R^{23} and R^{24} combine to form a dioxolane optionally substituted with $-O(C_{1-4}alkyl)$ or $O(C=O)(C_{1-4}alkyl)$; and

5 R^{25} and R^{26} are both hydrogen, or R^{25} and R^{26} are taken together to form $=CH(OC_{1-4}alkyl)$ or $=CH(O(C=O)C_{1-4}alkyl)$.

47. The compound of Claim 43 wherein:

R^a is phenyl;

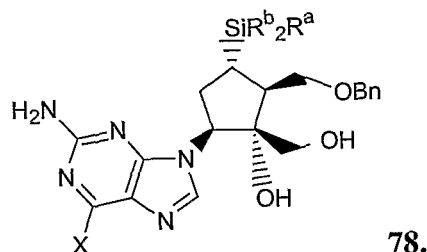
10 R^b is methyl;

X is benzyloxy;

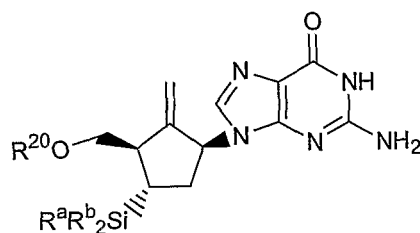
R^y and R^z are taken together to form methylene; and

R^{25} is hydrogen and R^{26} is acyl.

15 48. The compound of Claim 43 having the formula,



49. A compound of formula



or a salt thereof, wherein:

20 R^a is alkyl, phenyl, C_1 to C_6 alkylphenyl, or C_1 to C_6 alkoxyphenyl;

R^b is C_1 to C_6 alkyl; and

R^{20} is hydrogen or benzyl.

50. The compound of Claim 49 wherein:

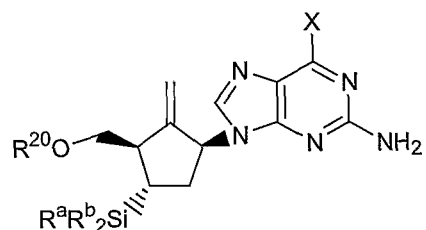
R^a is phenyl;
 R^b is methyl; and
 R^{20} is hydrogen.

5 51. The compound of Claim 49 wherein:

R^a is phenyl;
 R^b is methyl; and
 R^{20} is benzyl.

10 52. The methanesulfonate salt of the compound of Claim 51.

53. A compound of formula



or a salt thereof, wherein:

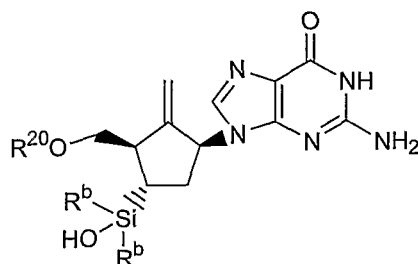
X is Cl or I;

15 R^a is alkyl, phenyl, C_1 to C_6 alkylphenyl, or C_1 to C_6 alkoxyphenyl;

R^b is C_1 to C_6 alkyl; and

R^{20} is hydrogen or benzyl.

54. A compound of formula

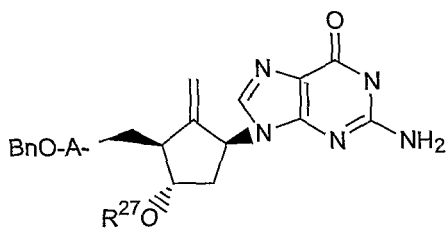


20

wherein R^b is C_1 to C_6 alkyl; and R^{20} is hydrogen or benzyl, or a salt thereof.

55. The compound of Claim 54 wherein R^b is methyl.

56. A compound of formula



or a salt thereof, wherein:

A is CH₂ or a bond;

R²⁷ is hydrogen, benzyl, or SiR^d₂R^c;

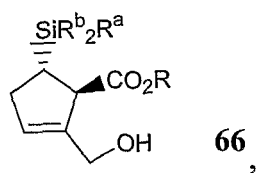
R^c is C₁ to C₄ alkyl or phenyl; and

R^d is C₁ to C₃ alkyl.

57. A compound of claim 56, in which A is a bond, and R²⁷ is hydrogen.

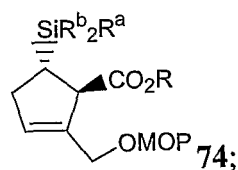
58. A method for making a compound of formula **78**, according to Claim 48, comprising,

(a) treating an ester of the formula



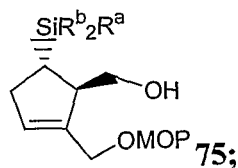
wherein R^a is allyl, phenyl, C₁ to C₆ alkylphenyl, or C₁ to C₆ alkoxyphenyl; R^b

is C₁ to C₆ alkyl; and R is C₁ to C₄ alkyl or benzyl; with 2-methoxypropene and a catalytic amount of a weak acid to provide a compound of formula

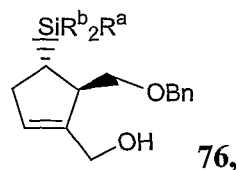


(b) reducing the carboxylic ester moiety of the compound **74** with at least one

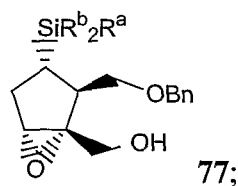
hydride reagent to provide a compound of formula,



