SYNTHESIS OF PURINE NUCLEOSIDES

This application is being filed on 23 December 2009, as a PCT International Patent application in the name of Pharmasset, Inc., a U.S. national corporation, applicant for the designation of all countries except the U.S., and Byoung-Kwon Chun, a citizen of South Korea; Jinfa Du, a citizen of the U.S.; Suguna Rachakonda, a citizen of India; Bruce S. Ross, a citizen of the U.S.; Michael Joseph Sofia, a citizen of the U.S.; Ganapati Reddy Pamulapati, a citizen of India; Wonsuk Chang, a citizen of South Korea; Hai-Ren Zhang, a citizen of the U.S.; and Dhanapalan Nagarathnam, a citizen of the U.S.; and claims priority to U.S. Provisional Patent Application No. 61/140,317, filed December 23, 2008, the content of which are incorporated by reference in its entirety.

BACKGROUND

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be 2-15% of the world's population. There are an estimated 4.5 million infected people in the United States alone, according to the U.S. Center for Disease Control. According to the World Health Organization, there are more than 200 million infected individuals worldwide, with at least 3 to 4 million people being infected each year. Once infected, about 20% of people clear the virus, but the rest can harbor HCV the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. The viral disease is transmitted parenterally by contaminated blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their offspring. Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection.

Purine phosphoramidates have been shown to be potent inhibitors of the HCV virus (US Patent Application 12/053,015, see also WO 2008/121634). However, preparation of these compounds has been made difficult due to poor yields

associated with the coupling of the ribose sugar to the purine base and because of poor C-1' beta-stereoselectivity associated with the ribose to purine base coupling step.

Generally, there are two ways to prepare a nucleoside analogue. The first way follows a linear synthetic sequence in which the target nucleoside is prepared from an appropriate nucleoside. In this approach, usually there is less concern about stereoselective chemistry as most if not all of the stereocenters are set. However, the synthesis can be lengthy if extensive modification of the sugar is required.

An alternative approach toward the synthesis of novel nucleosides utilizes a convergent synthesis where a sugar portion is separately modified and later coupled with an appropriate silylated base (Vorbrueggen et al., J. Org. Chem. **1976**, *41*, 2084). In the case of ribose derivatives in which there is a 2-α-O-acyl group present, the desired β stereochemistry at the 1'-position is secured by neighboring group participation in the presence of a Lewis acid such as $SnCl_4$ or TMSOTf. However, if the sugar has no 2-α-O-acyl group as for 2-deoxy nucleoside, the Vorbrueggen conditions would be expected to generate an isomeric mixture which is then often difficult to separate. A common way to avoid this stereochemical problem is to employ an α-halosugar so that an S_N2 type coupling with a salt of a purine base or a silylated pyrimidine base would generate the desired β isomer enriched mixture (Kazimierczuk, Z. et al. J. Am. Chem. Soc. **1984**, *106*, 6379-6382; Chun, B. K. et al J. Org. Chem, **2000**, *65*, 685-693; Zhong, M. et al. J. Org. Chem. **2006**, *71*, 7773-7779). However, the main problem of this approach from a process chemistry point of view is that, in many cases, it is difficult to obtain the desired reactive α-halosugar in a good yield without any difficult purification steps. There are many literature and patent examples of reacting salts of purine bases with α-halosugars.

Another possible way to do an S_N2 type coupling is enzymatic glycosylation in which the sugar-1-α-O-phosphate is coupled with purine base using either isolated enzymes or whole cells. The phosphate intermediate can be generated enzymatically from another nucleoside containing the desired sugar. This coupled reaction is called transglycosylation. This conversion is highly stereospecific. Unfortunately, natural enzymes only work with a limited number of modified sugars. For custom sugars, existing enzymes from a range of microorganisms need to be screened for activity or through extensive research there is a possibility that a mutated enzyme can be selected and produced though genetic engineering (Komatsu, H. et al

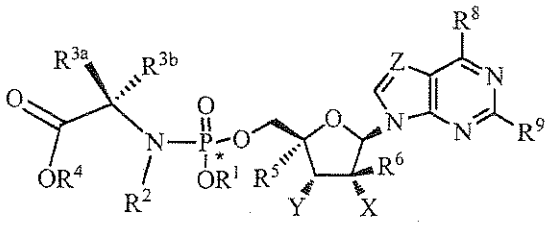
Tetrahedron Lett. 2003, 44, 2899-2901; Okuyama, K. et al. Biosci. Biotechnol. Biochem. 2003, 67(5), 989-995). 2'-Fluorinated nucleosides are difficult to enzymatically glycosylate but it has been accomplished using specialized natural enzymes (Krenitsky et al., J. Med. Chem. **1993**, *36*, 119-12) or with proprietary genetically engineered enzymes (Metkinen Chemistry, Kuusisto, Finland). There is no literature report of using enzymatic glycosylation for the 2'-fluoro-2'-*C*-methyl sugar. If it were possible, it would be necessary to start with 2'-fluoro-2'-*C*-methyluridine for transglycosylation or the 1-*O*-α-phosphate of the sugar for glycosylation. The cost of the synthesis of these starting materials approaches the cost of the final purines made chemically by the proposed route.

A final alternative method to couple a sugar with a purine base is through the use of Mitsunobu chemistry. This approach uses a condensing reagent such as *N,N*-dicyclohexylcarbodiimide (DCC) and triphenylphosphine. Although this reaction accepts a wide variety of substrates, yields are typically lower and there is no stereoselectivity. Purification of the product from the Mitsunubo reagents and by-products is often challenging as well.

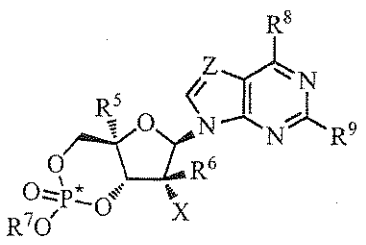
2'-deoxy-2'-fluoro-2'-C-methyl purine nucleosides and their corresponding nucleotide phosphoramidates belong to the 2'-deoxy nucleoside category since there is no directing α-acyloxy group in 2'-position. A close derivative of the purine analogs was first prepared using the linear nucleoside route in a less than 5% overall yield due to the complexity of forming the 2' quaternary center. The lowest yielding step, fluorination, was done late in the sequence. This route was unsuitable for large scale synthesis (Clark, J. L. et al. Bioorg. Med. Chem. Lett. **2006**, *16*, 1712-1715).

SUMMARY OF THE INVENTION

Disclosed is compound **I** or salts thereof or compound **II** or salts thereof:



I



II

wherein

(a) R^1 is hydrogen, n-alkyl; branched alkyl; cycloalkyl; or aryl, which includes, but is not limited to, phenyl or naphthyl,

where phenyl or naphthyl are optionally substituted with at least one of

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, F, Cl, Br, I, nitro, cyano, C_{1-6} haloalkyl, $-N(R^{1'})_2$, C_{1-6} acylamino, $-NHSO_2C_{1-6}$ alkyl, $-SO_2N(R^{1'})_2$, $COR^{1''}$, and $-SO_2C_{1-6}$ alkyl; ($R^{1'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{1''}$ is –OR' or $-N(R^{1'})_2$);

(b) R^2 is hydrogen, C_{1-10} alkyl, or R^{3a} or R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, where n is 2 to 4;

(c) R^{3a} and R^{3b} are

(i) independently selected from hydrogen, C_{1-10} alkyl, cycloalkyl, $-(CH_2)_c(NR^{3'})_2$, C_{1-6} hydroxyalkyl, $-CH_2SH$, $-(CH_2)_2S(O)_dMe$, $-(CH_2)_3NHC(=NH)NH_2$, (1H-indol-3-yl)methyl, (1H-imidazol-4-yl)methyl, $-(CH_2)_eCOR^{3''}$, aryl and aryl C_{1-3} alkyl, said aryl groups optionally substituted with a group selected from hydroxyl, C_{1-10} alkyl, C_{1-6} alkoxy, halogen, nitro and cyano;

(ii) R^{3a} and R^{3b} both are C_{1-6} alkyl;

(iii) R^{3a} and R^{3b} together are$(CH_2)_f$ so as to form a spiro ring;

(iv) R^{3a} is hydrogen and R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms

(v) R^{3b} is hydrogen and R^{3a} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, where c is 1 to 6, d is 0 to 2, e is 0 to 3, f is 2 to 5, n is 2 to 4, and where $R^{3'}$ is independently hydrogen or C_{1-6} alkyl and $R^{3''}$ is -OR' or $-N(R^{3'})_2$);

(vi) R^{3a} is H and R^{3b} is H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2-indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-Ph), CH_2SH, or lower cycloalkyl; or

(vii) R^{3a} is CH_3, $-CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2-indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H,

$CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, -$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-Ph), CH_2SH, or lower cycloalkyl and R^{3b} is H, where $R^{3'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{3''}$ is –OR' or -$N(R^{3'})_2$);

(d) R^4 is hydrogen, C_{1-10} alkyl, C_{1-10} alkyl optionally substituted with a lower alkyl, alkoxy, di(lower alkyl)-amino, or halogen, C_{1-10} haloalkyl, C_{3-10} cycloalkyl, cycloalkyl alkyl, cycloheteroalkyl, aminoacyl, aryl, such as phenyl, heteroaryl, such as, pyridinyl, substituted aryl, or substituted heteroaryl;

(e) R^5 is H, a lower alkyl, CN, vinyl, O-(lower alkyl), hydroxyl lower alkyl, i.e., -$(CH_2)_pOH$, where p is 1 -6, including hydroxyl methyl (CH_2OH), CH_2F, N_3, CH_2CN, CH_2NH_2, CH_2NHCH_3, $CH_2N(CH_3)_2$, alkyne (optionally substituted), or halogen, including F, Cl, Br, or I;

(f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, F, CN, vinyl, or ethynyl;

(g) R^7 is hydrogen, n-alkyl, branched alkyl, cycloalkyl, alkaryl, or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of H, F, Cl, Br, I, OH, $OR^{7'}$, SH, $SR^{7'}$, NH_2, $NHR^{7'}$, $NR^{7'}_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6, lower alkynyl of C_2-C_6, such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, $CO_2R^{7'}$, $CONH_2$, $CONHR^{7'}$, $CONR^{7'}_2$, CH=$CHCO_2H$, or CH=$CHCO_2R^{7'}$ wherein $R^{7'}$ is an optionally substituted alkyl, cycloalkyl, alkenyl, alkynyl, or alkoxyalkyl, which includes, but is not limited to, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and C_{1-10} alkoxyalkyl,

(h) X is H, OH, OMe, halogen, CN, NH_2, or N_3;

(i) Y is OH;

(j) Z is N or CR^{10};

(k) R^8 and R^9 are independently H, F, Cl, Br, I, OH, OR', SH, SR', NH_2, NHR', NR'_2, nitrogen heterocycle, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, lower alkenyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower

alkoxy of C_1-C_6, CO_2H, CO_2R', $CONH_2$, CONHR', $CONR'_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$,

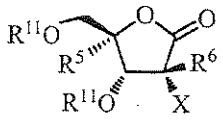
and

(l) R^{10} is H, halogen (including F, Cl, Br, I), OH, OR', SH, SR', NH_2, NHR', NR'_2, NO_2 lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, lower alkenyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6 , lower alkynyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, CO_2R', $CONH_2$, CONHR', $CONR'_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$;

wherein R' is an optionally substituted alkyl, which includes, but is not limited to, an optionally substituted C_{1-20} alkyl, an optionally substituted C_{1-10} alkyl, an optionally substituted lower alkyl; an optionally substituted cycloalkyl; an alkaryl; an optionally substituted alkynyl of C_2-C_6; an optionally substituted lower alkenyl of C_2-C_6, or optionally substituted acyl, which includes but is not limited to C(O) alkyl, C(O)(C_{1-20} alkyl), C(O)(C_{1-10} alkyl), or a C(O)(lower alkyl).

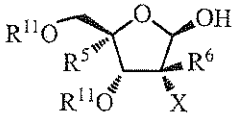
Also disclosed is a process for preparing compound **I** or compound **II**, as defined above, wherein said process comprises:

(a) stereoselective reduction of a protected ribonolactone **III** using a hydride reducing agent



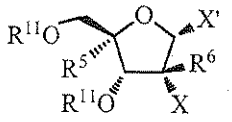
III

to provide a beta-lactol derivative **IV**; and



IV

(b) stereoselective conversion of the lactol derivative using a reagent to obtain an anomeric alpha-derivative **V**



V,

wherein R^5, R^6, and X have the meanings as defined above, X' is a leaving group and R^{11} is a protecting group.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. X-Ray Crystal Structure (ORTEP drawing with 30% probability thermal ellipsoids) for R_P-17.

Figure 2. XRD of R_P-17.

Figure 3. FT-IR spectrum of R_P-17.

DEFINITIONS

The phrase "a" or "an" entity as used herein refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound. As such, the terms "a" (or "an"), "one or more", and "at least one" can be used interchangeably herein.

The phrase "as defined herein above" or "as defined above" with respect to the substituents refers to the first definition provided in the Summary of the Invention or if no definitions there, then the DEFINITIONS, if if none there, the meaning understood by one of ordinary skill.

The terms "optional" or "optionally" as used herein means that a subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optional bond" means that the bond may or may not be present, and that the description includes single, double, or triple bonds.

The term "about" (also represented by ~) means that the recited numerical value is part of a range that varies within standard experimental error.

The term "halo," as used herein, includes chloro, bromo, iodo and fluoro.

The term "independently" is used herein to indicate that a variable is applied in any one instance without regard to the presence or absence of a variable having that same or a different definition within the same compound. Thus, in a compound in which R appears twice and is defined as "independently carbon or nitrogen", both

R's can be carbon, both R's can be nitrogen, or one R' can be carbon and the other nitrogen.

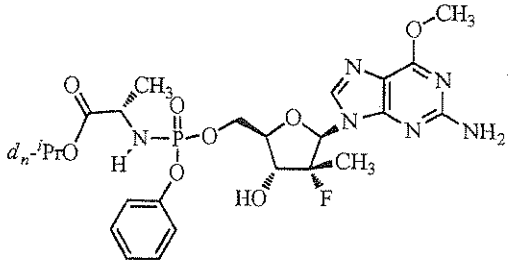
The term "purified," as described herein, refers to the purity of a given compound. For example, a compound is "purified" when the given compound is a major component of the composition, i.e., at least 50% w/w pure. Thus, "purified" embraces at least 50% w/w purity, at least 60% w/w purity, at least 70% purity, at least 80% purity, at least 85% purity, at least 90% purity, at least 92% purity, at least 94% purity, at least 96% purity, at least 97% purity, at least 98% purity, and at least 99% purity.

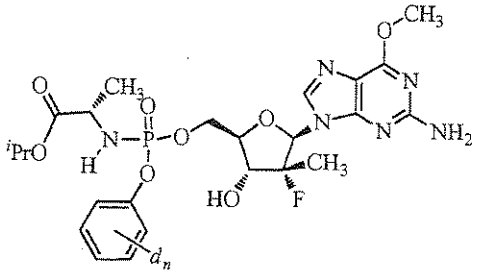
The term "tautomerism" and "tautomers" have their accepted plain meanings.

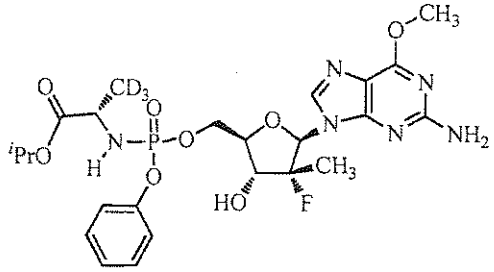
The term "P*" means that the phosphorus atom is chiral and that it has a corresponding Cahn-Ingold-Prelog designation of "R" or "S" which have their accepted plain meanings. It is contemplated that the phosphoramidate nucleoside **I** and the cyclic phosphate nucleotide **II** can exist as a mixture of diastereomers due to the chirality at phosphorus. Applicants contemplate use of the mixture of disastereomers and/or the resolved diastereomers. In some instances, an asterisk does not appear next to the phosphoroamidate or cyclic phosphate phosphorus atom. In these instances, it is understood that the phosphorus atom is chiral and that one of ordinary skill understands this to be so unless the substituents bound to the phosphorus exclude the possibility of chirality at phosphorus, such as in $P(O)Cl_3$.

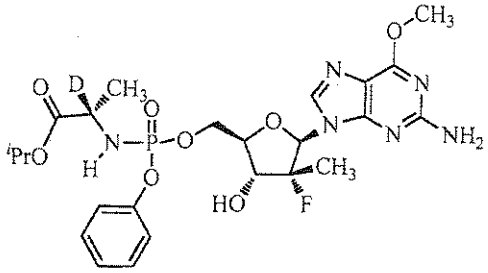
Also contemplated are isotopically-enriched analogs of compounds **I** and **II**. The term "isotopically-enriched" means that at least one atom of compounds **I** and **II** is enriched with a particular isotope, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{15}N, ^{32}P, etc. The term "deuterated analogs" means a compound described herein or its salts thereof, whereby a hydrogen atom is enriched with its ^{2}H-isotope, i.e., deuterium (D). Deuterium substitution can be partial or complete. Partial deuterium substitution means that at least one hydrogen is substituted by at least one deuterium. For instance, for a compound **11**, one of ordinary skill can contemplate at least the following partial deuterated analogs (where "d_n" represents n-number of deuterium atoms, such as, for an isopropyl group n = 1-7, while for a phenyl group, n = 1-5). Although the methyl groups depicted below are shown as being

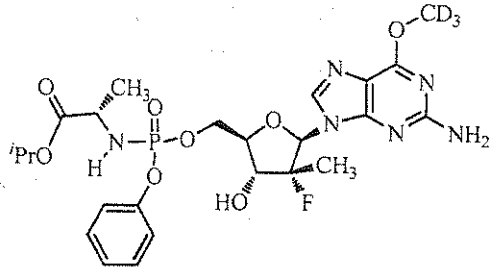
completely deuterated, one will recognize that partial-deuterated variations are also possible, such as, $-CDH_2$ and $-CD_2H$.

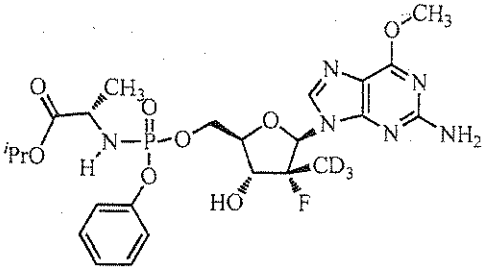












These are but a few deuterated analogs that are synthetically accessible by procedures and reagents that are known to one of ordinary skill.

The term "alkenyl" refers to an unsubstituted hydrocarbon chain radical having from 2 to 10 carbon atoms having one or two olefinic double bonds, preferably one olefinic double bond. The term "C_{2-N} alkenyl" refers to an alkenyl comprising 2 to N carbon atoms, where N is an integer having the following values: 3, 4, 5, 6, 7, 8, 9, or 10. The term "C_{2-10} alkenyl" refers to an alkenyl comprising 2 to 10 carbon atoms. The term "C_{2-4} alkenyl" refers to an alkenyl comprising 2 to 4 carbon atoms. Examples include, but are not limited to, vinyl, 1-propenyl, 2-propenyl (allyl) or 2-butenyl (crotyl).

The term "halogenated alkenyl" refers to an alkenyl comprising at least one of F, Cl, Br, and I.

The term "alkyl" refers to an unbranched or branched chain, saturated, monovalent hydrocarbon residue containing 1 to 30 carbon atoms. The term "C_{1-M} alkyl" refers to an alkyl comprising 1 to M carbon atoms, where M is an integer having the following values: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30. The term "C_{1-4} alkyl" refers to an alkyl containing 1 to 4 carbon atoms. The term "lower alkyl" denotes a straight or branched chain hydrocarbon residue comprising 1 to 6 carbon atoms, which is also designated by the expression "C_{1-6}-alkyl." "C_{1-20} alkyl" as used herein refers to an alkyl comprising 1 to 20 carbon atoms. "C_{1-10} alkyl" as used herein refers to an alkyl comprising 1 to 10 carbons. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.. Examples of lower alkyl groups include, but are not limited to, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, pentyl, isopentyl, neopentyl, hexyl, etc. The term (ar)alkyl or (heteroaryl)alkyl indicate the alkyl group is optionally substituted by an aryl or a heteroaryl group respectively.

The term "halogenated alkyl" (or "haloalkyl") refers to an unbranched or branched chain alkyl comprising at least one of F, Cl, Br, and I. The term "C_{1-M} haloalkyl" refers to an alkyl comprising 1 to M carbon atoms that comprises at least one of F, Cl, Br, and I, where M is an integer having the following values: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30. "C_{1-3} haloalkyl" refers to a haloalkyl comprising 1 to 3 carbons and at least one of F, Cl, Br, and I. The term "halogenated lower alkyl" (or "lower haloalkyl") refers to a haloalkyl comprising 1 to 6 carbon atoms and at least one of F, Cl, Br, and I. Examples include, but are not limited to, fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, dichloromethyl, dibromomethyl, diiodomethyl, trifluoromethyl, trichloromethyl, tribromomethyl, triiodomethyl, 1-fluoroethyl, 1-chloroethyl, 1-bromoethyl, 1-iodoethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2-difluoroethyl, 2,2-dichloroethyl, 2,2-dibromomethyl, 2-2-diiodomethyl, 3-fluoropropyl, 3-chloropropyl, 3-bromopropyl, 2,2,2-trifluoroethyl or 1,1,2,2,2-pentafluoroethyl.

The term "alkynyl" refers to an unbranched or branched hydrocarbon chain radical having from 2 to 10 carbon atoms, preferably 2 to 5 carbon atoms, and having one triple bond. The term "$C_{2\text{-}N}$ alkynyl" refers to an alkynyl comprising 2 to N carbon atoms, where N is an integer having the following values: 3, 4, 5, 6, 7, 8, 9, or 10. The term "C $C_{2\text{-}4}$ alkynyl" refers to an alkynyl comprising 2 to 4 carbon atoms. The term "$C_{2\text{-}10}$ alkynyl" refers to an alkynyl comprising 2 to 10 carbons. Examples include, but are limited to, ethynyl (i.e., –C≡CH), 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl or 3-butynyl.

The term "halogenated alkynyl" refers to an unbranched or branched hydrocarbon chain radical having from 2 to 10 carbon atoms, preferably 2 to 5 carbon atoms, and having one triple bond and at least one of F, Cl, Br, and I.

The term "alkoxy" refers to an -O-alkyl group, an –O-cycloalkyl group, an –O-lower cycloalkyl, wherein alkyl, cycloalkyl, and lower cycloalkyl are as defined above. Examples of –O-alkyl groups include, but are not limited to, methoxy, ethoxy, *n*-propyloxy, *i*-propyloxy, *n*-butyloxy, *i*-butyloxy, *t*-butyloxy. "Lower alkoxy" as used herein denotes an alkoxy group with a "lower alkyl" group as previously defined. "$C_{1\text{-}10}$ alkoxy" refers to an-O-alkyl wherein alkyl is $C_{1\text{-}10}$. Examples of –O-cycloalkyl groups include, but are not limited to, -O-*c*-propyl, -O-*c*-butyl, -O-*c*-pentyl, and –O-*c*-hexyl.

The term "halogenated alkoxy" refers to an –O-alkyl group in which the alkyl group comprises at least one of F, Cl, Br, and I.

The term "halogenated lower alkoxy" refers to an –O-(lower alkyl) group in which the lower alkyl group comprises at least one of F, Cl, Br, and I.

The term "cycloalkyl" refers to an unsubstituted or substituted carbocycle, in which the carbocycle contains 3 to 10 carbon atoms; preferably 3 to 8 carbon atoms; more preferably 3 to 6 carbon atoms (i.e., lower cycloalkyls). Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, 2-methyl-cyclopropyl, cyclobutyl, cyclopentyl, cycloheptyl, or cyclooctyl. The term "$C_{3\text{-}7}$ cycloalkyl" as used herein refers to a cycloalkyl comprising 3 to 7 carbons in the carbocyclic ring. The term "lower cycloalkyl" refers to $C_{3\text{-}6}$ cycloalkyl rings, which include, but are not limited to, cyclopropyl (^{c}Pr), 2-methyl-cyclopropyl, etc., cyclobutyl (^{c}Bu), 2-

methyl-cyclobutyl, 3-methyl-cyclobutyl, etc., cyclopentyl (^{c}Pn), 2-methyl-cyclopentyl, 3-methyl-cyclopentyl, 4-methyl-cyclopentyl, etc., cyclohexyl (^{c}Hx), etc.

The term "cycloalkyl alkyl" refers to an additionally unsubstituted or substituted alkyl substituted by a lower cycloalkyl. Examples of cycloalkyl alkyls include, but are not limited to, any one of methyl, ethyl, propyl, i-propyl, n-butyl, i-butyl, t-butyl or pentyl, isopentyl, neopentyl, hexyl, heptyl, and octyl that is substituted with cyclopropyl, 2-methyl-cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The term "cycloheteroalkyl" refers to an unsubstituted or substituted heterocycle, in which the heterocycle contains 2 to 9 carbon atoms; preferably 2 to 7 carbon atoms; more preferably 2 to 5 carbon atoms. Examples of cycloheteroalkyls include, but are not limited to, aziridin-2-yl, *N*-C_{1-3}-alkyl-aziridin-2-yl, azetidinyl, *N*-C_{1-3}-alkyl-azetidin-m'-yl, pyrrolidin-m'-yl, *N*-C_{1-3}-alkyl-pyrrolidin-m'-yl, piperidin-m'-yl, and *N*-C_{1-3}-alkyl-piperidin-m'-yl, where m' is 2, 3, or 4 depending on the cycloheteroalkyl. Specific examples of N-C_{1-3}-alkyl-cycloheteroalkyls include, but are not limited to, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-2-yl, N-methyl-piperidin-3-yl, and N-methyl-piperidin-4-yl. In the instance of R^4, the point of attachment between the cycloheteroalkyl ring carbon and the oxygen occurs at any one of m'.

The term "acyl" refers to a substituent containing a carbonyl moiety and a non-carbonyl moiety. The carbonyl moiety contains a double-bond between the carbonyl carbon and a heteroatom, where the heteroatom is selected from among O, N and S. When the heteroatom is N, the N is substituted by a lower alkyl. The non-carbonyl moiety is selected from straight, branched, and cyclic alkyl, which includes, but is not limited to, a straight, branched, or cyclic C_{1-20} alkyl, C_{1-10} alkyl, or lower alkyl; alkoxyalkyl, including methoxymethyl; aralkyl, including benzyl; aryloxyalkyl, such as phenoxymethyl; or aryl, including phenyl optionally substituted with halogen (F, Cl, Br, I), hydroxyl, C_1 to C_4 alkyl, or C_1 to C_4 alkoxy, sulfonate esters, such as alkyl or aralkyl sulphonyl, including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxytrityl, substituted benzyl,

trialkylsilyl (e.g. dimethyl-t-butylsilyl) or diphenylmethylsilyl. When at least one aryl group is present in the non-carbonyl moiety, it is preferred that the aryl group comprises a phenyl group.

The term "lower acyl" refers to an acyl group in which the non-carbonyl moiety is lower alkyl.

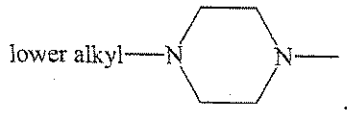
The term "aryl," as used herein, and unless otherwise specified, refers to substituted or unsubstituted phenyl (Ph), biphenyl, or naphthyl, preferably the term aryl refers to substituted or unsubstituted phenyl. The aryl group can be substituted with one or more moieties selected from among hydroxyl, F, Cl, Br, I, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, and phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in T.W. Greene and P.G. M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., John Wiley & Sons, 1999.

The terms "alkaryl" or "alkylaryl" refer to an alkyl group with an aryl substituent, such as benzyl. The terms "lower alkaryl" or "lower alkylaryl" refer to a lower alkyl group with an aryl substituent, such as benzyl. The terms "aralkyl" or "arylalkyl" refer to an aryl group with an alkyl substituent.

The term "di(lower alkyl)amino-lower alkyl" refers to a lower alkyl substituted by an amino group that is itself substituted by two lower alkyl groups. Examples include, but are not limited to, $(CH_3)_2NCH_2$, $(CH_3)_2NCH_2CH_2$, $(CH_3)_2NCH_2CH_2CH_2$, etc. The examples above show lower alkyls substituted at the terminus carbon atom with an N,N-dimethyl-amino substituent. These are intended as examples only and are not intended to limit the meaning of the term "di(lower alkyl)amino-lower alkyl" so as to require the same. It is contemplated that the lower alkyl chain can be substituted with an N,N-di(lower alkyl)-amino at any point along the chain, e.g., $CH_3CH(N\text{-(lower alkyl)}_2)CH_2CH_2$.

The term "heterocycle" refers to an unsubstituted or substituted heterocycle containing carbon, hydrogen, and at least one of N, O, and S, where the C and N can be trivalent or tetravalent, i.e., sp^2- or sp^3-hybridized. Examples of heterocycles include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine,

imidazole, oxazole, piperazine, etc. The term "nitrogen heterocycle" as used for R^8 and R^9 represents a heterocycle containing a nitrogen where the nitrogen is the point of attachment to the purine. Examples of a nitrogen heterocycle, as used for R^8 or R^9, include, but are not limited to, –N(-CH_2CH_2-) (aziridin-1-yl), –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), –N(-$CH_2CH_2CH_2CH_2$-) (pyrrolidin-1-yl), etc. In the instance of piperazine, as related to R^{10} for NR'_2, the corresponding opposite nitrogen atom of the piperazinyl is substituted by a lower alkyl represented by the following structure:



Preferably, the opposite nitrogen of the piperazinyl is substituted by a methyl group.

The term "amino acid" includes naturally occurring and synthetic α, β γ or δ amino acids, and includes but is not limited to, amino acids found in proteins, i.e. glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine. In a preferred embodiment, the amino acid is in the L-configuration. Alternatively, the amino acid can be a derivative of alanyl, valinyl, leucinyl, isoleucinyl, prolinyl, phenylalaninyl, tryptophanyl, methioninyl, glycinyl, serinyl, threoninyl, cysteinyl, tyrosinyl, asparaginyl, glutaminyl, aspartoyl, glutaroyl, lysinyl, argininyl, histidinyl, β-alanyl, β-valinyl, β-leucinyl, β-isoleucinyl, β-prolinyl, β-phenylalaninyl, β-tryptophanyl, β-methioninyl, β-glycinyl, β-serinyl, β-threoninyl, β-cysteinyl, β-tyrosinyl, β-asparaginyl, β-glutaminyl, β-aspartoyl, β-glutaroyl, β-lysinyl, β-argininyl or β-histidinyl. When the term amino acid is used, it is considered to be a specific and independent disclosure of each of the esters of α, β γ or δ glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine in the D and L-configurations.

The term "aminoacyl" includes unsubstituted, N -monosubstituted, and N,N-disubstituted derivatives of naturally occurring and synthetic α, β γ or δ amino acyls, where the amino acyls are derived from amino acids. The amino-nitrogen can be substituted or unsubstituted. When the amino-nitrogen is substituted, the nitrogen is

either mono- or di-substituted, where the substituent bound to the amino-nitrogen is a lower alkyl or an alkaryl.

The terms "alkylamino" or "arylamino" refer to an amino group that has one or two alkyl or aryl substituents, respectively.

The term "protected," as used herein and unless otherwise defined, refers to a group that is added to an oxygen, nitrogen, or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis. Non-limiting examples include: C(O)-alkyl, C(O)Ph, C(O)aryl, CH_3, CH_2-alkyl, CH_2-alkenyl, CH_2Ph, CH_2-aryl, CH_2O-alkyl, CH_2O-aryl, SO_2-alkyl, SO_2-aryl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, and 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

The term "purine" or "pyrimidine" base includes, but is not limited to, adenine, N^6-alkylpurines, N^6-acylpurines (wherein acyl is C(O)(alkyl, aryl, alkylaryl, or arylalkyl), N^6-benzylpurine, N^6-halopurine, N^6-vinylpurine, N^6-acetylenic purine, N^6-acyl purine, N^6-hydroxyalkyl purine, N^6-alkylaminopurine, N^6-thioalkyl purine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, including 6-azacytosine, 2- and/or 4-mercaptopyrmidine, uracil, 5-halouracil, including 5-fluorouracil, C^5-alkylpyrimidines, C^5-benzylpyrimidines, C^5-halopyrimidines, C^5-vinylpyrimidine, C^5-acetylenic pyrimidine, C^5-acyl pyrimidine, C^5-hydroxyalkyl purine, C^5-amidopyrimidine, C^5-cyanopyrimidine, ,C^5-iodopyrimidine, C^6-Iodo-pyrimidine, C^5-Br-vinyl pyrimidine, C^6-Br-vinyl pyrimidine, C^5-nitropyrimidine, C^5-amino-pyrimidine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl. Purine bases include, but are not limited to, guanine, adenine, hypoxanthine, 2,6-diaminopurine, and 6-chloropurine. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, and *t*-butyldiphenylsilyl, trityl, alkyl groups, and acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

The term "protecting group" refers to a chemical group which exhibits the following characteristics. The group must react selectively in good yield to give a protected substrate that is stable to the projected reactions; and the protective group must be selectively removable in good yield by readily available, preferably nontoxic reagents that do not attack the functional group(s) generated in such projected reactions (see Protective Groups in Organic Synthesis, 3rd ed. T. W. Greene and P. G. M. Wuts, John Wiley & Sons, New York, N.Y., 1999). Examples of protecting groups include, but are not limited to: benzoyl, substituted benzoyl, acetyl, phenyl-substituted benzoyl, trityl, DMT (4,4'-dimethoxytrityl), MMT (4-monomethoxytrityl), pixyl (9-phenylxanthen-9-yl) group, thiopixyl (9-phenylthioxanthen-9-yl). The substituted benzoyl groups can be partially substituted or fully substituted. For instance, one of ordinary skill would recognize that the 2-, 3-, 4-, 5-, and 6-positions of the benzoyl ring can be substituted with either hydrogen (an unsubstituted position) or another substituent (a substituted position), such as the substituents contemplated above and throughout the present disclosure. Examples of substituted benzoyl groups include, but are not limited to: 2-halo-benzoyl, 3-halo-benzoyl, 4-halo-benzoyl; 2,4-dihalo-benzoyl, 3,4-dihalo-benzoyl, and 3,5-dihalo-benzoyl; 2-(C_{1-6}-alkyl)-benzoyl, 3-(C_{1-6}-alkyl)-benzoyl, and 4-(C_{1-6}-alkyl)-benzoyl; 2,4-(diC_{1-6}-alkyl)-benzoyl, 3,4-(diC_{1-6}-alkyl)-benzoyl, and 3,5-(diC_{1-6}-alkyl)-benzoyl; 2-nitro-benzoyl, 3-nitro-benzoyl, 4-nitro-benzoyl; 2,4-(dinitro)-benzoyl, 3,4-(dinitro)-benzoyl, and 3,5-(dinitro)-benzoyl, etc.

The term "leaving group", (see also "Lv") as used herein, has the same meaning to the skilled artisan (Advanced Organic Chemistry: reactions, mechanisms and structure–Fourth Edition by Jerry March, John Wiley and Sons Ed.; 1992 pages 351-357) and represents a group which is part of and attached to a substrate molecule; in a reaction where the substrate molecule undergoes a displacement reaction (with for example a nucleophile), the leaving group is then displaced. Examples of leaving groups include, but are not limited to: halogen (F, Cl, Br, and I), preferably Cl, Br, or I; tosylate, mesylate, triflate, acetate, etc.

The term "hydride reducing agent", as used herein, has the meaning of at least one compound capable of reducing the carbonyl (C=O) group of the lactone to a hydroxy group (C–OH). Hydride reducing agents include, but are not limited to: (^{t}BuO)$_3$AlH, sodium (bis(2-methoxyethoxy)(2,2,2-trifluoro-ethoxy)aluminum hydride, Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride), sodium

borohydride, lithium aluminum hydride, diborane, borane-tetrahydrofuran complex, borane-dimethylsulfide complex, aluminum tri-isopropoxide, boron triacetoxy hydride, alcohol dehydrogenase enzymes, (–)- or (+)-diisopinocampheylchloroborane, lithium (2,3-Dimethyl-2-butyl)-t-butoxyborohydride, Diisobutylaluminum 2,6-Di-t-butyl-4-methylphenoxide. Preferably, the hydride reducing agent is $(^{t}BuO)_3AlH$ or sodium (bis(2-methoxyethoxy)(2,2,2-trifluoro-ethoxy)aluminum hydride.

The term "reagent" standing alone, as used herein, has the meaning of at least one compound capable of reacting with the lactol derivative by introducing a leaving group at the anomeric carbon atom. The at least one compound includes, but is not limited to, Ph_3P/CBr_4, $Ph_3P/CHBr_3$, $Ph_3P/CHBr_3$/imidazole, Ph_3P/Br_2, Ph_3P/Br_2/imidazole, N-bromosuccinimide/ Ph_3P, HBr in acetic acid, PBr_3/DMF, PBr_3/sodium bicarbonate, PBr_3/imidazole, PBr_5/DMF, PBr_5/sodium bicarbonate, PBr_5/imidazole, N-chlorosuccinimide/Ph_3P, $POBr_3$/imidazole, $POCl_3$/imidazole, $SOCl_2$, SO_2Cl_2, N-chlorosuccinimide, Ph_3P/CCl_4, HCl (g)/ether, acid chlorides and anhydrides such as acetyl chloride, acetic anhydride, benzoyl chloride, benzoic anhydride, triflic anhydride and trichloroacetonitrile/DBU. Other trivalent phosphorus compounds may be used in place of triphenylphosphine, such as triphenyl phosphite and (4-dimethylaminophenyl)diphenylphosphine.

The term "basic reagent", as used herein, means a compound that is capable of abstracting a proton from an acidic reagent, such as a purine base, whereby the "acidic" functional group of the purine base includes the N–H of the fused imidazole ring. Examples of basic reagents include, but are not limited to, a (lower alk)oxide ((lower alkyl)OM) in combination with an alcoholic solvent, where (lower alk)oxides include, but are not limited to, MeO^-, EtO^-, $^{n}PrO^-$, $^{i}PrO^-$, $^{t}BuO^-$, $^{i}AmO^-$ (iso-amyloxide), etc., and where M is an alkali metal cation, such as Li^+, Na^+, K^+, etc. Alcoholic solvents include (lower alkyl)OH,, such as, for example, MeOH, EtOH, $^{n}PrOH$, $^{i}PrOH$, $^{t}BuOH$, $^{i}AmOH$, etc. Non-alkoxy bases can also be used such as sodium hydride, sodium hexamethyldisilazane, lithium hexamethyldisilazane, lithium diisopropylamide, calcium hydride, sodium carbonate, potassium carbonate, cesium carbonate, DBU, and DBN.

The term "nucleophilic reagent", as used herein, means a compound that contains a radical that is capable of replacing another radical, e.g., by way of a nucleophilic-substitution reaction. An example of a nucleophilic reagent includes,

but is not limited to, a (lower alk)oxide ((lower alkyl)OM) in combination with an alcoholic solvent, where (lower alk)oxides include, but are not limited to, MeO^-, EtO^-, $^nPrO^-$, $^iPrO^-$, $^tBuO^-$, etc., and where M is an alkali metal cation, such as Li^+, Na^+, K^+, etc. Alcoholic solvents include (lower alkyl)OH, such as, for example, MeOH, EtOH, ^{n}PrOH, ^{i}PrOH, ^{t}BuOH, etc. Another example of a nucleophilic reagent includes, but is not limited to, an (aralkyl)oxide in combination with an aralkanol solvent, such as, for example, BnONa/BnOH, where "Bn" represents a benzyl radical ($C_6H_5CH_2$–). Another example of a nucleophilic reagent includes, but is not limited to, an unsubstituted or substituted heterocycle containing carbon, hydrogen, and at least one of N, O, and S, where the C and N can be trivalent or tetravalent, i.e., sp^2- or sp^3-hybridized in the presence of a basic reagent or lower alkyl amine, such as triethylamine or diisopropyl ethyl amine, etc. Specific examples of heterocycles include (see also a preceding paragraph), but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, imidazole, oxazole, piperazine, etc. Thus, any one of aziridine, azetidine, pyrrolidine, piperidine, imidazole, oxazole, piperazine can be used in combination with triethylamine or diisopropyl ethyl amine, etc. Yet another example of a nucleophilic reagents includes primary and secondary amines, which includes, but is not limited to, H_2NR' or HNR'_2, wherein R' is an optionally substituted alkyl, which includes, but is not limited to, an optionally substituted $C_{1\text{-}20}$ alkyl, an optionally substituted $C_{1\text{-}10}$ alkyl, an optionally substituted lower alkyl; or an optionally substituted cycloalkyl. The term "nucleophilic reagent" also provides for functional groups, which when introduced at the 6 position of the purine moiety, are capable of being coverted to a hydroxy group. The term "a group capable of being converted to OH," as used in the process described herein, means a substituent comprised of –OZ, where –OZ is converted to –OH on exposure to certain chemical reagents. Z includes, but is not limited to, an unsubstituted or substituted benzyl, such as, benzyl or p-methoxy-benzyl; a silyl, such as, trimethylsilyl-, t-butyl-diphenylsilyl-, t-butyl-dimethylsilyl, etc.; and an unsubstituted or substituted allyl, such as, $-CH_2CH{=}CH_2$.

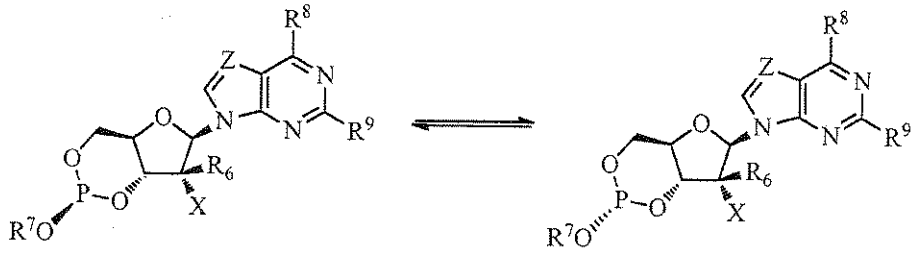
The term P(III)-reagent as used in the process described herein means a chemical reagent whereby the phosphorus atom has a +3-oxidation state. Examples of such P(III)-reagents include, but are not limited to, $P(Lv)_3$, $R^7OP(Lv)_2$, $R^7OP(Lv)(N(C_{1\text{-}6}\ alkyl)_2)$, $R^7OP[N(C_{1\text{-}6}\ alkyl)_2]_2$, and mixtures thereof, where Lv is a leaving group, R^7 and $C_{1\text{-}6}$ alkyl are defined herein.

The term activator reagent as used in the process described herein means a compound that promotes the reaction involving a P(III)-reagent. Examples of activators include, but are not limited to, 1H-tetrazole, 5-ethylthiotetrazole, imidazolium triflate, and 4,5-dicyano-imidazole, as well as those disclosed in U.S. Patent No. 6,274,725.

The term P(V)-reagent as used in the process described herein means a P(III)-reagent having an additional oxo (P=O, depicted also as –P(O)–) substituent, whereby the phosphorus atom has a +5-oxidation state. Examples of such P(V)-reagents include, but are not limited to, $P(O)(Lv)_3$, $R^7OP(O)(Lv)_2$, $R^7OP(O)(Lv)(N(C_{1\text{-}6}\ alkyl)_2)$, $R^7OP(O)[N(C_{1\text{-}6}\ alkyl)_2]_2$, and mixtures thereof, where Lv is a leaving group, R^7 and $C_{1\text{-}6}$ alkyl are defined herein.

The term oxidizing agent as used in the process described herein means a chemical reagent that increases the oxidation state of an atom, i.e., an oxidizing agent promotes "oxidizing" or "oxidation." In a particular embodiment, the atom that is oxidized is phosphorus, as in a phosphite derivative of **II**. Examples of oxidizing agents include, but are not limited to, hydrogen peroxide, hydroperoxides, peroxides, peracids, iodine, and mixtures thereof. Hydrogen peroxide can be used in the presence of a solvent, such as acetonitrile, as disclosed in Cvetovich, R. J. Organic Process Research & Development, Article ASAP, Publication Date (Web): May 11, 2009. Hydroperoxides, ROOH, include peroxides in which R is an alkyl or an aryl and salts thereof, which include, but is not limited to t-butylperoxide (^{t}BuOOH). Peroxides include alkyl, aryl, or mixed alkyl/aryl peroxides and salts thereof. Peracids include alkyl and aryl peracids, which include, but are not limited to, m-chloroperoxybenzoic acid (mCPBA). Use of an elemental halogent, such as, bromine (Br_2), chlorine (Cl_2), or iodine (I_2), can be done in the presence of water and other components, such as, pyridine, tetrahydrofuran, and water. Alternatively, an aqueous Cl_2 solution in the presence of TEMPO is contemplated as well.

The expression "equilibrating the phosphite derivative of **II**" as used herein refers to a process where a composition comprising the two isomers (*cis* and *trans*) of the phosphite derivative of **II** is allowed to equilibrate, as depicted in the following equation.



cis *trans*

The terms *cis* and *trans* refer to the spatial position of the –OR^7 substituent relative to the spatial position of the nucleobase on the furanose ring system. One of ordinary skill will recognize that the equilibrium position, i.e., the ratio of *cis*-to-*trans*, may be influenced by solvent, temperature, etc. and that the conditions to obtain a certain equilibrium position can be determined experimentally, such experimental techniques include, but are not limited to, ^{1}H- or ^{31}P-NMR spectroscopy.

The term amine reagent as used herein means a composition containing at least one compound comprising nitrogen in its protonated or unprotonated form. One of ordinary skill will understand that this term embraces ammonia, mono-, and di-substituted alkyl amines, such as methyl amine, di-isopropyl amine, cyclopentyl-amine, as well as heterocyclic compounds that include, but are not limited to, pyrrolidine, piperidine, morpholine, etc., imidazole, N-(C_{1-6} alkyl)-imidazole, such as, N-methyl-imidazole, pyrazole, N-(C_{1-6} alkyl)- pyrazole, such as, N-methyl-pyrazole, triazole, N-(C_{1-6} alkyl)-triazole, such as N-methyl-triazole, tetrazole, N-(C_{1-6} alkyl)-tetrazole, such as N-methyl-tetrazole, oxazole, etc. Additional examples of heterocyclic amines are disclosed in T.L. Gilchrist, Heterocyclic Chemistry, 1985, Longman Scientific & Technical, which is hereby incorporated by reference.

The terms "purine" or "derivatized purine", as used in the process described herein, means, in addition to the compounds specifically disclosed in a preceding paragraph, a precursor compound of the "Base" of the compounds represented by the structures of formula I and formula II.

The term "salts thereof" includes acid or basic additions salts, as well as pharmaceutically acceptable salts. The phrase "pharmaceutically acceptable salt" means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include, but are not limited to: (1) acid addition salts, formed with inorganic acids such as hydrochloric

acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as glycolic acid, pyruvic acid, lactic acid, malonic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, salicylic acid, muconic acid, and the like or (2) basic addition salts formed with the conjugate bases of any of the inorganic acids listed above, wherein the conjugate bases comprise a cationic component selected from among Na^+, K^+, Mg^{2+}, Ca^{2+}, $NH_gR'''_{4-g}{}^+$, in which R''' is a C_{1-3} alkyl and g is a number selected from among 0, 1, 2, 3, or 4. It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same acid addition salt.

The term "preparation" or "dosage form" is intended to include both solid and liquid formulations of the active compound and one skilled in the art will appreciate that an active ingredient can exist in different preparations depending on the desired dose and pharmacokinetic parameters.

The term "excipient" as used herein refers to a compound that is used to prepare a pharmaceutical composition, and is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipients that are acceptable for veterinary use as well as human pharmaceutical use.

The term "crystalline" refers to a situation where a solid sample of compound **I** or **II** has crystalline characteristics when determined by X-ray powder diffraction or a single crystal X-ray technique.

The term "crystal-like" refers to a situation where a solid sample of compound **I** or **II** has crystalline characteristics when determined by one means, e.g., visually or by optical or polarizing microscopy, but does not have crystalline characteristics when determined by another means, e.g., x-ray powder diffraction. Methods of visually determining the crystallinity of a solid sample by visual or by optical or by polarizing microscopy are disclosed in USP <695> and <776>, both of which are incorporated by reference. A solid sample of compound **I** or **II** that is "crystal-like" may be crystalline under certain conditions but may become non-crystalline when subjected to other conditions.

The term "amorphous" refers to a situation where a solid sample of compound **I** or **II** is neither crystalline nor crystal-like.

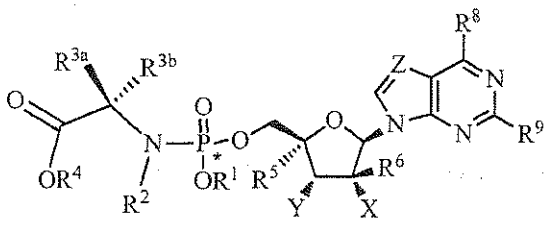
The term "co-crystallates" include co-crystallates of compound **I** or **II** in combination with salts, which embraces pharmaceutically acceptable salts.

The term "substantially anhydrous" means that a substance contains at most 10% by weight of water, preferably at most 1% by weight of water, more preferably at most 0.5% by weight of water, and most preferably at most 0.1% by weight of water.

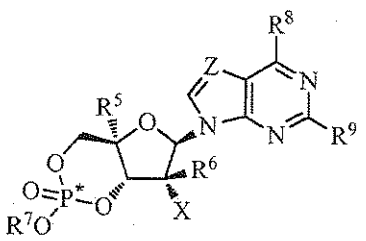
A (lattice or adsorbed) solvent (designated in some instances by the symbol *S*) or anti-solvent includes at least one of a C_1 to C_8 alcohol, a C_2 to C_8 ether, a C_3 to C_7 ketone, a C_3 to C_7 ester, a C_1 to C_2 chlorocarbon, a C_5 to C_{12} saturated hydrocarbon, and a C_6 to C_{12} aromatic hydrocarbon.

DETAILED DESCRIPTION OF THE INVENTION

Disclosed is compound I or salts thereof or compound **II** or salts thereof:



I



II

wherein

(a) R^1 is hydrogen, n-alkyl; branched alkyl; cycloalkyl; or aryl, which includes, but is not limited to, phenyl or naphthyl,

where phenyl or naphthyl are optionally substituted with at least one of

$C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, $C_{1\text{-}6}$ alkoxy, F, Cl, Br, I, nitro, cyano, $C_{1\text{-}6}$ haloalkyl, $-N(R^{1'})_2$, $C_{1\text{-}6}$ acylamino, $-NHSO_2C_{1\text{-}6}$ alkyl, $-SO_2N(R^{1'})_2$, $COR^{1''}$, and $-SO_2C_{1\text{-}6}$ alkyl; ($R^{1'}$ is independently hydrogen or alkyl, which includes, but is not limited to, $C_{1\text{-}20}$ alkyl, $C_{1\text{-}10}$ alkyl, or $C_{1\text{-}6}$ alkyl, $R^{1''}$ is –OR' or $-N(R^{1'})_2$);

(b) R^2 is hydrogen, $C_{1\text{-}10}$ alkyl, or R^{3a} or R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, where n is 2 to 4;

(c) R^{3a} and R^{3b} are

(i) independently selected from hydrogen, C_{1-10} alkyl, cycloalkyl, -$(CH_2)_c(NR^{3'})_2$, C_{1-6} hydroxyalkyl, -CH_2SH, -$(CH_2)_2S(O)_dMe$, -$(CH_2)_3NHC(=NH)NH_2$, (1H-indol-3-yl)methyl, (1H-imidazol-4-yl)methyl, -$(CH_2)_eCOR^{3''}$, aryl and aryl C_{1-3} alkyl, said aryl groups optionally substituted with a group selected from hydroxyl, C_{1-10} alkyl, C_{1-6} alkoxy, halogen, nitro and cyano;

(ii) R^{3a} and R^{3b} both are C_{1-6} alkyl;

(iii) R^{3a} and R^{3b} together are$(CH_2)_f$ so as to form a spiro ring;

(iv) R^{3a} is hydrogen and R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms

(v) R^{3b} is hydrogen and R^{3a} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, where c is 1 to 6, d is 0 to 2, e is 0 to 3, f is 2 to 5, n is 2 to 4, and where $R^{3'}$ is independently hydrogen or C_{1-6} alkyl and $R^{3''}$ is -OR' or $-N(R^{3'})_2$);

(vi) R^{3a} is H and R^{3b} is H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2-indol-3-yl, -$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, -$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-Ph), CH_2SH, or lower cycloalkyl; or

(vii) R^{3a} is CH_3, -CH_2CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2-indol-3-yl, -$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, -$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-Ph), CH_2SH, or lower cycloalkyl and R^{3b} is H, where $R^{3'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{3''}$ is –OR' or -$N(R^{3'})_2$);

(d) R^4 is hydrogen, C_{1-10} alkyl, C_{1-10} alkyl optionally substituted with a lower alkyl, alkoxy, di(lower alkyl)-amino, or halogen, C_{1-10} haloalkyl, C_{3-10} cycloalkyl, cycloalkyl alkyl, cycloheteroalkyl, aminoacyl, aryl, such as phenyl, heteroaryl, such as, pyridinyl, substituted aryl, or substituted heteroaryl;

(e) R^5 is H, a lower alkyl, CN, vinyl, O-(lower alkyl), hydroxyl lower alkyl, i.e., -$(CH_2)_pOH$, where p is 1 -6, including hydroxyl methyl (CH_2OH), CH_2F,

N_3, CH_2CN, CH_2NH_2, CH_2NHCH_3, $CH_2N(CH_3)_2$, alkyne (optionally substituted), or halogen, including F, Cl, Br, or I;

(f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, F, CN, vinyl, or ethynyl;

(g) R^7 is hydrogen, n-alkyl, branched alkyl, cycloalkyl, alkaryl, or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of H, F, Cl, Br, I, OH, $OR^{7'}$, SH, $SR^{7'}$, NH_2, $NHR^{7'}$, $NR^{7'}_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6, lower alkynyl of C_2-C_6, such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, $CO_2R^{7'}$, $CONH_2$, $CONHR^{7'}$, $CONR^{7'}_2$, $CH=CHCO_2H$, or $CH=CHCO_2R^{7'}$ wherein $R^{7'}$ is an optionally substituted alkyl, cycloalkyl, alkenyl, alkynyl, or alkoxyalkyl, which includes, but is not limited to, $C_{1\text{-}10}$ alkyl, $C_{3\text{-}7}$ cycloalkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, and $C_{1\text{-}10}$ alkoxyalkyl,

(h) X is H, OH, OMe, halogen, CN, NH_2, or N_3;

(i) Y is OH;

(j) Z is N or CR^{10};

(k) R^8 and R^9 are independently H, F, Cl, Br, I, OH, OR', SH, SR', NH_2, NHR', NR'_2, nitrogen heterocycle, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, lower alkenyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, CO_2R', $CONH_2$, CONHR', $CONR'_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$,

and

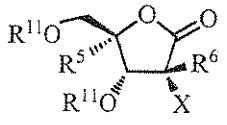
(l) R^{10} is H, halogen (including F, Cl, Br, I), OH, OR', SH, SR', NH_2, NHR', NR'_2, NO_2 lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, lower alkenyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6 , lower alkynyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, CO_2R', $CONH_2$, CONHR', $CONR'_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$;

wherein R' is an optionally substituted alkyl, which includes, but is not limited to, an optionally substituted $C_{1\text{-}20}$ alkyl, an optionally substituted $C_{1\text{-}10}$ alkyl,

an optionally substituted lower alkyl; an optionally substituted cycloalkyl; an alkaryl; an optionally substituted alkynyl of C_2-C_6; an optionally substituted lower alkenyl of C_2-C_6, or optionally substituted acyl, which includes but is not limited to C(O) alkyl, C(O)(C_{1-20} alkyl), C(O)(C_{1-10} alkyl), or a C(O)(lower alkyl).

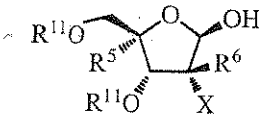
Also disclosed is a process for preparing compound **I** or compound **II**, as defined above, wherein said process comprises:

(a) stereoselective reduction of a protected ribonolactone **III** using a hydride reducing agent



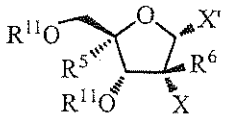
III

to provide a beta-lactol derivative **IV**; and



IV

(b) stereoselective conversion of the lactol derivative using a reagent to obtain an anomeric alpha-derivative **V**



V ,

wherein R^5, R^6, and X have their meanings as described above, X' is a leaving group, and R^{11} is a protecting group.

A first embodiment is directed to compound **I**,

wherein

(a) R^1 is hydrogen, n-alkyl; branched alkyl; cycloalkyl; or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, F, Cl, Br, I, nitro, cyano, C_{1-6} haloalkyl, -$N(R^{1'})_2$, C_{1-6} acylamino, -$NHSO_2C_{1-6}$ alkyl, -$SO_2N(R^{1'})_2$, $COR^{1''}$, and -SO_2C_{1-6} alkyl; ($R^{1'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{1''}$ is –OR' or -$N(R^{1'})_2$);

(b) R^2 is hydrogen or CH_3;

(c) R^{3a} and R^{3b} are

(i) independently selected from hydrogen, C_{1-10} alkyl, cycloalkyl, -$(CH_2)_c(NR^{3'})_2$, C_{1-6} hydroxyalkyl, -CH_2SH, -$(CH_2)_2S(O)_dMe$, -$(CH_2)_3NHC(=NH)NH_2$, (1H-indol-3-yl)methyl, (1H-imidazol-4-yl)methyl, -$(CH_2)_eCOR^{3''}$, aryl and aryl C_{1-3} alkyl, said aryl groups optionally substituted with a group selected from hydroxyl, C_{1-10} alkyl, C_{1-6} alkoxy, halogen, nitro and cyano; (ii) R^{3a} and R^{3b} both are C_{1-6} alkyl; (iii) R^{3a} and R^{3b} together are$(CH_2)_f$ so as to form a spiro ring; (iv) R^{3a} is hydrogen and R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms; (v) R^{3b} is hydrogen and R^{3a} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, where c is 1 to 6, d is 0 to 2, e is 0 to 3, f is 2 to 5, n is 2 to 4, and where $R^{3'}$ is independently hydrogen or C_{1-6} alkyl and $R^{3''}$ is -OR' or –$N(R^{3'})_2$); (vi) R^{3a} is H and R^{3b} is H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2-indol-3-yl, -$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, -$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-Ph), CH_2SH, or lower cycloalkyl; or (vii) R^{3a} is CH_3, -CH_2CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2-indol-3-yl, -$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, -$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-Ph), CH_2SH, or lower cycloalkyl and R^{3b} is H, where $R^{3'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{3''}$ is –OR' or -$N(R^{3'})_2$);

(d) R^4 is hydrogen, C_{1-10} alkyl, C_{1-10} alkyl optionally substituted with a lower alkyl, alkoxy or halogen, C_{1-10} haloalkyl, C_{3-10} cycloalkyl, cycloalkyl alkyl, cycloheteroalkyl, aminoacyl, di(lower alkyl)amino-lower alkyl, aryl, such as phenyl, heteroaryl, such as, pyridinyl, substituted aryl, or substituted heteroaryl;

(e) R^5 is H, a lower alkyl, CN, vinyl, O-(lower alkyl), hydroxyl lower alkyl, i.e., -$(CH_2)_pOH$, where p is 1 -6, including hydroxyl methyl (CH_2OH), CH_2F, N_3, CH_2CN, CH_2NH_2, CH_2NHCH_3, $CH_2N(CH_3)_2$, alkyne (optionally substituted), or halogen, including F, Cl, Br, or I;

(f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, F, CN, vinyl, ethynyl;

(g) X is H, OH, OMe, CN, F, Cl, Br, I, NH_2, or N_3;

(h) Y is OH;

(i) R^8 and R^9 are independently H, F, Br, I, OH, OR', NH_2, NHR', NR'$_2$, nitrogen heterocycle, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$;

(j) Z is N or CR^{10}; and

(k) R^{10} is an H, halogen (including F, Cl, Br, I), OR', NH_2, NHR', NR'$_2$, NO_2, lower alkyl of C_1-C_6, –C≡CH, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$;

wherein R' is a lower alkyl, a lower cycloalkyl, a lower alkaryl, or a C(O)(lower alkyl);

A first aspect of the first embodiment is directed to compound I

wherein

(a) R^1 is hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, phenyl, p-tolyl, p-bromo-phenyl, p-chloro-phenyl, p-fluorophenyl;

(b) R^2 is hydrogen or CH_3;

(c) R^{3a} is H and R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2-indol-3-yl, -$CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, -$CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-Ph), CH_2SH, or lower cycloalkyl;

(d) R^4 is hydrogen, CH_3, Et, ^{i}Pr, ^{n}Pr, ^{n}Bu, 2-butyl, ^{t}Bu, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-4-yl, lower haloalkyl, or di(lower alkyl)amino-lower alkyl;

(e) R^5 is H, CN, CH_3, OCH_3, CH_2OH, CH_2F, N_3, halogen, including F, Cl, Br, or I;

(f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, F, CN, vinyl, or ethynyl;

(g) X is H, OH, OCH_3, CN, F, Cl, Br, I, NH_2, or N_3;

(h) Y is OH;

(i) R^8 and R^9 are independently H, F, Br, I, OH, OR', NH_2, NHR', NR'$_2$, nitrogen heterocycle, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH{=}CHCO_2H$, or $CH{=}CHCO_2R'$;

(j) Z is N or CR^{10}; and

(k) R^{10} is an H, halogen (including F, Cl, Br, I), OR', NH_2, NHR', NR'$_2$, NO_2, lower alkyl of C_1-C_6, $-C{\equiv}CH$, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH{=}CHCO_2H$, or $CH{=}CHCO_2R'$;

wherein R' is a lower alkyl, a lower cycloalkyl, a lower alkyaryl, or a C(O)(lower alkyl).

A second aspect of the first embodiment is directed to compound **I**

wherein

(a) R^1 is hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, phenyl, p-tolyl, p-bromo-phenyl, p-chloro-phenyl, or p-fluorophenyl;

(b) R^2 is hydrogen or CH_3;

(c) R^{3a} is H and R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, or lower cycloalkyl;

(d) R^4 is hydrogen, CH_3, Et, ^{i}Pr, ^{n}Pr, ^{n}Bu, 2-butyl, ^{t}Bu, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-4-yl, lower haloalkyl, or di(lower alkyl)amino-lower alkyl;

(e) R^5 is H, CN, CH_2F, N_3, F, Cl, Br, or I;

(f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, F, vinyl, or ethynyl;

(g) X is H, OH, OCH_3, CN, F, Cl, Br, I, NH_2 or N_3;

(h) Y is OH;

(i) R^8 and R^9 are independently H, F, Br, I, OH, OR', NH_2, NHR', NR'$_2$, nitrogen heterocycle, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH{=}CHCO_2H$, or $CH{=}CHCO_2R'$;

(j) Z is N or CR^{10}; and

(k) R^{10} is a H, halogen (including F, Cl, Br, I), OR', NH_2, NHR', NR'$_2$, NO_2, lower alkyl of C_1-C_6, $-C{\equiv}CH$, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH{=}CHCO_2H$, or $CH{=}CHCO_2R'$;

wherein R' is a lower alkyl, a lower cycloalkyl, a lower alkaryl, or a C(O)(lower alkyl).

A third aspect of the first embodiment is directed to compound **I**,

wherein

(a) R^1 is hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, phenyl, p-tolyl, p-bromo-phenyl, p-chloro-phenyl, or p-fluorophenyl;

(b) R^2 is hydrogen;

(c) R^{3a} is H and R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, or lower cycloalkyl;

(d) R^4 is hydrogen, CH_3, Et, ^{i}Pr, ^{n}Pr, ^{n}Bu, 2-butyl, ^{t}Bu, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-4-yl, lower haloalkyl, or di(lower alkyl)amino-lower alkyl;

(e) R^5 is H or N_3;

(f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, F, vinyl or ethynyl;

(g) X is H, OH, OCH_3, CN, F, NH_2 or N_3;

(h) Y is OH;

(i) R^8 and R^9 are independently H, F, Br, I, OH, OR', NH_2, NHR', NR'$_2$, nitrogen heterocycle, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH{=}CHCO_2H$, or $CH{=}CHCO_2R'$;

(j) Z is N or CR^{10}; and

(k) R^{10} is an H, halogen (including F, Cl, Br, I), OR', NH_2, NHR', NR'$_2$, NO_2, lower alkyl of C_1-C_6, $-C{\equiv}CH$, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH{=}CHCO_2H$, or $CH{=}CHCO_2R'$;

wherein R' is a lower alkyl, a lower cycloalkyl, a lower alkyaryl, or a C(O)(lower alkyl).

A fourth aspect of the first embodiment is directed to compound **I**,

wherein

(a) R^1 is hydrogen, methyl, phenyl, p-bromo-phenyl, p-chloro-phenyl, or p-fluorophenyl;

(b) R^2 is hydrogen;

(c) R^{3a} is H and R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, or lower cycloalkyl;

(d) R^4 is hydrogen, CH_3, Et, ^{i}Pr, ^{n}Pr, ^{n}Bu, 2-butyl, ^{t}Bu, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-4-yl, lower haloalkyl, or di(lower alkyl)amino-lower alkyl;

(e) R^5 is H or N_3;

(f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, F, vinyl, or ethynyl;

(g) X is H, OH, OCH_3, CN, F, NH_2 or N_3;

(h) Y is OH;

(i) R^8 and R^9 are independently H, F, Br, I, OH, OR', NH_2, NHR', NR'$_2$, nitrogen heterocycle, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH{=}CHCO_2H$, or $CH{=}CHCO_2R'$;

(j) Z is N or CR^{10}; and

(k) R^{10} is an H, halogen (including F, Cl, Br, I), OR', NH_2, NHR', NR'$_2$, NO_2, lower alkyl of C_1-C_6, –C≡CH, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH{=}CHCO_2H$, or $CH{=}CHCO_2R'$;

wherein R' is a lower alkyl, a lower cycloalkyl, a lower alkyaryl, or a C(O)(lower alkyl).

A fifth aspect of the first embodiment is directed to compound **I**,

wherein

(a) R^1 is hydrogen, methyl, phenyl, p-bromo-phenyl, p-chloro-phenyl, or p-fluorophenyl;

(b) R^2 is hydrogen;

(c) R^{3a} is H and R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, or lower cycloalkyl;

(d) R^4 is hydrogen, CH_3, Et, ^{i}Pr, ^{n}Pr, ^{n}Bu, 2-butyl, ^{t}Bu, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-4-yl, lower haloalkyl, or di(lower alkyl)amino-lower alkyl;

(e) R^5 is H or N_3;

(f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, F, vinyl, or ethynyl;

(g) X is H, OH, OCH_3, CN, F, NH_2 or N_3;

(h) Y is OH;

(i) R^8 and R^9 are independently H, F, Br, I, OH, OR', NH_2, NHR', NR'$_2$, nitrogen heterocycle, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$;

(j) Z is N or CR^{10}; and

(k) R^{10} is an H, halogen (including F, Cl, Br, I), OR', NH_2, NHR', NR'$_2$, NO_2, lower alkyl of C_1-C_6, $-C\equiv CH$, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$;

wherein R' is a lower alkyl, a lower cycloalkyl, a lower alkyl, or a C(O)(lower alkyl).

A sixth aspect of the first embodiment is directed to compound **I**,

wherein

(a) R^1 is hydrogen, phenyl, p-tolyl, p-bromo-phenyl, p-chloro-phenyl, or p-fluorophenyl;

(b) R^2 is hydrogen or CH_3;

(c) R^{3a} is H and R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2OH, CH_2((4'-OH)-Ph), or lower cycloalkyl;

(d) R^4 is hydrogen, CH_3, Et, ^{i}Pr, ^{n}Pr, ^{n}Bu, 2-butyl, ^{t}Bu, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl;

(e) R^5 is H or N_3;

(f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, F, CN, vinyl or ethynyl;

(g) X is H, OH, OCH_3, CN, F, Cl, Br, I, NH_2, or N_3;

(h) Y is OH;

(i) R^9 is NH_2 and R^8 is H, F, Br, I, OH, OR', NH_2, NHR', NR'$_2$, nitrogen heterocycle, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$;

(j) Z is N or CR^{10}; and

(k) R^{10} is an H, F, Cl, Br, I, OR', NH_2, NHR', NR'_2, or lower alkyl of C_1-C_6, or –C≡CH;

wherein R' is a lower alkyl, a lower cycloalkyl, a lower alkaryl, or a C(O)(lower alkyl).

A seventh aspect of the first embodiment is directed to compound **I**,

wherein

(a) R^1 is hydrogen, phenyl, p-tolyl, p-bromo-phenyl, or p-chloro-phenyl;

(b) R^2 is hydrogen or CH_3;

(c) R^{3a} is H and R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2OH, or lower cycloalkyl;

(d) R^4 is hydrogen, CH_3, Et, ^{i}Pr, ^{n}Pr, ^{n}Bu, 2-butyl, ^{t}Bu, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl;

(e) R^5 is H of N_3;

(f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, F, CN, vinyl or ethynyl;

(g) X is H, OH, OCH_3, CN, F, Cl, Br, or N_3;

(h) Y is OH;

(i) R^9 is NH_2 and R^8 is H, F, OH, O(lower alkyl), O(lower alkyaryl), NH_2, NHR', NR'_2, or nitrogen heterocycle; and

(j) Z is N;

wherein R' is a lower alkyl, a lower cycloalkyl, a lower alkaryl, or a C(O)(lower alkyl).

An eighth aspect of the first embodiment is directed to compound **I**,

wherein

(a) R^1 is hydrogen, phenyl, p-bromo-phenyl, p-chloro-phenyl, or p-fluorophenyl;

(b) R^2 is hydrogen;

(c) R^{3a} is H and R^{3b} is H, CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, or $CH(CH_3)CH_2CH_3$;

(d) R^4 is hydrogen, CH_3, Et, ^{i}Pr, ^{n}Pr, ^{n}Bu, 2-butyl, or cyclopentyl;

(e) R^5 is H or N_3;

(f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, F, CN, vinyl, or ethynyl;

(g) X is H, OH, CN, F, or N_3;

(h) Y is OH;

(i) R^9 is NH_2 and R^8 is H, F, OH, O(lower alkyl), O(lower alkaryl), NH_2, NHR', NR'$_2$, or nitrogen heterocycle; and

(j) Z is N;

wherein R' is a lower alkyl, a lower cycloalkyl, a lower alkaryl, or a C(O)(lower alkyl).

A ninth aspect of the first embodiment is directed to compound **I**

wherein

(a) R^1 is hydrogen, phenyl, p-bromo-phenyl, p-chloro-phenyl, or p-fluorophenyl;

(b) R^2 is hydrogen;

(c) R^{3a} is H and R^{3b} is H, CH_3, $CH(CH_3)_2$, or $CH_2CH(CH_3)_2$;

(d) R^4 is hydrogen, CH_3, Et, ^{i}Pr, ^{n}Pr, ^{n}Bu, 2-butyl, or cyclopentyl;

(e) R^5 is H;

(f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, F, CN, vinyl, or ethynyl;

(g) X is H, OH, CN, F, or N_3;

(h) Y is OH;

(i) R^9 is NH_2 and R^8 is H, F, OH, O(lower alkyl), O(lower alkaryl), NH_2, NHR', NR'$_2$, or nitrogen heterocycle; and

(j) Z is N;

wherein R' is a lower alkyl, a lower cycloalkyl, a lower alkaryl, or a C(O)(lower alkyl).

A tenth aspect of the first embodiment is directed to compound **I** wherein (a) R^1 is hydrogen, phenyl, p-bromo-phenyl, p-chloro-phenyl, or p-fluorophenyl; (b) R^2 is hydrogen; (c) R^{3a} is H and R^{3b} is CH_3; (d) R^4 is hydrogen, CH_3, ^{i}Pr, or cyclopentyl; (e) R^5 is H; (f) R^6 is CH_3; (g) X is F; (h) Y is OH; (i) R^8 is independently OH, OMe, OEt, O^{i}Pr, OBn, or–N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), and R^9 is NH_2; (j) Z is N.

An eleventh aspect of the first embodiment is directed to compound **I** wherein (a) R^1 is phenyl; (b) R^2 is hydrogen; (c) R^{3a} is H and R^{3b} is CH_3;(d) R^4 is ^{i}Pr; (e) R^5 is H; (f) R^6 is CH_3; (g) X is F; (h) Y is OH; R^8 is OMe; and (j) Z is N.

A twelfth aspect of the first embodiment is directed to compound **I** wherein (a) R^1 is phenyl; (b) R^2 is hydrogen; (c) R^{3a} is H and R^{3b} is CH_3;(d) R^4 is ^{i}Pr; (e) R^5 is H; (f) R^6 is CH_3; (g) X is F; (h) Y is OH; R^8 is OEt; and (j) Z is N.

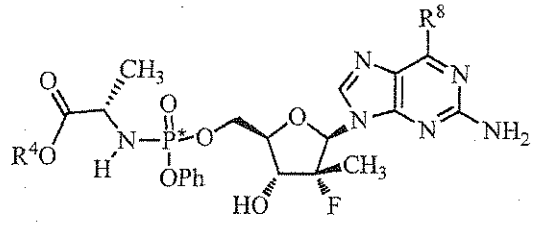
A thirteenth aspect of the first embodiment is directed to compound **I** wherein (a) R^1 is phenyl; (b) R^2 is hydrogen; (c) R^{3a} is H and R^{3b} is CH_3;(d) R^4 is ^{i}Pr; (e) R^5 is H; (f) R^6 is CH_3; (g) X is F; (h) Y is OH; R^8 is O^{i}Pr; and (j) Z is N.

A fourteenth aspect of the first embodiment is directed to compound **I** wherein (a) R^1 is phenyl; (b) R^2 is hydrogen; (c) R^{3a} is H and R^{3b} is CH_3;(d) R^4 is CH_3; (e) R^5 is H; (f) R^6 is CH_3; (g) X is F; (h) Y is OH; R^8 is –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), and R^9 is NH_2; and (j) Z is N.

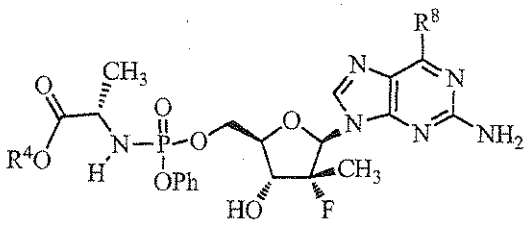
A fifteenth aspect of the first embodiment is directed to compound I wherein (a) R^1 is phenyl; (b) R^2 is hydrogen; (c) R^{3a} is H and R^{3b} is CH_3;(d) R^4 is cyclopentyl; (e) R^5 is H; (f) R^6 is CH_3; (g) X is F; (h) Y is OH; R^8 is independently OBn; and R^9 is NH_2; and (j) Z is N.

A sixteenth aspect of the first embodiment is directed to compound I wherein (a) R^1 is phenyl; (b) R^2 is hydrogen; (c) R^{3a} is H and R^{3b} is CH_3;(d) R^4 is cyclopentyl; (e) R^5 is H; (f) R^6 is CH_3; (g) X is F; (h) Y is OH; R^8 is OH and R^9 is NH_2; and (j) Z is N.

Preferred compounds of the first embodiment include compounds represented by the following structure:



where R^4 is a lower alkyl and R^8 is a O(lower alkyl). Additionally preferred compounds include:



11: $R^4 = {}^i$Pr, R^8 = -OMe
11a: $R^4 = {}^i$Pr, R^8 = -OEt
11b: $R^4 = {}^i$Pr, R^8 = -O^{i}Pr
12: R^4 = Me. R^8 = -N(-$CH_2CH_2CH_2$-)
13: $R^4 = {}^c$Pn, R^8 = -OBn
14: $R^4 = {}^c$Pn, R^8 = -OH

R^8 = N(-$CH_2CH_2CH_2$-) = 

Of the preferred compounds, compound **11** is particularly preferred. One of ordinary skill will recognize that **11** comprises a mixture of diastereomers designated S_P-**11** and R_P-**11**. Contemplated herein is a composition that comprises S_P-**11**, R_P-**11**, or mixtures thereof.

The composition that comprises S_P-**11**, R_P-**11**, or mixtures thereof can also be part of a solvate, a hydrate, or a mixed solvate/hydrate. The solvate is designated as S_P-**11**·n*S*, R_P-**11**·n*S*, or **11**·n*S*; while the hydrate is designated as S_P-**11**·mH_2O, R_P-**11**·mH_2O, or **11**·mH_2O, where *S* is a lattice solvent, n varies by an integer or non-integer amount from about 0 to about 3 and m varies by an integer or non-integer amount from about 0 to about 5. The composition that comprises S_P-**11**, R_P-**11**, or mixtures thereof and its salts, solvates, and hydrates thereof is crystalline, crystal-like, or amorphous.

A second embodiment is directed to compound **II**,

wherein

(a) R^5 is H, a lower alkyl, cyano (CN), vinyl, O-(lower alkyl), including OCH_3, OCH_2CH_3, hydroxyl lower alkyl, i.e., -$(CH_2)_pOH$, where p is 1 -6, including hydroxyl methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHCH_3, $CH_2N(CH_3)_2$, F, Cl, Br, or I

(b) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, F, vinyl, or ethynyl;

(c) R^7 is H, n-alkyl, branched alkyl, cycloalkyl, alkaryl, alkenyl, or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of H, F, Cl, Br, I, OH, $OR^{7'}$, SH, $SR^{7'}$, NH_2, $NHR^{7'}$, $NR^{7'}{}_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I), halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, $CO_2R^{7'}$, $CONH_2$, $CONHR^{7'}$, $CONR^{7'}{}_2$, CH=$CHCO_2H$, or CH=$CHCO_2R^{7'}$ wherein $R^{7'}$ is an optionally substituted alkyl, cycloalkyl, alkenyl, alkynyl, or alkoxyalkyl, which includes, but is not limited to, $C_{1\text{-}10}$ alkyl, $C_{3\text{-}7}$ cycloalkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, or $C_{1\text{-}10}$ alkoxyalkyl;

(d) X is H, OH, F, OMe, NH_2, or N_3;

(e) R^8 and R^9 are independently H, F, Cl, Br, I, OH, OR', SH, SR', NH_2, NHR', NR'$_2$, nitrogen heterocycle, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2H, CO_2CH_3, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$,

(f) Z is N or CR^{10}; and

(g) R^{10} is an H, halogen (including F, Cl, Br, I), OH, OR', SH, SR', NH_2, NHR', NR'_2, NO_2 lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, lower alkenyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6 , lower alkynyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, CO_2R', $CONH_2$, CONHR', $CONR'_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$

wherein R' is a C_{1-20} alkyl; a C_{1-20} cycloalkyl; an alkaryl, a C_2-C_6 alkenyl, a C_2-C_6 alkynyl.

A first aspect of the second embodiment is directed to compound **II**,

wherein

(a) R^5 is H, a lower alkyl, cyano (CN), vinyl, O-(lower alkyl), including OCH_3, OCH_2CH_3, hydroxyl lower alkyl, i.e., $-(CH_2)_pOH$, where p is 1 -6, including hydroxyl methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHCH_3, $CH_2N(CH_3)_2$, F, Cl, Br, or I

(b) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or F;

(c) R^7 is H, n-alkyl, branched alkyl, cycloalkyl, alkaryl, alkenyl, or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of H, F, Cl, Br, I, OH, $OR^{7'}$, SH, $SR^{7'}$, NH_2, $NHR^{7'}$, $NR^{7'}_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I), halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, $CO_2R^{7'}$, $CONH_2$, $CONHR^{7'}$, $CONR^{7'}_2$, $CH=CHCO_2H$, or $CH=CHCO_2R^{7'}$ wherein $R^{7'}$ is an optionally substituted alkyl, cycloalkyl, alkenyl, alkynyl, or alkoxyalkyl, which includes, but is not limited to, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or C_{1-10} alkoxyalkyl;

(d) X is H, OH, F, OMe, NH_2, or N_3;

(e) R^8 and R^9 are independently H, F, Cl, Br, I, OH, OR', SH, SR', NH_2, NHR', NR'$_2$, nitrogen heterocycle, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2H, CO_2CH_3, $CONH_2$, $CONHCH_3$, or $CON(CH_3)_2$,

(f) Z is N or CR^{10}; and

(g) R^{10} is an H, F, OH, OR', NH_2, NHR', NR'$_2$, NR"$_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, or –C≡CH;

wherein R' is a C_{1-20} alkyl; a C_{1-20} cycloalkyl; an alkaryl, a C_2-C_6 alkenyl, a C_2-C_6 alkynyl.