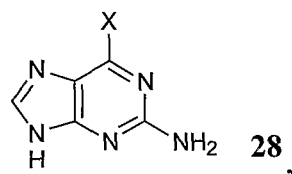
(c) protecting the unprotected hydroxy moiety of compound **75**, as a benzyl ether upon treatment of compound **75** with a base and a benzyl halide, then removing the MOP group of the compound **75**, to provide the allylic alcohol having the formula,



5 (d) epoxidizing the product from step (c) with a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst, or with a peracid, to give a cyclopentane epoxide having the formula

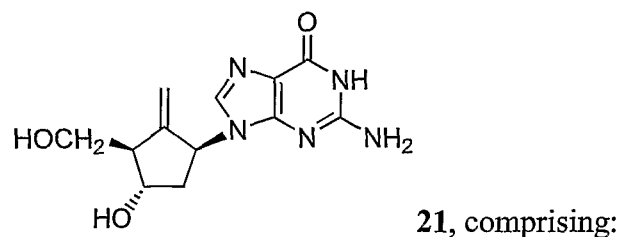


10 (e) treating the cyclopentane epoxide from step (d) with an alkali metal salt of a purine compound of formula

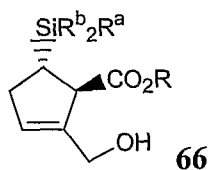


wherein X is benzyloxy; I, or Cl, to give a compound of formula **78**.

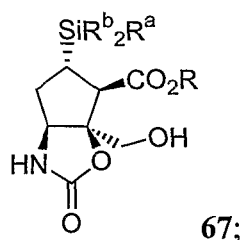
15 59. A process for the preparation of entecavir having the formula



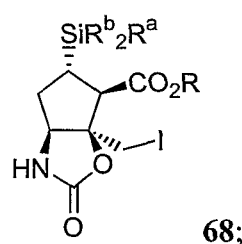
(a) converting an ester having the formula



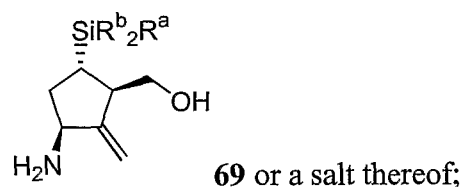
wherein R is C₁ to C₄ alkyl, or benzyl; R^a is allyl, phenyl, C₁ to C₆ alkylphenyl or C₁ to C₆ alkoxyphenyl, and R^b is C₁ to C₆ alkyl, under aminohydroxylation conditions to give an oxazolidinone having the formula



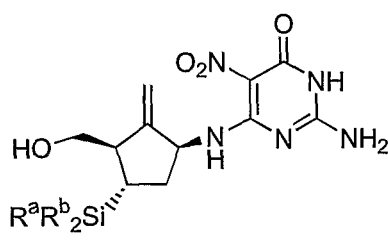
- 5 (b) converting the alcohol of the oxazolidinone of formula **67** with an iodide salt to give an iodide having the formula



- (c) treating the iodide of formula **68** with zinc and acetic acid;
 (d) treating the product of step (c) with a hydride reagent to reduce the ester moiety to an alcohol and give a methylene compound of formula
- 10

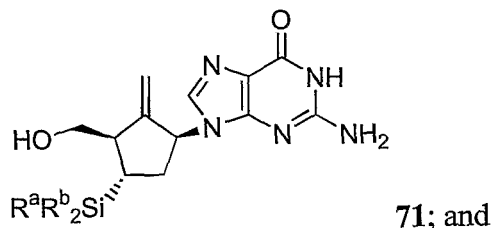


- (e) reacting the methylene compound of formula **69** with 6-chloro-2-amino-5-nitro-4(3H)-pyrimidinone in the presence of base to give a pyrimidine compound having the formula



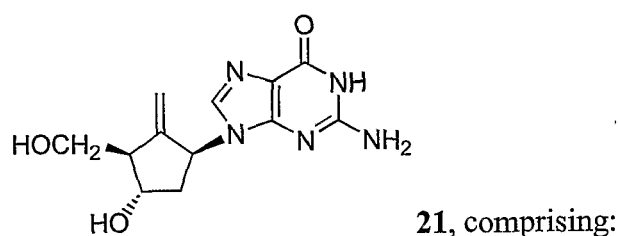
- 15 (f) treating the pyrimidine compound of formula **70** with a reducing agent to reduce the nitro moiety to an amine;

(g) cyclizing the product of step (f) with an orthoformate derivative and an acid to give a methylene compound having the formula

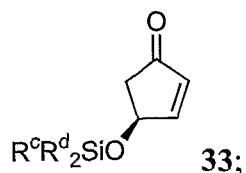


(h) converting the silane moiety of the compound of formula **71** to a hydroxy moiety and providing the compound of formula **21**.

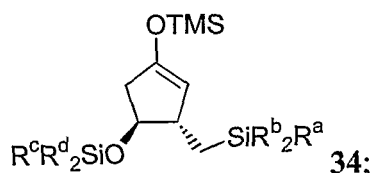
60. A process for the preparation of entecavir having the formula



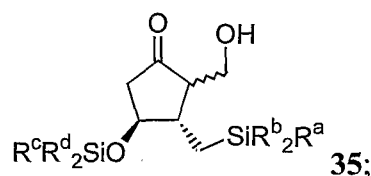
(a) treating 4-(S)-hydroxy-2-cyclopenten-1-one with a silylating reagent of the formula $R^c R^d SiY$ and a trialkylamine base wherein R^c is C_1 to C_4 alkyl or phenyl, R^d is C_1 to C_3 alkyl, and Y is a leaving group to give the compound of formula



(b) treating the product from step (a) with a Grignard reagent prepared from a (halomethyl)silane reagent of the formula $R^a R^b SiCH_2X'$, wherein R^a is allyl, phenyl, C_1 to C_6 alkylphenyl or C_1 to C_6 alkoxyphenyl; R^b is C_1 to C_6 alkyl; and X' is chloro, bromo, or iodo followed by treatment with trimethylsilylating reagent to give a compound of formula

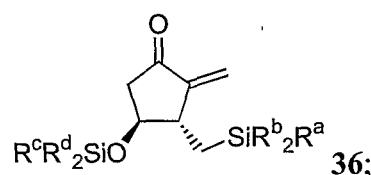


(c) formylating the compound of formula **34** to give a compound of formula

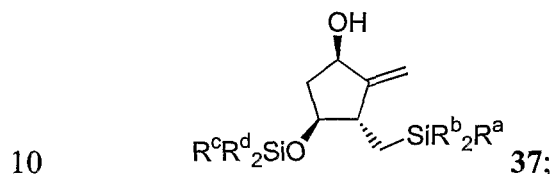


(d) treating the compound of formula **35** with a sulfonylating reagent having the formula R^3SO_2Cl , wherein R^3 is C_1 to C_4 alkyl, trifluoromethyl, phenyl or phenyl substituted by C_1 to C_6 alkyl or C_1 to C_6 alkoxy;

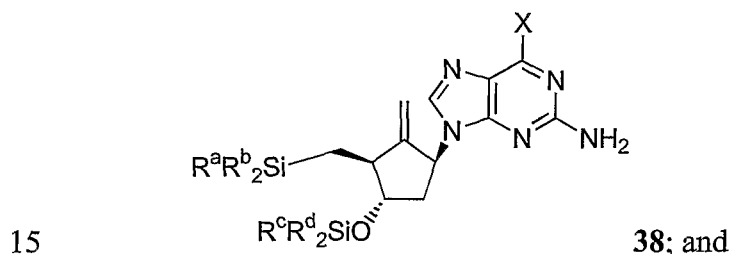
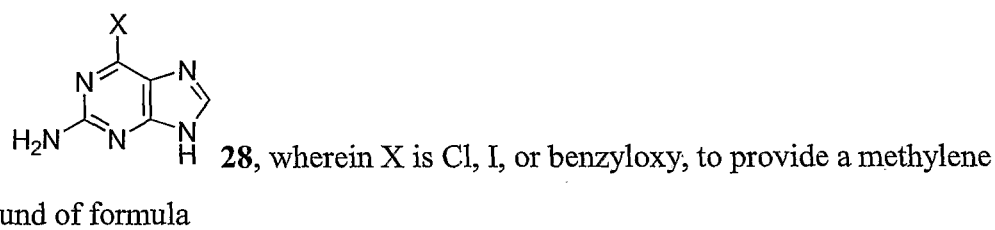
- 5 (e) reacting the product of step (d) with a strong base to eliminate a sulfonate group to provide a methylene compound of formula



(f) selectively reducing the methylene compound of formula **36** with a hydride reagent to provide an allylic alcohol of the formula

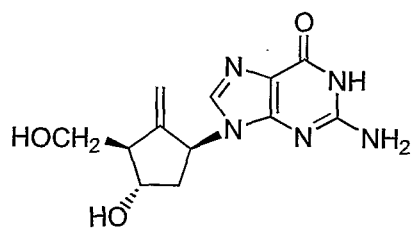


(g) condensing the allylic alcohol of the formula **37** under Mitsunobu conditions with a purine compound of formula



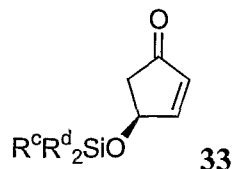
(h) converting the compound of formula **38** to the compound of formula **21**.

61. A process for the preparation of entecavir having the formula



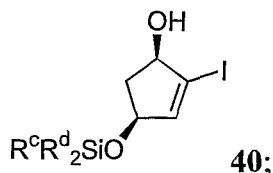
21, comprising:

- (a) reacting a cyclopentenone of the formula

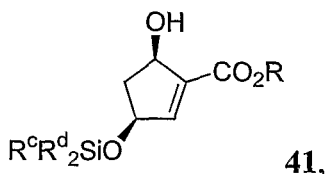


with iodine, wherein R^c is C_1 to C_4 alkyl, or phenyl, and R^d is C_1 to C_3 alkyl;

- 5 (b) reducing the carbonyl group of the product of step (a) to provide an iodo compound of formula



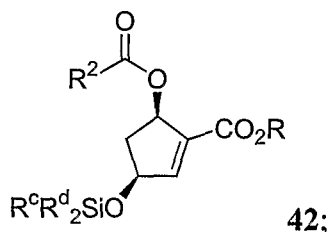
- (c) converting the iodo compound of formula 40 to give a compound of formula



10

wherein R is C_1 to C_4 alkyl, or benzyl;

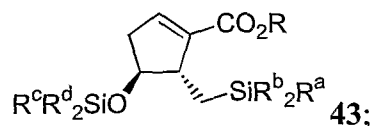
- (d) acylating the compound of formula **41** with an activated acyl agent of the formula $R^2C(O)-Y$ wherein R^2 is C_1 to C_6 alkyl, arylalkyl or aryl, and Y is a leaving group to give a compound of formula