A second aspect of the second embodiment is directed to compound **II**,

wherein

(a) R^5 is H, a lower alkyl, cyano (CN), vinyl, O-(lower alkyl), including OCH_3, OCH_2CH_3, hydroxyl lower alkyl, i.e., $-(CH_2)_pOH$, where p is 1 -6, including hydroxyl methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHCH_3, $CH_2N(CH_3)_2$, F, Cl, Br, or I

(b) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, or CH_2CH_3;

(c) R^7 is H, n-alkyl, branched alkyl, cycloalkyl, alkaryl, alkenyl, or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of H, F, Cl, Br, I, OH, $OR^{7'}$, SH, $SR^{7'}$, NH_2, $NHR^{7'}$, $NR^{7'}_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I), halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, $CO_2R^{7'}$, $CONH_2$, $CONHR^{7'}$, $CONR^{7'}_2$, $CH=CHCO_2H$, or $CH=CHCO_2R^{7'}$ wherein $R^{7'}$ is an optionally substituted alkyl, cycloalkyl, alkenyl, alkynyl, or alkoxyalkyl, which includes, but is not limited to, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or C_{1-10} alkoxyalkyl;

(d) X is H, OH, F, OMe, NH_2, or N_3;

(e) R^8 and R^9 are independently H, F, Br, OH, OR', NH_2, NHR', NR'$_2$, nitrogen heterocycle, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2CH_3, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$;

(f) Z is N or CR^{10}; and

(g) R^{10} is an H, F, OH, OR', NH_2, NHR', NR'$_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, or –C≡CH;

wherein R' is a C_{1-20} alkyl; a C_{1-20} cycloalkyl; an alkaryl, a C_2-C_6 alkenyl, a C_2-C_6 alkynyl.

A third aspect of the second embodiment is directed to compound **II**,

wherein

(a) R^5 is H, a lower alkyl, cyano (CN), vinyl, O-(lower alkyl), including OCH_3, OCH_2CH_3, hydroxyl lower alkyl, i.e., $-(CH_2)_pOH$, where p is 1 -6, including hydroxyl methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHCH_3, $CH_2N(CH_3)_2$, F, Cl, Br, or I

(b) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, or CH_2CH_3;

(c) R^7 is H, n-alkyl, branched alkyl, cycloalkyl, alkaryl, alkenyl, or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of H, F, Cl, Br, I, OH, $OR^{7'}$, SH, $SR^{7'}$, NH_2, $NHR^{7'}$, $NR^{7'}_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I), halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, $CO_2R^{7'}$, $CONH_2$, $CONHR^{7'}$, $CONR^{7'}_2$, CH=$CHCO_2H$, or CH=$CHCO_2R^{7'}$ wherein $R^{7'}$ is an optionally substituted alkyl, cycloalkyl, alkenyl, alkynyl, or alkoxyalkyl, which includes, but is not limited to, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or C_{1-10} alkoxyalkyl;

(d) X is F;

(e) R^8 and R^9 are independently H, F, Br, OH, OR', NH_2, NHR', NR'_2, nitrogen heterocycle, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2CH_3, $CONH_2$, $CONHCH_3$, or CON $(CH_3)_2$;

(f) Z is N or CR^{10}; and

(g) R^{10} is an H, F, OH, OR', NH_2, NHR', NR'_2, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, or –C≡CH;

wherein R' is a lower alkyl; a lower cycloalkyl; a lower alkaryl, a C_2-C_6 alkenyl, a C_2-C_6 alkynyl.

A fourth aspect of the second embodiment is directed to compound **II**,

wherein

(a) R^5 is H, -CH_3, cyano (CN), vinyl, -OCH_3, -CH_2OH, -CH_2F, azido (N_3), CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHCH_3, $CH_2N(CH_3)_2$, F, Cl, Br, or I

(b) R^6 is H, CH_3, or CH_2CH_3;

(c) R^7 is H, n-alkyl, branched alkyl, cycloalkyl, alkaryl, alkenyl, or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of H, F, Cl, Br, I, OH, $OR^{7'}$, SH, $SR^{7'}$, NH_2, $NHR^{7'}$, $NR^{7'}_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I), halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, $CO_2R^{7'}$, $CONH_2$, $CONHR^{7'}$, $CONR^{7'}_2$, $CH{=}CHCO_2H$, or $CH{=}CHCO_2R^{7'}$ wherein $R^{7'}$ is an optionally substituted alkyl, cycloalkyl, alkenyl, alkynyl, or alkoxyalkyl, which includes, but is not limited to, $C_{1\text{-}10}$ alkyl, $C_{3\text{-}7}$ cycloalkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, or $C_{1\text{-}10}$ alkoxyalkyl;

(d) X is F;

(e) R^8 and R^9 are independently H, F, OH, OR', SH, SCH_3, NH_2, NHR', NR'_2, nitrogen heterocycle, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2H, CO_2CH_3, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$;

(f) Z is N or CR^{10}; and

(g) R^{10} is an H, F, OH, OR', NH_2, NHR', NR'_2, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, or –C≡CH;

wherein R' is a lower alkyl; a lower cycloalkyl; a lower alkaryl, a C_2-C_6 alkenyl, a C_2-C_6 alkynyl.

A fifth aspect of the second embodiment is directed to compound **II**,

wherein

(a) R^5 is H, -CH_3, cyano (CN), vinyl, -OCH_3, -CH_2OH, -CH_2F, azido (N_3), CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHCH_3, $CH_2N(CH_3)_2$, F, Cl, Br, or I

(b) R^6 is H or CH_3;

(c) R^7 is H, lower alkyl, lower alkylaryl, lower cycloalkyl, lower alkenyl, or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of H, F, Cl, Br, I, OH, $OR^{7'}$, SH, $SR^{7'}$, NH_2, $NHR^{7'}$, $NR^{7'}_2$, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, wherein $R^{7'}$ is an optionally substituted alkyl, cycloalkyl, alkenyl, alkynyl, or alkoxyalkyl, which includes, but is not limited to, $C_{1\text{-}10}$ alkyl, $C_{3\text{-}7}$ cycloalkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, or $C_{1\text{-}10}$ alkoxyalkyl;

(d) X is F;

(e) R^8 and R^9 are independently H, F, OH, OR', NH_2, NHR', NR'_2, nitrogen heterocycle, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2H, CO_2CH_3, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$;

(f) Z is N or CR^{10}; and

(g) R^{10} is an H, F, OH, OR', NH_2, NHR', NR'_2, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, or –C≡CH;

wherein R' is a lower alkyl; a lower cycloalkyl; a lower alkaryl, a C_2-C_6 alkenyl, a C_2-C_6 alkynyl.

A sixth aspect of the second embodiment is directed to compound **II**,

wherein

(a) R^5 is H or N_3;

(b) R^6 is H, CH_3, or CH_2CH_3;

(c) R^7 is H, lower alkyl, lower alkylaryl, lower cycloalkyl, lower alkenyl, or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of H, F, Cl, Br, I, OH, $OR^{7'}$, SH, $SR^{7'}$, NH_2, $NHR^{7'}$, $NR^{7'}_2$, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, wherein $R^{7'}$ is an optionally substituted alkyl, cycloalkyl, alkenyl, alkynyl, or alkoxyalkyl, which includes, but is not limited to, $C_{1\text{-}10}$ alkyl, $C_{3\text{-}7}$ cycloalkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, or $C_{1\text{-}10}$ alkoxyalkyl;

(d) X is F;

(e) R^8 and R^9 are independently H, F, OH, OR', NH_2, NHR', NR'_2, nitrogen heterocycle, CH_3, $CH_{3-q}X_q$, where X is F, Cl, Br, or I and q is 1 to 3, vinyl, CO_2H, CO_2CH_3, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$,

(f) Z is N or CR^{10}; and

(g) R^{10} is an H, F, OH, OR', NH_2, NHR', NR'_2, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, or $-C{\equiv}CH$;

wherein R' is a lower alkyl; a lower cycloalkyl; a lower alkaryl, a C_2-C_6 alkenyl, a C_2-C_6 alkynyl.

A seventh aspect of the second embodiment is directed to compound II, wherein (a) R^5 is H; (b) R^6 is H, CH_3, or CH_2CH_3; (c) R^7 is lower alkyl or lower cycloalkyl; (d) X is F; (e) R^8 and R^9 are independently H, F, OH, OR', NH_2, NHR', NR'_2, nitrogen heterocycle, and (f) Z is N; wherein R' is a lower alkyl; a lower cycloalkyl; a lower alkaryl, a C_2-C_6 alkenyl, a C_2-C_6 alkynyl.

An eighth aspect of the second embodiment is directed to compound II, wherein (a) R^5 is H; (b) R^6 is H, CH_3, or CH_2CH_3; (c) R^7 is lower alkyl or

lower cycloalkyl; (d) X is F; (e) R^9 is NH_2 and R^8 OH, OR', or nitrogen heterocycle, and (f) Z is N; wherein R' is a lower alkyl; a lower cycloalkyl; a lower alkaryl, a C_2-C_6 alkenyl, a C_2-C_6 alkynyl.

A ninth aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is H, CH_3, or CH_2CH_3; (c) R^7 is lower alkyl or lower cycloalkyl; (d) X is F; (e)R^9 is NH_2 and R^8 is O(lower alkyl), O(lower cycloalkyl), or nitrogen heterocycle; and (f) Z is N.

A tenth aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is is lower alkyl or lower cycloalkyl; (d) X is F; (e) R^9 is NH_2 and R^8 is O(lower alkyl), O(lower cycloalkyl), or nitrogen heterocycle; and (f) Z is N.

An eleventh aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is is lower alkyl or lower cycloalkyl; (d) X is F; (e) R^9 is NH_2 and R^8 is O(lower alkyl), O(lower cycloalkyl) or –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and (f) Z is N.

A twelfth aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is CH_3, ^{i}Pr, ^{c}Bu, or ^{c}Pn; (d) X is F; (e) R^9 is NH_2 and R^8 is O(lower alkyl) or –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and (f) Z is N.

A thirteenth aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is CH_3, ^{i}Pr, ^{c}Bu, or ^{c}Pn; (d) X is F; (e) R^9 is NH_2 and R^8 is OMe, OEt, O^{i}Pr, or –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and (f) Z is N.

A fourteenth aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is CH_3, ^{i}Pr, ^{c}Bu, or ^{c}Pn; (d) X is F; (e) R^9 is NH_2 and R^8 is OMe, OEt, or O^{i}Pr; and (f) Z is N.

A fifteenth aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is CH_3, ^{i}Pr, ^{c}Bu, or ^{c}Pn; (d) X is F; (e) R^8 is OMe and R^9 is NH_2; and (f) Z is N.

A sixteenth aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is CH_3, ^{i}Pr, ^{c}Bu, or ^{c}Pn; (d) X is F; (e) R^8 is OEt and R^9 is NH_2; and (f) Z is N.

A seventeenth aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is CH_3, ^{i}Pr, ^{c}Bu, or ^{c}Pn; (d) X is F; (e) R^8 is O^{i}Pr and R^9 is NH_2; and (f) Z is N.

An eighteenth aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is CH_3; (d) X is F; (e) R^8 is –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and R^9 is NH_2; and (f) Z is N.

A nineteenth aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is CH_3; (d) X is F; (e) R^8 is OEt and R^9 is NH_2; and (f) Z is N.

A twentieth aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is ^{i}Pr; (d) X is F; (e) R^8 is OEt and R^9 is NH_2; and (f) Z is N.

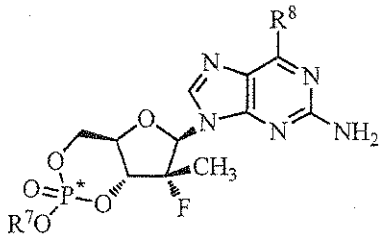
A twenty-first aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is ^{c}Bu; (d) X is F; (e) R^8 is OMe and R^9 is NH_2; and (f) Z is N.

A twenty-second aspect of the second embodiment is directed to a compound **II** wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is ^{c}Pn; (d) X is F; (e) R^8 is OMe and R^9 is NH_2; and (f) Z is N.

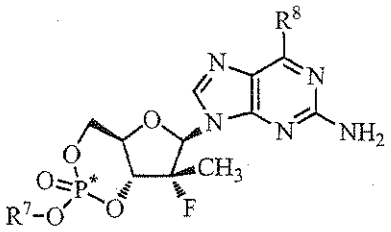
A twenty-third aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is ^{c}Bu; (d) X is F; (e) R^8 is OEt and R^9 is NH_2; and (f) Z is N.

A twenty-fourth aspect of the second embodiment is directed to compound **II**, wherein (a) R^5 is H; (b) R^6 is CH_3; (c) R^7 is ^{c}Pn; (d) X is F; (e) R^8 is OEt and R^9 is NH_2; and (f) Z is N.

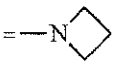
Preferred compounds to be prepared by way of the second embodiment, or by another suitable process, include compounds represented by the following structure



where R^7 is a lower alkyl or a lower cycloalkyl and R^8 is an O(lower alkyl). Additionally preferred compounds include:



15: R^7 = Me, R^8 = -N(-$CH_2CH_2CH_2$-)
16: R^7 = Me, R^8 = -OEt
17: R^7 = ^{i}Pr, R^8 = -OEt
23: R^7 = ^{c}Bu, R^8 = -OMe
24: R^7 = ^{c}Pn, R^8 = -OMe

R^8 = N(-$CH_2CH_2CH_2$-) = 

Of these preferred compounds, **17** is particularly preferred. One of ordinary skill will recognize that **17** comprises a mixture of diastereomers designated as R_P-**17** and S_P-**17**. Contemplated herein is a composition that comprises S_P-**17**, R_P-**17**, or mixtures thereof. It is preferred that the composition comprises purified R_P-**17**. It is further preferred that the composition comprises substantially pure R_P-**17**.

The composition that comprises S_P-**17**, R_P-**17**, or mixtures thereof can also be part of a solvate, a hydrate, or a mixed solvate/hydrate. The solvate is designated as S_P-**17**·n*S*, R_P-**17**·n*S*, or **17**·n*S*; while the hydrate is designated as S_P-**17**·mH_2O, R_P-**17**·mH_2O, or **17**·mH_2O, where *S* is a lattice solvent, n varies by an integer or non-integer amount from about 0 to about 3 and m varies by an integer or non-integer amount from about 0 to about 5. The composition that comprises S_P-**17**, R_P-**17**, or mixtures thereof and its salts, solvates, and hydrates thereof is crystalline, crystal-like, or amorphous.

A first aspect of the preferred compounds of formula **II** is directed to crystalline *R*P-**17**.

A second aspect of the preferred compounds of formula **II** directed to crystalline *R*P-**17** having an XRD 2θ-reflections (°) at about 12.2.

A third aspect of the preferred compounds of formula **II** directed to crystalline *R*P-**17** having XRD 2θ-reflections (°) at about 12.2, 14.3, 15.5, and 19.9.

A fourth aspect of the preferred compounds of formula **II** directed to crystalline *R*P-**17** having XRD 2θ-reflections (°) at about 12.2, 14.3, 15.5, 17.4, 18.1, 19.9, 22.8, 23.6, 24.5, 25.1, and 27.35.

A fifth aspect of the preferred compounds of formula **II** directed to crystalline *R*P-**17** having an XRD diffraction pattern substantially as that shown in Fig. 1.

A sixth aspect of the preferred compounds of formula II directed to orthorhombic, crystalline *R*P-**17**.

A sixth aspect of the preferred compounds of formula **II** directed to crystalline *R*P-**17** having orthorhombic ($P2_12_12_1$) unit cell parameters of a ~ 11.4 Å, b ~ 12.4 Å, and c ~ 14.2 Å.

A seventh aspect of the preferred compounds of formula **II** directed to crystalline *R*P-**17** having the following FT-IR peaks (cm^{-1}): ~1581, ~1295, ~1065, ~999, ~798, and ~79`.

An eighth aspect of the preferred compounds of formula **II** is directed to crystalline *R*P-**17** having an FT-IR spectrum substantially as that shown in Fig. 2.

A ninth aspect of the preferred compounds of formula **II** is directed to substantially pure *R*P-**17**.

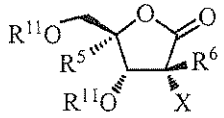
A tenth aspect of the preferred compounds of formula **II** is directed to substantially pure, crystalline *R*P-**17**.

An eleventh aspect of the preferred compounds of formula **II** is directed to substantially pure, crystal-like *R*P-**17**.

A twelfth aspect of the preferred compounds of formula **II** is directed to substantially pure, amorphous *R*P-**17**.

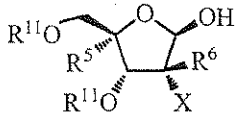
A third embodiment is directed to a process for preparing compound **I** or compound **II** or any of the compounds recited in any one of the aspects of the first and second embodiments, wherein said process comprises:

(a) stereoselective reduction of a protected ribonolactone **III** using a hydride reducing agent



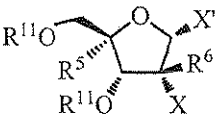
III

to provide a beta-lactol derivative **IV**; and



IV

(b) stereoselective conversion of the lactol derivative using a reagent to obtain an anomeric alpha-derivative **V**



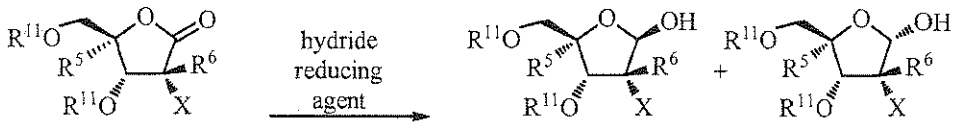
V ,

wherein R^5, R^6, and X have their meanings as described above, X' is a leaving group, and R^{11} is a protecting group.

A first aspect of the third embodiment directed to a process for preparing a compound **I** or compound **II** or any of the compounds recited in any one of the aspects of the first and second embodiments, wherein for the compound **III** or the compound **IV**, R^{11} is benzoyl or substituted benzoyl (preferably R^{11} is 4-chloro-benzoyl), R^5 is H, R^6 is CH_3, and X is F. The hydride reducing agent is $(^tBuO)_3AlH$, sodium (bis(2-methoxyethoxy)(2,2,2-trifluoro-ethoxy)aluminum hydride, or Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride). The stereoselective reduction can be performed in a solvent comprising tetrahydrofuran (THF) or diethyl ether, preferably the solvent is THF at a temperature ranging from about (-78°C) to about 25°C, preferably at a temperature ranging from about (-78°C) to about 0°C, and most preferably at a temperature from about (-30°C) to about 0°C.

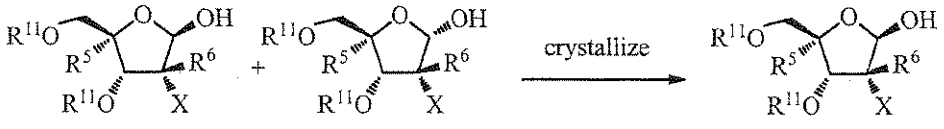
A second aspect of the third embodiment is directed to a process for preparing a compound **I** or a compound **II** or any of the compounds recited in any

one of the aspects of the first and second embodiments, said process comprising stereoselective reduction of a protected ribonolactone **III** using a hydride reducing agent to provide a mixture comprising a beta-lactol derivative **IV** and an alpha-lactol derivative **IV-α**:



III **IV** **IV-α**

and crystallizing the beta-lactol derivative **IV** from the mixture comprising the beta-lactol derivative and the alpha-lactol derivative



IV **IV-α** **IV**

wherein R^5, R^6, and X have the meanings as defined herein above and R^{11} is a protecting group.

A third aspect of the third embodiment is directed to a process for preparing a compound **I** or a compound **II** or any of the compounds recited in any one of the aspects of the first and second embodiments, wherein for the compound **III**, the compound **IV**, or the compound **IV-α**, R^5 is H, R^6 is CH_3, R^{11} is benzoyl or a substituted benzoyl (preferably R^{11} is 4-chloro-benzoyl), and X is F. The hydride reducing agent is $(^tBuO)_3AlH$, sodium (bis(2-methoxyethoxy)(2,2,2-trifluoro-ethoxy)aluminum hydride, or Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride). The stereoselective reduction can be performed in a solvent comprising tetrahydrofuran (THF) or diethyl ether, preferably the solvent is THF at a temperature ranging from about (-78°C) to about 25°C, preferably at a temperature ranging from about (-78°C) to about 0°C, and most preferably at a temperature from about (-30°C) to about 0°C. The crystallization occurs by a process comprising adding to the mixture seed crystals of the beta-lactol derivative and then heating the mixture comprising the seed crystals of the beta-lactol derivative at a temperature

that ranges from about 25°C to about 80°C, preferably about 50°C with (about 0.2 mmHg) or without applied vacuum.

A fourth aspect of the third embodiment is directed to a process for preparing a compound **I** or a compound **II** or any of the compounds recited in any one of the aspects of the first and second embodiments, comprising stereoselective conversion of a lactol derivative **IV** using a reagent to obtain an anomeric alpha-derivative **V**

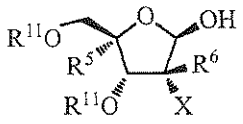


IV V

wherein R^5, R^6, and X, have the meanings as defined herein above, R^{11} is a protecting group and X' is a leaving group.

A fifth aspect of the third embodiment is directed to a process for preparing a compound **I** or a compound **II** or any of the compounds recited in any one of the aspects of the first and second embodiments, wherein for the compound **IV** or the compound **V**, R^5 is H, R^6 is CH_3, R^{11} is benzoyl or a substituted benzoyl (preferably R^{11} is 4-chloro-benzoyl), X is F, and X" is Br. The reagent is defined as above. Preferably, the reagent is at least one of Ph_3P/CBr_4, $Ph_3P/CHBr_3$, $Ph_3P/CHBr_3$/imidazole, Ph_3P/Br_2, Ph_3P/Br_2/imidazole, N-bromosuccinimide/ Ph_3P, HBr in acetic acid, PBr_3/DMF, PBr_3/sodium bicarbonate, PBr_3/imidazole, PBr_5/DMF, PBr_5/sodium bicarbonate, PBr_5/imidazole, and $POBr_3$/imidazole. More preferably, the reagent is Ph_3P/CBr_4. The stereoselective conversion can be performed in the presence of certain solvents, which include, but are not limited to, CH_2Cl_2, 1,2-dichloroethane, toluene, chlorobenzene, tetrahydrofuran, dioxane, diethyl ether, dimethylformamide, acetonitrile, N-methylpyrrolidine, dimethoxyethane, preferably the solvent used is CH_2Cl_2. The stereoselective conversion can be performed at a temperature that ranges from about (-78°C) to about 0°C. Preferably, the temperature ranges from about (-78°C) to about (-10°C). Most preferably, the temperature ranges from about (-30°C) to about (-10°C).

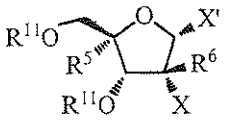
A fourth embodiment is directed to a compound **IV**.



IV

wherein R^5, R^6, and X have the meanings as defined herein above and R^{11} is a protecting group. Preferably, R^5 is H, R^6 is CH_3, R^{11} is a protecting group, preferably R^{11} is is benzoyl or a substituted benzoyl and more preferably R^{11} is 4-chloro-benzoyl, and X is F, preferably R^{11} is 4-chloro-benzoyl. The compound **IV** can be purified or unpurified. The compound **IV** is useful for preparing compound **I** and compound **II**.

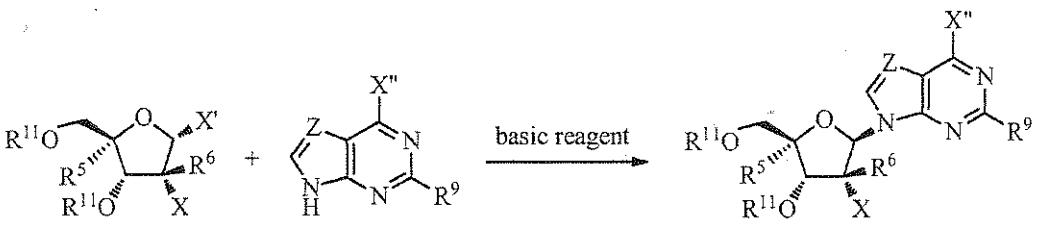
A fifth embodiment is directed to a compound **V**.



V

wherein R^5, R^6, R^{11}, X, and X' have the meanings set forth above. Preferably, R^5 is H, R^6 is CH_3, R^{11} is a protecting group, preferably R^{11} is is benzoyl or a substituted benzoyl and more preferably R^{11} is 4-chloro-benzoyl, X is F, and X' is Cl, Br, or I (most preferably X' is Br). The compound **V** can be purified or unpurified. The compound **V** is useful for preparing a compound **I** and a compound **II**.

An sixth embodiment is directed to a process for preparing a compound **I** or a compound **II** or any of the compounds recited in any one of the aspects of the first and second embodiments, comprising stereoselective coupling of an alpha-derivative **V** with a purine or a derivatized purine base using a basic reagent to produce a beta-nucleoside **VI**

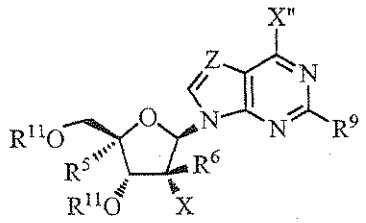


V VI

wherein R^5, R^6, R^9 X, and Z have the meanings as defined herein above R^{11} is a protecting group, X' and X" independent of each other are leaving groups.

A first aspect of the sixth embodiment is directed to a process for preparing a compound **I** or a compound **II** or any of the compounds recited in any one of the aspects of the first and second embodiments, wherein for the compound **V** or the compound **VI**, R^5 is H, R^6 is CH_3, R^9 is NH_2, R^{11} is a protecting group, preferably R^{11} is is benzoyl or a substituted benzoyl and more preferably R^{11} is 4-chloro-benzoyl, X is F, X' is Br, X" is Cl, and Z is N. The basic reagent is as defined above. Preferably, the basic reagent comprises a (lower alk)oxide ((lower alkyl)OM) and an alcoholic solvent. Preferably, the basic reagent is MeONa/MeOH, EtONa/EtOH, or ^{t}BuOK/^{t}BuOH. Most preferably, the basic reagent is ^{t}BuOK/^{t}BuOH. The stereoselective coupling can be performed in a solvent comprising at least one of a polar aprotic solvent, a non-polar solvent, and a polar solvent. Examples of polar aprotic solvents include, but are not limited to, acetonitrile, dimethylsulfoxide, N,N-dimethylformamide, hexamethylphosphoramide, etc. The stereoselective coupling can be performed at a temperature that ranges from about 0°C up to about the reflux temperature of the solvent. Preferably, the temperature ranges from about 25°C to about 75°C. More preferably, the temperature ranges from about 40°C to about 60°C. Most preferably, the temperature is about 50°C.

A seventh embodiment is directed to a compound **VI**.

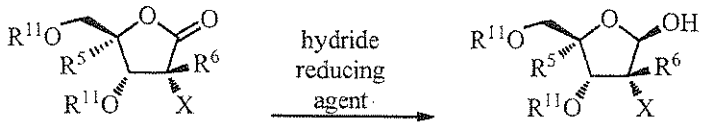


VI

wherein R^5, R^6, R^9 X, and Z have the meanings as defined herein above R^{11} is a protecting group, X" is a leaving group. Preferably, R^{11} is benzoyl or a substituted benzoyl, more preferably R^{11} is 4-chloro-benzoyl, R^5 is H, R^6 is CH_3, X is F, X" is Cl, R^9 is NH_2, and Z is N. Compound **VI** can be purified or unpurified. Compound **VI** is useful for preparing compound **I** and compound **II**.

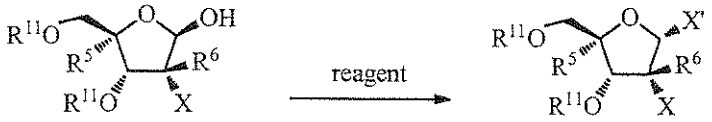
A first aspect of the seventh embodiment is directed to a process for preparing compound **VI**, wherein said process comprises:

(a) stereoselective reduction of a protected ribonolactone **III** using a hydride reducing agent to provide a beta-lactol derivative **IV**; and



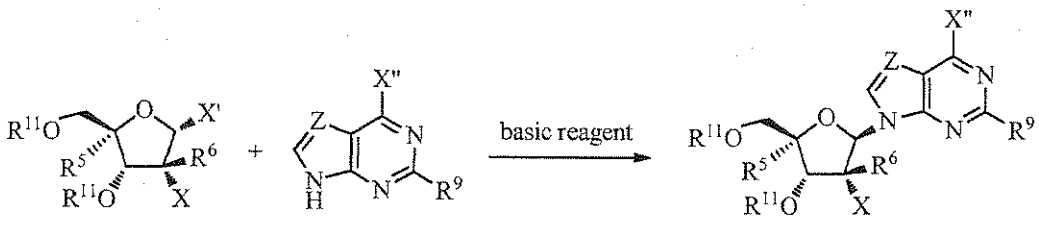
III **IV**

(b) stereoselective conversion of the lactol derivative using a reagent to obtain an anomeric alpha-derivative **V**



IV **V** , and

(c) stereoselective coupling of an alpha- derivative **V** with a purine or a derivatized purine base using a basic reagent to produce a beta-nucleoside **VI**



V **VI**

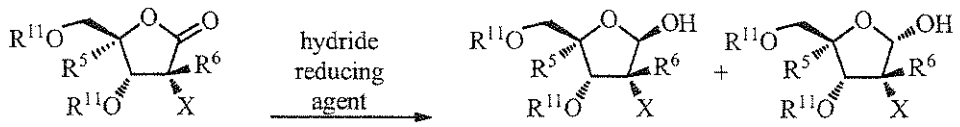
wherein R^5, R^6, R^9, and Z have the meanings as defined above, each of X' and X" independent of each other is a leaving group, and R^{11} is a protecting group.

A second aspect of the seventh embodiment is directed to a process for preparing compound **VI**, where R^5 is H, R^6 is CH_3, R^9 is NH_2, R^{11} is a protecting group, preferably R^{11} is benzoyl or a substituted benzoyl and more preferably R^{11} is 4-chloro-benzoyl, X is F, X' is Br, X" is Cl, and Z is N. The stereoselective reduction can be performed in a solvent comprising tetrahydrofuran (THF) or diethyl ether, preferably the solvent is THF at a temperature ranging from about (-78°C) to about 25°C, preferably at a temperature ranging from about (-78°C) to about 0°C, and most preferably at a temperature from about (-30°C) to about 0°C. The hydride reducing agent is $(^tBuO)_3AlH$, sodium (bis(2-methoxyethoxy)(2,2,2-trifluoro-ethoxy)aluminum hydride, or Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride). The stereoselective coupling can be performed in a solvent comprising at

least one of a polar aprotic solvent, a non-polar solvent, and a polar solvent. Examples of polar aprotic solvents include, but are not limited to, acetonitrile, dimethylsulfoxide, N,N-dimethylformamide, hexamethylphosphoramide, etc. The stereoselective coupling can be performed at a temperature that ranges from about 0°C up to about the reflux temperature of the solvent. Preferably, the temperature ranges from about 25°C to about 75°C. More preferably, the temperature ranges from about 40°C to about 60°C. Most preferably, the temperature is about 50°C. The basic reagent is as defined above. Preferably, the basic reagent comprises a (lower alk)oxide ((lower alkyl)OM) and an alcoholic solvent. Preferably, the basic reagent is MeONa/MeOH, EtONa/EtOH, EtOK/EtOH, ^{i}PrONa/^{i}PrOH, ^{i}PrOK/^{i}PrOH, or ^{t}BuOK/^{t}BuOH. Most preferably, the basic reagent is ^{t}BuOK/^{t}BuOH.

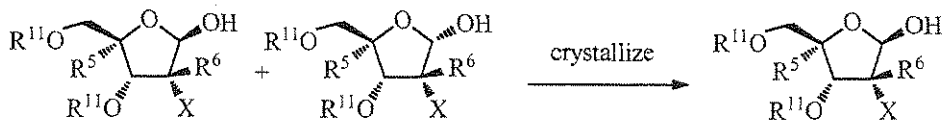
A third aspect of the seventh embodiment is directed to a process for preparing compound **VI** said process comprising:

(a) stereoselective reduction of a protected ribonolactone **III** using a hydride reducing agent to provide a mixture comprising a beta-lactol derivative **IV** and an alpha-lactol derivative **IV-α**:



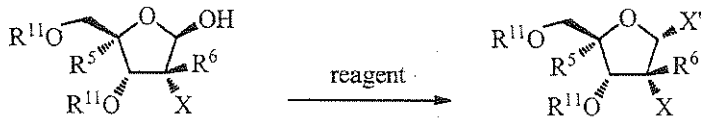
III IV IV-α

(b) crystallizing the beta-lactol derivative **IV** from the mixture comprising the beta-lactol derivative and the alpha-lactol derivative;



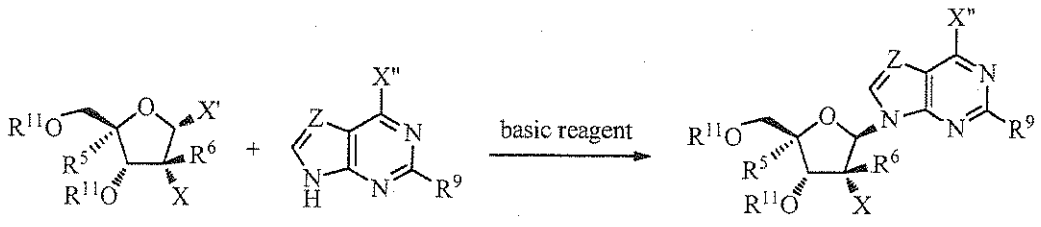
IV IV-α IV

(c) stereoselective conversion of the lactol derivative **IV** using a reagent to obtain an anomeric alpha-derivative **V**



IV V , and

(c) stereoselective coupling of an alpha- derivative **V** with a purine or a derivatized purine base using a basic reagent to produce a beta-nucleoside **VI**

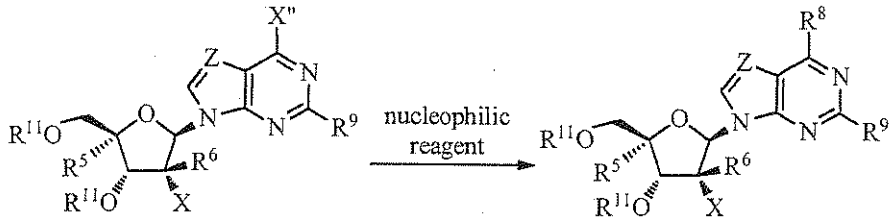


V VI

wherein R^5, R^6, R^9, X, and Z have the meanings as defined above, each of X' and X" independent of each other is a leaving group, and R^{11} is a protecting group. Preferably, R^5 is H, R^6 is CH_3, R^{11} is benzoyl or a substituted benzoyl (preferably R^{11} is 4-chloro-benzoyl), X is F, X' is Br, X" is Cl, Z is N, and R^9 is NH_2. The hydride reducing agent is $(^tBuO)_3AlH$, sodium (bis(2-methoxyethoxy)(2,2,2-trifluoro-ethoxy)aluminum hydride, or Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride). The stereoselective reduction can be performed in a solvent comprising tetrahydrofuran (THF) or diethyl ether, preferably the solvent is THF at a temperature ranging from about (-78°C) to about 25°C, preferably at a temperature ranging from about (-78°C) to about 0°C, and most preferably at a temperature from about (-30°C) to about 0°C. The crystallization occurs by a process comprising adding to the mixture seed crystals of the beta-lactol derivative and then heating the mixture comprising the seed crystals of the beta-lactol derivative at a temperature that ranges from about 25°C to about 80°C, preferably about 50°C with (about 0.2 mmHg) or without applied vacuum. The stereoselective coupling can be performed in a solvent comprising at least one of a polar aprotic solvent, a non-polar solvent, and a polar solvent. Examples of polar aprotic solvents include, but are not limited to, acetonitrile, dimethylsulfoxide, N,N-dimethylformamide, hexamethylphosphoramide, etc. The stereoselective coupling can be performed at a temperature that ranges from about 0°C up to about the reflux temperature of the solvent. Preferably, the temperature ranges from about 25°C to about 75°C. More preferably, the temperature ranges from about 40°C to about 60°C. Most preferably, the temperature is about 50°C. The basic reagent is as defined above. Preferably, the basic reagent comprises a (lower alk)oxide ((lower alkyl)OM) and an alcoholic solvent. Preferably, the basic reagent is MeONa/MeOH,

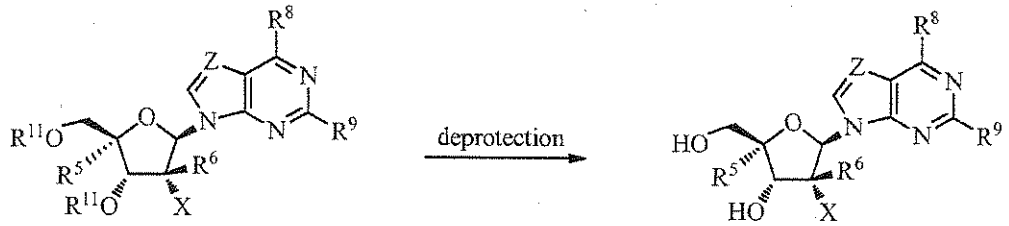
EtONa/EtOH, EtOK/EtOH, ^{i}PrONa/^{i}PrOH, ^{i}PrOK/^{i}PrOH, or ^{t}BuOK/^{t}BuOH. Most preferably, the basic reagent is ^{t}BuOK/^{t}BuOH.

An eight embodiment is directed to a process for preparing a compound **I** or a compound **II** or any of the compounds recited in any one of the aspects of the first and second embodiments, comprising reacting a beta-nucleoside derivative **VI** with a nucleophilic reagent to produce a 6-substituted nucleoside **VII**;



VI **VII**

deprotecting the 6-substituted nucleoside **VII** to produce a free purine nucleoside derivative **VIII**;



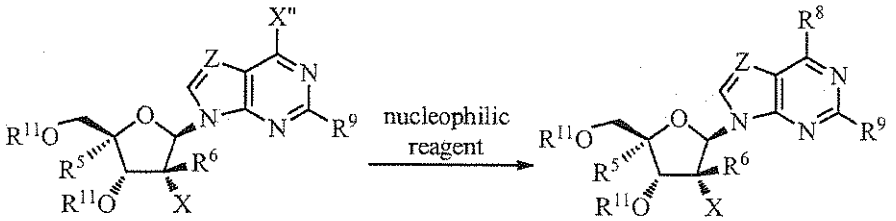
VII **VIII**

wherein R^5, R^6, R^8, R^9, X, Z have the meanings as defined herein above, R^{11} is a protecting group, and X" is a leaving group.

A first aspect of the eighth embodiment is directed to a process for preparing a compound **I** or a compound **II**, wherein for the the compound **VI**, the compound **VII**, or the compound **VIII**, R^5 is H, R^6 is CH_3, R^8 is any one –OMe, –OEt, –O^{i}Pr, –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), and –OBn, R^9 is NH_2, R^{11} is a protecting group (preferably benzoyl or substituted benzoyl, more preferably 4-chlor-benzoyl), X is F, X" is Cl, and Z is N. The nucleophilic reagent is as defined above. Preferably, the nucleophilic reagent is one that provides for R^8 which is any one –OMe, –OEt, –O^{i}Pr, –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), and –OBn. The reacting can be performed in at least one solvent comprising at least one of a polar aprotic solvent, a non-polar

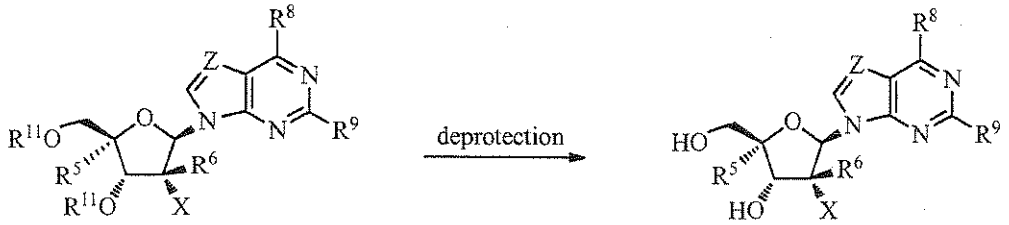
solvent, and a polar solvent. Examples of polar solvents include, but are not limited to, methanol, ethanol, t-butanol, benzyl alcohol. Examples of polar aprotic solvents include, but are not limited to, acetonitrile, dimethylsulfoxide, N,N-dimethylformamide, hexamethylphosphoramide, etc. The reacting can be performed at a temperature that ranges from about 0°C up to about the reflux temperature of the at least one solvent. Preferably, the temperature ranges from about 25°C to about 75°C. More preferably, the temperature ranges from about 40°C to about 60°C. Most preferably, the temperature is about 50°C. The deprotecting can occur as described herein.

A second aspect of the eight embodiment is directed to a process for preparing a compound **I** or a compound **II**, comprising reacting a beta-nucleoside derivative **VI** with a nucleophilic reagent to produce a 6-substituted nucleoside **VII**;



VI VII

deprotecting the 6-substituted nucleoside **VII** to produce a free purine nucleoside derivative **VIII**;

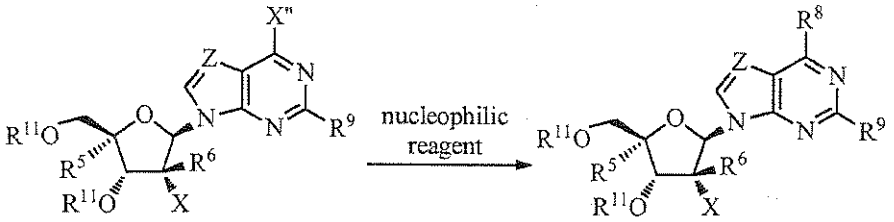


VII VIII

wherein for the compound **VI**, the compound **VII**, or the compound **VIII**, R^5 is H, R^6 is CH_3, R^8 is –OMe, R^9 is NH_2, R^{11} is a protecting group (preferably benzoyl or substituted benzoyl), X is F, X" is Cl, and Z is N (see compound (7) below). The nucleophilic reagent is MeONa/MeOH. The reacting can be performed in a solvent comprising methanol. The reacting can be performed at a temperature that ranges from about 0°C up to about 65°C. Preferably, the temperature ranges

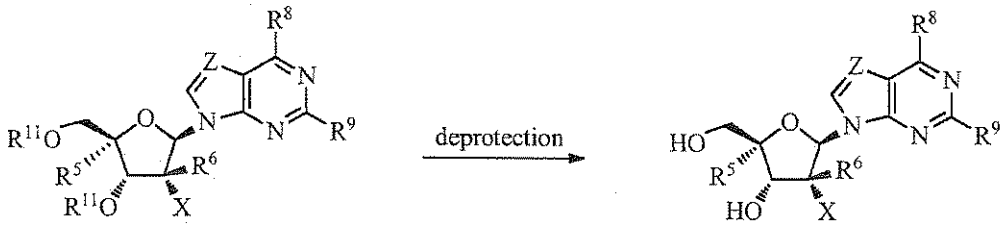
from about 25°C to about 65°C or alternatively from a temperature above room temperature to the boiling point of the alcoholic solvent/reagent. More preferably, the temperature ranges from about 40°C to about 60°C. Most preferably, the temperature is about 50°C. The deprotecting can occur as described herein.

A third aspect of the eighth embodiment is directed to a process for preparing a compound **I** or a compound **II**, comprising reacting a beta-nucleoside derivative **VI** with a nucleophilic reagent to produce a 6-substituted nucleoside **VII**;



VI **VII**

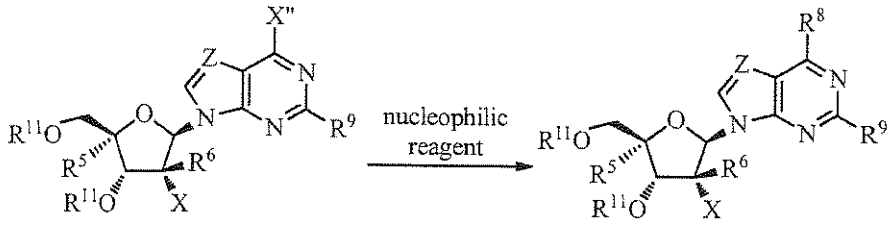
deprotecting the 6-substituted nucleoside **VII** to produce a free purine nucleoside derivative **VIII**;



VII **VIII**

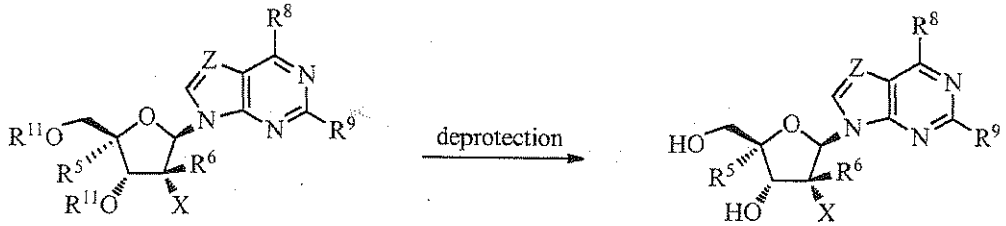
wherein for the compound **VI**, the compound **VII**, or the compound **VIII**, R^5 is H, R^6 is CH_3, R^8 is –OEt, R^9 is NH_2, R^{11} is a protecting group (preferably benzoyl or substituted benzoyl), X is F, X" is Cl, and Z is N (see compound (**10**) below). The nucleophilic reagent is as defined above. In the instance where the nucleophilic reagent is KOEt/EtOH, the nucleophilic reagent can be prepared in situ by reacting EtOH a base, such as potassium carbonate. The reacting can be performed in ethanol and at a temperature that ranges from about 0°C up to about 78°C. Preferably, the temperature ranges from about 25°C to about 78°C. More preferably, the temperature ranges from about 40°C to about 60°C. Most preferably, the temperature is about 50°C. The deprotecting can occur as described herein.

A fourth aspect of the eighth embodiment is directed to a process for preparing a compound **I** or a compound **II** comprising reacting a beta-nucleoside derivative **VI** with a nucleophilic reagent to produce a 6-substituted nucleoside **VII**;



VI **VII**

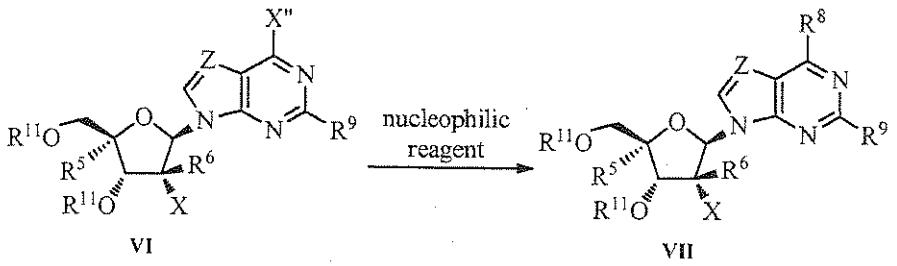
deprotecting the 6-substituted nucleoside **VII** to produce a free purine nucleoside derivative **VIII**;



VII **VIII**

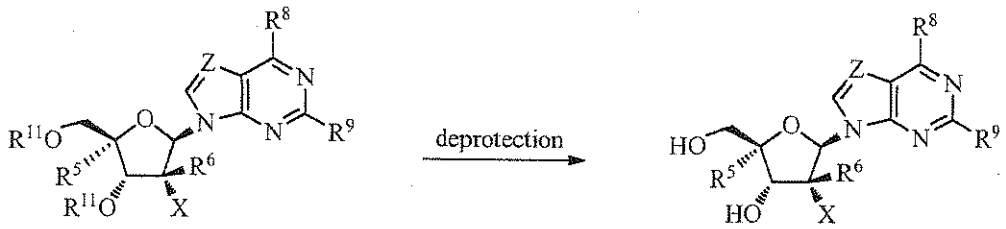
wherein for the compound **VI**, the compound **VII**, or the compound **VIII**, R^5 is H, R^6 is CH_3, R^8 is –OBn, R^{11} is a protecting group (preferably benzoyl or substituted benzoyl), X is F, X" is Cl, and Z is N (see compound (**9**) below). The nucleophilic reagent is BnONa/BnOH, wherein BnONa is obtained by a process comprising reacting benzyl alcohol with sodium hydride in a N,N-dimethylformamide solution at a temperature achieved using an ice bath (about 0°C). The reacting can be performed in a solvent comprising benzyl alcohol. The reacting can be performed at a temperature that ranges from about 0°C up to about 75°C. Preferably, the temperature ranges from about 25°C to about 65°C. More preferably, the temperature ranges from about 40°C to about 60°C. Most preferably, the temperature is about 50°C. The deprotecting can occur as described herein.

A fifth aspect of the eighth embodiment is directed to a process for preparing a compound **I** or a compound **II** comprising reacting a beta-nucleoside derivative **VI** with a nucleophilic reagent to produce a 6-substituted nucleoside **VII**;



VI VII

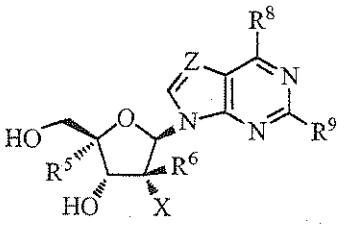
deprotecting the 6-substituted nucleoside **VII** to produce a free purine nucleoside derivative **VIII**;



VII VIII

wherein for the compound **VI**, the compound **VII**, or the compound **VIII**, R^5 is H, R^6 is CH_3, R^8 is -N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), R^9 is NH_2, R^{11} is a protecting group (preferably benzoyl or substituted benzoyl), X is F, X" is Cl, and Z is N (see compound (**8**) below). The nucleophilic reagent is azetidine/triethyl amine. The reacting can be performed in a solvent comprising ethanol. The reacting can be performed at a temperature that ranges from about 0°C up to about 78°C. Preferably, the temperature ranges from about 25°C to about 75°C. More preferably, the temperature ranges from about 40°C to about 60°C. Most preferably, the temperature is about 50°C. The deprotecting can occur as described herein.

A ninth embodiment is directed to a compound **VIII**.

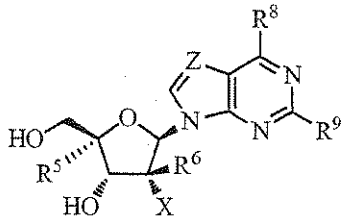


VIII

wherein for the compound **VIII**, R^5, R^6, X, R^8, R^9, and Z have the meanings as defined herein above. Preferably, R^5 is H, R^6 is CH_3, X is F, R^8 is a –O(lower alkyl),

–O(lower cycloalkyl), –O(lower alkaryl), or nitrogen heterocycle, R^9 is NH_2, and Z is N. More preferably, R^5 is H, R^6 is CH_3, X is F, R^8 is any one of OMe, OEt, O^{i}Pr, OBn, and N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), R^9 is NH_2, and Z is N. The compound **VIII** can be purified or unpurified. Preferably the compound **VIII** is purified.

A preferred compound **VIII** is represented by one of compounds **7**, **8**, **9**, and **10** (see below).



VIII

7, R^8 = -OMe
7a, R^8 = -O^{i}Pr
8, R^8 = -N(-$CH_2CH_2CH_2$-)
9, R^8 = -OBn
10, R^8 = -OEt

wherein, R^5 is H, R^6 is CH_3, X is F, Z is N, and R^9 is NH_2. The compound **VIII** is useful for preparing a compound **I** and a compound **II**.

A tenth embodiment of is directed to a process comprising converting a free purine nucleoside derivative **VIII** to compound **I** or converting the free purine nucleoside derivative to compound **II**. Procedures for converting a free purine nucleoside derivative **VIII** to compound **I** are disclosed herein, as well as U.S. Patent Application No. 12/053,015, filed March 21, 2008 (see also WO 2008/121634). Procedures for converting a free purine nucleoside derivative **VIII** to compound **II** are disclosed herein and U.S. Provisional Patent Application No. 61/060,683, filed June 11, 2008.

A first aspect of the tenth embodiment related to preparing compound **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with either a P(III)-reagent or a P(V)-reagent.

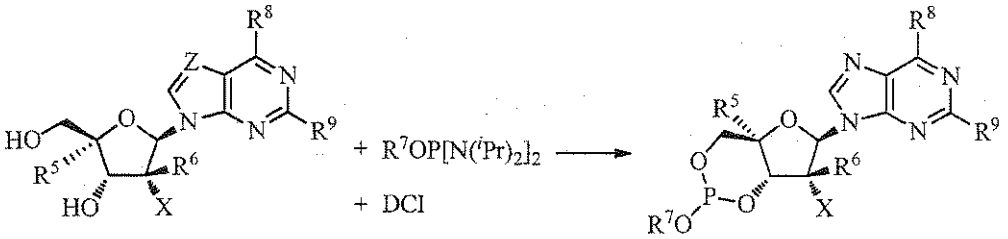
A second aspect of the tenth embodiment related to preparing the compound **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with a P(III)-reagent to obtain a phosphite derivative of **II**, wherein the phosphite derivative of **II** comprises a mixture of isomers.

A third aspect of the tenth embodiment related to preparing the compound **II** is directed to a process which comprises reacting the free purine nucleoside

derivative **VIII** with a P(III)-reagent in the presence of an activator reagent to obtain a phosphite derivative of **II**, wherein the phosphite derivative of **II** comprises a mixture of isomers.

A fourth aspect of the tenth embodiment related to preparing the compound **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with a P(III)-reagent in the presence of an activator reagent to obtain a phosphite derivative of **II**, wherein the phosphite derivative of **II** comprises a mixture of isomers; and equilibrating the phosphite derivative of **II** to provide an equilibrium mixture of phosphite isomer derivatives of **II**.

A fifth aspect of the tenth embodiment related to preparing the 3',5'-cyclic phosphate derivative **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with a $R^7OP[N(^iPr)_2]_2$ in the presence of 4,5-dicyanoimidazole to obtain a phosphite derivative of **II**

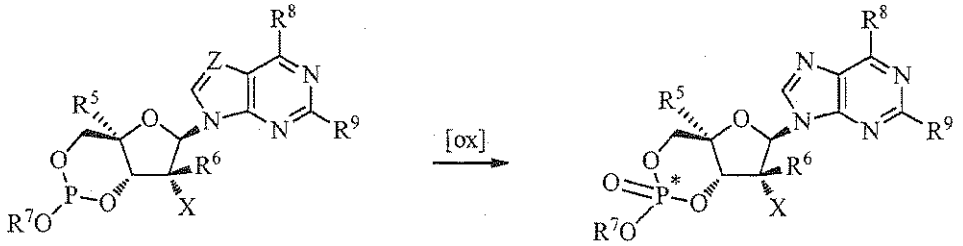


VIII phosphite derivative of **II**

wherein the phosphite derivative of **II** comprises a mixture of isomers and R^5, R^6, R^7, R^8, R^9, X and Z are defined herein;

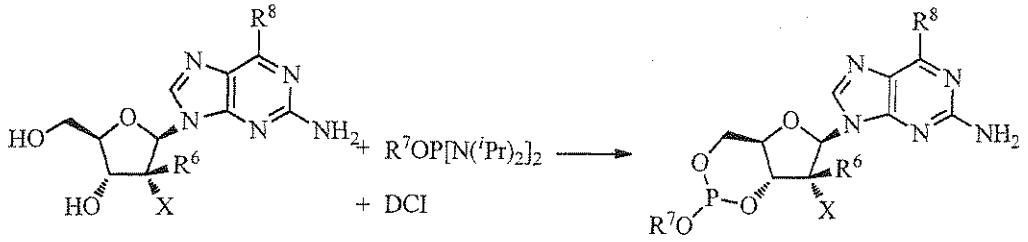
and equilibrating the phosphite derivative of **II** to obtain an equilibrium mixture of phosphite isomer derivatives of **II**.

A sixth aspect of the tenth embodiment is related to the fifth aspect further comprising oxidizing the equilibrium mixture of phosphite isomer derivatives of **II** to obtain the 3',5'-cyclic phosphate derivative **II**



phosphite derivative of **II** **II**

A seventh aspect of the tenth embodiment related to preparing the 3',5'-cyclic phosphate derivative **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with a $R^7OP[N(^iPr)_2]_2$ in the presence of 4,5-dicyanoimidazole to obtain a phosphite derivative of **II**

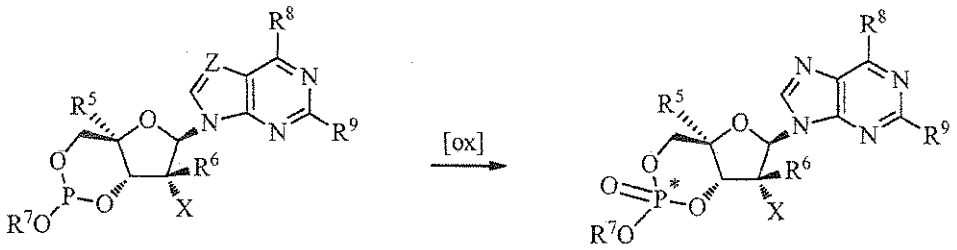


VIII phosphite derivative of **II**

wherein the phosphite derivative of **II** comprises a mixture of isomers, R^5 is H, R^6 is CH_3, X is F, Z is N, and R^9 is NH_2, while R^7 and R^8 are defined herein;

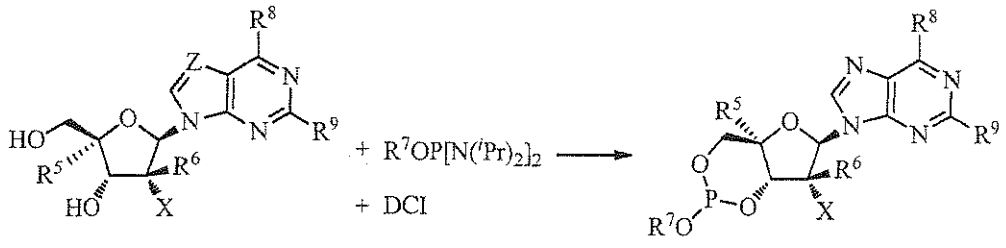
and equilibrating the phosphite derivative of **II** to obtain an equilibrium mixture of phosphite isomer derivatives of **II**.

An eighth aspect of the tenth embodiment is related to the seventh aspect further comprising oxidizing the equilibrium mixture of phosphite isomer derivatives of **II** to obtain the 3',5'-cyclic phosphate derivative **II**



phosphite derivative of **II** **II**

A ninth aspect of the tenth embodiment related to preparing the 3',5'-cyclic phosphate derivative **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with a $R^7OP[N(^iPr)_2]_2$ in the presence of 4,5-dicyanoimidazole to obtain a phosphite derivative of **II**

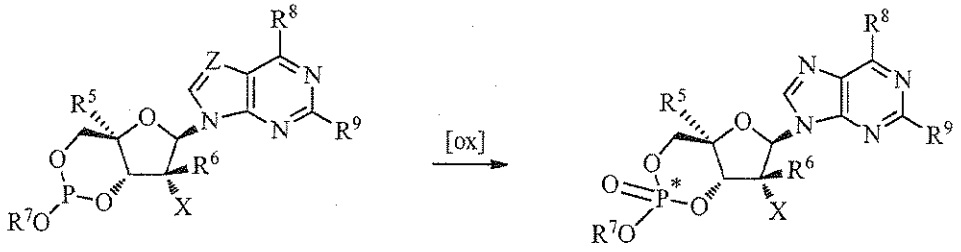


VIII phosphite derivative of **II**

wherein the phosphite derivative of **II** comprises a mixture of isomers and R^5 is H, R^6 is CH_3, R^7 is Me, ^{i}Pr, ^{c}Bu, or ^{c}Pn, R^8 is OMe, OEt, or O^{i}Pr, R^9 is NH_2, X is F, and Z is N.

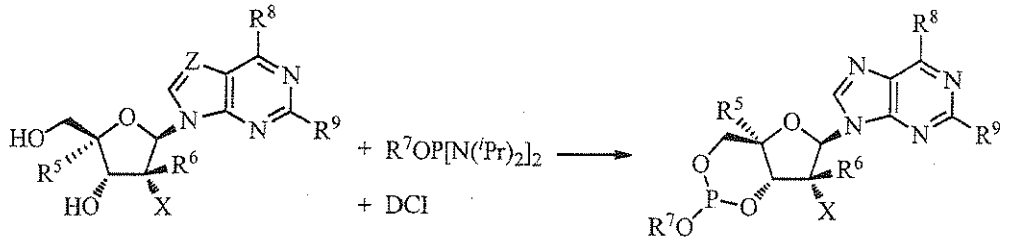
and equilibrating the phosphite derivative of **II** to obtain an equilibrium mixture of phosphite isomer derivatives of **II**.

A tenth aspect of the tenth embodiment is related to the ninth aspect further comprising oxidizing the equilibrium mixture of phosphite isomer derivatives of **II** to obtain the 3',5'-cyclic phosphate derivative **II**



phosphite derivative of **II** **II**

An eleventh aspect of the tenth embodiment related to preparing the 3',5'-cyclic phosphate derivative **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with a ^{i}PrOP[N(^{i}Pr)$_2$]$_2$ in the presence of 4,5-dicyanoimidazole to obtain a phosphite derivative of **II**



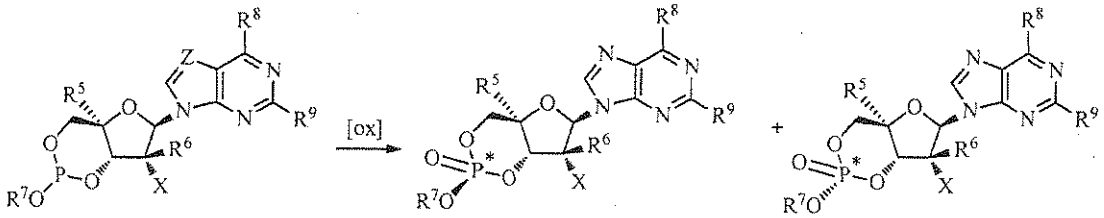
VIII phosphite derivative of **II**

wherein the phosphite derivative of **II** comprises a mixture of isomers and R^5 is H, R^6 is CH_3, R^7 is Me, ^{i}Pr, ^{c}Bu, or ^{c}Pn, R^8 is OMe, OEt, or O^{i}Pr, R^9 is NH_2, X is F, and Z is N;

and equilibrating the phosphite derivative of **II** to obtain an equilibrium mixture of phosphite isomer derivatives of **II**.

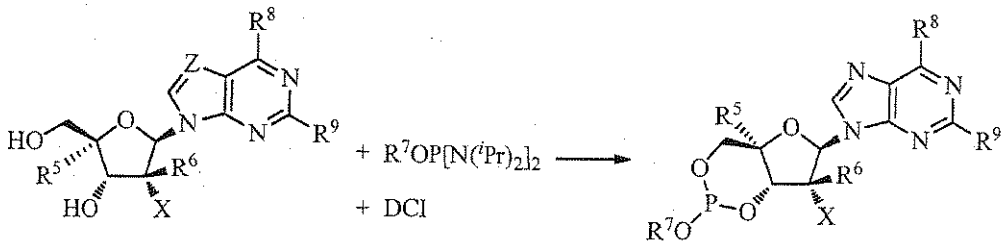
A twelfth aspect of the tenth embodiment is related to the eleventh aspect further comprising oxidizing the equilibrium mixture of phosphite isomer

derivatives of **II** to obtain a disasteromeric mixture of the 3',5'-cyclic phosphate derivatives s shown below.



phosphite derivative of **II**

A thirteenth aspect of the tenth embodiment related to preparing the 3',5'-cyclic phosphate derivative **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with a $^{i}PrOP[N(^{i}Pr)_2]_2$ in the presence of 4,5-dicyanoimidazole to obtain a phosphite derivative of **II**



VIII

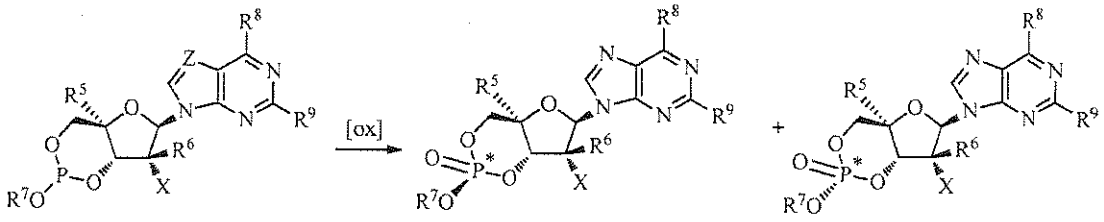
phosphite derivative of **II**

wherein the phosphite derivative of **II** comprises a mixture of isomers and R^5 is H, R^6 is CH_3, R^7 is Me, ^{i}Pr, ^{c}Bu, or ^{c}Pn, R^8 is OMe, OEt, or $O^{i}Pr$, R^9 is NH_2, X is F, and Z is N;

and equilibrating the phosphite derivative of **II** in a solution at a temperature to obtain an equilibrium mixture of phosphite isomer derivatives of **II**. The above-noted solution comprises a polar solvent, a non-polar solvent, and mixtures thereof. Examples of polar solvents include, but are not limited to, water, dimethylsulfoxide, N,N-dimethylformamide, hexamethylphosphoramidate, acetonitrile, ethyl acetate, tetrahydrofuran, etc. and mixtures thereof. Examples of non-polar solvents include, but are not limited to, hexane, heptane, benzene, toluene, methylene chloride, chloroform, etc., and mixtures thereof. The temperature can range over the entire available temperature range for the solution, which entails a temperature range where the solution does not solidify due to freezing, the solution does not evaporate due to boiling, or the solution components do not decompose. The solution temperature is determined experimentally based on the equilibrium position of the

mixture of isomers of the phosphite derivative of **II**. For instance, if the *cis* isomer is desired, then the desirable temperature or temperature range is one where the mole (or molar) ratio of the *cis*-isomer to the *trans*-isomer is at an acceptable maximum.

A fourteenth aspect of the tenth embodiment is related to the eleventh aspect further comprising optionally isolating the equilibrium mixture as a solid and contacting an oxidizing agent and the equilibrium mixture of phosphite isomer derivatives of **II** in a solution comprising an organic solvent to obtain the 3',5'-cyclic phosphate derivatives s shown below.



phosphite derivative of **II**

In a preferred aspect, the mole ratio of oxidizing agent to the phosphite derivative **II** ranges from about 0.9 to about 1.5, preferably from about 0.9 to about 1.2, more preferably from about 0.9 to about 1.1, most preferably the mole ratio of oxidizing agent to the phosphite derivative **II** is about 1. In a preferred aspect, the solution comprises tetrahydrofuran ("THF"), and the oxidizing agent comprises iodine (I_2). In a first preferred aspect, the solution comprises THF, pyridine ("pyr"), and water in at least about one-molar equivalent relative to the phosphite derivative of **II**. In a second preferred aspect, the solution comprises about 60 v/v % to about 80 v/v % of THF and about 39 v/v % to about 17 v/v % of pyr, and about 1 v/v% to about 3 v/v % of water, with the proviso that the amount of water is at least about one-molar equivalent relative to the phosphite derivative of II. In a second preferred aspect, the solution comprises about 65 v/v % to about 75 v/v % of THF and about 34 v/v % to about 22 v/v % of pyr, and about 1 v/v% to about 3 v/v % of water, with the proviso that the amount of water is at least about one-molar equivalent relative to the phosphite derivative of **II**. In a third preferred aspect, the solution comprises about 70 v/v % of THF, about 28 v/v of pyr, and about 2 v/v % of water, with the proviso that the amount of water is at least about one-molar equivalent relative to the phosphite derivative of II. .

A fifteenth aspect of the tenth embodiment related to preparing the compound **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with a P(V)-reagent.

A sixteenth aspect of the tenth embodiment related to preparing the compound **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with a P(V)-reagent and an amine reagent.

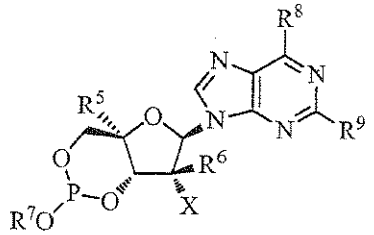
A seventeenth aspect of the tenth embodiment related to preparing the compound **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with a P(V)-reagent selected from among $P(O)(Lv)_3$, $R^7OP(O)(Lv)_2$, $R^7OP(O)(Lv)(N(C_{1\text{-}6}\ alkyl)_2)$, $R^7OP(O)[N(C_{1\text{-}6}\ alkyl)_2]_2$ and an amine reagent.

An eighteenth aspect of the tenth embodiment related to preparing the compound **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with a $R^7OP(O)(Lv)_2$ and an amine reagent.

A nineteenth aspect of the tenth embodiment related to preparing the compound **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with a $R^7OP(O)(Lv)_2$ and an amine reagent, wherein R^5 is H, R^6 is CH_3, R^7 is Me, ^{i}Pr, ^{c}Bu, or ^{c}Pn, R^8 is OMe, OEt, or O^{i}Pr, R^9 is NH_2, X is F, and Z is N.

A twentieth aspect of the tenth embodiment related to preparing the 3',5'-cyclic phosphate derivative **II** is directed to a process which comprises reacting the free purine nucleoside derivative **VIII** with a $R^7OP(O)(Lv)_2$ and an amine reagent, wherein R^5 is H, R^6 is CH_3, R^7 is Me, ^{i}Pr, ^{c}Bu, or ^{c}Pn, R^8 is OMe, OEt, O^{i}Pr, R^9 is NH_2, X is F, and Z is N, Lv is Cl, and the amine reagent comprises triethyl amine and N-methylimidazole.

A tenth embodiment is directed to a phosphite derivative of **II** represented by the following formula:

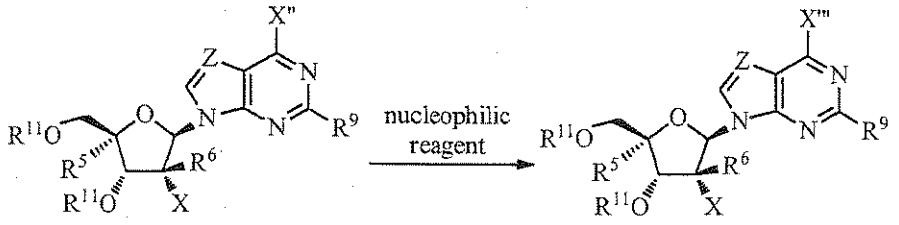


phosphite derivative of **II**

wherein the phosphite derivative of **II** where R^5, R^6, R^7, R^8, R^9, X, and Z are as defined herein. In a preferred aspect, the phosphite derivative of **II** has R^5 is H, R^6 is CH_3, R^7 is lower alkyl or lower cycloalkyl, R^8 is a –O(lower alkyl), –O(lower cycloalkyl), or –OBn, R^9 is NH_2, X is F, and Z is N. In an additionally preferred aspect, the phosphite derivative of **II** has R^5 is H, R^6 is CH_3, R^7 is Me, ^{i}Pr, ^{c}Bu, or ^{c}Pn, R^8 is OMe, OEt, or O^{i}Pr, R^9 is NH_2, X is F, and Z is N.

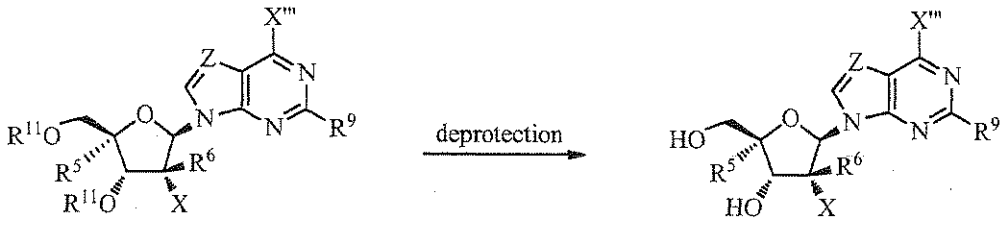
An eleventh embodiment is directed to a process for preparing the comound **I** or the compound **II**, where for both R^8 is OH, said process comprising

reacting a beta-nucleoside derivative **VI** with a nucleophilic reagent to produce a 6-X'''-substituted nucleoside **VII'**;



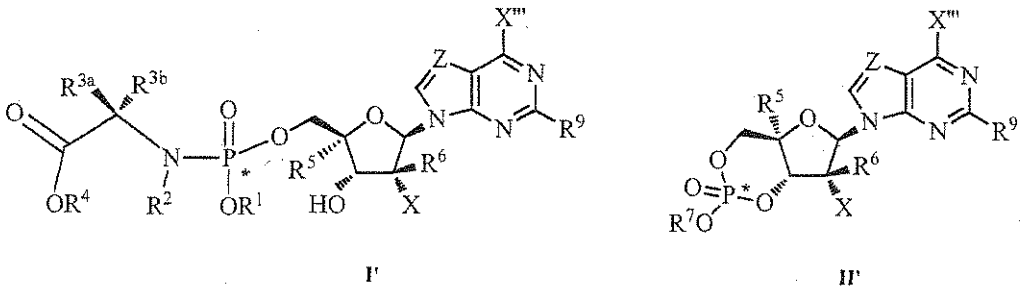
VI **VII'**

deprotecting the 6-X'''-substituted nucleoside **VII'** to produce a 6-X'''-substituted nucleoside **IX**;



VII' **IX**

converting the 6-X'''-substituted nucleoside **IX** to obtain a 6-X'''-phosphoramidate nucleoside **I'** or a 6-X'''-cyclic phosphate nucleotide **II'**



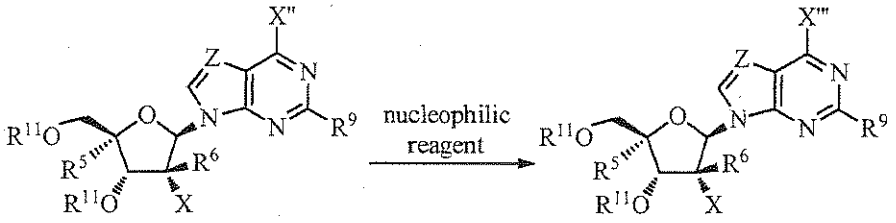
I' **II'**

converting the 6-X'''-phosphoramidate nucleoside **I'** or the 6-X'''-cyclic phosphate nucleotide **II'** to the phosphoramidate nucleoside **I** (where R^8 = OH) or the cyclic phosphate nucleotide **II** (where R^8 = OH),

wherein for the compounds **VI**, **VII'**, **IX**, **I'**, or **II'**, R^1, R^2, R^{3a}, R^{3b}, R^4, R^5, R^6, R^7, R^9, X and Z are as defined herein above, R^{11} is a protecting group (preferably benzoyl or 4-chloro-benzoyl, and more preferably 4-chloro-benzoyl), X'' is a leaving group, and X'''' is a group capable of being converted to OH.

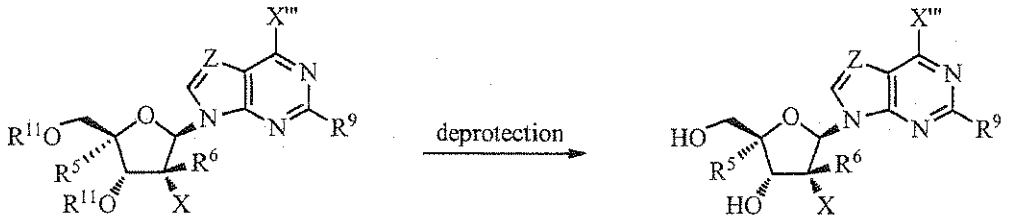
A first aspect of the eleventh embodiment is directed to a process for preparing a compound **I**, where R^8 is OH, said process comprising

reacting the beta-nucleoside derivative **VI** with a nucleophilic reagent to produce a 6-X'''-substituted nucleoside **VII'**;



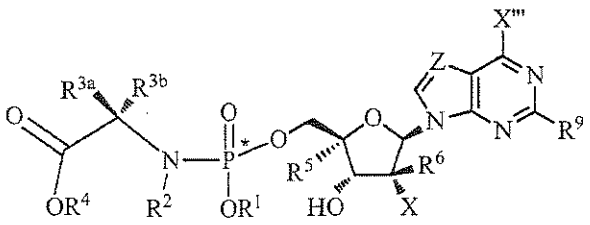
VI **VII'**

deprotecting a 6-X'''-substituted nucleoside **VII'** to produce a 6-X'''-substituted nucleoside **IX**;



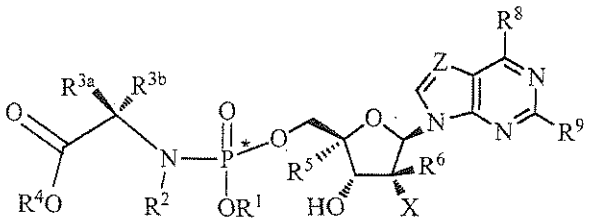
VII' **IX**

converting the 6-X'''-substituted nucleoside **IX** to obtain a 6-X'''-phosphoramidate nucleoside **I'**;



I'

converting the 6-X'''-phosphoramidate nucleoside **I'** to the phosphoramidate nucleoside **I** (where R^8 = OH);



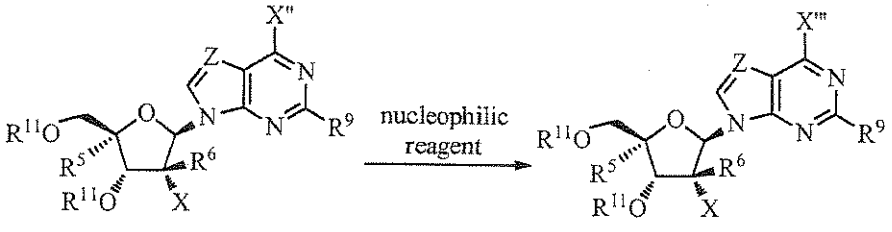
I

wherein for the compounds **VI**, **VII'**, **IX**, **I'**, or **II'**, R^1, R^2, R^{3a}, R^{3b}, R^4, R^5, R^6, R^7, R^9, X and Z are as defined herein above, R^{11} is a protecting group (preferably benzoyl or 4-chloro-benzoyl, and more preferably 4-chloro-benzoyl), X'' is a leaving group, and X'''' is a group capable of being converted to OH;

wherein the reacting can be performed in a solvent comprising ethanol and at a temperature that ranges from about 0°C up to about 78°C. Preferably, the temperature ranges from about 25°C to about 75°C. More preferably, the temperature ranges from about 40°C to about 60°C. Most preferably, the temperature is about 50°C. The deprotecting can occur as described herein.