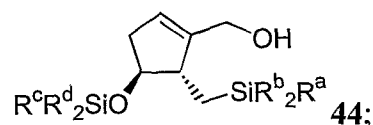
15

- (e) treating the product of step (d) with a Grignard reagent prepared from a (halomethyl)silane reagent of the formula $R^aR^bSiCH_2X'$, wherein R^a is allyl, phenyl,

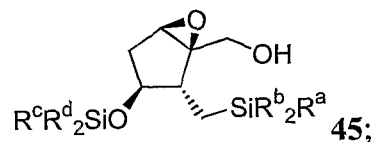
C₁ to C₆ alkylphenyl or C₁ to C₆ alkoxyphenyl; R^b is C₁ to C₆ alkyl; and X' is chloro, bromo, or iodo to give an ester of the formula



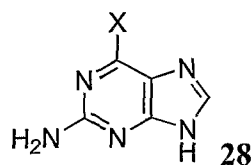
- (f) reducing the ester of formula **43** with a hydride reagent to provide an
5 allylic alcohol of the formula



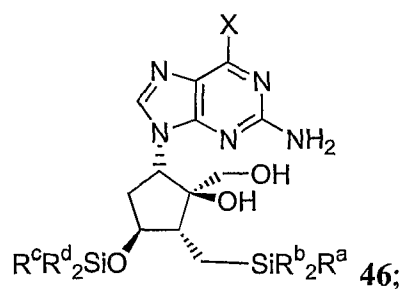
- (g) epoxidizing the allylic alcohol of formula **44** with an oxidizing agent to provide a cyclopentane epoxide of the formula



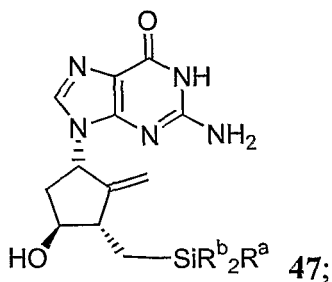
- 10 (h) reacting the cyclopentane epoxide of formula **45** with an alkali metal salt of a purine compound of formula



wherein X is Cl, I or benzyloxy, to give a compound of formula



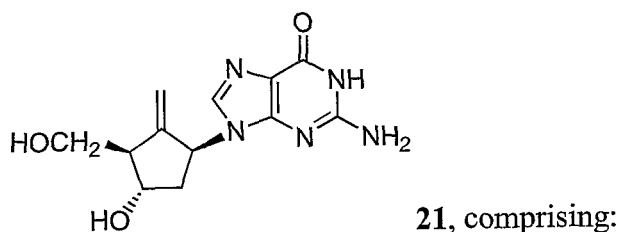
- 15 (i) converting the compound of formula **46** to a methylene compound of formula



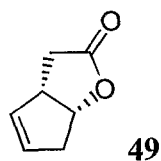
- (j) treating the compound of formula **47** with an acid or base effective for protodesilylation of the silyl moiety; and
- (k) oxidizing the product of step (j) to provide the compound of formula **21**.

5

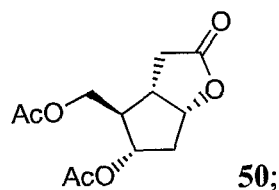
62. A process for the preparation of entecavir having the formula



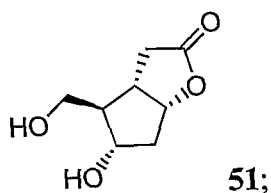
- (a) treating a homochiral bicyclic lactone of the formula



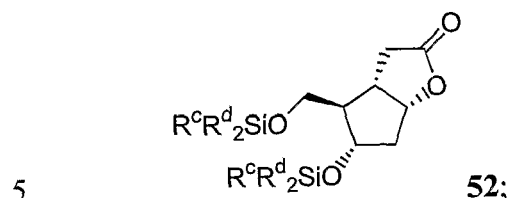
- 10 with paraformaldehyde, acetic acid, and sulfuric acid to provide a diacetate of the formula



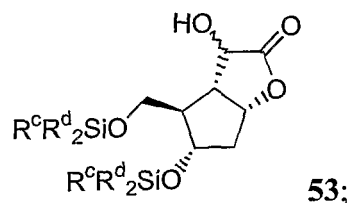
- (b) treating the diacetate product of step (a) using a base in an alcohol solvent to remove the acetate protecting groups to give the compound having the
- 15 formula



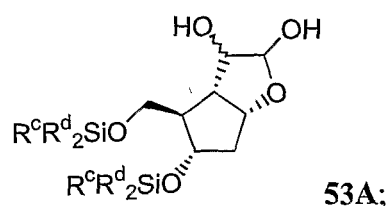
(c) treating the product of step (b) with a silylating reagent of the formula $R^cR^d_2SiY$, wherein R^c is linear or branched C_1 to C_4 alkyl, or phenyl, and R^d is linear or branched C_1 to C_3 alkyl and Y is a leaving group, to provide a compound of formula



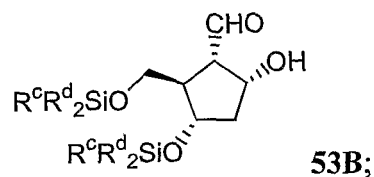
(d) treating the product of step (c) with a strong non-nucleophilic base and (1S)-(+)-(10-camphorsulfonyl)oxaziridine to give a compound of formula



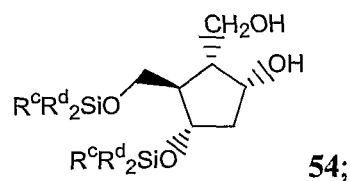
10 (e) reducing the lactone moiety of the product from step (d) with a hydride reagent to give a compound having the formula