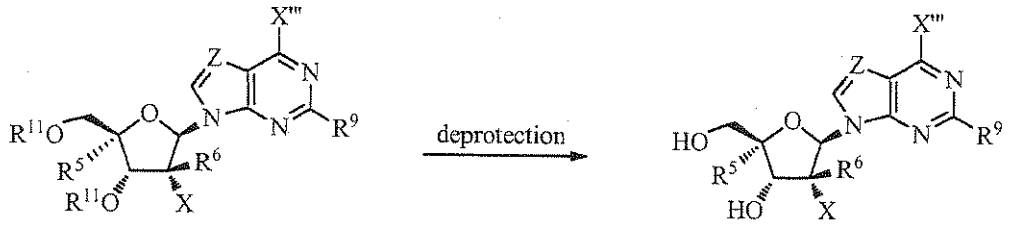
A second aspect of the eleventh embodiment is directed to a process for preparing a compound **I**, where R^8 is OH, said process comprising

reacting a beta-nucleoside derivative **VI** with a nucleophilic reagent to produce a 6-X'''-substituted nucleoside **VII'**;



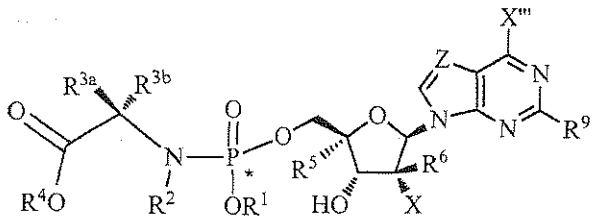
VI **VII'**

deprotecting the 6-X'''-substituted nucleoside **VII'** to produce a 6-X'''-substituted nucleoside **IX**;



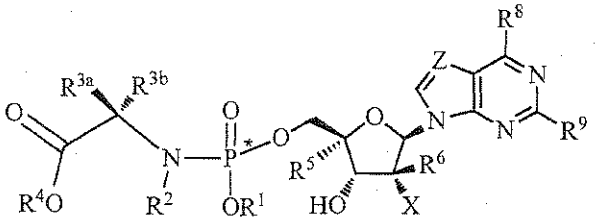
VII' **IX**

converting the 6-X'''-substituted nucleoside **IX** to obtain a 6-X'''-phosphoramidate nucleoside **I'**;



I'

converting the 6-X'''-phosphoramidate nucleoside **I'** to the phosphoramidate nucleoside **I** (where R^8 = OH);



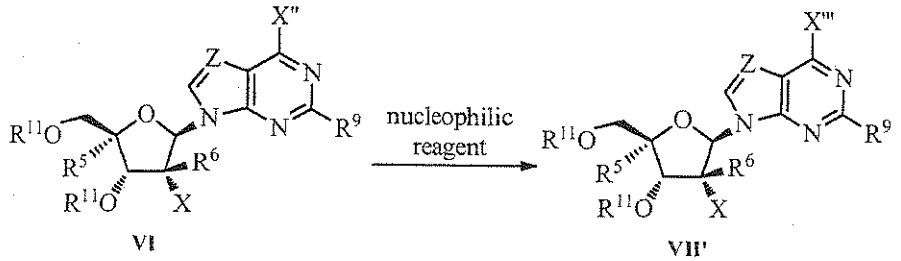
I

wherein for the compounds **VI**, **VII'**, **IX**, **I'**, or **II'**, R^1, R^2, R^{3a}, R^{3b}, R^4, R^5, R^6, R^7, R^9, X and Z are as defined herein above, R^{11} is a protecting group (preferably benzoyl or 4-chloro-benzoyl, and more preferably 4-chloro-benzoyl), X'' is a leaving group, and X'''' is a group capable of being converted to OH;

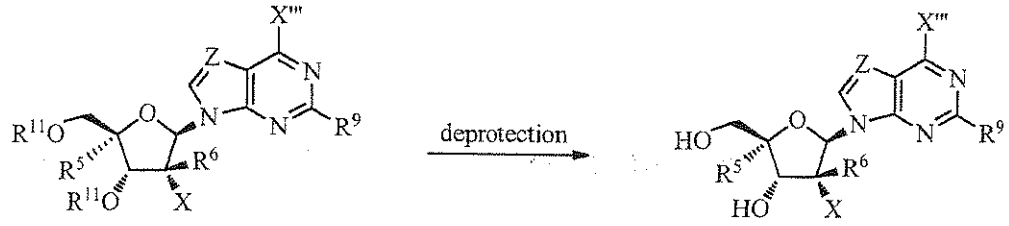
wherein the reacting can be performed in a solvent comprising ethanol and at a temperature that ranges from about 0°C up to about 78°C. Preferably, the temperature ranges from about 25°C to about 75°C. More preferably, the temperature ranges from about 40°C to about 60°C. Most preferably, the temperature is about 50°C. The group capable of being converted to OH (X'''') is –OBn, an –O-silyl, or an –O-allyl. The deprotecting can occur as described herein.

A third aspect of the eleventh embodiment is directed to a process for preparing a compound **I**, where R^8 is OH, said process comprising

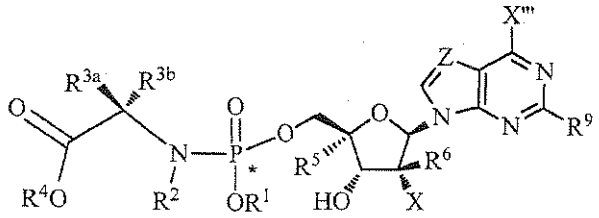
reacting a beta-nucleoside derivative **VI** with a nucleophilic reagent to produce a 6-X'''-substituted nucleoside **VII'**;



deprotecting the 6-X'''-substituted nucleoside **VII'** to produce a 6-X'''-substituted nucleoside **IX**;

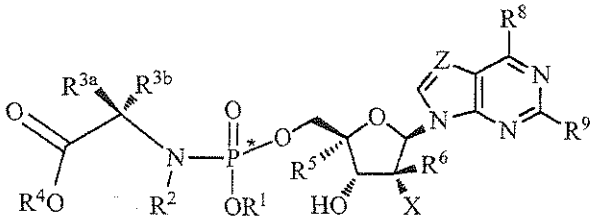


converting the 6-X'''-substituted nucleoside **IX** to obtain a 6-X'''-phosphoramidate nucleoside **I'**;



I'

converting the 6-X'''-phosphoramidate nucleoside **I'** to the phosphoramidate nucleoside **I** (where R^8 = OH);



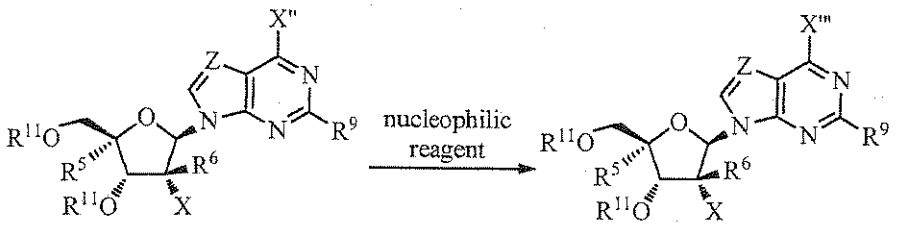
I

wherein for the compounds represented by formulas **VI**, **VII'**, **IX**, **I'**, or **II'**, R^1 is phenyl, R^2 is hydrogen, R^{3a} is hydrogen, R^{3b} is CH_3, R^4 is –lower alkyl or –lower cycloalkyl, R^5 is H, R^6 is CH_3, R^9 is NH_2, R^{11} is a protecting group (preferably benzoyl or 4-chloro benzoyl), X is F, X" is Cl, X''' is –OBn, –O-silyl, or –O-allyl, and Z is N;

wherein the reacting can be performed in a solvent comprising ethanol and at a temperature that ranges from about 0°C up to about 78°C. Preferably, the temperature ranges from about 25°C to about 75°C. More preferably, the temperature ranges from about 40°C to about 60°C. Most preferably, the temperature is about 50°C. The group capable of being converted to OH (X''') is –OBn, an –O-silyl, or an –O-allyl. The deprotecting can occur as described herein.

A fourth aspect of the eleventh embodiment is directed to a process for preparing a compound **I**, where R^8 is OH, said process comprising

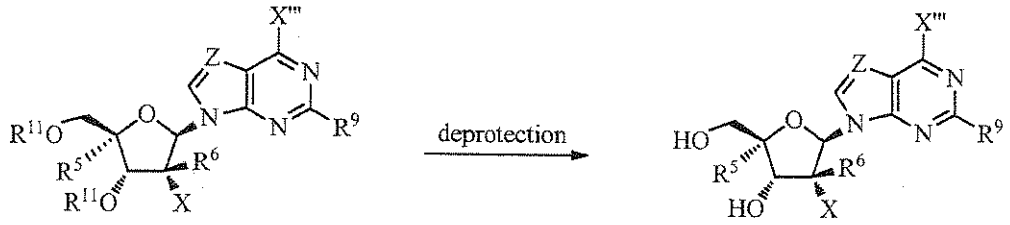
reacting a beta-nucleoside derivative **VI** with a nucleophilic reagent to produce a 6-X'''-substituted nucleoside **VII'**;



VI **VII'**

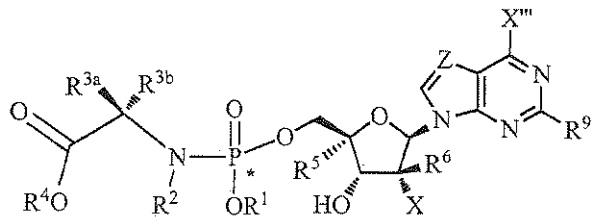
wherein X''' is a group capable of being converted to OH;

deprotecting the 6-X'''-substituted nucleoside **VII'** to produce a 6-X'''-substituted nucleoside **IX**;



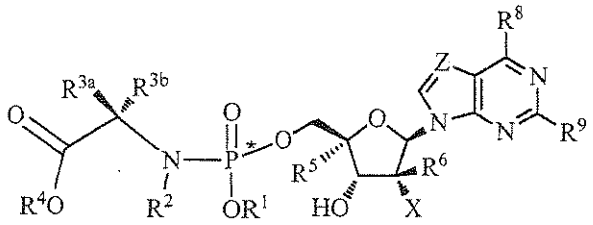
VII' **IX**

converting the 6-X'''-substituted nucleoside **IX** to obtain a 6-X'''-phosphoramidate nucleoside **I'**;



I'

converting the 6-X'''-phosphoramidate nucleoside **I'** to the phosphoramidate nucleoside **I** (where R^8 = OH);



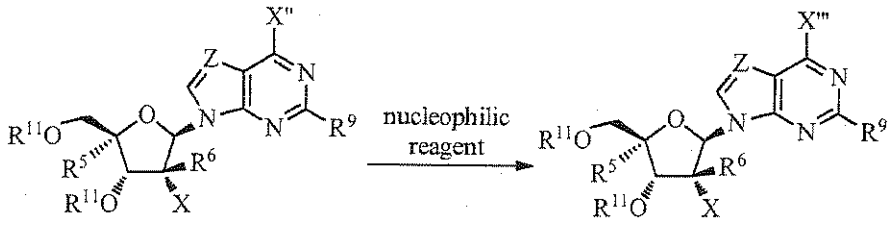
I

wherein for the compounds represented by formulas **VI**, **VII'**, **IX**, **I'**, or **II'**, R^1 is phenyl, R^2 is hydrogen, R^{3a} is hydrogen, R^{3b} is CH_3, R^4 is –lower alkyl or –lower cycloalkyl, R^5 is H, R^6 is CH_3, R^9 is NH_2, R^{11} is a protecting group (preferably benzoyl or 4-chloro-benzoyl), X is F, X'' is Cl, X''' is –OBn or –O-allyl, and Z is N;

wherein the reacting can be performed in a solvent comprising ethanol and at a temperature that ranges from about 0°C up to about 78°C. Preferably, the temperature ranges from about 25°C to about 75°C. More preferably, the temperature ranges from about 40°C to about 60°C. Most preferably, the temperature is about 50°C. The deprotecting can occur as described herein.

A fifth aspect of the eleventh embodiment is directed to a process for preparing a compound **I**, where R^8 is OH, said process comprising

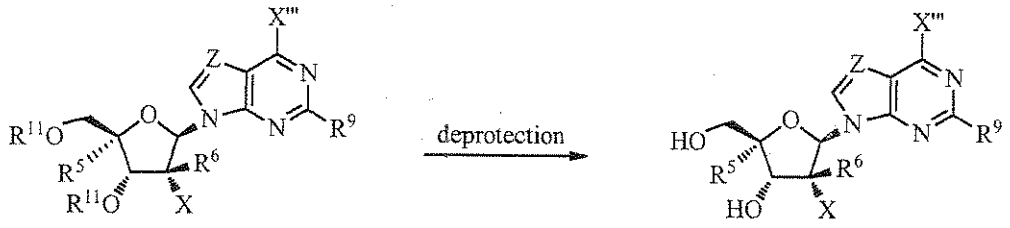
reacting a beta-nucleoside derivative **VI** with a nucleophilic reagent to produce a 6-X'''-substituted nucleoside **VII'**;



VI **VII'**

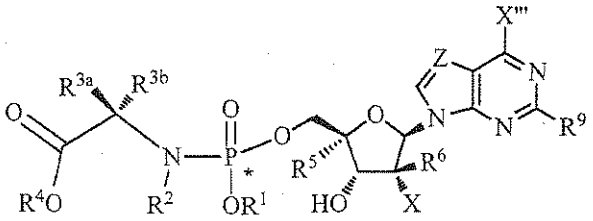
wherein X''' is a group capable of being converted to OH;

deprotecting the 6-X'''-substituted nucleoside **VII'** to produce a 6-X'''-substituted nucleoside **IX**;



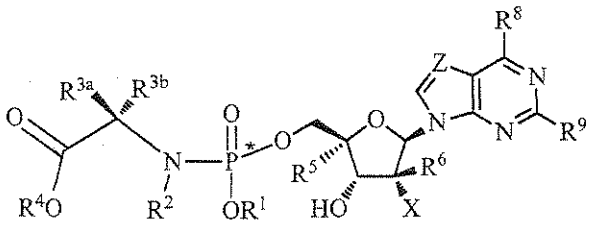
VII' **IX**

converting the 6-X'''-substituted nucleoside **IX** to obtain a 6-X'''-phosphoramidate nucleoside **I'**;



I'

converting the 6-X'''-phosphoramidate nucleoside **I'** to the phosphoramidate nucleoside **I** (where R^8 = OH);



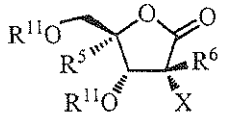
I

wherein for the compounds represented by formulas **VI**, **VII'**, **IX**, **I'**, or **II'**, R^1 is phenyl, R^2 is hydrogen, R^{3a} is hydrogen, R^{3b} is CH_3, R^4 is –Me, –Et, $-^nPr$, $-^iPr$, $-^cPn$, or $-^cHx$, R^5 is H, R^6 is CH_3, R^9 is NH_2, R^{11} is a protecting group (preferably benzoyl or substituted benzoyl), X is F, X'' is Cl, X''' is –OBn or –O-allyl, and Z is N;

wherein the reacting can be performed in a solvent comprising ethanol and at a temperature that ranges from about 0°C up to about 78°C. Preferably, the temperature ranges from about 25°C to about 75°C. More preferably, the temperature ranges from about 40°C to about 60°C. Most preferably, the temperature is about 50°C. The deprotecting can occur as described herein.

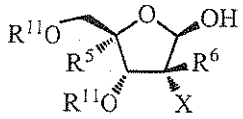
A twelfth embodiment is directed to a process for preparing a compound **I** or compound **II**: said process comprising:

(a-1) stereoselective reduction of a protected ribonolactone **III** using a hydride reducing agent



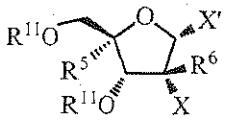
III

to provide a beta-lactol derivative of **IV**;



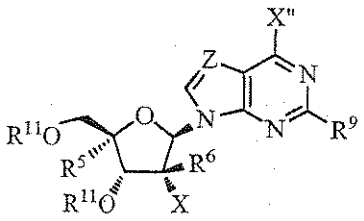
IV

(b-1) stereoselective conversion of the lactol derivative using a reagent to obtain an anomeric alpha-derivative **V**;



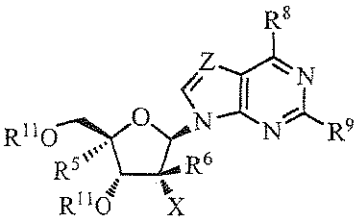
V

(c-1) stereoselective coupling of the anomeric alpha-derivative with a purine base or a derivatized purine base using a basic reagent to produce a beta-nucleoside derivative **VI**;



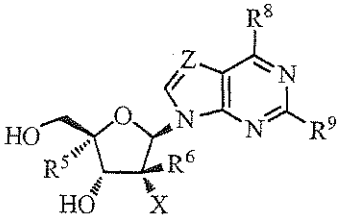
VI

(d-1) reacting the beta-nucleoside derivative with a nucleophilic reagent to produce a 6-substituted nucleoside **VII**;



VII

(e-1) deprotecting the 6-substituted nucleoside to produce a free purine nucleoside derivative **VIII**

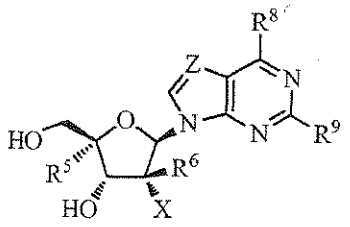


VIII

(f-1) converting the free purine nucleoside derivative to its corresponding 5'-phosphoramidate derivative **I** or

(g-1) converting the free purine nucleoside derivative to its corresponding 3',5'-cyclic phosphate derivative **II**; or

(d-2) reacting the beta-nucleoside derivative with a nucleophilic reagent to produce a free purine nucleoside derivative **VIII**;



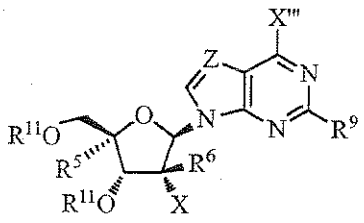
VIII

(f-2) converting the free purine nucleoside derivative to its corresponding 5'-phosphoramidate derivative **I** or

(g-2) converting the free purine nucleoside derivative to its corresponding 3',5'-cyclic phosphate derivative **II**; or

in the alternative for the preparation of the compound **I** or the compound **II**, where for both R^8 is OH,

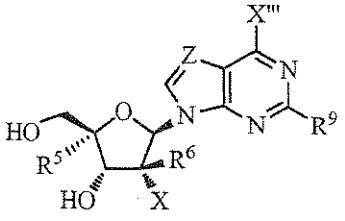
(d-3) reacting the beta-nucleoside derivative **VI** with a nucleophilic reagent to produce a 6-X'''-substituted nucleoside **VII'**;



VII'

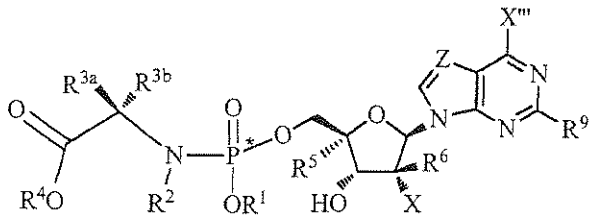
(h-3) deprotecting the 6-X'''-substituted nucleoside **VII'** to produce a 6-X'''-substituted nucleoside **VIII'**;

wherein X''' is a group capable of being converted to OH;

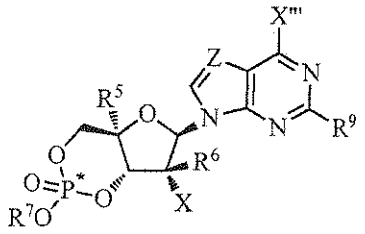


VIII'

(i-3) converting the 6-X'''-substituted nucleoside **VIII'** to obtain a 6-X'''-phosphoramidate nucleoside **I'** or a 6-X'''-cyclic phosphate nucleotide **II'**



I'



II'

(j-3) converting the 6-X'''-phosphoramidate nucleoside **I'** or the 6-X'''-cyclic phosphate nucleotide **II'** to the phosphoramidate nucleoside I (where R^8 = OH) or the cyclic phosphate nucleotide II (where R^8 = OH),

wherein X' is a leaving group;

wherein X'' is a leaving group;

wherein R^{11} is a protecting group; and

X''' is a group capable of being converted to –OH.

UTILITY

Compounds prepared by the processes disclosed herein are useful for the treatment of any condition the result of an infection by any one of the following viral agents: hepatitis C virus, West Nile virus, yellow fever virus, degue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus and Japanese encephalitis virus.

Dosage, Administration, and Use

In a thirteenth embodiment, the invention is related to a composition for the treatment and/or prophylaxis of any of the viral agents using compound **I** or **II**. Possible viral agents include, but are not limited to: hepatitis C virus, hepatitus B virus, Hepatitis A virus, West Nile virus, yellow fever virus, dengue virus, rhinovirus, polio virus, bovine viral diarrhea virus, Japanese encephalitis virus, or those viruses belonging to the groups of Pestiviruses, hepaciviruses, or flavaviruses. In the fourteenth embodiment, a preferred compound of formula **I** is represented by compound **11**, while a preferred compound of formula **II** is represented by compound **17**, more preferably R_P-**17**.

An aspect of this embodiment is directed to a composition for the treatment of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, and equivalent medium and compound **I** or **II**.

The compound **I** or **II** may be independently formulated in a wide variety of oral administration dosage forms and carriers. Oral administration can be in the form of tablets, coated tablets, hard and soft gelatin capsules, solutions, emulsions, syrups, or suspensions. The compound **I** or **II** is efficacious when administered by suppository administration, among other routes of administration. The most convenient manner of administration is generally oral using a convenient daily dosing regimen which can be adjusted according to the severity of the disease and the patient's response to the antiviral medication.

The compound **I** or **II**, as well as their pharmaceutically acceptable salts, together with one or more conventional excipients, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as suspensions, emulsions, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration. A typical preparation will contain from about 5% to about 95% active compound or compounds (w/w).

The compound **I** or **II** can be administered alone but will generally be administered in admixture with one or more suitable pharmaceutical excipients, diluents or carriers selected with regard to the intended route of administration and standard pharmaceutical practice.

A pharmaceutically acceptable salt form of an active ingredient may also initially confer a desirable pharmacokinetic property on the active ingredient which were absent in the non-salt form, and may even positively affect the

pharmacodynamics of the active ingredient with respect to its therapeutic activity in the body.

Solid form preparations include, for example, powders, tablets, pills, capsules, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. Solid form preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like. Examples of solid formulations are exemplified in EP 0524579; US 6,635,278; US 2007/0099902; US 7,060,294; US 2006/0188570; US 2007/0077295; US 2004/0224917; US 7,462,608; US 2006/0057196; US 6,267,985; US 6,294,192; US 6,569,463; US 6,923,988; US 2006/0034937; US 6,383,471; US 6,395,300; US 6,645,528; US 6,932,983; US 2002/0142050; US 2005/0048116; US 2005/0058710; US 2007/0026073; US 2007/0059360; and US 2008/0014228, each of which is incorporated by reference.

Liquid formulations also are suitable for oral administration include liquid formulation including emulsions, syrups, elixirs and aqueous suspensions. These include solid form preparations which are intended to be converted to liquid form preparations shortly before use. Examples of liquid formulation are exemplified in U.S. Patent Nos. 3,994,974; 5,695,784; and 6,977,257. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins,

methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

The compound **I** or **II** may be independently formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

The compound **I** or **II** may be independently formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate. Certain of these formulations may also be used in conjunction with a condom with or without a spermicidal agent.

Suitable formulations along with pharmaceutical carriers, diluents and excipients are described in *Remington: The Science and Practice of Pharmacy* **1995**, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania, which is hereby incorporated by reference. A skilled formulation scientist may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration without rendering the compositions unstable or compromising their therapeutic activity.

Additionally, the purified compound **I** or **II** may be independently formulated in conjunction with liposomes or micelles. As to liposomes, it is contemplated that the purified compounds can be formulated in a manner as disclosed in U.S. Patent Nos. 5,013,556; U.S. 5,213,804; 5,225,212; 5,891,468;6,224,903; 6,180,134; 5,192,549; 5,316,771; 4,797,285; 5,376,380; 6,060,080; 6,132,763; 6,653,455; 6,680,068; 7,060,689; 7,070,801; 5,077,057; 5,277,914; 5,549,910; 5,567,434; 5,077,056; 5,154,930; 5,736,155; 5,827,533; 5,882,679; 6,143,321; 6,200,598; 6,296,870; 6,726,925; and 6,214,375, each of which is incorporated by reference. As to micelles, it is contemplated that the purified compounds can be formulated in a manner as disclosed in U.S. Patent Nos. 5,145,684 and 5,091,188, both of which are incorporated by reference.

The fourteenth embodiment is directed to a use compound **I** or **II** in the manufacture of a medicament for the treatment of any condition the result of an infection by any one of the following viral agents: hepatitis C virus, West Nile virus, yellow fever virus, degue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus and Japanese encephalitis virus. In the fourteenth embodiment, a preferred compound of formula **I** is represented by compound **11**, while a preferred compound of formula **II** is represented by compound **17**, more preferably R_P-**17**.

The term "medicament" means a substance used in a method of treatment and/or prophylaxis of a subject in need thereof, wherein the substance includes, but is not limited to, a composition, a formulation, a dosage form, and the like, comprising compound **I** or **II**. It is contemplated that the use of any of compound **I** or **II** in the manufacture of a medicament, for the treatment of any of the antiviral conditions disclosed herein, either alone or in combination with another compound. A medicament includes, but is not limited to, any one of the compositions contemplated by the thirteenth embodiment.

A fifteenth embodiment is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises administering a therapeutically effective amount of any of compound **I** or **II** to the subject. In the fifteenth embodiment, a preferred compound of formula **I** is represented by compound **11**, while a preferred compound of formula **II** is represented by compound **17**, more preferably R_P-**17**.

It is intended that a subject in need thereof is one that has any condition the result of an infection by any of the viral agents disclosed herein, which includes, but is not limited to, hepatitis C virus, West Nile virus, yellow fever virus, degue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus or Japanese encephalitis virus, flaviviridae viruses or pestiviruses or hepaciviruses or a viral agent causing symptoms equivalent or comparable to any of the above-listed viruses.

The term "subject" means a mammal, which includes, but is not limited to, cattle, pigs, sheep, chicken, turkey, buffalo, llama, ostrich, dogs, cats, and humans, preferably the subject is a human. It is contemplated that in the method of treating a

subject thereof of the fifteenth embodiment can be any of the compounds contemplated herein, either alone or in combination with another compound.

The term "therapeutically effective amount" as used herein means an amount required to reduce symptoms of the disease in an individual. The dose will be adjusted to the individual requirements in each particular case. That dosage can vary within wide limits depending upon numerous factors such as the severity of the disease to be treated, the age and general health condition of the patient, other medicaments with which the patient is being treated, the route and form of administration and the preferences and experience of the medical practitioner involved. For oral administration, a daily dosage of between about 0.001 and about 10 g, including all values in between, such as 0.001, 0.0025, 0.005, 0.0075, 0.01, 0.025, 0.050, 0.075, 0.1, 0.125, 0.150, 0.175, 0.2, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, and 9.5, per day should be appropriate in monotherapy and/or in combination therapy. A particular daily dosage is between about 0.01 and about 1 g per day, including all incremental values of 0.01 g (i.e., 10 mg) in between, a preferred daily dosage about 0.01 and about 0.8 g per day, more preferably about 0.01 and about 0.6 g per day, and most preferably about 0.01 and about 0.25 g per day, each of which including all incremental values of 0.01 g in between. Generally, treatment is initiated with a large initial "loading dose" to rapidly reduce or eliminate the virus following by a decreasing the dose to a level sufficient to prevent resurgence of the infection. One of ordinary skill in treating diseases described herein will be able, without undue experimentation and in reliance on personal knowledge, experience and the disclosures of this application, to ascertain a therapeutically effective amount of the compound **I** or salt thereof or the compound **II** or salt thereof for a given disease and patient.

Therapeutic efficacy can be ascertained from tests of liver function including, but not limited to protein levels such as serum proteins (e.g., albumin, clotting factors, alkaline phosphatase, aminotransferases (e.g., alanine transaminase, aspartate transaminase), 5'-nucleosidase, γ-glutaminyltranspeptidase, etc.), synthesis of bilirubin, synthesis of cholesterol, and synthesis of bile acids; a liver metabolic function, including, but not limited to, carbohydrate metabolism, amino acid and ammonia metabolism. Alternatively the therapeutic effectiveness may be monitored

by measuring HCV-RNA. The results of these tests will allow the dose to be optimized.

A first aspect of the fifteenth embodiment is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises administering to the subject a therapeutically effective amount of a compound represented by any of compound **I** (preferably compound **11**) or **II** (preferably compound **17**, more preferably R_P-**17**) and a therapeutically effective amount of another antiviral agent; wherein the administration is concurrent or alternative. It is understood that the time between alternative administration can range between 1-24 hours, which includes any sub-range in between including, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 23 hours.

Examples of "another antiviral agent" include, but are not limited to: HCV NS3 protease inhibitors (see WO 2008010921, WO 2008010921, EP 1881001, WO 2007015824, WO 2007014925, WO 2007014926, WO 2007014921, WO 2007014920, WO 2007014922, US 2005267018, WO 2005095403, WO 2005037214, WO 2004094452, US 2003187018, WO 200364456, WO 2005028502, and WO 2003006490); HCV NS5B Inhibitors (see US 2007275947, US20072759300, WO2007095269, WO 2007092000, WO 2007076034, WO 200702602, US 2005-98125, WO 2006093801, US 2006166964, WO 2006065590, WO 2006065335, US 2006040927, US 2006040890, WO 2006020082, WO 2006012078, WO 2005123087, US 2005154056, US 2004229840, WO 2004065367, WO 2004003138, WO 2004002977, WO 2004002944, WO 2004002940, WO 2004000858, WO 2003105770, WO 2003010141, WO 2002057425, WO 2002057287, WO 2005021568, WO 2004041201, US 20060293306, US 20060194749, US 20060241064, US 6784166, WO 2007088148, WO 2007039142, WO 2005103045, WO 2007039145, WO 2004096210, and WO 2003037895); HCV NS4 Inhibitors (see WO 2007070556 and WO 2005067900); HCV NS5a Inhibitors (see US 2006276511, WO 2006120252, WO 2006120251, WO 2006100310, WO 2006035061); Toll-like receptor agonists (seeWO 2007093901); and other inhibitors (see WO 2004035571, WO 2004014852, WO 2004014313, WO 2004009020, WO 2003101993, WO 2000006529); and compounds disclosed in U.S. Patent Application No. 12/053,015, filed March 21, 2008 (the contents of which are

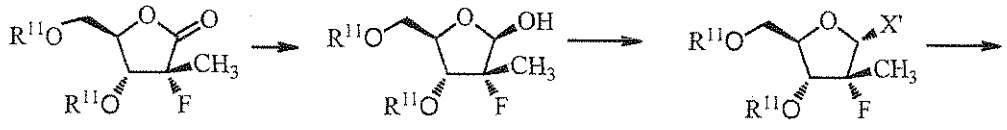
incorporated by reference), interferon-α, interferon-β, pegylated interferon-α, ribavirin, levovirin, viramidine, another nucleoside HCV polymerase inhibitor, a HCV non-nucleoside polymerase inhibitor, a HCV protease inhibitor, a HCV helicase inhibitor or a HCV fusion inhibitor.

When compound **I** or **II** is administered in combination with another antiviral agent the activity may be increased over the parent compound. When the treatment is combination therapy, such administration may be concurrent or sequential with respect to that of the nucleoside derivatives. "Concurrent administration" as used herein thus includes administration of the agents at the same time or at different times. Administration of two or more agents at the same time can be achieved by a single formulation containing two or more active ingredients or by substantially simultaneous administration of two or more dosage forms with a single active agent.

It will be understood that references herein to treatment extend to prophylaxis as well as to the treatment of existing conditions. Furthermore, the term "treatment" of a HCV infection, as used herein, also includes treatment or prophylaxis of a disease or a condition associated with or mediated by HCV infection, or the clinical symptoms thereof.

EXAMPLES

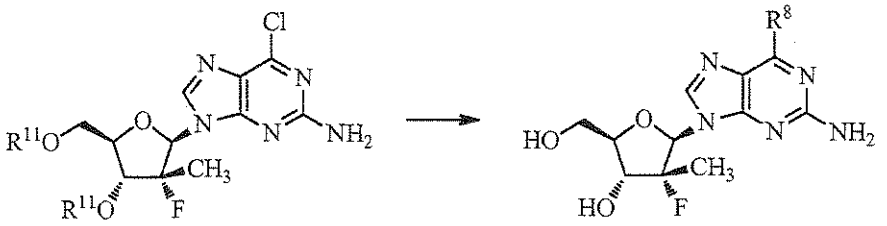
A further understanding of the disclosed embodiments will be appreciated by consideration of the following examples, which are only meant to be illustrative, and not limit the disclosed invention.



1a: R^{II} = Bz
1a': R^{II} = H
1b: R^{II} = 4-Cl-Bz

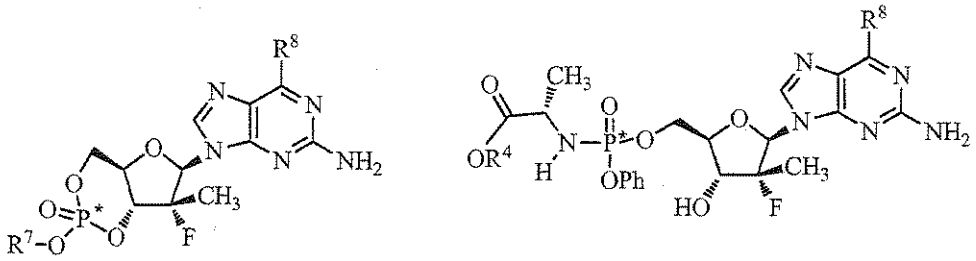
2a: R^{II} = Bz
2b: R^{II} = 4-Cl-Bz

3, X' = Cl, R^{II} = Bz
4a: X' = Br, R^{II} = Bz
4b: X' = Br, R^{II} = 4-Cl-Bz
5, X' = I, R^{II} = Bz



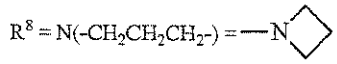
6a: R^{11} = Bz
6b: R^{11} = 4-Cl-Bz

7, R^8 = -OMe
7a, R^8 = -O^{i}Pr
8, R^8 = -N(-$CH_2CH_2CH_2$-)
9, R^8 = -OBn
10, R^8 = -OEt



15: R^7 = Me, R^8 = -N(-$CH_2CH_2CH_2$-)
16: R^7 = Me, R^8 = -OEt
17: R^7 = ^{i}Pr, R^8 = -OEt
23: R^7 = ^{c}Bu, R^8 = -OMe
24: R^7 = ^{c}Pn, R^8 = -OMe

11: R^4 = ^{i}Pr, R^8 = -OMe
11a: R^4 = ^{i}Pr, R^8 = -OEt
11b: R^4 = ^{i}Pr, R^8 = -O^{i}Pr
12: R^4 = Me. R^8 = -N(-$CH_2CH_2CH_2$-)
13: R^4 = ^{c}Pn, R^8 = -OBn
14: R^4 = ^{c}Pn, R^8 = -OH



The use of the convergent glycosylation route to prepare 2'-deoxy-2'-fluoro-2'-C-methyl purine nucleosides and their corresponding nucleotide phosphoramidates came about with the development of the synthesis of 3,5-di-O-benzoyl-2-deoxy-2-fluoro-2-*C*-methylribonolactone (**1a**) (Chun, K.; Wang, P. Intl. Pat. Appl. WO 2006/031725). An alternative common intermediate is the 4-chlorobenzoyl analog **1a**, which can be produced either by debenzoylation of **1a** to form the intermediate lactone diol, **1a'**, followed by 4-chlorobenzoylation, or by substituting 4-chlorobenzoyl chloride directly to react with **1a'**. An unexpected feature of the 3,5-di(4-chloro-benzoylated) intermediates is that they tend to have better crystalline properties, compared to the 3,5-di(benzoylated) intermediates, and so provides for an alternative means of purification in addition to chromatography.

After several attempts using Vorbrueggen-type Lewis acid mediated coupling and the ribonolactol 1-*O*-acetate of 3,5-di-O-benzoyl-2-deoxy-2-fluoro-2-

C-methylribonolactone, we observed very low coupling yields and the undesired α-anomer was the major product. Mitsunobu coupling with the ribonolactol (**2a/2b**) did give the desired product but with no stereoselectivity and very difficult chromatographic separation resulting in isolated yields of 6-10% for this step alone and the method was not scaleable.

The preferred approach became the S_N2 type reaction using a halo-sugar and a salt of the purine base. Again, the challenge of this approach was how to obtain an α halo-sugar stereospecifically in high yield to take advantage the inversion of configuration expected with S_N2 type reactions. A typical method treats an anomeric mixture of the 1-*O*-acetate of a sugar with HCl or HBr in acetic acid. However, this method resulted in production of unfavorable anomeric mixtures. Reducing the lactone (e.g., with $LiAlH(t\text{-}BuO)_3$ or Red-Al) initially generates at 2:1 ratio of β/α anomers but after initial purification through a silica gel filtration column, the resulting oil slowly anomerizes to form pure crystalline β-anomer of the lactol (**2a/2b**). This can be accelerated from several days at ambient temperature to 5-17 h at 50°C with seeding β-crystals. We observed that once the lactol is in solution, it slowly anomerizes back towards the 2:1 equilibrium in solvents such as dichloromethane or chloroform at ambient temperature. This process can be slowed considerable by chilling the solution (eg -20°C).

Chlorination through an S_N2 mechanism with N-chlorosuccinimide (NCS) produced an α-chlorosugar (**3**) in a stereospecific manner in almost quantitative yield.

To obtain an α-bromosugar (**4a**), many bromination conditions were tried including N-bromosuccinimide (NBS) and HBr in acetic acid. Among them, we followed a general bromination reaction using a combination of triphenylphosphine (PPh_3) and carbon tetrabromide (CBr_4) (eg. Hooz et al, *Can. J. Chem.*, **1968**, *46*, 86-87). Under the conditions of using methylene chloride as the solvent and maintaining a low temperature (-10 to -20°C) we obtained the best result where the desired α/β isomer ratio was greater than 10:1, in a yield of greater than 80%. Applicants believe that there are no literature precedents describing this level of stereoselectivity for this reaction type. Another practical observation was that by conducting the bromination under sub-ambient temperature conditions, such as, most preferably about -20°C) and exposing the cold reaction solution to silica gel as

soon as possible after the completion of the reaction minimizes anomerization of the bromosugar. The bromosugar can be purified through a silica gel filtration column. Once treated with silica gel, the bromosugar it is practically stable even at elevated temperatures.

The iodosugar (**5a**) was prepared in a similar manner, which can be coupled with the purine to produce a key intermediate (**6a**).

Following the general purine coupling method of Bauta et al (Intl. Pat. Appl. WO 2003/011877), we coupled the α-bromosugar (**4a**) with the potassium salt of 6-chloro-2-amino-purine in t-butanol in acetonitrile. The reaction took over a week at ambient temperatures. The reaction was optimized to go to completion in 24 h at 50°C. After partial purification through a silica gel filtration column, the anomeric mixture was isolated in 63% yield in a ratio of 14:1 β/α. The β-anomer (**6a**) could be selectively crystallized out from a methanolic solution to give the pure desired β-anomer (**6a**) in 55% yield from the bromosugar (**4a**).

With a key intermediate **6a** in hand, conversion to unprotected 2-amino-6-substituted purines (e.g., **7-10**) was accomplished. Further conversion to the phosphoramidate derivatives (e.g., **11-14**) proceeded by an adaptation of the method of Lehsten et al., Org. *Proc. Res. Dev.*, **2002**, *6*, 819-822 or as disclosed in U.S. Patent Application No. 12/053,015, filed March 21, 2008, pp. 651-675. Cyclic phosphate derivatives (e.g., **15-17**) were prepared as described in *Can J. Chem.*, **1993**, *71*, 855 or as disclosed in U.S. Provisional Patent Application No. 61/060,683, filed June 11, 2008, pp. 79-89. As the phosphoramidate group can also react to a minor extent on the secondary 3' hydroxyl, the potential exists for 3' monophosphoramidate and 3', 5' bis-phosphoramidate impurities. The 3' isomer would be expected to have similar physical properties to the desired 5' isomer making purification by chromatography difficult. This is ameliorated by further reacting the crude product mixture with sub-stoichiometric amounts of protecting groups which are selective for primary hydroxyls over secondary hydroxyls such as t-butyldimethylsilyl chloride, t-butyldiphenylsilyl chloride or 4,4'-dimethoxytrityl chloride in the presence of pyridine or similar base to generate 5' protected 3' phosphoramidate. The resulting product and the bis substituted phosphoramidate are less polar than the desired 5' phosphoramidate and can be separated readily by chromatography.

Compound (**1a**) can be obtained by a process disclosed at page 5 in U.S. Published Application No. 2008/0139802 (which corresponds to WO 2008/045419), at pages 11-13 in WO 2006/012440, and at pages 20-22 and 30-31 in WO 2006/031725, each of which is hereby incorporated by reference. Alternatively, the 4-chlorobenzoyl lactone analog (**1b**) can be produced either by debenzoylation of 1a to form the intermediate lactone diaol, **1a'**, followed by 4-chlorobenzoylation, or by substituting 4-chlorobenzoyl chloride directly to react with **1a'**.

Example 1. ((2R,3R,4R)-3-(4-chlorobenzoyloxy)-4-fluoro-4-methyl-5-oxotetrahydrofuran-2-yl)methyl 4-chlorobenzoate (1b)

((2R,3R,4R)-3-(benzoyloxy)-4-fluoro-4-methyl-5-oxotetrahydrofuran-2-yl)methyl benzoate (**1a**, 44.50 g, 119.5 mmol) was suspended in anhydrous methanol (240 mL). A catalytic amount of 25 wt. % sodium methoxide in methanol (2.3 mL, 10 mmol, 8.3 mol%) was added at room temperature. After 2 h, the reaction was complete as shown by TLC (20% EtOAc in hexanes). After concentration of the solvent under reduced pressure, the residue was triturated with a mixture of ethyl ether and hexanes (1:2 v/v) (200 mL) to afford crude intermediate lactone, **a**. The solid was collected via filtration and rinsed with hexanes (3x 40 mL). To a dry 1 L of round flask was loaded the crude intermediate and it was dissolved in anhydrous THF (500 mL). 4-Chlorobenzoyl chloride (46 mL, 358 mmol) was added at room temperature. The mixture was cooled in an ice-water bath and then triethylamine (100 mL, 717 mmol) was added. The cloudy mixture was stirred at room temperature for overnight. The reaction was quenched via addition of water (60 mL) and then the solution was concentrated under reduced pressure. The residue was diluted with ethyl acetate (200 mL)and washed with water, brine (2x100 mL each). The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography (20% EtOAc in hexanes) to afford the product as a light yellow fluffy solid. The product was dried under (0.2 mmHg, 50°C, 2 h) to afford 24.3 g (46%), mp: 138-141°C. ^{1}H NMR ($CDCl_3$): δ 7.99 (m, 2 H, arom.), 7.91 (m, 2 H, arom.), 7.45 (m, 2 H, arom.), 7.39 (m, 2 H, arom.), 5.45 (dd, 1 H, J = 17.6 Hz, J = 7.2 Hz, C3-H), 4.97 (m, 1 H, C4-H), 4.73 (m, 1 H, C5-Ha), 4.58 (m, 1 H, C5-Hb), 1.73 (d, 3 H, CH_3).

Example 2. ((2R,3R,4R,5R)-3-(benzoyloxy)-4-fluoro-5-hydroxy-4-methyltetrahydrofuran-2-yl)methyl benzoate (2a)

To a 5 L of dry three-neck round-bottomed flask fit with a mechanical stirrer, addition funnel and thermometer was charged the lactone ((2R,3R,4R)-3-(benzoyloxy)-4-fluoro-4-methyl-5-oxotetrahydrofuran-2-yl)methyl benzoate) (**1a**, 379 g, 1.018 mol). The solid was dissolved in anhydrous THF (1.75 L) and cooled to -30°C under a nitrogen atmosphere. A solution of lithium tri-tert-butoxyaluminohydride (1.0 M in THF, 1.527 L) was added to the lactone solution while stirring over 1 h and maintaining the -30°C temperature. After finishing the addition, the temperature was slowly increased and the reaction was followed by TLC (lactol R_f 0.4, 30% EtOAc in hexanes). The reaction was complete after 1h 15 min (temperature reached -10°C). The reaction was quenched by addition of Ethyl acetate (900 mL) via addition funnel. Sat. NH_4Cl (40 mL) was added at 0°C. The cloudy mixture was decanted into a 10 L round-bottomed flask. The solid residue left behind was filtered and washed with ethyl acetate (2x200 mL). The filtrate was combined with the decanted solution and the combined solution was concentrated under reduced pressure. The oily residue was dissolved in ethyl acetate (2 L) and washed with 3 *N* HCl (600 mL). The aqueous layer was back-extracted with ethyl acetate (3x400 mL). The combined organic layer was washed with water (3x800 mL), sat. $NaHCO_3$ (400 mL) and brine (400 mL). The organic solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a light brown oily residue. The residue was purified by plug column (2.2 kg of 40-63 micron silica gel, packed in a 6 L sintered glass funnel, 22 cm length of silica gel, diameter 15 cm) using suction and a step-gradient of 5%, 10%, 20%, and 30% ethyl acetate in hexanes –ca 5 L of each). The product containing fractions were combined and concentrated under reduced pressure to a colorless, very thick liquid (310.4 g).

The liquid slowly solidified after adding crystalline beta product as seeds (ca 100 mg spread out) under vacuum (0.2 mmHg) at 50°C. The process of solidification was complete in 20 hours at 50°C with or without vacuum. The white solid thus collected (293.8 g, 77%) has a mp of 79-80°C and ratio of β/α is 20:1 based on NMR.

^{1}H-NMR (DMSO-d_6) β-isomer, δ = 5.20 (dd, 1 H, OH); α-isomer, δ = 5.40 (dd, 1 H, OH). (β-lactol) .(DMSO-d_6): δ 7.99 (m, 2 H, arom.), 7.93 (m, 2 H, arom.),

7.70 (m, 1 H, arom.), 7.61 (m, 1 H, arom.), 7.55 (m, 2 H, arom.), 7.42 (m, 2 H, arom.), 7.32 (dd, 1 H, C1-H), 5.54 (dd, 1 H, C3-H), 5.20 (dd, 1 H, OH), 4.55-4.50 (m, 1 H, C5-Ha), 4.46-4.40 (m, 2 H, C5-Hb and C4-H), 1.42 (d, 3 H, CH_3).

Example 3. ((2R,3R,4R,5R)-3-(4-chlorobenzoyloxy)-4-fluoro-5-hydroxy-4-methyltetrahydrofuran-2-yl)methyl 4-chlorobenzoate (2b)

To a 1 liter dry round-bottomed flask was loaded ((2R,3R,4R)-3-(4-chlorobenzoyloxy)-4-fluoro-4-methyl-5-oxotetrahydrofuran-2-yl)methyl 4-chlorobenzoate (**1b,** 50.0 g, 113 mmol) and the solid was dissolved in anhydrous THF (200 mL). The solution was cooled to -20°C. Lithium tri-tert-butoxyaluminohydride (1.0 M in THF) (170 mL, 170 mmol) was added via an addition funnel over 20 min and the resulting mixture was stirred for an additional one hour at -20°C. Ethyl acetate (120 mL) was added and the mixture was allowed to warm up slowly to 0°C. Sat. aq ammonium chloride (4.5 mL) was added. The mixture was concentrated under reduced pressure and then diluted with EtOAc (500 mL). Aqueous HCl (3 N, 300 mL) was added to dissolve all solids. After separation, the organic layer was washed with water (2x 200 mL), brine (100 mL), and dried over sodium sulfate. The organic layer was concentrated under reduced pressure to furnish an amorphous solid. The solid was dissolved in methanol (169 mL) heated to reflux. After cooling to room temperature, water was added portionwise (37 mL total) until a slightly turbid mixture formed. After standing, the precipitated β-lactol product was filtered and washed with methanol (2x 20 mL) and dried (0.2 mmHg, 50°C, 17 h) to 30.5 g (61%) of an off-white solid with an anomeric ratio of $\beta/\alpha > 35:1$. ^{1}H NMR (DMSO-d_6): δ 7.95 (m, 2 H, arom.), 7.90 (m, 2 H, arom.), 7.61 (m, 2 H, arom.), 7.51 (m, 2 H, arom.), 7.31 (dd, 1 H, C1-H, J = 5.2 Hz, J = 0.8 Hz), 5.50 (dd, 1 H, C3-H, J = 24 Hz, J = 7.2 Hz), 5.19 (dd, 1 H, C4-H, J = 10.8 Hz, J = 5.6 Hz), 4.56 (m, 1 H, C5-Ha), 4.42 (m, 2 H, C5-Hb and OH), 1.42 (d, 3 H, CH_3, J = 22.8 Hz).

Example 4. ((2R,3R,4R,5R)-3-(benzoyloxy)-5-chloro-4-fluoro-4-methyltetrahydrofuran-2-yl)methyl benzoate (3)

To a solution of mixture of compound **2a** (1.0 g, 2.67 mmol) and PPh_3 (1.4 g, 5.34 mmol) in CH_2Cl_2 (15 mL) was added NCS (1.07 g, 8.01 mmol) portionwise at 0°C. Then the resulting mixture was stirred at rt for 1h and poured into a silica gel

column and eluted with EtOAc-hexanes (1:4) using pressure. The collected right fractions were combined, concentrated, and co-evaporated with CH_2Cl_2 several times and used next step (1.0 g, 95%).

^{1}H-NMR ($CDCl_3$) δ = 8.13-8.02 (m, 4H, aromatic), 7.78-7.50 (m, aromatic, 2H), 7.53-7.43 (m, 4H, aromatic), 6.01 (s, 1H, H-1), 5.28 (dd, 1H, J = 3.2, 5.6 Hz, H-3), 4.88 (m, 1H, H-H-4), 4.77 (dd, 1H, J = 3.2, 12.4 Hz, H-5), 4.61 (dd, 1H, J = 4.0, 12.4 Hz, H-5'), 1.73 (d, 3H, J = 21.6 Hz, CH_3).

Example 5. ((2R,3R,4R,5R)-3-(benzoyloxy)-5-bromo-4-fluoro-4-methyltetrahydrofuran-2-yl)methyl benzoate (4a)

Anhydrous dichloromethane (5.6 L) was charged into a reactor and cooled to -22°C or below. Triphenylphosphine (205.4 g, 0.783 mol) was added to the cold solvent and the suspension was stirred to form a solution. The lactol (**2a**, 209.4 g, 0.559 mol) in solid form was added to the cold solution and stirred for 15 mins. Carbon tetrabromide (278.2 g, 0.839 mol) was added portion-wise while maintaining the temperature of the solution between -22°C to -20°C under a flow of nitrogen gas (approx. 30 min). After finishing the addition of CBr_4, the temperature was slowly raised to -17°C over 20 mins. The reaction was judged to be >95% complete by TLC (R_fs 0.61 (α), 0.72 (β), 0.36 lactol; 20% EtOAc in hexanes). The reaction solution was immediately transferred to a vessel containing 230 g of flash chromatography grade silica gel (40-63 microns). The stirred mixture was immediately passed through a pad of silica gel (680 g) in a 2.5 L sintered glass Buchner funnel. The filtrate was concentrated under reduced pressure to about 800 mL and the ratio of α/β isomers of the crude product was 10:1 as determined by ^{1}H-NMR. ($CDCl_3$) δ = 6.35, (s, α C1-H), 6.43, (d, β C1-H). The residue was purified by plug column chromatography using 2.1 kg of silica gel in a 6 L sintered glass Buchner funnel and eluted (via suction) with a stepwise gradient elution of 1%, 5%, 8% 12% EtOAc in hexane (ca 4 L each) to remove non-polar impurities followed by 12%, 25% EtOAc in hexane (6 L total) to elute the product. The product containing fractions were combined into two fractions, concentrated under reduced pressure, dried under vacuum (0.1 mmHg, ambient temp., 20 h) to colorless oils. Main fraction (197 g, 89% α/β = 20:1). The alpha isomer crystallized from a small portion of the oil upon standing at 0°C for several weeks to give large, thin plates,

mp 59-61°C. The pure beta isomer crystallized from a mixture of alpha and beta product oil from an earlier less selective run to give needles, mp 77-79°C.

^{1}H-NMR (β-bromide) ($CDCl_3$): δ = 8.08 (m, 2 H, arom.), 8.04 (m, 2 H, arom.), 7.62 (m, 1 H, arom.), 7.54-7.45 (m, 3 H, arom.), 7.35 (m, 2 H, arom.), 6.43 (d, 1 H, C1-H), 6.04 (dd, 1 H, C3-H), 4.78-4.73 (m, 2 H, C4-H and C5-Ha), 4.63-4.58 (m, 1 H, C5-Hb), 1.76 (d, 3 H, CH_3). α-bromide, α/β = 20:1) ($CDCl_3$): δ 8.13 (m, 2 H, arom.), 8.02 (m, 2 H, arom.), 7.63-7.56 (m, 2 H, arom.), 7.50-7.42 (m, 4 H, arom.), 6.34 (s, 1 H, C1-H), 5.29 (dd, 1 H, C3-H), 4.88 (m, 1 H, C4-H), 4.78 (dd, 1 H, C5-Ha), 4.63 (dd, 1 H, C5-Hb), 1.72 (d, 3 H, CH_3).

Example 6. (2R,3R,4R,5R)-5-bromo-2-((4-chlorobenzoyloxy)methyl)-4-fluoro-4-methyltetrahydrofuran-3-yl 4-chlorobenzoate (4b)

Anhydrous dichloromethane (530 mL) was added to a 1 L of dry round-bottomed flask and cooled to -22°C. Triphenylphosphine (19.5 g, 74 mmol) was added and then added the β-lactol (**2b**, 23.5 g, 53 mmol). To that solution, carbon tetrabromide (26.3 g, 79.5 mmol, solid) was added portionwise over 5 min. at -22°C. The reaction was slowly warmed up to room temperature and once reaction was complete, the solution was passed through a short pad of silica gel (148 g in a 600 mL of fritted disc Buchner funnel) to remove any brown color polar impurities. The colorless filtrate was concentrated to dryness under reduced pressure and the solid residue was dissolved in ethyl ether (170 mL). Hexanes (50 mL) was added slowly until a precipitate started to form. The product was collected as a light yellow solid via filtration and dried (0.2 mm Hg, 25°C, 17 h) to afford 21.23 g, (79%) with an anomeric ratio of α/β > 65:1. The product was contaminated with 3-4% of triphenylphosphine oxide which had no effect on the next reaction step. ^{1}H NMR ($CDCl_3$) : δ 8.05 (m, 2 H, arom.), 7.95 (m, 2 H, arom.), 7.47-7.40 (m, 4 H, arom.), 6.33 (s, 1 H, C1-H), 5.22 (m, 1 H, C3-H), 4.84 (m, 1 H, C4-H), 4.76 (m, 1 H, C5-Ha), 4.62 (m, 1 H, C5-Hb), 1.69 (d, 3 H, CH_3, J = 21.6 Hz).

Example 7. ((2R,3R,4R,5R)-3-(benzoyloxy)-4-fluoro-5-iodo -4-methyltetrahydrofuran-2-yl)methyl benzoate (5)

To a solution of compound **2** (1 g, 2.67 mmol), triphenylphosphine (700 mg, 2.67 mmol), and imidazole (180 mg, 2.67 mmol) in anhydrous CH_2Cl_2 (10 mL) iodine (680 mg, 2.68 mmol) was added. The resulting mixture was stirred for 30

min and poured into a silica gel column and eluted with EtOAc-hexanes (1:4) to give a syrupy product (1.3 g, quantitatve) and used in next reaction without further characterization.

Example 8. (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (6a)

To a 12 L of three-neck round-bottomed flask was charged 6-chloro-2-aminopurine (225.4 g, 1.329 mol). Anhydrous tert-BuOH (4.5 L) was added and the solution was stirred with a mechanical stirrer at ambient temperature. Potassium tert-butoxide (solid, 151.6 g, 1.35 mol) was added portion-wise under a flow of nitrogen gas while stirring. The mixture was stirred at RT for an additional 30 min. To a 5 L round-bottomed flask was loaded the α-bromide (**4a**, 197 g, 0.451 mol) and 3 L of anhydrous acetonitrile at ambient temperature. The bromide solution was added to the purine base suspension over 1 min at ambient temperature. The 5L flask was rinsed with acetonitrile (2x1L) to transfer bromide completely to the reaction mixture. The mixture was heated gradually to 50°C over 2 h with a heating mantle and controller, and stirred for 20 h. The reaction was almost complete as shown by TLC beta (R_f 0.28, 30% EtOAc in hexanes). The reaction was quenched by the addition of sat. NH_4Cl (200 mL) to form a suspension. The suspended solid[1] was removed by filtration through a 3 cm pad of Celite in a 2.5 L porcelain Buchner funnel. The solid was washed with toluene (3x100 mL). The combined filtrate was neutralized by adding 6 N HCl solution until pH 7 (approx 220 mL). The mixture was concentrated under reduced pressure. When the volume of mixture was reduced to about one-third volume, additional precipitated solid was removed by filtration in a similar manner. The filtrate was further concentrated to a volume of about 800 mL. The residue was loaded onto a plug column (1.6 kg flash grade silica gel in a 6 L sintered glass Buchner funnel) and eluted (via suction) with a gradient of 10% ethyl acetate in hexanes (6 L) to remove non-polar impurities, 30% ethyl acetate in hexanes to afford a small amount of lactol (6 L), and then 40%~45% ethyl acetate in hexanes (4 L) to elute the main amount of product. The product containing fractions were combined, concentrated under reduced pressure and dried under vacuum (0.2 mmHg, 24 h, ambient temp.) to a white foam solid (150.7 g, β/α = 14:1 by NMR.

^{1}H-NMR. ($CDCl_3$) beta: δ = 1.33 (d, 22.4 Hz, 2'-*C*-CH_3), alpha: 1.55 (d, 22 Hz, 2'-*C*-CH_3).

The product mixture foam was dissolved in methanol (700 mL) at ambient temperature. Upon standing, a solid slowly formed over 2 h. The suspension was cooled in a freezer to -5°C for 17 h. The resulting white solid was collected by filtration and washed with cold MeOH (-5°C, 3x60 mL) and ethyl ether (3x100 mL). The solid was dried under vacuum (0.2 mmHg, 24 h, ambient temp.) to afford 110.5 g of β-product with excellent de (β/α 99.8:1 by HPLC). The filtrate was partially concentrated (ca. 400 mL) and then diluted with more MeOH (400 mL) while heating to 60°C. The solution was cooled down to ambient temperature, seeded and the cooled to -5°C. The second crop was collected, washed and dried in a similar manner to give more product as a white solid (12.26 g) with similar diastereomeric purity. The mother liquor was concentrated to dryness under reduced pressure (ca. 25 g). The residue was a mixture of β and α-isomers. It was subjected to automated silica gel column chromatography (Analogix, 240 g cartridge, 40% to 50% ethyl acetate in hexanes) to afford 14.52 g of product foam which was recrystallized from MeOH, washed and dried in a similar manner to afford an additional 8.46 g of product in high purity.

The three solids were judged to be of similar purity and they were combined to give 131.2 g of white crystalline product **6a**, (55% from bromosugar, 49% from lactol). Mp 160.5-162.0°C. HPLC purity 99.5% including 0.20 % alpha.

^{1}H-NMR (pure β-anomer, $CDCl_3$): δ = 8.03 (m, 2 H, arom.), 7.93 (m, 2 H, arom.), 7.88 (s, 1 H, C8-H), 7.60 (m, 1 H, arom.), 7.50 (m, 1 H, arom.), 7.44 (m, 2 H, arom.), 7.33 (m, 2 H, arom.), 6.44 (dd, 1 H, C1'-H), 6.12 (d, 1 H, C3'-H), 5.35 (s, 2 H, NH_2), 5.00 (dd, 1 H, C5'-Ha), 4.76 (m, 1 H, C4'-H), 4.59 (dd, 1 H, C5'-Hb), 1.33 (d, 3 H, CH_3).

^{1}H-NMR (α-isomer, $CDCl_3$): δ = 8.11-8.09 (m, 3 H, arom. and C8-H), 8.01 (m, 2 H, arom.), 7.63 (m, 1 H, arom.), 7.55 (m, 1 H, arom.), 7.48 (m, 2 H, arom.), 7.39 (m, 2 H, arom.), 6.35 (d, 1 H, C1'-H), 5.76 (dd, 1 H, C3'-H), 5.18 (s, 2 H, NH_2), 4.93-4.89 (m, 1 H, C4'-H), 4.75-4.71 (m, 1 H, C5'-Ha), 4.58-4.54 (m, 1 H, C5'-Hb), 1.55 (d, 3 H, CH_3).

Example 9. (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-((4-chlorobenzoyloxy)methyl)-4-fluoro-4-methyltetrahydrofuran-3-yl-4-chlorobenzoate (6b)

To a 250 mL of dry round-bottomed flask was charged 2-amino-6-chloropurine (2.57 g, 15.1 mmol, 2.95 eq). Anhydrous tert-BuOH (51 mL) was added, followed by potassium tert-butoxide (1.73g, 15.4 mmol). The suspension was stirred at room temperature for 30 min. and then added to a solution of the bromide (**4b**, 2.60 g, 5.14 mmol) in anhydrous acetonitrile (86 mL). The mixture was heated at 50°C for 43 hours. The reaction was quenched by the addition of aq. sat'd ammonium chloride (3 mL). A precipitated solid consisting mostly of excess starting purine base was removed by filtration and the product containing filtrate was concentrated under reduced pressure. The resulting solid residue was triturated with ethyl acetate (110 mL). After removal of the remaining solid by filtration, the filtrate was washed with water (3x 40 mL), brine (1x 40 mL) and dried over sodium sulfate. The organic solution was concentrated under reduced pressure to afford 2.96 g of crude products with an anomeric ratio of β/α about 10:1. The crude product was purified through column chromatography (25% ethyl acetate in hexanes) to give 1.98 g (65%) of product as an oil. A portion was dissolved in methanol (8 ml/g) to furnish crystalline white solid (β/α = 26:1) mp shrinks 155, melts 167-175°C. ^{1}H NMR ($CDCl_3$) : δ 7.91 (m, 2 H, arom.), 7.84 (m, 2 H, arom.), 7.84 (s, 1 H, C8-H), 7.40 (m, 2 H, arom.), 7.28 (m, 2 H, arom.), 6.48 (dd, 1 H, C3'-H, J = 22.8 Hz, J = 9.2 Hz), 6.09 (d, 1 H, C1'-H, J = 18 Hz), 5.39 (s, 2 H, NH_2), 5.06 (m, 1 H, C5'-Ha), 4.73 (m, 1 H, C4'-H), 4.56 (m, 1 H, C5'-Hb), 1.32 (d, 3 H, CH_3, J = 22.4 Hz).

Example 10. (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (6a) from compound 3

To a solution of compound **3** (450 mg, 2.68 mmol) in chlorobenzene (1.5 mL) were added potassium salt of the base (1.37 g, 8.05 mmol) in t-butanol (5 mL) and subsequently anhydrous acetonitrile (5 mL) at rt. The resulting mixture was stirred at 80-140°C in a sealed tube for 7 days and concentrated *in vacuo* after neutralization with HCl. The residue was purified by silica gel column

chromatography (hexanes:EtOAc = 2:1) to give compound **6a** (90 mg, 15%) as a white foam.

Example 11. (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (6a) from compound 5

To a solution of compound **5** (1.3 g, 2.68 mmol) in t-butanol (10 mL) was added sodium salt of the base (1.37 g, 8.05 mmol) in DMF (10 mL) at ambient temperature. The resulting mixture was stirred for 15h and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 2:1) to give compound **6** (220 mg, 16%) as a white foam.

Example 12. (2R,3R,4R,5R)-5-(2-amino-6-methoxy-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol (7) from 6a

To a 250 mL dry round-bottomed flask was charged (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (**6a**, 7.50 g, 14.26 mmol). Anhydrous methanol (30 mL) was added and a white suspension was formed. At 50°C, a solution of sodium methoxide in methanol (25%, 19.7 mL, 64.17 mmol) was added via a dry syringe under a nitrogen atmosphere. A white cloudy reaction mixture was formed. After 3.5 h at 50°C, the reaction was complete with no starting material left as shown by TLC test. The mixture was cooled down to room temperature and neutralized by addition of glacial acetic acid (3 mL). A white solid was filtered out and washed with methanol (3x5 mL). The filtrate was mixed with 20 g of silica gel and concentrated to dryness. The mixture was loaded in line with a silica gel cartridge and separated via column chromatography using a gradient of methanol in dichloromethane 0 to 15% MeOH. The product eluted out at 12% methanol in dichloromethane. The product containing fractions were combined, concentrated under reduced pressure and dried under vacuum (0.2 mmHg, 50°C, 24 h) to a white powder solid (4.45 g, 98% yield), mp 199-202°C.

^{1}H-NMR (DMSO-d_6): δ = 8.18 (1 H, s, C8-H), 6.61 (2 H, s, NH_2), 6.05 (1 H, d, C1'-H), 5.68 (1 H, d, 3'-OH), 5.26 (1 H, m, 5'-OH), 4.23-4.13 (1 H, m, C3'-H), 3.96 (3 H, s, OCH_3), 3.92-3.83 (2 H, m, C4'-H and C5'-H_a), 3.70-3.67 (1 H, m, C5'-H_b), 1.06 (3 H, d, C2'-CH_3).

Example 13. (2R,3R,4R,5R)-5-(2-amino-6-methoxy-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol (7) from 6b

To a dry 5 L three-necked round flask fitted with a mechanical stirrer and an addition funnel was loaded (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(((4-chlorobenzoyl)oxy)methyl)-4-fluoro-4-methyltetrahydrofuran-3-yl 4-chlorobenzoate (**6b**, 313.2 g , 526.5 mmol). The solid was suspended in anhydrous methanol (2.1 L) and cooled in an ice-water bath under an atmosphere of nitrogen. A solution of sodium 25 wt.% methoxide in methanol (361 mL, 1.58 mol) was added via an additional funnel over 20 min to give a clear solution. The reaction was allowed to warm to room temperature for 6 hours to form a turbid solution. The completion of the reaction was confirmed by LC/MS by the lack of any remaining 6-chloro deprotected nucleoside. The reaction solution was acidified with con. HCl (132 mL, 1.58 mol). After standing at room termperature (1 h), the solution was filtered to remove a white precipitate. The precipitate was washed with methanol (3x 50 mL). The combined filtrate was concentrated under reduced pressure to afford a sticky solid residue. The residue was mixed with 420 mL of 2 N HCl (420 mL) and dichloromethane (1 L). The organic layer was separated and the aqueous layer was extracted with additional dichloromethane (3x 500 mL). To the aqueous layer, ethyl acetate (1.4 L) was added and solid sodium carbonate (86 g) was added portion-wise to neutralize the aqueous layer to ca pH 8 (caution: foaming). After separation of the organic layer, the solid in aqueous layer was dissolved by adding more water (200 mL). The aqueous layer was extracted with ethyl acetate (3x 700 mL and 400 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to a light yellow color solid that was redissolved in acetone (820 mL) at 50°C and stirred until new solid formation initiated. The saturated solution was cooled in a freezer and product was collected by filtration. The white solid was rinsed with acetone (2x 150 mL) and ethyl ether (3x 80 mL) and dried (0.2mm Hg, 50°C, 4 h) to a white crystalline solid, 151.6 g (92%) of material with NMR and HPLC matching material purified by chromatography.

Compound (**7a**) is prepared in a manner analogous to either Examples 12-13 for the preparation of compound (7).

Example 14. (2S)-isopropyl 2-((((2R,3R,4R,5R)-5-(2-amino-6-methoxy-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy) (phenoxy) phosphorylamino)propanoate (11)

To a 250 mL dry round-bottomed flask were loaded phenyl dichlorophosphate (2.66 g, 12.61 mmol) and anhydrous dichloromethane (40 mL). The amino ester salt (2.60 g, 15.53 mmol) was added to the solution and the mixture was cooled to -5°C. *N*-Methyl imidazole (7.7 mL, 97 mmol) was then added quickly via a dry syringe at -5°C and the solution was stirred at -5°C for 1 h. The nucleoside (7, 3.04 g, 9.7 mmol) was added from a vial in one portion at -5°C and the solid was slowly dissolved in 20 minutes. The reaction temperature was allowed to rise to ambient temperature over 2 h. After 17 h, the reaction was not complete. More chemical reagents were made (as described above from phosphate (2.66g), aminoester (2.60g), and NMI (3.8 mL, 48 mmol)) and added to the reaction mixture at -5°C. The reaction was stirred at room temperature for 2 more hours. The reaction was almost complete as shown by TLC result and diluted with 70 mL of dichloromethane·HCl solution (1 *N*, 70 mL) was added. The aqueous layer was separated and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$, water, brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the sticky residue was purified through automated column chromatography using a 240 g cartridge and a gradient of 0-8% 2-PrOH in dichloromethane to afford product as a foam solid (4.16 g, 7.14 mmol, 73% yield). HPLC purity 97.4%. NMR spectra of product showed it is a mixture of two diastereoisomers with a ratio of 1.2 : 1.

^{1}H-NMR (DMSO-d_6): δ = 7.98 (1 H, s, 8-H of one isomer), 7.95 (1 H, s, 8-H of another isomer), 7.37-7.32 (2 H, m, arom-H), 7.22-7.15 (3 H, m, arom-H), 6.6 (2 H, s, NH_2), 6.11 (1 H, d, C1'-H of one isomer), 6.09 (1 H, d, C1'-H of another isomer), 6.09-5.98 (1 H, m, amide NH), 5.88 (1 H, d, 3'-OH of one isomer), 5.81 (1 H, d, 3'-H of another isomer), 4.85-4.75 (1 H, hepta, methine H of *iso*-propyl), 4.46-4.27 (2 H, m, C4'-H, α-H of amino ester), 4.15-4.07 (1 H, m, C3'-H), 3.96 (3 H, s, OCH_3), 3.82-3.72 (2 H, m, C5'-H_a and C5'-H_b), 1.23-1.06 (9 H, m, CH_3's of amino ester), 1.03 (3 H, d, C2'-CH_3).

^{31}P-NMR (DMSO-d_6): δ = 4.91 (one isomer), 4.72 (another isomer).

An alternate purification method is to chemically alter the minor 3' phosphoramidate by-product in order to simplify the chromatographic separation.

The crude phosphoramidate product is dissolved in anhydrous pyridine (5 mL/g), and is treated with 0.5 molar equivalents of t-butyldimethylsilyl chloride at ambient temperature to react selectively with the free 5' primary hydroxyl of the 3' isomer impurity. Reaction progress can be monitored by LC/MS. Once the 3' isomer is converted to a 5'-tBDMS-3'-phosphoramidate derivative, the reaction is quenched with methanol (3 eq), concentrated under reduced pressure, partitioned between ethyl acetate and 5% citric acid and then the organic layer is concentrated. The residue is then subjected to chromatography which can now be done with a higher loading and a faster gradient and achieve a higher purity.

Compounds (**11a**) and (**11b**) are prepared by an analogous method as Example 14 using compounds (**10**) and (**7a**) as starting reagents.

Example 15. (2R,3R,4R,5R)-5-(2-amino-6-(azetidin-1-yl)-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol (8)

To a 350 mL of dry seal pressure flask (Chemglass) were added (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (**6a**, 3.6 g, 6.85 mmol) and 150 mL of absolute ethanol. Azetidine hydrochloride (2.56 g, 27.4 mmol) was added and then followed by triethylamine (4.16 g, 41.1 mmol). The supension was stirred and heated to 70°C while sealed for 5 hours. All the starting material was consumed but the benzoyl groups remained as shown by TLC. Sodium methoxide (7.8 mL, 34.3 mmol, 25% solution in methanol) was added to the mixture and heated at 50°C. The reaction was complete after 3.5 h. The reaction mixture was allowed to cool to room temperature and neutralized by addition of glacial acetic acid (0.41 g, 6.85 mmol). The mixture was concentrated under reduced pressure and then the residue was triturated with ethyl acetate. The resulting solid was removed by filtration and the solid was washed with EtOAc (2x 15 mL). The filtrate was concentrated under reduced pressure and the residue was purified via column chromatography (Analogix, 120 g cartridge, gradient of 0 to15% MeOH in DCM). The pure product containing fractions were combined, concentrated under reduced pressure and dried (50°C, 0.2 mmHg, 17 h) to a light pink colored foam solid (2.15 g, 6.35 mmol, 93%).

^{1}H-NMR (DMSO-d_6) δ = 8.00 (s, 1 H, C8-H), 6.03 (s, 2 H, NH_2), 6.00 (d, 1 H, C1'-H), 5.64 (d, 1 H, 3'-OH), 5.24 (t, 1 H, 5'-OH), 4.24-4.10 (m, 5 H, N-CH_2 of

azetidine, C3'-H), 3.90-3.81 (m, 2 H, C4'-H and C5'-H_a), 3.69-3.64 (m, 1 H, C5'-H_b), 2.37 (penta, 2 H, center CH_2 of azetidine), 1.05 (d, 3 H, C2'-CH_3).

Example 16. (2S)-methyl 2-((((2R,3R,4R,5R)-5-(2-amino-6-(azetidin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (12)

To a 100 mL dry round-bottomed flask were added phenyl dichlorophosphate (1.72 g, 8.15 mmol) and anhydrous dichloromethane (17 mL). The amino ester (1.42 g, 10.2 mmol) was added and the suspension was cooled to -5°C. *N*-Methylimidazole (3.34 g, 40.7 mmol) was added via a syringe in one portion and the solution was stirred at -5°C for 1 h under a nitrogen atmosphere. The nucleoside (**8**, 1.38 g, 4.07 mmol) (foam solid) was then added in one portion and the solution was allowed to warm up over 1 h to ambient temperature. After 4 h at ambient temperature, TLC (5% MeOH in DCM) indicated an incomplete reaction (about 30% SM remained) but also a growing less polar impurity. The reaction was quenched by the addition of sat NH_4Cl (20 mL) and diluted with dichloromethane (20 mL). The organic layer was separated and washed with water (5x 30 mL), brine (20 mL) and dried over Na_2SO_4. The product containing solution was filtered and concentrated under reduced pressure to a crude oily residue, 3.26 g. This was purified by column chromatography (Analogix, 40 g cartridge, gradient of MeOH in DCM from 0% to 10%). The product eluted at 4% MeOH in DCM. The pure product containing fractions were combined, concentrated under reduced pressure and dried (50°C, 0.2 mmHg, 17 h) to a white foam solid (1.322 g, 2.28 mmol, 56%). HPLC purity 99.25%. NMR spectra of product showed it is a mixture of two diastereoisomers with a ratio of 55:45.

^{1}H-NMR (DMSO-d_6) δ = 7.80 (s, 1 H, 8-H of one isomer), 7.80 (s, 1 H, 8-H of another isomer), 7.38-7.33 (m, 2 H, arom-H), 7.22-7.14 (m, 3 H, arom-H), 6.09 (s, 2 H, NH_2), 6.12-6.02 (m, 2 H, C1'-H and NH), 5.83 (d, 1 H, 3'-OH of one isomer), 5.77 (d, 1 H, 3'-OH of another isomer), 4.46-4.05 (m, 8 H, NCH_2 of azetidine, α-H of aminoester, C3'-H, C4'-H, C5'-H_a), 3.89-3.79 (m, 1 H, C5'-H_b), 3.56 (s, 3 H, OCH_3 of aminoester in one isomer), 3.54 (s, 3 H, OCH_3 of aminoester in another isomer), 2.37 (penta, 2 H, center CH_2 of azetidine), 1.21 (d, 3 H, α-CH_3 of aminoester in one isomer), 1.19 (d, 3 H, α-CH_3 of aminoester in another isomer), 1.08 (d, 3 H, C2'-CH_3).

^{31}P NMR (DMSO-d_6): δ 4.85 (one isomer), 4.77 (other isomer).

Example 17. (2R,3R,4R,5R)-5-(2-amino-6-(benzyloxy)-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol (9)

To a 500 mL of dry round-bottomed flask were added (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (**6a**, 8.0 g, 15.2 mmol) and anhydrous benzyl alcohol (128 mL). To another 250 mL of dry round-bottomed flask were charged NaH (60% in mineral oil, 2.44 g, 60.8 mmol) and anhydrous DMF (40 mL). The suspension was stirred at 0°C in an ice-water bath. Benzyl alcohol (27 mL) was added drop-wise via a syringe. A solution was slowly formed and it was transferred to the nucleoside suspension quickly under a nitrogen atmosphere at room temperature. The mixture was heated to 50°C and stirred. The reaction was complete after 3 h and cooled to ambient temperature. It was neutralized by the addition of 4 *N* HCl to *ca.* pH=7 (12 mL). The solution was concentrated under reduced pressure (4 mbar, 90°C bath). The cloudy residue was diluted with dichloromethane (100 mL) and washed with water (3x 30 mL), brine (30 mL) and dried over Na_2SO_4. The suspension was filtered and the filtrate was concentrated under reduced pressure to an oily residue. This was purified by column chromatography (Analogix, 0 to 8% gradient of MeOH in DCM). The product eluted at 4% MeOH in DCM. The product containing fractions were combined, concentrated under reduced pressure and dried (50°C, 0.2 mmHg, 17 h) to a white foam solid (4.57 g, 11.7 mmol, 77.2%).

^{1}H-NMR (DMSO-d_6) δ = 8.18 (s, 1 H, 8-H), 7.53-7.51 (m, 2 H, arom-H), 7.43-7.34 (m, 3 H, arom-H), 6.66 (s, 2 H, NH_2), 6.05 (d, 1 H, C1'-H), 5.67 (d, 1 H, 3'-OH), 5.48 (dd, 2 H, CH_2 of Benzyl), 5.25 (t, 1 H, 5'-OH), 4.18 (dt, 1 H, C3'-H), 3.92-3.82 (m, 2 H, C4'-H and C5'-H_a), 3.71-3.66 (m, 1 H, C5'- H_b), 1.07 (d, 3 H, C2'-CH_3).

Example 18. (2S)-cyclopentyl 2-((((2R,3R,4R,5R)-5-(2-amino-6-(benzyloxy)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (13)

To a 100 mL of dry round-bottomed flask were charged phenyl dichlorophosphate (3.29 g, 15.58 mmol) and anhydrous dichloromethane (24 mL).

The aminoester tosylate (white powder) was added and the solution was cooled to -5°C under nitrogen. *N*-Methylimidazole (4.92 g, 59.94 mmol) was added via a dry syringe in one portion and the resulted colorless clear solution was stirred at -5°C for one hour. Then the nucleoside (**9**) solid was added (2.334 g, 5.99 mmol) to the solution under nitrogen in one portion and the mixture was allowed to warm to ambient temperature to give a colorless solution. Reaction progress was monitored by TLC (5% methanol in dichloromethane). TLC indicated an incomplete reaction after 20 h (about 30% starting material left). The reaction was still quenched by the addition of dichloromethane (30 mL) and 1 *N* HCl (60 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2x20 mL). The combined organic layer was washed with water (2x40 mL), sat $NaHCO_3$ (30 mL), water, and brine. The organic layer was dried over Na_2SO_4. After removal of solid by filtration, the filtrate was concentrated under reduced pressure to a gummy residue (7.28 g). The residue was purified via column chromatography (Analogix, 80 g cartridge, gradient of 0 to 10% MeOH in DCM). The product eluted at 2% MeOH in DCM. The product containing fractions were combined, concentrated under reduced pressure and dried (50°C, 0.2 mmHg, 17 h) to a white foam solid (2.249 g, a mixture of two isomers, 60:40). A portion of the starting nucleoside (0.257 g) was also recovered. Yield is 62% based on consumed starting material.

^{1}H-NMR (DMSO-d_6): δ = 7.98 (s, 1 H, 8-H of one isomer), 7.96 (s, 1 H, 8-H of another isomer), 7.52-7.50 (m, 2 H, arom-H), 7.42-7.31 (m, 5 H, arom-H), 7.21-7.12 (m, 3 H, arom-H), 6.68 (s, 2 H, NH_2), 6.12 (d, 1 H, C1'-H of one isomer), 6.10 (d, 1 H, C1'-H of another isomer), 6.04-5.96 (m, 1 H, NH), 5.87 (d, 1 H, 3'-OH of one isomer), 5.81 (d, 1 H, 3'-OH of another isomer), 5.48 (dd, 2 H, CH_2 of Benzyl), 4.99-4.93 (m, 1 H, α-H of aminoester), 4.46-4.27 (m, 3 H, C3'-H, C4'-H, OCH of aminoester), 4.15-4.06 (m, 1 H, C5'-H_a), 3.81-3.71 (m, 1 H, C5'- H_b), 1.74-1.43 (m, 8 H, methylene CH_2 of *c*-pentyl), 1.18 (d, 3 H, α-CH_3 of aminoester), 1.09 (d, 3 H, C2'-CH_3 of one isomer), 1.08 (d, 3 H, C2'-CH_3 of another isomer).

^{31}P NMR (DMSO-d_6): δ = 4.91 (one isomer), 4.73 (other isomer).