(f) cleaving the product from step (e) with an oxidizing agent to give a compound of formula

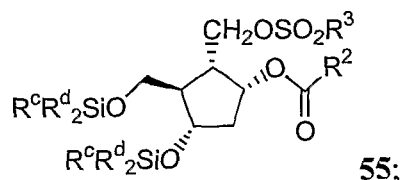


15 (g) reducing the product from step (f) with a hydride reagent to give a diol of the formula

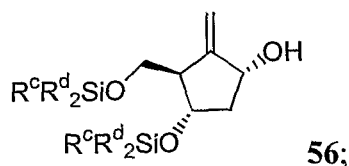


(h) selectively sulfonylating the primary alcohol of the product from step (g) with a reagent of the formula R^3SO_2Cl , wherein R^3 is C_1 to C_4 alkyl, trifluoromethyl, phenyl, or phenyl substituted by C_1 to C_6 alkyl or C_1 to C_6 alkoxy;

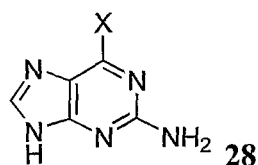
(i) acylating the secondary alcohol of the product of step (h) with an acylating agent of the formula $R^2C(O)-Y$, wherein R^2 is C_1 to C_6 alkyl, arylalkyl or aryl, and Y is a leaving group to give a compound having the formula



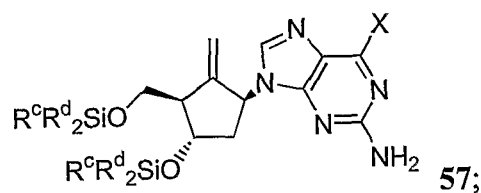
(j) treating the product from step (i) with a strong base to effect elimination and hydrolysis of the carboxylic acid ester to give the compound of formula



(k) condensing the product from step (j) with a purine compound of formula



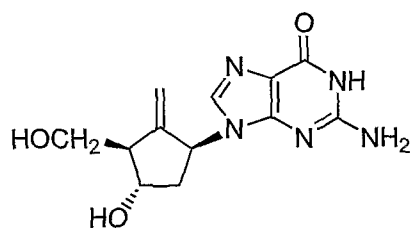
wherein X is Cl, I or benzyloxy, under Mitsunobu conditions to give a methylene compound of formula



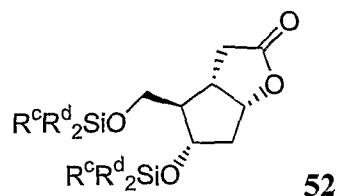
(l) removing the silyl ether protecting groups of the methylene compound of formula **57**; and

(m) hydrolyzing the 6-X group to give the compound of formula **21**.

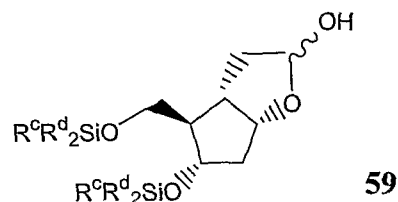
63. A process for the preparation of entecavir having the formula



(a) reducing the compound of formula



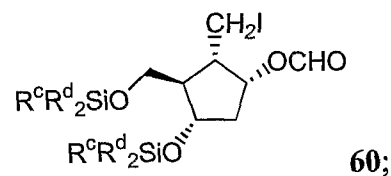
to give a lactol of the formula



5

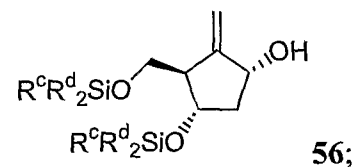
wherein R^c is a linear or branched C_1 to C_4 alkyl, or phenyl, and R^d is a linear or branched C_1 to C_3 alkyl;

(b) iodinating the lactol product of step (a) by free radical oxidation to give an iodide compound having the formula

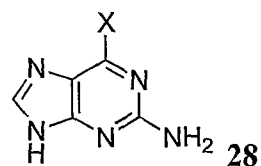


10

(c) treating the product from step (b) with a strong base to give the methylene compound of formula

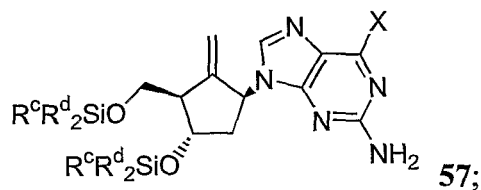


(d) condensing the product from step (c) with a purine compound of formula



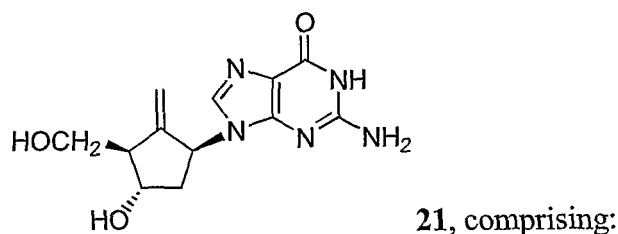
15

wherein X is Cl, I or benzyloxy, under Mitsunobu conditions to give a methylene compound of formula

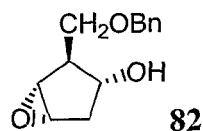


- (e) removing the silyl ether protecting groups of the methylene compound of formula **57**; and
- (f) hydrolyzing the 6-X group to give the compound of formula **21**.