Example 19. (2S)-cyclopentyl 2-((((2R,3R,4R,5R)-5-(2-amino-6-hydroxy-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (14)

To a 250 mL of dry round-bottomed flask with starting material (**13**, 1.92 g, 2.8 mmol) was added anhydrous absolute ethanol (50 mL). Palladium on charcoal (10%, 120 mg) was added. The atmosphere in the flask was exchanged with hydrogen and the mixture was stirred under 1 atm of hydrogen gas for 3.5 h at room temperature. The reaction was judged complete by TLC and the Pd on charcoal was removed by filtration and washed with ethanol (2x 10 mL). The filtrate was concentrated under reduced pressure to a solid residue. The solid was mixed with silica gel (10 g) and purified by column chromatography (Analogix, 40 g cartridge, gradient of 1% to 16% MeOH in DCM). The product containing fractions were combined, concentrated under reduced pressure and dried (50°C, 0.2 mmHg, 17 h) to a white powder (1.43 g, 86%). HPLC purity 99.55%. NMR spectra of product showed it is a mixture of two diastereoisomers with a ratio of 60:40. Mp =133~150°C.

^{1}H-NMR (DMSO-d_6): δ = 10.70 (s, 1 H, NH of imide), 7.81 (s, 1 H, 8-H of one isomer), 7.79 (s, 1 H, 8-H of another isomer), 7.38-7.33 (m, 2 H, arom-H), 7.22-7.14 (m, 3 H, arom-H), 6.62 (s, 2 H, NH_2), 6.08-5.97 (m, 2 H, C1'-H and NH of aminoester), 5.88 (b, 1 H, 3'-OH of one isomer), 5.82 (b, 1 H, 3'-OH of another isomer), 5.01-4.94 (m, 1 H, α-H of aminoester), 4.44-4.25 (m, 3 H, C3'-H, C4'-H, OCH of aminoester), 4.12-4.04 (m, 1 H, C5'-H_a), 3.82-3.72 (m, 1 H, C5'- H_b), 1.77-1.46 (m, 8 H, methylene CH_2 of *c*-pentyl), 1.21-1.19 (m, 3 H, α-CH_3 of aminoester), 1.09 (d, 3 H, C2'-CH_3 of one isomer), 1.08 (d, 3 H, C2'-CH_3 of another isomer).

^{31}P-NMR (DMSO-d_6): δ = 4.95 (one isomer), 4.72 (another isomer).

Example 20. (2R,3R,4R,5R)-5-(2-amino-6-ethoxy-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol (10) from 6a

To a 500 mL of dry round-bottomed flask was loaded (**6a**, 11 g, 20.92 mmol). Anhydrous absolute ethanol (210 mL) was added and followed by anhydrous K_2CO_3 (28.91 g, 209.2 mmol). The suspension was stirred and heated at 75°C under nitrogen for 5.5 h. All the starting material was consumed at that time by TLC test. The mixture was cooled to room temperature and solid was filtered out. The filtrate was neutralized by addition of glacial acetic acid (2.52 g) to pH~7

and concentrated under reduced pressure. The residue was dissolved in methanol and mixed with silica gel (15 g). The dried mixture of crude product and silica gel was transferred to an empty cartridge and separated through column chromatography (Analogix 220 g, gradient of 0 to 15% MeOH in DCM) to afford product (5% MeOH in DCM) as a white foam solid (3.73 g, 54.5%). A second white solid was isolated from column (10% MeOH in DCM, 1.44 g) and it is a mixture of two dimers of nucleoside. A more polar, third white solid was collected from column (15% MeOH in DCM, 0.47 g) and it is a mixture of trimers of nucleoside. HPLC purity of product 99.94%.

^{1}H-NMR (DMSO-d_6): δ 8.16 (s, 1 H, 8-H), 6.55 (s, 2 H, NH_2), 6.04 (d, 1 H, C1'-H), 5.66 (d, 1 H, 3'-OH), 5.24 (m, 1 H, 5'-OH), 4.44 (q, 2 H, 6-OCH_2), 4.23-4.08 (m, 1 H, C3'-H), 3.91-3.82 (m, 2 H, C4'-H and C5'-H_a), 3.71-3.66 (m, 1 H, C5'- H_b), 1.36 (t, 3 H, CH_3 of ethyl), 1.06 (d, 3 H, C2'-CH_3).

Example 21. (2R,3R,4R,5R)-5-(2-amino-6-ethoxy-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol (10) from 6b

(2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(((benzoyl)oxy)methyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (**6b**, 9.66 g, 18.4 mmol) was coevaporated with abs. ethanol (50 mL) under reduced pressure to remove any traces of methanol. Sodium ethoxide solution was prepared by adding sodium hydride (60 wt.% in mineral oil, 2.21 g, 55.2 mmol) in small portions to abs. ethanol (50 mL) cooled in an ice bath under a nitrogen atmosphere (caution, hydrogen gas evolution). This was added to the starting material and the resulting mixture was heated to reflux for one hour and then neutralized by addition of concentrated HCl at 5°C. The solution was concentrated under reduced pressure and to the residue was added was added 1N HCl (18 mL) and dichloromethane (18 mL). The layers were separated and the aqueous layer was washed with dichloromethane (2x10 mL). To the aqueous solution, ethyl acetate was added and sat. sodium carbonate solution was added to adjust the pH of aqueous layer to *ca* 8. The organic layer was separated and the aqueous layer was extracted with EtOAc (4x10 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to a light yellow foam solid. The crude mixture was purified by crystallization from acetone (10 mL) to give pure product in two crops. The

combined solid product was dried (50°C, 0.2 mmHg, 24 h) to 5.04 g (84%) of material with NMR and HPLC matching material purified by chromatography.

Example 22. N^6,N^6-Diethyl-9-((4aR,6R,7R,7aR)-7-fluoro-2-methoxy-7-methyl-tetrahydro-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl)-9H-purine-2,6-diamine (phosphite precursor to 15)

(2R,3R,4R,5R)-5-(2-Amino-6-azetidin-1-yl-purin-9-yl)-4-fluoro-2-hydroxymethyl-4-methyl-tetrahydro-furan-3-ol (**8**, 340 mg, 1.0 mmol) was dissolved in anhydrous pyridine (6 ml) at ambient temperature. A solution of 0.45 M 1H-tetrazole in acetonitrile (5.5 mL, 2.5 mmol) was added followed by bis (N,N-diisopropylamino)methylphosphoramidite (317 µL, 1.1 mmol). The mixture was stirred at ambient temperature for 17 h. The solvent was concentrated under reduced pressure and the residue was triturated with ethyl acetate (20 mL). The resulting precipitant of salts was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate in hexanes (40-80%). The product containing fractions were combined and concentrated to a white solid, 47 mg (12% yield).

Example 23. 6-Azetidin-1-yl-9-((4aR,6R,7R,7aR)-7-fluoro-2-methoxy-7-methyl-2-oxo-tetrahydrofuro[3,2-d][1,3,2]dioxaphosphinin-6-yl)-9H-purin-2-ylamine (15)

To a stirred solution of the cyclic phosphite (47 mg, 0.12 mmol) in dichloromethane (2 mL) was added 77% mCPBA (32mg, 0.14 mmol) at ambient temperature. After 5 min, the solution was concentrated under reduced pressure the residue was purified by silica gel column chromatography (4 g) using a gradient of ethyl acetate in hexanes (80-100%). The pure product fractions were combined and concentrated under reduced pressure to a white solid, 21 mg (43%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.45 and 7.44 (two s, 1H), 5.45 (d, J=20Hz, 1H), 4.89-4.41 (m, 10H), 3.93 (app. t, J=13.0Hz, 3H), 2.49 (bs, 2H), 1.39 (overlapping d, J=22.4Hz, 3H); MS (ESI) *m/z* 415 $(M+H)^+$.

^{31}P-NMR (162 MHz, $CDCl_3$): δ = -1.26, -3.58;

Example 24. 6-Ethoxy-9-((4aR,6R,7R,7aR)-7-fluoro-2-methoxy-7-methyl-2-oxo-tetrahydro-2,5-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl)-9H-purin-2-ylamine (16)

(2R,3R,4R,5R)-5-(2-Amino-6-ethoxy-purin-9-yl)-4-fluoro-2-hydroxymethyl-4-methyl-tetrahydro-furan-3-ol (**10**, 150 mg, 0.46 mmol) was dissolved in anhydrous pyridine (2 ml) at 0°C. A solution of 0.45 M 1H-tetrazole in acetonitrile (2.55 mL) was added followed by bis (N,N-diisopropylamino)methylphosphoramidite (0.16 mL, 0.55 mmol). The mixture was allowed to slowly warm to ambient temperature over 5 h. TLC indicated a complete reaction. The reaction was quenched upon the addition of water (0.1 mL). The reaction solution was concentrated under reduced pressure and then the residue was triturated with ethyl acetate (5 mL). The resulting white precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting intermediate cyclic phosphite residue was dissolved in acetonitrile (2 mL) and then treated with t-butyl hydroperoxide (70% in water, 0.25 mL) for 17 at ambient temperature. TLC indicated a complete reaction. The reaction solution was concentrated under reduced pressure and the residue was purified by column chromatography (Analogix using a gradient of 0 to 10% IPA in DCM). The product containing fractions were combined and concentrated under reduced pressure to a white solid, 80 mg (34% yield) as a mixture of two diastereomers ~2:1.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.16 (s, 1.5H), 6.65 (s, 2H), 6.55 (bs, 1H), 6.28 (d, J = 20.8 Hz, 1.5H), 4.78-4.60 (m, 4.5H), 4.45 (q, J = 6.8 Hz, 1H), 4.44 (q, J = 6.8 Hz, 2H), 4.28-4.22 (m, 1.5H), 3.83 (d, J = 11.6 Hz, 1.5H), 3.76 (d, J = 11.6 Hz, 3H), 1.36 (t, J = 7.2 Hz, 1.5H), 1.36 (t, J = 7.2 Hz, 3H), 2.46 (d, J = 22.4 Hz, 1.5H), 2.44 (d, J = 22.8 Hz, 3H).

^{31}P-NMR (162 MHz, DMSO-d_6): δ -3.25, -4.16; t_R = 0.86 (35.0%), 0.89 (64.4%).

LRMS (ESI): $[M + H]^+$ calculated for $C_{14}H_{20}FN_5O_6P$ 404.3, found 404.3.

Example 25. 6-Ethoxy-9-((4aR,6R,7R,7aR)-7-fluoro-2-isopropoxy-7-methyl-2-oxo-tetrahydro-2,5-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl)-9H-purin-2-yl amine (17)

(2R,3R,4R,5R)-5-(2-Amino-6-ethoxy-purin-9-yl)-4-fluoro-2-hydroxymethyl-4-methyl-tetrahydro-furan-3-ol (**10**, 150 mg, 0.46 mmol) was

dissolved in anhydrous pyridine (2 ml) at 0°C. A solution of 0.45 M 1H-tetrazole in acetonitrile (2.55 mL) was added followed by bis (N,N-diisopropylamino)ispropylphosphoramidite (0.16 mL, 0.55 mmol, 1.2 eq). The mixture was allowed to slowly warm to ambient temperature over 3 h. TLC indicated a complete reaction. The reaction was quenched upon the addition of water (0.1 mL). The reaction solution was concentrated under reduced pressure and then the residue was triturated with ethyl acetate (5 mL). The resulting white precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting intermediate cyclic phosphite residue was dissolved in acetonitrile (2 mL) and then treated with t-butyl hydroperoxide (70% in water, 0.19 mL) for 5 h at ambient temperature. TLC indicated a complete reaction. The reaction solution was concentrated under reduced pressure and the residue was purified by column chromatography (Analogix using a gradient of 0 to 5% IPA in DCM). The two diastereomers were separable. Fractions containing each diastereomer were separately combined and concentrated under reduced pressure to white solids to give 20 mg of each diastereomer (combined yield 20%).

*R*P-**17**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H, C8-*H*), 6.02 (br d, 1H, J= 19.6 Hz, C1'-*H*), 5.46 (br s, 1H, 3'-*H*), 4.90 (sept, 1H, J = 6.4 Hz, C*H*$(CH_3)_2$), 4.84 (br s, 2H, N*H*$_2$), 4.69-4.42 (m, 4H, 5'-*Ha* and *Hb*, C*H*$_2CH_3$), 4.40-4.37 (m, 1H, 4'-*H*), 1.48-1.33 (m, 9H, CH(C*H*$_3)_2$) and CH_2CH_3), 1.35 (d, 3H, J= 22 Hz, 2'-C-C*H*$_3$). ^{31}P-NMR (162 MHz, $CDCl_3$ with respect to an external standard of triphenylphosphate in $CDCl_3$ set to -17.80): δ -7.18 (s). LRMS (ESI) $[M + H]^+$ calculated for $C_{16}H_{24}FN_5O_6P$ 432.4, found 432.4. Optical rotation $[\alpha]^{25}_D$ -80.3 (*c* 1.00, methanol). Elemental analysis: Calcd: C, 44.15; H, 5.37; N, 16.24. Fd: C, 44.21; H, 5.21; N, 15.90. Mp 193.5-197.0 (melt with decomp.)

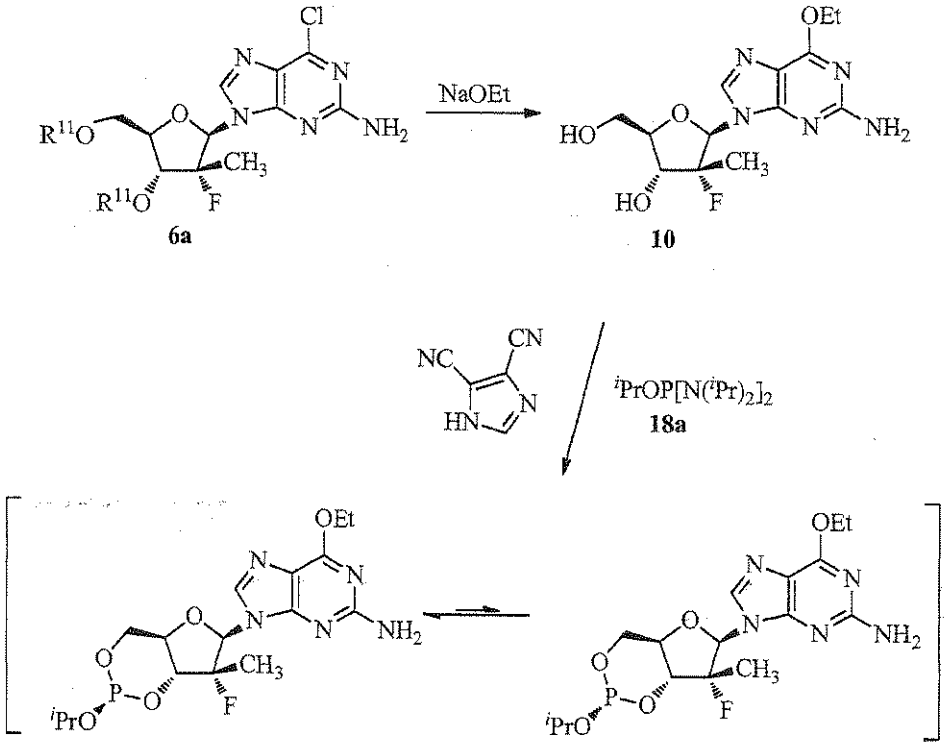
*S*P-**17**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H, C8-*H*), 5.98 (br d, 1H, J= 20.0 Hz, C1'-*H*), 5.78 (br s, 1H, 3'-*H*), 5.10 (br s, 2H, N*H*$_2$), 4.83 (sept, 1H, J = 6.4 Hz, C*H*$(CH_3)_2$), 4.63-4.48 (m, 4H, 5'-*Ha* and *Hb*, C*H*$_2CH_3$), 4.45-4.38 (m, 1H, 4'-*H*), 1.47-1.21 (m, 12H, CH(C*H*$_3)_2$), CH_2CH_3 and 2'-C-C*H*$_3$). ^{31}P-NMR (162 MHz, $CDCl_3$ with respect to an external standard of triphenylphosphate in $CDCl_3$ set to -17.80) δ -3.74 (s). LRMS (ESI) $[M + H]^+$ calculated for $C_{16}H_{24}FN_5O_6P$ 432.4, found 432.4.

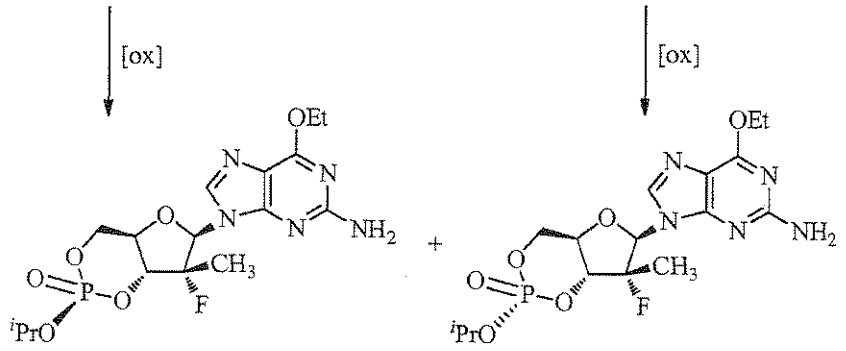
Alternative Synthetic Process for Cyclic Phosphate Nucleotide, **17**. (**Scheme 2**.)

We have found that the cylic phosphate nucleotide, such as **17**, can be prepared using either P(III)- or P(V)-reagents, as evidenced by the following discussion and accompanying schemes.

The P(III)-reagent cyclization reaction incorporating nucleoside **10** and a P(III)-reagent, such as **18** using 1H-tetrazole as the activator initially gives an approximately equimolar mixture of cyclic phosphite diastereomers, but with elevated reaction temperature (50-60°C) for 6-24 hours, the mixture equilibrates predominantly to the cis isomer as reported in the literature. We have found that 4,5-dicyanoimidazole, DCI, accelerates this conversion rate and drives the equilibrium from initially approximately 80% to greater than 95% cis at 40-60°C after 6 h. The *cis*-phosphite diastereomer leads to R_P-**17** upon oxidation and also doubles the effective yield of this diastereomer and also simplifies the purification away from S_P-**17**. We have found it more efficient to oxidize the crude cyclic phosphite esters directly, but it is possible to isolate them as well. The cyclic phosphate esters do not equilibrate under the reaction conditions.

Scheme 2. Cyclic Phosphate Nucleotide By P(III)-Reagent



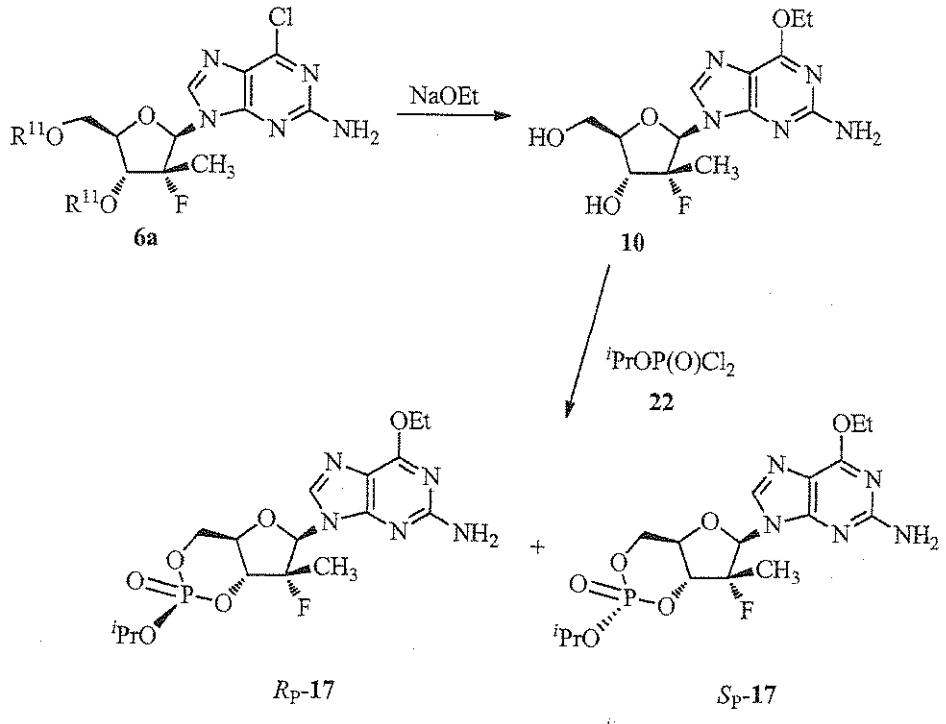


R_P-17 S_P-17

Oxidation [ox] of the phosphite esters to the phosphate esters can be accomplished in many ways. Peroxides such as m-chloroperbenzoic acid, t-butylhydroperoxide, hydrogen peroxide work well but are potentially explosive. Urea hydrogen peroxide is a safer peroxide form that works well for this conversion. One can envision using potassium persulfate, bleach and air-oxidation with or without catalysts such as TEMPO. We have chosen to use an iodine-THF-pyridine-water based oxidation reagent commonly used in automated oligonucleotide synthesis. The reaction is nearly instantaneous and can be monitored colorimetrically based on the brown color of iodine.

Alternatively, the diastereomers, R_P-**17**and S_P-**17**, can be prepared directly from compound (**10**) by using an appropriate P(V)-reagent, as illustrated in **Scheme 3**.

Scheme 3. Cyclic Phosphate Nucleotide By P(V)-Reagent



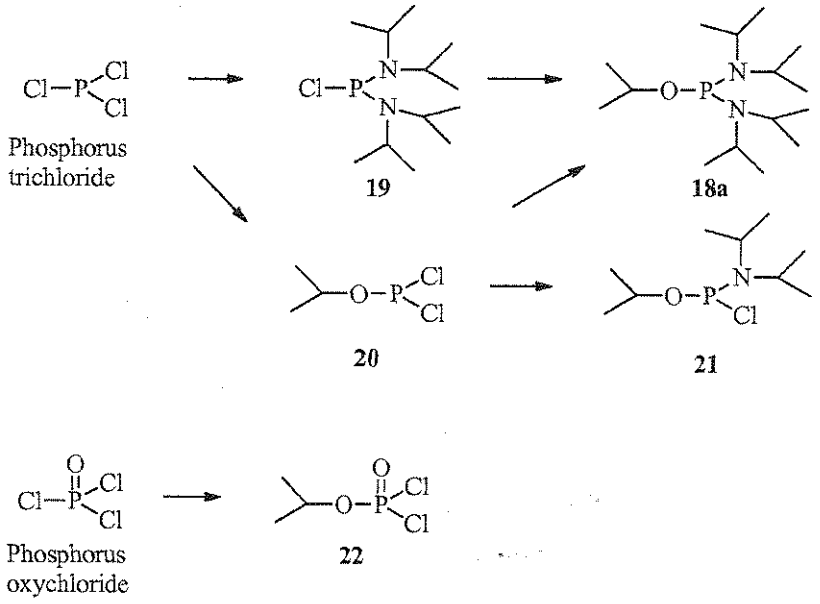
For P(V)-reagent-based chemistry, one can start with phosphorus oxychloride and monsubstitute one chloride with isopropanol. The resulting dichlorophosphate isopropanoate reagent **22** (Grunze et al., US Patent 2,960,527) can be purified by vacuum distillation and can then be reacted with nucleoside **10** to form R_P-**17**directly in approximately 50-70% isolated yield. Using the described conditions with triethylamine and N-methylimidazole, only traces of S_P-**17** can be observed. The resulting crude product after an aqueous workup is also more amenable to direct crystallization without pre-purification by chromatography.

Purification of R_P-**17**from S_P-**17** and other by-products such as ring opened phosphates can be accomplished through washing an organic solution of the crude product with dilute base to remove free phosphates and the activating reagents followed by silica gel chromatography or crystallization or by a combination of both. As noted earlier, the desired product R_P-**17**crystallizes readily from several solvents that include ethyl acetate, acetone and isopropanol. Although the gross form of the crystals vary, an XPRD study of crystals from the three solvents showed a single polymorph which is the same as could be mathematically predicted from the single crystal x-ray from ethyl acetate.

The synthesis of the cyclic phosphate ester can be done either through P(III)- or P(V)-reagents. Chemistry involving the use of the P(III)-reagent requires an

oxidation step for the intermediate cyclic phosphite esters as shown in **Scheme 2**. For the P(III)-reagent chemistry, the preferred route is to make the phosphorus reagent, isopropyl-N,N, N',N'-tetraisopropylphosphorodiamidite (**18**), which is not commercially available, but can be prepared readily by reacting commercially available chloro-N,N,N',N'-tetraisopropylphosphorodiamidite (**19**) with isopropanol in the presence of a tertiary amine base as described below. Reagent **18** can be used as crude or it can be purified by vacuum distillation. Based on an analogous compound known in the literature, 2-cyanoethyl-N,N, N',N'-tetraisopropylphosphorodiamidite commonly used in oligonucleotide chemistry, one can envision also synthesizing **18** by reacting isopropanol or its trimethylsilyl ether with phosphorus trichloride to form the dichloro intermediate **20** which could then be converted to **18** or the monoamine reagent **21**. Intermediate **20** can be reacted directly with the nucleoside in pyridine to make the intermediate cyclic phosphite esters although in a poor yield. The diisopropylamine groups in **18** can be activated for displacement by acidic and/or nucleophilic reagents. This method is well-documented in the literature for automated synthesis of oligonucleotides and their nucleoside phosphoramidite precursor reagents. 1H-tetrazole is the most commonly used activator reagent historically, but this activator reagent is no longer readily available in the US due to hazardous shipping regulations of a potentially explosive compound. We have found that non-explosive known activator reagent DCI gives superior yields for our cyclic phosphate ester derivatives. Other known activators such as 5-ethylthiotetrazole and imidazolium triflate also work as well as 1H-tetrazole.

Scheme 4. Synthesis of Selected P(III)- and P(V) Reagents



Example 26. Isopropyl-N,N,N',N'-tetraisopropylphosphorodiamidite (18a)

Bis(diisopropylamino)chlorophosphine (**19**, 250.1 g, 937 mmol) was dissolved in anhydrous ethyl ether (3.6 L) and triethylamine (190 g, 1.87 mol) was introduced. The turbid mixture was cooled at 0°C and a solution of 2-propanol (225 g, 287 mL) in ether (200 mL) was added via a funnel. The resulting cloudy mixture was stirred at room temperature for 5.5 hours. The reaction was complete by checking with ^{31}P NMR (δ = 116.10 ppm, S). White solid (triethylamine HCl salt) was removed by filtration. The filtrate was concentrated to furnish a pale brown liquid (272 g, quantitative) and used for next step without further purification. Note that the P(III)-reagent can be purified by vacuum distillation (bp 84-86°C, 5 mm Hg) if desired to furnish a colorless clear oil. ^{1}H NMR ($CDCl_3$): δ 3.91 (m, 1H), 3.51 (m, 4 H), 1.19 (d, 6 H, J = 6 Hz), 1.16 (24 H, m). . ^{31}P NMR ($CDCl_3$): δ 116.1.

Example 27. 6-Ethoxy-9-((2*R*,4a*R*,6*R*,7*R*,7a*R*)-7-fluoro-2-isopropoxy-7-methyl-2-oxo-tetrahydro-2λ^5-furo[3,2-*d*][1,3,2]dioxaphosphinin-6-yl)-9H-purin-2-ylamine (17-R_P) and 6-Ethoxy-9-((2S,4a*R*,6*R*,7*R*,7a*R*)-7-fluoro-2-isopropoxy-7-methyl-2-oxo-tetrahydro-2λ^5-furo[3,2-*d*][1,3,2]dioxaphosphinin-6-yl)-9H-purin-2-ylamine (S_P-17)

To a stirred suspension of (2R,3R,4R,5R)-5-(2-amino-6-ethoxy-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol (**10**, 65.0 g, 0.199 mol) and 4,5-dicyanoimidazole (59 g, 496 mol) in acetonitrile (1000 mL) at 0-5°C was added P(III)-reagent **18** (62.35 mL, 0.199 mol), drop-wise over a period of 20

min. The solid was dissolved after the completion of the addition of the P(III)-reagent and a clear solution was observed. After 30 min, the solution was warmed to room temperature and stirred for 3h. The reaction mixture was then heated at 50°C (bath) for 6h. (A small aliquot of the reaction was solution was diluted with an equal volume of $CDCl_3$ and tested by P-NMR to show less than 5% of the minor trans isomer at δ 127.91 ppm. The solvent was evaporated to dryness and the residue was stirred with EtOAc (500mL) to form a white solid suspension of the DCI salt. The solid was removed by filtration and washed with EtOAc (250mL). The combined filtrate was concentrated to dryness. To the residue was added a 0.1M solution of iodine in 70:28:2 (each in v/v %) THF:Pyridine:H_2O (2L) over a period of 30min at 5-10°C After 2h, more white DCI salt solid was collected by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (1L), washed with a 10% aqueous sodium thiosulfate (200mL) and then saturated aq.$NaHCO_3$ (3 x 250mL) until DCI was mostly removed as judged by TLC. The organic layer was washed with water (250mL). (Also note that saturated sodium carbonate solution can remove DCI more efficiently). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give 86g of foam. This was combined with similar material from two additional runs totaling 259 mmol of starting nucleoside. The combined crude foams were dissolved in a minimum of dichloromethane and subjected to silica gel chromatography using 3 L of silica gel in a 6 L sintered glass Buchner funnel with a step gradient of 30-75 % EtOAc/hexanes to give 83 g of purified product as a foam as the primary fraction and 16 g of a secondary partially purified fraction. The primary fraction was suspended in ethyl ether (250 mL) which immediately gave a fine granular solid. The solid was collected by filtration and dried (40°C, 0.2mmHg, 17 h) to 73.5 g of slightly off white powder containing 20 mole% of ethyl ether. The solid was co-evaporated with acetone (200 mL) and re-dried in a similar manner to 71.5 g of white solid with 2 mole% of acetone, and HPLC purity of 98.5%. The secondary contaminated fractions were purified by chromatography to afford an additional 9.0 g for a total recovery of 80.5 g (41%) of pure product. Portions of the desired R_P-**17**solid could be re-crystallized into large irregular prisms by slow evaporation of product solutions in ethyl acetate, isopropanol and acetone. A small portion of the lower isomer (S_P-**17** 250 mg) was also isolated as an amorphous white foam solid.

R_P-**17**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H, C8-*H*), 6.02 (br d, 1H, J= 19.6 Hz, C1'-*H*), 5.46 (br s, 1H, 3'-*H*), 4.90 (sept, 1H, J = 6.4 Hz, C*H*$(CH_3)_2$), 4.84 (br s, 2H, N*H*$_2$), 4.69-4.42 (m, 4H, 5'-*Ha* and *Hb*, C*H*$_2$CH$_3$), 4.40-4.37 (m, 1H, 4'-*H*), 1.48-1.33 (m, 9H, CH(C*H*$_3$)$_2$) and CH$_2$C*H*$_3$), 1.35 (d, 3H, J= 22 Hz, 2'-C-C*H*$_3$). ^{31}P-NMR (162 MHz, $CDCl_3$ with respect to an external standard of triphenylphosphate in $CDCl_3$ set to -17.80) δ -7.18 (s). LRMS (ESI) $[M + H]^+$ calculated for $C_{16}H_{24}FN_5O_6P$ 432.4, found 432.4. Optical rotation $[\alpha]^{25}_D$ -80.3 (*c* 1.00, methanol). Elemental analysis: Calcd: C, 44.15; H, 5.37; N, 16.24. Fd: C, 44.21; H, 5.21; N, 15.90. Mp 193.5-197.0 (melt with decomp.)

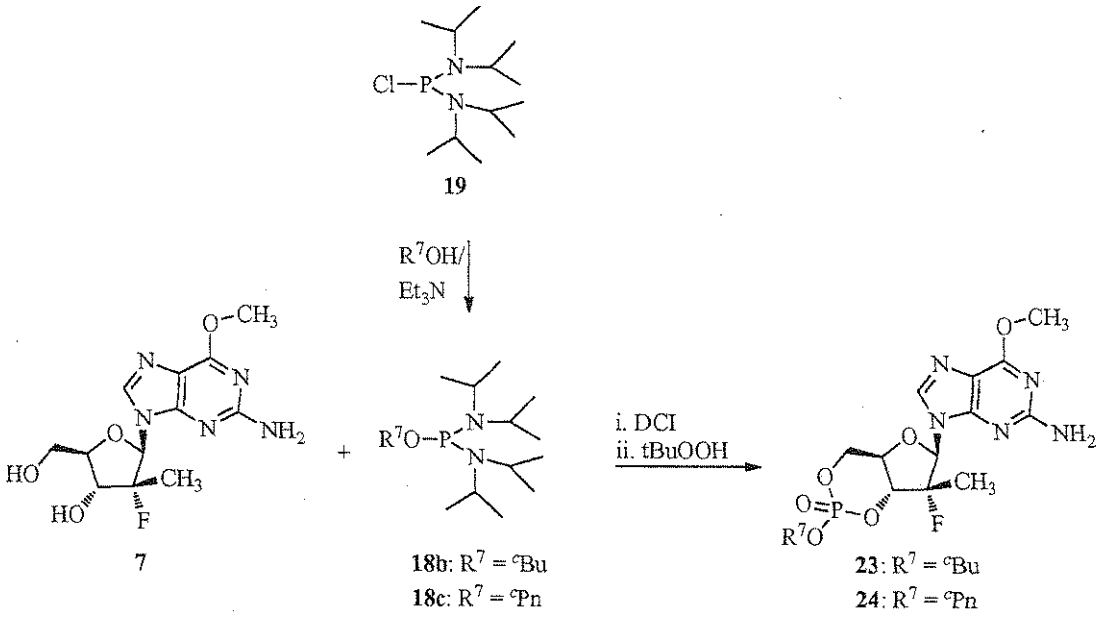
S_P-**17**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H, C8-*H*), 5.98 (br d, 1H, J= 20.0 Hz, C1'-*H*), 5.78 (br s, 1H, 3'-*H*), 5.10 (br s, 2H, N*H*$_2$), 4.83 (sept, 1H, J = 6.4 Hz, C*H*$(CH_3)_2$), 4.63-4.48 (m, 4H, 5'-*Ha* and *Hb*, C*H*$_2$CH$_3$), 4.45-4.38 (m, 1H, 4'-*H*), 1.47-1.21 (m, 12H, CH(C*H*$_3$)$_2$), CH$_2$C*H*$_3$ and 2'-C-C*H*$_3$). ^{31}P-NMR (162 MHz, $CDCl_3$ with respect to an external standard of triphenylphosphate in $CDCl_3$ set to -17.80) δ -3.74 (s). LRMS (ESI) $[M + H]^+$ calculated for $C_{16}H_{24}FN_5O_6P$ 432.4, found 432.4

Alternate Synthesis of 17 via P(V)-Reagent Chemistry

Example 28. Synthesis of Isopropyl phoshorodichloridate (22)

A solution of isopropyl alcohol (38.6mL, 0.50mol) and triethylamine (69.83mL, 0.50mol) in dichloromethane (250 mL) was added to a stirred solution of $POCl_3$ (50.45 mL, 0.551mol) in DCM (250 mL), drop-wise over a period of 25min at -5°C. After stirring the mixture for 1h the solvent was evaporated and the residue was suspended in diethyl ether (400 mL). The triethylamine hydrochloride salt was filtered and washed with ether (100 mL). The filtrate was concentrated and the residue was distilled under high vacuum (~10mmHg) with a cow-head (bath temperature slowly raised to 85°C in 30min). The required product was collected at 42-48°C (distillation head temperature) as a colorless liquid (82.0g, 93% yield).

Scheme 5. Preparation of Selected Cyclophosphate Nucleotides



Example 29. Cyclobutyl-N,N,N',N'-tetraisopropylphosphorodiamidite (18b) and Cyclopentyl-N,N,N',N'-tetraisopropylphosphorodiamidite (18c)

To a solution of alcohol (R^7OH, 10 mmol) in dry ethyl ether (20 mL) was added Et_3N (10 mmol) followed by chloride 1 (10 mmol) and the mixture was stirred at room temperature for 16 h. Solid was removed by filtration. Solvent was evaporated to give reagents **18b** (for ^{c}BuOH) and **18c** (for ^{c}PnOH) that were used for the next reaction without further purification.

Example 30. 6-Methoxy-9-((2R,4aR,6R,7R,7aR)-7-fluoro-2-cyclobutoxy-7-methyl-2-oxo-tetrahydro-2λ^5-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl)-9H-purin-2-ylamine (23)

Preparation of cyclophosphates **23**. To a solution of 7 (0.63 g, 2.00 mmol) in dry acetonitrile (30 mL) were added dicyanoimidazole (DCI, 0.59 g, 5 mmol) then reagent **18b** (0.58 g, 2.00 mmol), and the mixture was stirred at room temperature for 30 min then at 45 °C for 1 h. To the mixture was added additional reagent **18b** (1 mmol) and dicyanoimidazole (1.25 mmol). The resulting solution was stirred at 45 °C for 4 h. Solvent was evaporated and the residue was dissolved in CH_2Cl_2 (30 mL). To the solution was added *t*-BuOOH (70%, 1 mL) followed by Na_2SO_4 to dry the solution. The mixture was stirred at room temperature for 1 h. Toluene (20 mL) was added and the solvents were evaporated and the residue was dissolved in EtOAc (150 mL). The solution was washed with aq. K_2CO_3 to remove diacyanoimidazole

and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-100% EtOAc in hexanes) to give compound **23** was white solid (0.19 g, 22%). δ_H (400MHz, $CDCl_3$): 7.59 (s, 1H), 6.01 (d, J = 19.2Hz, 1H), 5.50 (br. s, 1H), 4.89 (m, 3H), 4.36-4.67 (m, 3H), 4.08 (s, 3H), 2.23-2.50 (m, 4H), 1.67, 1.83 (mm, 2H), 1.34 (d, J = 22.0Hz, 3H). MS (ESI): 430 ($M+H^+$). ^{31}P (CDCl3): -6.98.

Example 31. 6-Methoxy-9-((2R,4aR,6R,7R,7aR)-7-fluoro-2-cyclopentoxy-7-methyl-2-oxo-tetrahydro-2λ^5-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl)-9H-purin-2-ylamine (24)

Preparation of cyclophosphate **24**. The above procedure was applied for the preparation of compound **24** except that **18c** was used instead of **18b** obtaining a 21% yield of crystalline **24**. δ_H (400MHz, $CDCl_3$): 7.59 (s, 1H), 6.02 (d, J = 19.4Hz, 1H), 5.30 (br. s, 1H), 5.08 (m, 1H), 4.85 (br.s, 2H), 4.35-4.66 (m, 3H), 4.07 (s, 3H), 1.65-1.99 (m, 8H), 1.34 (d, J = 22.0Hz, 3H). MS (ESI): 444 ($M+H^+$). ^{31}P (CDCl3): -6.00.

Example 32. 6-Ethoxy-9-((2R,4aR,6R,7R,7aR)-7-fluoro-2-isopropoxy-7-methyl-2-oxo-tetrahydro-2λ^5-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl)-9H-purin-2-ylamine (R_P-17)

To a stirred suspension of (2R,3R,4R,5R)-5-(2-amino-6-ethoxy-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol (**10**, 5.00 g, 15.28 mmol) in dichloromethane (75mL) was added triethylamine (8.52 mL, 61.1 mmol) at room temperature. The reaction mixture was cooled to -30°C and then was added isopropyl phoshorodichloridate (**22**), drop-wise over a period of 5min. The mixture was stirred at this temperature for 15min and then was added NMI (2.54 mL, 32.1 mmol), drop-wise over a period of 5min. The mixture was stirred between -25°C and -15 for 1h and then slowly warmed to room temperature in 20h. The solvent was evaporated and the residue was triturated with EtOAc (500 mL). The off-white solid was filtered and washed with ethyl acetate (100 mL). Only a trace (< 2%) of the other isomer S_P-**17** was visible in the crude reaction. The filtrate was evaporated and

the residue was chromatographed using 20-85% ethyl acetate/hexanes gradient to give pure R_P-17as a white solid (4.65g, 70.6%% yield).