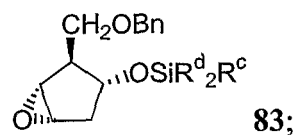
64. A process for the preparation of entecavir having the formula



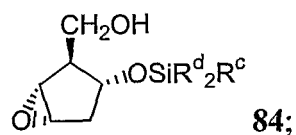
- (a) silylating a compound of formula



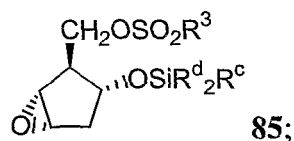
with a compound of formula $R^cR^d_2SiY$, wherein R^c is linear or branched C_1 to C_4 alkyl, or phenyl, R^d is linear or branched C_1 to C_3 alkyl, and Y is a leaving group, to provide a compound of formula



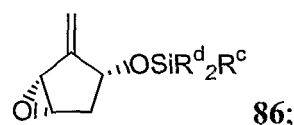
- (b) reducing the product from step (a) under conditions sufficient to remove the benzyl protecting group to give a compound of formula



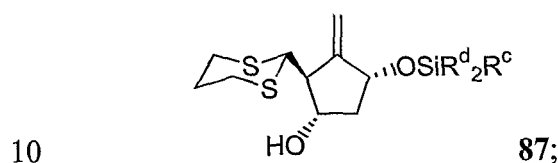
(c) converting the alcohol moiety of the product from step (b) to a sulfonate ester of the formula SO_2R^3 , wherein R^3 is C_1 to C_4 alkyl, trifluoromethyl, or phenyl substituted by C_1 to C_6 alkyl or C_1 to C_6 alkoxy to give a compound of formula



- 5 (d) treating the product from step (c) with a strong base to effect elimination of the $\text{R}^3\text{SO}_3\text{H}$ to provide the methylene compound of formula



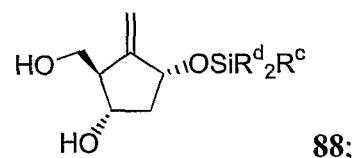
(e) treating the product from step (d) with a lithium salt of 1,3-dithiane to provide the compound of formula



10

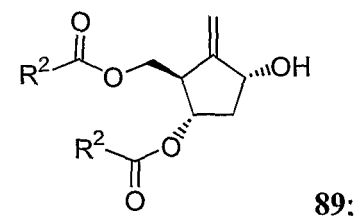
(f) hydrolyzing the dithioacetal moiety of the compound of formula **87**; and

(g) treating the product of step (f) with a hydride reagent to provide a compound of formula

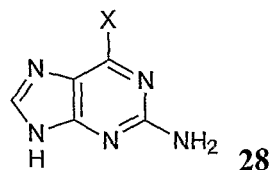


15

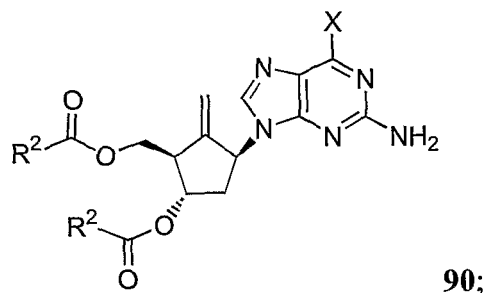
(h) acylating the compound of formula **88** with a compound having the formula $\text{R}^2\text{C}(\text{O})-\text{Y}$, wherein Y is a leaving group and R^2 is C_1 to C_6 alkyl or aryl, to give the compound of formula



(i) condensing the product from step (h) with a purine compound of formula

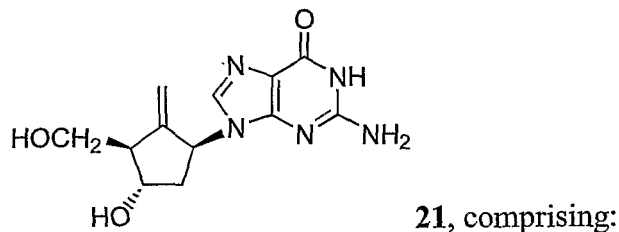


wherein X is Cl, I, or benzyloxy under Mitsunobu conditions to give a methylene compound of formula

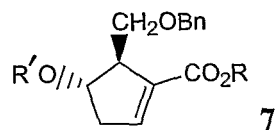


- 5 (j) removing the acyl ester protecting groups from the methylene compound of formula **90**; and
- (k) hydrolyzing the X group to give the compound of formula **21**.

10 65. A process of preparing entecavir having the formula

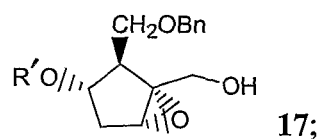


- (a) reducing an ester of the formula

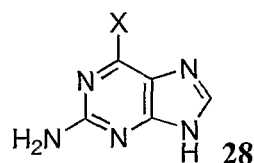


15 wherein R is C₁ to C₄ alkyl, or benzyl, and R' is benzyl, benzyl substituted on the phenyl moiety by C₁ to C₆ alkyl or C₁ to C₆ alkoxy, or R^cR^d₂Si wherein R^c is linear or branched C₁ to C₄ alkyl or phenyl, and R^d is linear or branched C₁ to C₃ alkyl, with a hydride reagent;

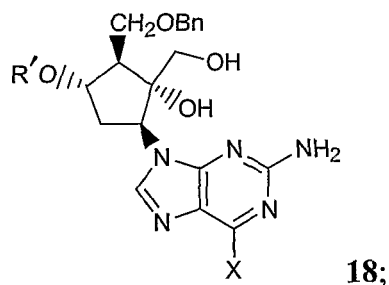
(b) asymmetrically epoxidizing the product from step (a) with a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst to provide the cyclopentane epoxide of the formula



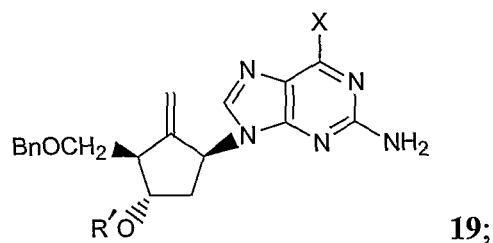
- 5 (c) treating the product of step (b) with an alkali metal salt of a purine compound of formula



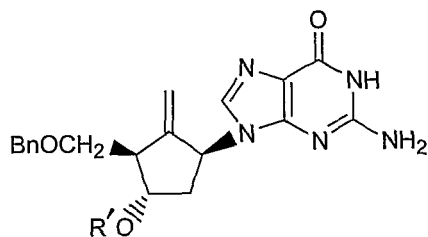
wherein X is Cl, I or BnO, to provide a compound of formula



- 10 (d) converting the vicinal diol product of step (c) to an alkene to provide the methylene compound of formula

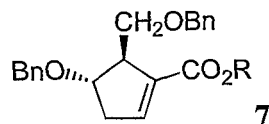


(e) hydrolyzing the X group of the compound of formula **19** to provide the methylene compound of formula



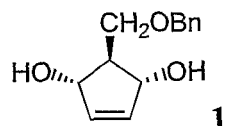
(f) removing the benzyl ether protecting group(s) to provide the compound of formula **21**.

5 66. A process for the preparation of an ester of the formula

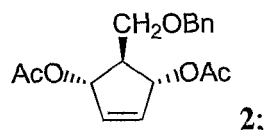


wherein R is C₁ to C₄ alkyl or benzyl, comprising:

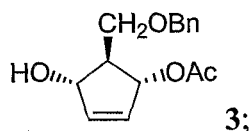
(a) acetylating a diol of the formula



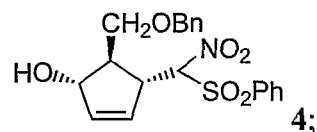
10 with an anhydride to provide the diacetate of the formula



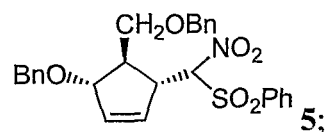
(b) hydrolyzing the product from step (c) with a hydrolase enzyme to give a compound of formula



15 (c) coupling the product from step (b) with phenylsulfonylnitromethane to give a compound of formula

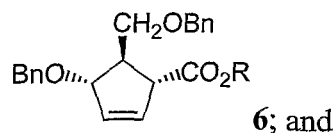


(d) alkylating the product from step (c) with a benzyl halide to provide the compound of formula



20

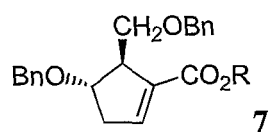
(e) converting the product from step (d) to an ester of the formula



(f) isomerizing the ester of the formula **6** under basic conditions to provide the ester of the formula **7**.

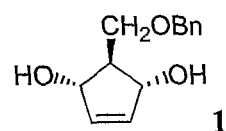
5

67. A process for the preparation of an ester of the formula



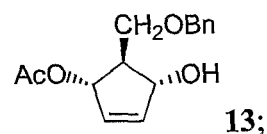
wherein R is C₁ to C₄ alkyl or benzyl, comprising:

(a) asymmetrically acetylating the diol of the formula



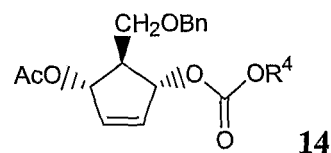
10

with a C₁ to C₆ alkyl acetate ester and hydrolase enzyme to obtain a compound of formula



(b) acylating the product from step (a) to give an alkyl carbonate of the

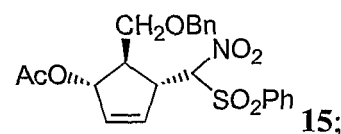
15 formula



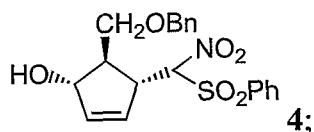
wherein R⁴ is C₁ to C₆ alkyl, benzyl, phenyl, or phenyl substituted by C₁ to C₆ alkyl or C₁ to C₆ alkoxy;

(c) coupling the product from step (b) with phenylsulfonylnitromethane to

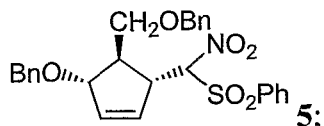
20 obtain a compound of formula



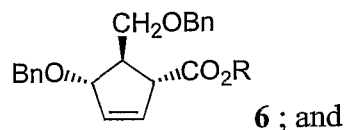
(d) hydrolyzing the product from step (c) with a base to obtain a compound of formula



(e) alkylating the product from step (d) with a benzyl halide in the presence
5 of strong non-nucleophilic base to give the compound of formula

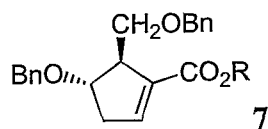


(f) converting the product from step (e) to an ester of the formula



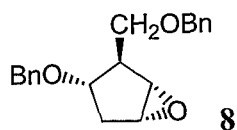
(g) isomerizing the ester of the formula **6** under basic conditions to provide
10 the ester of the formula **7**.

68. A process for the preparation of an ester of the formula

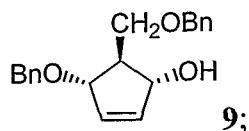


15 wherein R is C₁ to C₄ alkyl or benzyl, comprising:

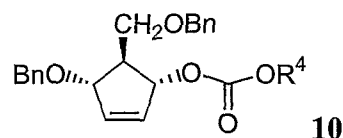
(a) reacting a cyclopentane epoxide of the formula



with a strong non-nucleophilic base to form an allylic alcohol of the formula

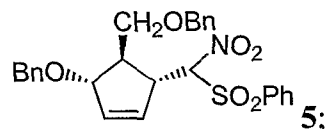


(b) acylating the product from step (a) to give an alkyl carbonate ester of the
20 formula

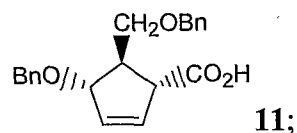


wherein R^4 is C_1 to C_6 alkyl, benzyl, phenyl, or phenyl substituted by C_1 to C_6 alkyl or C_1 to C_6 alkoxy;

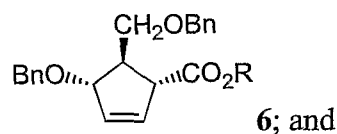
- (c) coupling the product of step (b) with phenylsulfonylnitromethane to give
5 the compound of formula



- (d) converting the product from step (c) to an acid of the formula



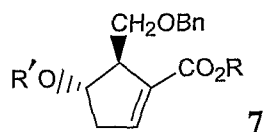
- (e) converting the product from step (d) to an ester of the formula



10

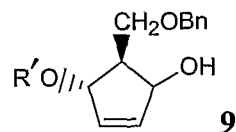
- (f) isomerizing the product from step (e) under basic conditions to provide
the ester of formula 7.

- 15 69. A process of preparing an ester of the formula

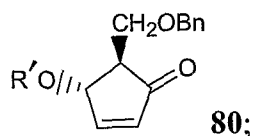


wherein R is C_1 to C_4 alkyl, or benzyl; R' is benzyl, or benzyl substituted on the phenyl moiety by C_1 to C_6 alkyl or C_1 to C_6 alkoxy, or $R^c R^d Si$, wherein R^c is C_1 to C_4 alkyl, or phenyl, and R^d is C_1 to C_3 alkyl; comprising:

- 20 (a) oxidizing an allylic alcohol of the formula

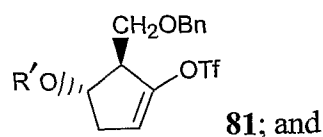


with an oxidizing agent to give a cyclopentenone of the formula



(b) reducing the cyclopentenone of the formula **80** with lithium tri-*sec*-butylborohydride;

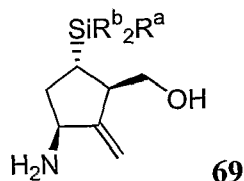
5 (c) sulfonylating the product of step (b) with a triflating reagent to give a compound of formula



(d) converting the triflate moiety of the compound of formula **81** to an alkoxy carbonyl moiety to give the ester of the formula **7**.

10

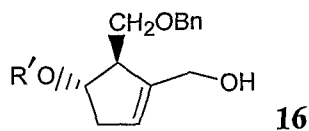
70. A compound of formula



wherein R^a is allyl, phenyl, C_1 to C_6 alkylphenyl or C_1 to C_6 alkoxyphenyl; and R^b is

15 C_1 to C_6 alkyl; or a salt thereof.

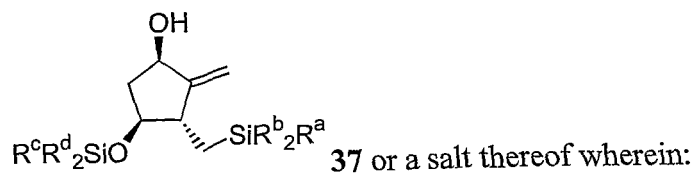
71. A compound of formula



or a salt thereof wherein R^1 is benzyl or $R^cR^d_2Si-$, R^c is C_1 to C_4 alkyl or phenyl, and

20 R^d is C_1 to C_3 alkyl.

72. A compound of formula



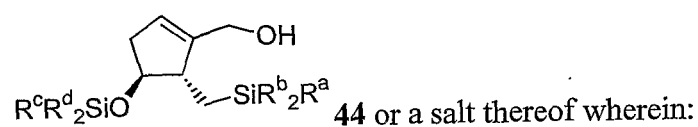
R^a is allyl, phenyl, C_1 to C_6 alkylphenyl or C_1 to C_6 alkoxyphenyl;

R^b is C_1 to C_6 alkyl;

R^c is C_1 to C_4 alkyl or phenyl; and

5 R^d is C_1 to C_3 alkyl.

73. A compound of formula



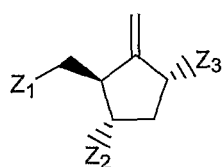
10 R^a is allyl, phenyl, C_1 to C_6 alkylphenyl or C_1 to C_6 alkoxyphenyl;

R^b is C_1 to C_6 alkyl;

R^c is C_1 to C_4 alkyl or phenyl; and

R^d is C_1 to C_3 alkyl.

15 74. A compound of formula



wherein Z_1 and Z_2 are both $R^cR^d_2SiO-$ and Z_3 is hydroxy or

Z_1 and Z_2 are both hydroxy and Z_3 is $R^cR^d_2SiO-$;

R^c is C_1 to C_4 alkyl or phenyl; and

R^d is C_1 to C_3 alkyl.

20