As an alternative non-chromatographic isolation method, the crude reaction mixture from a same scale reaction was diluted with dichloromethane (100 mL) and washed with 1 N HCl (2x100 mL) and water (2x50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure followed by high vacuum for 2 h to give 5.1 g of crude R_P-**17**. One portion of the crude (750 mg) was dissolved in ethyl acetate (2,0 mL) and heated to reflux with stirring for 6 h. The resulting suspension was cooled to ambient temperature and stirred for 20h. The solid was collected by filtration and dried under high vacuum to give 482 mg (50% yield from **10**) R_P-**17** as a white solid, HPLC purity 99.03%. A second portion (1.0 g) was treated in a similar manner with isopropanol (2 mL) to afford 671 mg (52% from **10**) of R_P-**17** as a white solid, HPLC purity 98.64%.

Example 33. X-Ray Crystallography of R_P-17

R_P-**17**, crystallized from _ethyl acetate_through slow partial evaporation at ambient temperature starting at 20 mL/g, ($C_{16}H_{23}N_5PO_6F$) crystallizes in the orthorhombic space group (systematic absences 0k0: k=odd, and h0l: l=odd) with a=11.3544(13)Å, b=12.4153(14)Å, c=14.1622(15)Å, V=1996.4(4)Å^3, Z=4, and d_{calc}=1.435 g/cm^3 X-ray intensity data were collected on a Rigaku Mercury CCD area detector employing graphite-monochromated Mo-Kα radiation (λ=0.71073 Å) at a temperature of 150(1)K. Preliminary indexing was performed from a series of twelve 0.5° rotation images with exposures of 30 seconds. A total of 860 rotation images were collected with a crystal to detector distance of 35 mm, a 2θ swing angle of -10°, rotation widths of 0.5° and exposures of 5 seconds: scan no. 1 was a φ-scan from 0° to 310° at ω = 10° and χ = 20°; scan no. 2 was an ω-scan from -20° to 20° at χ = -90° and φ = 0°; scan no. 3 was an ω-scan from -20° to 20° at χ = -90° and φ = 90°; scan no. 4 was an ω-scan from -20° to 20° at χ = -90° and φ = 135°. Rotation images were processed using CrystalClear (CrystalClear: Rigaku Corporation, 1999), producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the CrystalStructure program package for further processing and structure solution on a Dell Pentium 4 computer (CrystalStructure: Crystal Structure Analysis Package, Rigaku Corp. Rigaku/MSC (2002)). A total of 23016 reflections were

measured over the ranges $2.82 \leq \theta \leq 25.02°$, $-13 \leq h \leq 13$, $-14 \leq k \leq 14$, $-16 \leq l \leq 16$ yielding 3520 unique reflections (Rint = 0.0292). The intensity data were corrected for Lorentz and polarization effects and for absorption using REQAB (minimum and maximum transmission 0.8833, 1.0000).

The structure was solved by direct methods (SIR97) (SIR97: Altomare, A., M. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. Moliterni, G. Polidori & R. Spagna (1999). J. Appl. Cryst., 32, 115-119). Refinement was by full-matrix least squares based on F^2 using SHELXL-97 (SHELXL-97: Sheldrick, G.M. (2008) Acta Cryst., A64,112-122). All reflections were used during refinement. The weighting scheme used was $w=1/[\sigma^2(F_o^2)+ 0.0500P^2 + 1.0836 P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement converged to R1=0.0417 and wR2=0.0994 for 3376 observed reflections for which $F > 4\sigma(F)$ and R1=0.0440 and wR2=0.1020 and GOF =1.063 for all 3520 unique, non-zero reflections and 268 variables ($R1 = \Sigma||F_o| - |F_c|| / \Sigma |F_o|$; $wR2 = [\Sigma w(F_o^2 - F_c^2)2/\Sigma w(F_o^2)^2]^{½}$; $GOF = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{½}$; where n = the number of reflections and p = the number of parameters refined.). The maximum Δ/σ in the final cycle of least squares was 0.009 and the two most prominent peaks in the final difference Fourier were +0.487 and -0.291 e/Å^3.

Table 1 lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Table 2. Figure 1 is an ORTEP representation of *R*P-**17** with 30% probability thermal ellipsoids displayed (ORTEP-II: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations". C.K. Johnson (1976) ORNL-5138).

Table 1. Summary of Structure Determination of Compound *R*P-**17**.

Empirical formula	$C_{16}H_{23}N_5PO_6F$
Formula weight	431.36
Temperature	150(1) K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Cell constants:	
a	11.3544(13) Å
b	12.4153(14) Å

c	14.1622(15) Å
Volume	1996.4(4) $Å^3$
Z	4
Density (calculated)	1.435 Mg/m^3
Absorption coefficient	0.191 mm^{-1}
F(000)	904
Crystal size	0.42 x 0.30 x 0.25 mm^3
Theta range for data collection	2.82 to 25.02°
Index ranges	$-13 \leq h \leq 13, -14 \leq k \leq 14, -16 \leq l \leq 16$
Reflections collected	23016
Independent reflections	3520 [R(int) = 0.0292]
Completeness to theta = 25.02°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.8833
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3520 / 0 / 268
Goodness-of-fit on F^2	1.063
Final R indices [$I>2\sigma(I)$]	R1 = 0.0417, wR2 = 0.0994
R indices (all data)	R1 = 0.0440, wR2 = 0.1020
Absolute structure parameter	0.00(12)
Largest diff. peak and hole	0.487 and -0.291 $e.Å^{-3}$

Table 2. Refined Positional Parameters for Compound R_P-**17**

Atom	x	y	z	$U_{eq}, Å^2$
C1	0.2555(2)	0.83827(19)	0.78326(17)	0.0272(5)
C2	0.1938(2)	0.9120(2)	0.64894(17)	0.0301(5)
C3	0.2700(2)	1.0255(2)	0.76243(18)	0.0322(6)
C4	0.2878(2)	0.93680(19)	0.82096(17)	0.0302(6)
C5	0.3333(2)	0.82033(19)	0.92511(17)	0.0332(6)
H5	0.3610	0.7881	0.9801	0.044
H5a	0.1295	0.8410	0.5396	0.058
H5b	0.1386	0.9599	0.5274	0.058
C6	0.2826(3)	1.2144(2)	0.7297(2)	0.0412(7)
H6a	0.2744	1.2798	0.7666	0.055
H6b	0.2103	1.2039	0.6944	0.055
C7	0.3837(3)	1.2265(2)	0.6621(2)	0.0493(8)
H7a	0.4558	1.2338	0.6970	0.074
H7b	0.3718	1.2894	0.6239	0.074
H7c	0.3881	1.1641	0.6223	0.074
C8	0.2857(2)	0.64618(18)	0.84428(17)	0.0291(5)
H8	0.3230	0.6174	0.9013	0.039
C9	0.1647(2)	0.59037(19)	0.83228(17)	0.0300(5)
C10	0.1676(2)	0.56883(18)	0.72778(16)	0.0271(5)
H10	0.1524	0.6364	0.6941	0.036

Atom	x	y	z	U_{eq},Å^2
C11	0.3245(3)	0.5338(2)	0.6094(2)	0.0429(7)
H11a	0.3123	0.6037	0.5803	0.057
H11b	0.4058	0.5123	0.6002	0.057
C12	0.2940(2)	0.5370(2)	0.71253(17)	0.0304(5)
H12	0.3080	0.4660	0.7406	0.040
C13	0.0594(3)	0.6481(3)	0.8722(2)	0.0466(7)
H13a	-0.0097	0.6046	0.8635	0.070
H13b	0.0494	0.7157	0.8403	0.070
H13c	0.0714	0.6608	0.9384	0.070
C14	-0.0316(3)	0.6077(3)	0.4951(2)	0.0465(7)
H14	-0.0835	0.5450	0.4886	0.062
C15	-0.0061(4)	0.6550(4)	0.4010(3)	0.0822(14)
H15a	0.0552	0.7078	0.4069	0.123
H15b	-0.0760	0.6886	0.3766	0.123
H15c	0.0189	0.5992	0.3586	0.123
C16	-0.0817(4)	0.6858(4)	0.5660(4)	0.0911(15)
H16a	-0.0922	0.6500	0.6255	0.137
H16b	-0.1563	0.7120	0.5439	0.137
H16c	-0.0284	0.7452	0.5737	0.137
N1	0.28432(18)	0.76254(15)	0.85124(14)	0.0283(5)
N2	0.20704(19)	0.82043(16)	0.69836(14)	0.0292(5)
N3	0.22347(19)	1.01316(16)	0.67699(14)	0.0321(5)
N4	0.3370(2)	0.92399(17)	0.91070(15)	0.0353(5)
N5	0.1485(2)	0.90323(19)	0.56147(16)	0.0433(6)
O1	0.30100(19)	1.12352(13)	0.79270(13)	0.0396(5)
O2	0.08771(16)	0.48743(14)	0.69318(11)	0.0322(4)
O3	0.24398(19)	0.45382(16)	0.57040(13)	0.0452(5)
O4	0.35659(15)	0.61669(14)	0.76480(12)	0.0330(4)
O5	0.0411(2)	0.37249(17)	0.55075(14)	0.0509(6)
O6	0.0849(2)	0.57405(18)	0.53123(15)	0.0519(6)
F1	0.17654(15)	0.48997(12)	0.87802(10)	0.0419(4)
P1	0.10640(7)	0.46627(6)	0.58365(5)	0.0394(2)

$U_{eq}=^1/_3[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

Example 34. X-Ray Powder Diffraction of *R*P-17

Samples of *R*P-17 were analyzed by X-Ray Powder Diffraction (XRD) under the following regimen.

a. Bruker AXS/Siemens D5000

X-Ray Powder Diffraction patterns were collected on a Siemens D5000 diffractometer using Cu Kα radiation (40kV, 40mA), θ-θ goniometer, divergence of V20 and receiving slits, a graphite secondary monochromator and a scintillation counter. The instrument is performance checked using a certified Corundum standard (NIST 1976). The software used for data collection was Diffrac Plus XRD Commander v2.3.1 and the data were analyzed and presented using Diffrac *Plus* EVA v 11.0.0.2 or v 13.0.0.2.

Ambient conditions

Samples run under ambient conditions were prepared as flat plate specimens using powder as received. Approximately 35 mg of the sample was gently packed into a cavity cut into polished, zero-background (510) silicon wafer. The sample was rotated in its own plane during analysis. The details of the data collection are: angular range: 2 to 42°2θ; step size: 0.05°2θ; and collection time: 4 $s.step^{-1}$.

b. Bruker AXS C2 GADDS

X-Ray Powder Diffraction patterns were collected on a Bruker AXS C2 GADDS diffractometer using Cu Kα radiation (40 kV, 40 mA), automated XYZ stage, laser video microscope for auto-sample positioning and a HiStar 2-dimensional area detector. X-ray optics consists of a single Göbel multilayer mirror coupled with a pinhole collimator of 0.3 mm.

Figure 2 shows an XRD Diffractogram for R_P-17.

Table 3 provides a tabulation of XRD diffractogram peaks for R_P-17.

Table 3.

Angle 2-Theta (°)	Relative Intensity %	Angle 2-Theta (°)	Relative Intensity %	Angle 2-Theta (°)	Relative Intensity %
9.45	8.1	21.48	12.3	30.87	6.1
9.9	9.5	21.96	18.1	32.37	6.2
10.53	18.5	22.84	34	32.69	5.7
12.2	100	23.63	38.9	32.94	7.3
12.47	20.2	24.24	22.4	33.32	6.7
14.25	64	24.51	32.6	34.45	7.6
15.46	81.7	24.87	15.3	35.04	6.5
16.29	10.4	25.08	30.3	35.19	5.7
16.64	24.1	25.41	12	36.71	2.9
17.4	41.1	26.09	12.3	37.2	3.4
18.12	40.8	26.49	6.3	38.67	9.5
19.92	69.4	27.35	30.1	39.38	7.2
20.28	21.5	28.06	8.6	40.38	6
20.47	29.8	29.94	5.7	41.91	7.2
21.14	16.2	30.04	6.6		

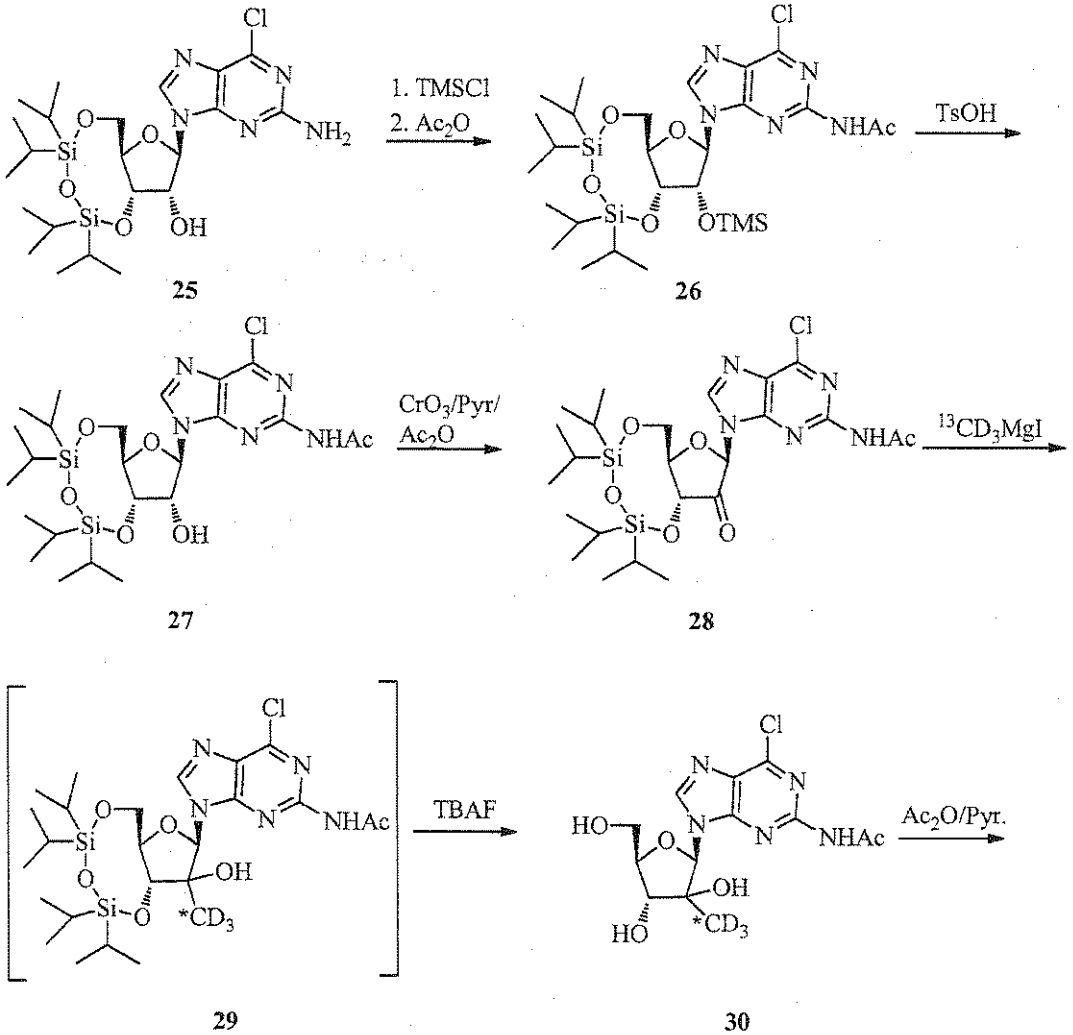
Example 35. Fourier Transform – Infrared (FT-IR) Spectrometry

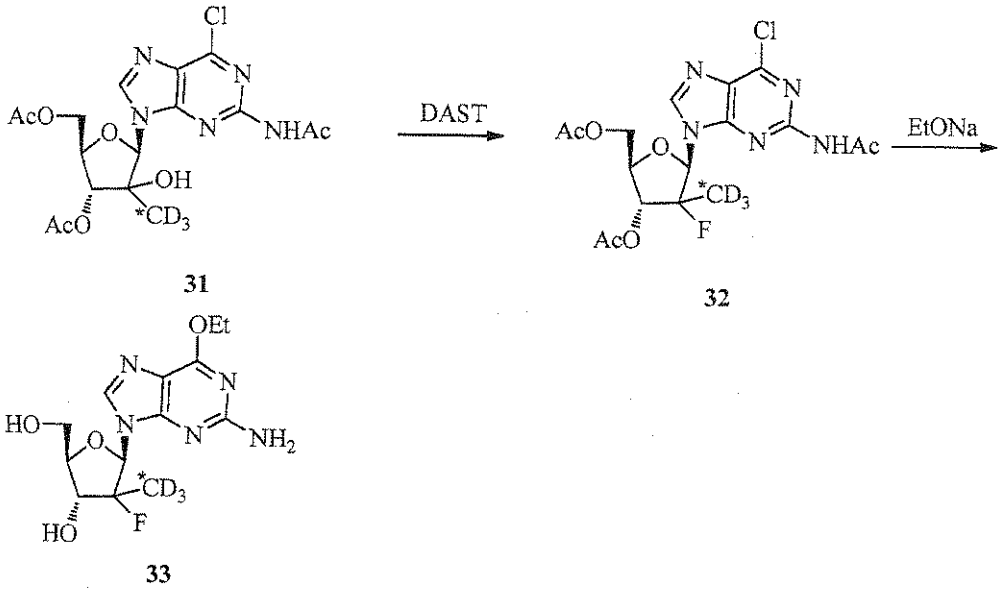
Data for R_P-**17** were collected on a Perkin-Elmer Spectrum One fitted with a universal Attenuated Total Reflectance (ATR) sampling accessory. The data were collected and analyzed using Spectrum v5.0.1 software.

The FT-IR spectrum obtained for R_P-**17** is shown in Figure 3. Selected peaks, in wave-numbers (cm^{-1}) are recited below:

~1607, ~1581, ~1295, ~1250, ~1238, ~1229, ~1079, ~1065, ~999, ~968, ~902, ~886, ~876, ~855, ~798, and ~791

Scheme 6. Preparation of Selected Isotopically Enriched Purine Analogs (* indicates ^{13}C-labeled position)





Example 36. (2R,3R,4R,5R)-5-(2-amino-6-ethoxy-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-perdeuterio-^{13}C-methyltetrahydrofuran-3-ol (33, *cf.* 10)

26. To a solution of compound **25** (5.70 g, 10.5 mmol) in pyridine (10 mL) and CH_2Cl_2 (90 mL) was added TMSCl (3.42 g, 31.5 mmol, 3 eq) at 0 °C and the solution was stirred at 0 °C for 30 min. To the resulting solution was added Ac_2O (3.21 g, 31.5 mmol, 3 eq) and the solution was stirred at 0 °C for 1 h then room temperature for 2 h. EtOAc (200 mL) was added and the mixture was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (10-60% EtOAc in hexane) to give compound **26** (5.0 g, 72%). δ_H (400MHz, $CDCl_3$): 8.45 (s, 1H), 7.95 (s, 1H), 5.93 (s, 1H), 4.00-4.41 (m, 5H), 2.60 (s, 3H), 0.91-1.11 (m, 28H), 0.21 s, 9H). MS (ESI): 658 ($M+H^+$).

27. To a solution of **26** (5.0 g, 7.6 mmol) in THF (100 mL) was added $TsOH.H_2O$ (1g) and the solution was stirred at room temperature for 3 h and neutralized with triethylamine. Solvent was evaporated and the residue was purified by silica gel column chromatography (10-80% EtOAc in hexanes) to give product **27** (3.5 g, 79%). δ_H (400MHz, $CDCl_3$): 8.21 (d, J = 1.2Hz, 1H), 8.00, 8.02 (ss, 1H), 6.00 (s, 1H), 4.68 (t, J = 7.2Hz, 1H), 4.45 (d, J = 4.8Hz, 1H), 4.05-4.19 (m, 3H), 3.17 (s, 1H), 2.54 (s, 3H), 1.03-1.10 (m, 28H). MS (ESI): 586 ($M+H^+$).

28. To a mixture of CrO_3 (2.2 g, 21.99 mmol, 3 mol eq) in CH_2Cl_2 (30 mL) were added pyridine (1.74 g, 22.0 mmol, 3 eq) then Ac_2O (2.24 g, 22 mmol, 3eq). To the resulting mixture was added a solution of **27** (4.3 g, 7.33 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 30 min. To the mixture was added EtOAc (200 mL) slowly and the mixture was stirred at room temperature for 1h. The solid was filtered off through silica gel pad. The filtrate was concentrated to dryness and the residue was co-evaporated with toluene. EtOAc (100 mL) was added and the mixture was filtered through silica gel pad. The filtrate was evaporated. The residue was co-evaporated with toluene to give white solid. The residue was purified by silica gel column chromatography (5-80% EtOAc in hexane) to give a syrup. The syrup (hydrated) was co-evaporated with toluene (2 x 50 mL) to give compound **28** which was dried under vacuum overnight (free ketone, 3.65 g, 85%). δ_H (400MHz, $CDCl_3$): 8.00 (s, 1H), 7.86 (s, 1H), 5.77 (s, 1H), 5.25 (d, J = 9.2Hz, 1H), 4.07-4.28 (m, 3H), 2.41 (s, 3H), 1.06-1.16 (m, 28H).

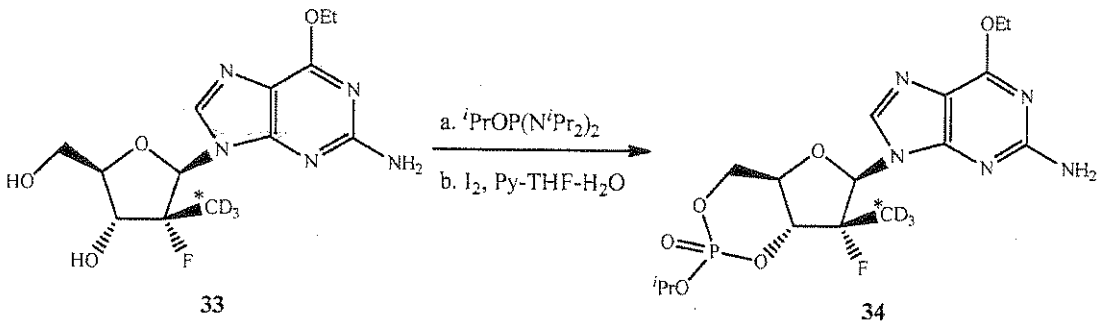
31. To a mixture of Mg (1.68 g, 69.14 mmom) in dry ethyl ether (40 mL) was added 1/3 of $^{13}CD_3I$ (8.70 g, 60.00 mmol) and the mixture was stirred at room temperature until reflux. To the mixture was added the rest of $^{13}CD_3I$ at the rate that kept the reaction under gentle reflux. After cooled down to room temperature, the solution was transferred to another flask in ice-bath. To the solution of the reagent was added $AlCl_3$ (2.67 g, 20.00 mmol) and the mixture was stirred at 0 °C for 1h. Ether was evaporated at room temperature to obtain syrup. To the syrup was added CH_2Cl_2 (100 mL). To the mixture was added a solution of compound **28** (5.84 g, 10.00 mmol) in CH_2Cl_2 (30 mL) slowly at 0 °C. The solution was stirred at 0 °C for 3 h. The reaction was quenched by addition of saturated NH_4Cl (10 mL). EtOAc (300 mL) was added and the mixture was stirred at room temperature for 10 min. Solid was removed by filtration. The filtrate was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was dissolved in THF (100 mL). To the mixture was added TBAF (30 mmol, 1M in THF) and the solution was stirred at room temperature for 2 h. Solvent was evaporated and the residue was purified by silica gel column (0-15% MeOH in CH_2Cl_2) to give nucleoside **30** which was dissolved in pyridine (30 mL) and CH_2Cl_2 (100 mL). To the solution was added Ac_2O (3 mL, excess) and the mixture was stirred at 0 °C for 16 h. Water (10 mL) was added and the mixture was stirred at room temperature for 10 min. EtOAc (200

mL) was added and the solution was washed with water, brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-8% MeOH in CH_2Cl_2) to give compound **31** as white solid 1.33 g, 29.9%). δ_H (400MHz, $CDCl_3$): 8.28 (s, 1H), 8.10 (s, 1H), 6.03 (d, J = 2.4Hz, 1H), 5.22 (d, J = 3.2Hz, 1H), 4.50 (m, 2H), 4.24 (m, 1H), 4.00 (s, 1H), 2.45 (s, 3H), 2.20, 2.12 (ss, 2 x 3H). MS (ESI): 446 ($M+H^+$).

32. To a solution of **31** (0.68 g, 1.53 mmol) in CH_2Cl_2 (68 mL) precooled at -78 °C was added DAST (0.74 g, 4.59 mmol) within 20 min and the solution was stirred at the same temperature for 30 min then at room temperature for 1 h. EtOAc (200 mL) was added and the solution was washed with aq. $NaHCO_3$, brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-90% EtOAc in hexanes) to give compound **32** (0.21 g, 30.6%) as white solid. δ_H (400MHz, $CDCl_3$): 8.26 (s, 1H), 8.11 (s, 1H), 6.23 (d, J = 17.2Hz, 1H), 5.75 (m, 1H), 4.39, 4.56 (m, 3H), 2.21, 2.17 (ss, 2 x 3H). MS (ESI): 448 ($M+H^+$).

33. To dry EtOH (25 mL) was added EtONa in EtOH (3.1 mL, 21%, 0.53 g, 7.83 mmol). To the solution was added a solution of compound **32** (0.35 g, 0.78 mmol) in EtOH (11 mL) and the solution was stirred at room temperature for 20 h. The reaction was quenched with AcOH to pH7. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-10% MeOH in CH_2Cl_2) to give compound **33** (0.21 g, 81%). δ_H (400MHz, CD_3OD): 8.22 (s, 1H), 6.15 (d, J = 18.0Hz, 1H), 4.52 (q, J = 6.8Hz, 2H), 4.38 (dd, J = 5.8, 23.6Hz, 1H), 4.03 (m, 2H), 3.86 (m, 1H). MS (ESI): 332 ($M+H^+$).

Example 37. Synthesis of R_p-6-Ethoxy-9-((4aR,6R,7R,7aR)-7-fluoro-2-isopropoxy-7-methyl-$^{13}CD_3$-2-oxo-tetrahydro-2,5-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl)-9H-purin-2-yl amine (34)

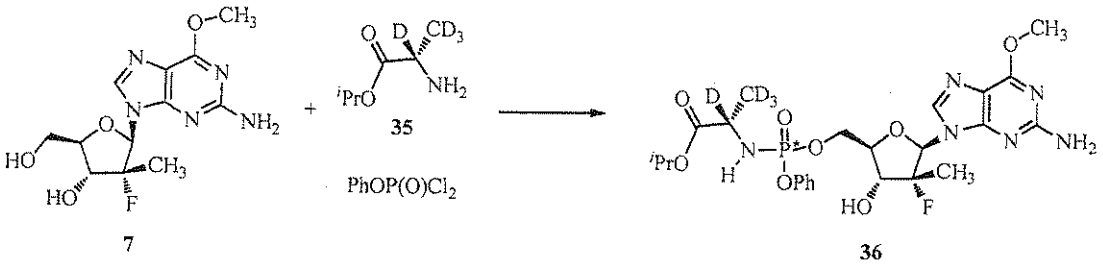


33 34

To a dry 50 mL round-bottomed flask was charged 205 mg of the nucleoside **33**. Anhydrous aceotonitrile (4 mL) was added and the suspension was cooled in an ice bath. To the mixture 4,5-dicyanoimidazole (183 mg) was added and followed by isopropyl tetraisopropylphosphorodiamidite (209 mg). The resulted clear solution was then heated at 45 °C for 6 hrs. The reaction mixture was concentrated and residue was triturated with 20 mL of ethyl acetate. White solid was removed by passing the supernatant through a short pad of cotton in a pipette. The flask and pipette were rinsed with ethyl acetate (4x5 mL). The combined solution was concentrated and the flask with the residue was cooled in an ice bath. A solution of iodine (*ca.* 0.1 M in a mixture of THF, pyridine and water, ~8 mL) was added and the brown solution was stirred at room temperature for 5 mins. An aqueous solution of sodium thiosulphate (10%) was added dropwise until a light brown solution was formed. After removal of solvents, the residue was triturated with ethyl acetate (20 mL) and solid was removed by passing the solution through a pad of cotton in a pipette and rinsed the flask and pipette with ethyl acetate (4x5 mL). The combined organic solution was washed with sat. sodium bicarbonate (2x15 mL) and sat sodium carbonate (15 mL). The combined aqueous layer was extracted with ethyl acetate (4x20 mL). The combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4. Solvent was removed and residue was purified by column chromatography (silica gel, 40% EtOAc in hexanes) to afford 98.7 mg of product **34** as a white solid with a yield of 34%. HPLC purity of product: 98.23%. ^{1}H NMR ($CDCl_3$): δ 7.59 (s, 1 H, 8-H), 6.01 (d, 1 H, C1'-H), 5.41 (br, 1 H, C3'-H), 4.88 (s, 2

H, NH2), 4.85 (m, 1 H, CH of ester), 4.64-4.46 (m, 4 H, 6-OCH_2, C4'-H and C5'-H_a), 4.38-4.32 (m, 1 H, C5'-H_b), 1.45-1.41 (m, 9 H, CH_3s). ^{31}P NMR ($CDCl_3$): δ -5.96.

Example 38. (2S)-isopropyl-2-((((2R,3R,4R,5R)-5-(2-amino-6-methoxy-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy) (phenoxy) phosphorylamino)-2-deuterio-propanoate-d_3 (36)



Isopropyl 2,3,3,3-d_4 L-alaninate, **35**. 2,3,3,3-d_4 L-alanine (Aldrich, 7.19 g, 77.2 mmol) was added to anhydrous isopropanol (50 mL) and stirred under a nitrogen atmosphere. Thionyl chloride (9.19 g, 77.2 mmol) was dropped in over 15 min and the warm reaction mixture was heated to reflux for 17 h. The reaction was concentrated under reduced pressure and then coevaporated with acetonitrile (40 mL) and then dried (25 °C, 0.1 mm) for 17 h. Upon standing for 3 days, a portion crystallized. Ethyl ether (50 mL) was added and the mixture was stirred for 2 h to break up into a fine suspension. The solid was collected by filtration and washed with ether (50 mL) and dried (50 °C, 0.1 mm) to give 6.3 g g (48%) of product as white, shiny plates. The product was used as is in the next step.

36. To a 100 mL dry round-bottomed flask was loaded phenyl dichlorophosphate (1.4 eq. 0.47 g, 2.24 mmol) and anhydrous dichloromethane (20 ml). The labeled-aminoacid isopropyl ester salt of L-alanine (1.8 eq., 0.492 g, 2.88 mmol) was added to the solution and the mixture was cooled to -5°C. A solution of *N*-Methyl imidazole (10. eq., 1.26 mL, 15.9 mmol) in anhydrous dichloromethane (5 ml) was then added quickly *via* a dry syringe at -5 °C and the solution was stirred at -5 °C for 1 h. The nucleoside (7, 0.5 g, 1.6 mmol) was added from a vial in one portion at -5 °C and the solid was slowly dissolved in 20 minutes. The reaction

temperature was allowed to rise to ambient temperature over 1h and stirred overnight. After 18h, the reaction was almost complete as shown by TLC result and diluted with 25 mL of dichloromethane. HCl solution (1 *N*, 20 mL) was added. The aqueous layer was separated and extracted with dichloromethane. The organic layer was washed with sat $NaHCO_3$, water, brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the off-white foam was purified through automated column chromatography using a 40 g cartridge and a gradient of 0-3% methanol in dichloromethane to afford product as a white foam solid (62% yield). HPLC purity 99.6%. NMR spectra of product showed it is a mixture of two diastereoisomers with a ratio of **1:3**. ^{1}H NMR (DMSO D_6): δ 7.97 (1 H, s) , 7.95 (1 H, s) 7.37-7.31 (2 H, m), 7.29-7.20 (3 H, m), 6.62 (2 H, s), 6.11 (1 H, d), 6.06 (1 H, d), 6.05-5.97 (1 H, m), 5.80 (1 H, d), 5.81 (1 H, d), 4.87-4.76 (1 H, hept), 4.45-4.28 (2 H, m), 4.10-4.00 (1 H, m), 3.95 (3 H, s), 3.82-3.72 (2 H, m), 1.13-1.09 (6 H, m), 1.03 (3 H, d). ^{31}P NMR ($CDCl_3$): δ 5.55, 4.71 (1:3); MS, m/e 587 $(M+1)^+$.

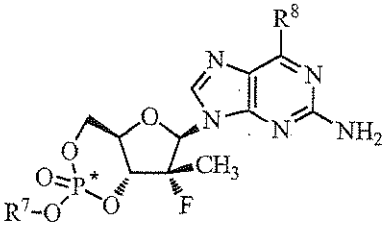
Example 39. Biological Data

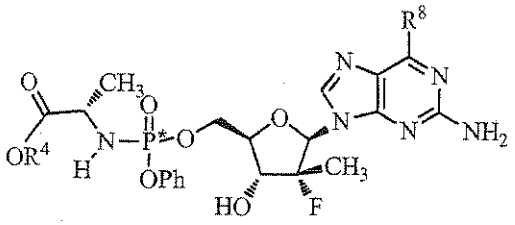
HCV replicon assay. HCV replicon RNA-containing Huh7 cells (clone A cells; Apath, LLC, St. Louis, Mo.) were kept at exponential growth in Dulbecco's modified Eagle's medium (high glucose) containing 10% fetal bovine serum, 4 mM L-glutamine and 1 mM sodium pyruvate, 1× nonessential amino acids, and G418 (1,000 μg/ml). Antiviral assays were performed in the same medium without G418. Cells were seeded in a 96-well plate at 1,500 cells per well, and test compounds were added immediately after seeding. Incubation time 4 days. At the end of the incubation step, total cellular RNA was isolated (RNeasy 96 kit; Qiagen). Replicon RNA and an internal control (TaqMan rRNA control reagents; Applied Biosystems) were amplified in a single-step multiplex RT-PCR protocol as recommended by the manufacturer. The HCV primers and probe were designed with Primer Express software (Applied Biosystems) and covered highly conserved 5′-untranslated region (UTR) sequences (sense, 5′-AGCCATGGCGTTAGTA(T)GAGTGT-3′, and antisense, 5′-TTCCGCAGACCACTATGG-3′; probe, 5′-FAM-CCTCCAGGACCCCCCCTCCC-TAMRA-3′).

To express the antiviral effectiveness of a compound, the threshold RT-PCR cycle of the test compound was subtracted from the average threshold RT-PCR

cycle of the no-drug control (ΔCt_{HCV}). A ΔCt of 3.3 equals a 1-log 10 reduction (equal to the 90% effective concentration [EC_{90}]) in replicon RNA levels. The cytotoxicity of the test compound could also be expressed by calculating the ΔCt_{rRNA} values. The $\Delta\Delta Ct$ specificity parameter could then be introduced ($\Delta Ct_{HCV} - \Delta Ct_{rRNA}$), in which the levels of HCV RNA are normalized for the rRNA levels and calibrated against the no-drug control.

Compounds **11**, **12**, **14**, **15**, **16**, and **17**, represented by the following structure(s),





15: R^7 = Me, R^8 = -N(-$CH_2CH_2CH_2$-)
16: R^7 = Me, R^8 = -OEt
17: R^7 = ^{i}Pr, R^8 = -OEt
23: R^7 = ^{c}Bu, R^8 = -OMe
24: R^7 = ^{c}Pn, R^8 = -OMe

11: R^4 = ^{i}Pr, R^8 = -OMe
12: R^4 = Me, R^8 = -N(-$CH_2CH_2CH_2$-)
14: R^4 = ^{c}Pn, R^8 = -OH

R^8 = N(-$CH_2CH_2CH_2$-) = 

were tested for their biological properties based on the preceding assay. The results of these tests are disclosed in the Table 4.

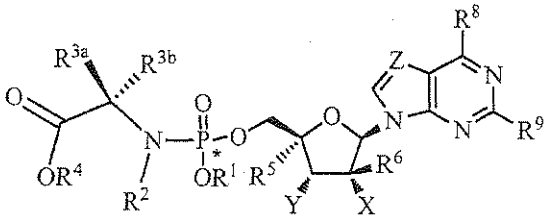
Table 4. Activity of Selected Compounds

Compd. No.	CloneA EC_{90} (μM)
11	0.02
12	0.07
14	0.13
15	0.71
16	0.48
17	0.60
23	0.13
24	0.037

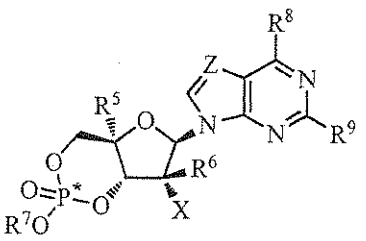
The contents of U.S. Patent Application No. 12/053,015, filed March 21, 2008 (see also WO 2008/121634), U.S. Patent Application No. 12/479,075, filed June 5, 2009, and U.S. Provisional Patent Application Nos. 61/060,683, filed June 11, 2008, 61/140,423, 61/140,441, 61/140,317, and 61/140,369, each of which being filed December 23, 2008 are hereby incorporated by reference in their entirety. Moreover, the patent and non-patent references disclosed herein are incorporated by reference. In the event that the incorporated subject matter contains a term that conflicts with a term disclosed in the present application text, the meaning of the term contained in the present application controls provided that the overall meaning of the incorporated subject matter is not lost.

CLAIMS

1. A compound **I** or salt thereof or compound **II** or salt thereof:



I



II

wherein

(a) R^1 is hydrogen, n-alkyl; branched alkyl; cycloalkyl; or aryl, which includes, but is not limited to, phenyl or naphthyl,

where phenyl or naphthyl are optionally substituted with at least one of

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, F, Cl, Br, I, nitro, cyano, C_{1-6} haloalkyl, $-N(R^{1'})_2$, C_{1-6} acylamino, $-NHSO_2C_{1-6}$ alkyl, $-SO_2N(R^{1'})_2$, $COR^{1''}$, and $-SO_2C_{1-6}$ alkyl; ($R^{1'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{1''}$ is –OR' or $-N(R^{1'})_2$);

(b) R^2 is hydrogen, C_{1-10} alkyl, or R^{3a} or R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, where n is 2 to 4;

(c) R^{3a} and R^{3b} are

(i) independently selected from hydrogen, C_{1-10} alkyl, cycloalkyl, $-(CH_2)_e(NR^{3'})_2$, C_{1-6} hydroxyalkyl, $-CH_2SH$, $-(CH_2)_2S(O)_dMe$, $-(CH_2)_3NHC(=NH)NH_2$, (1H-indol-3-yl)methyl, (1H-imidazol-4-yl)methyl, $-(CH_2)_eCOR^{3''}$, aryl and aryl C_{1-3} alkyl, said aryl groups optionally substituted with a group selected from hydroxyl, C_{1-10} alkyl, C_{1-6} alkoxy, halogen, nitro and cyano;

(ii) R^{3a} and R^{3b} both are C_{1-6} alkyl;

(iii) R^{3a} and R^{3b} together are$(CH_2)_f$ so as to form a spiro ring;

(iv) R^{3a} is hydrogen and R^{3b} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms

(v) R^{3b} is hydrogen and R^{3a} and R^2 together are $(CH_2)_n$ so as to form a cyclic ring that includes the adjoining N and C atoms, where c is 1 to 6, d is 0 to 2, e is 0 to 3, f is 2 to 5, n is 2 to 4, and where $R^{3'}$ is independently hydrogen or C_{1-6} alkyl and $R^{3''}$ is -OR' or $-N(R^{3'})_2$);

(vi) R^{3a} is H and R^{3b} is H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2-indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-Ph), CH_2SH, or lower cycloalkyl; or

(vii) R^{3a} is CH_3, $-CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CH_2Ph, CH_2-indol-3-yl, $-CH_2CH_2SCH_3$, CH_2CO_2H, $CH_2C(O)NH_2$, CH_2CH_2COOH, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, CH_2-imidazol-4-yl, CH_2OH, $CH(OH)CH_3$, CH_2((4'-OH)-Ph), CH_2SH, or lower cycloalkyl and R^{3b} is H, where $R^{3'}$ is independently hydrogen or alkyl, which includes, but is not limited to, C_{1-20} alkyl, C_{1-10} alkyl, or C_{1-6} alkyl, $R^{3''}$ is –OR' or $-N(R^{3'})_2$);

(d) R^4 is hydrogen, C_{1-10} alkyl, C_{1-10} alkyl optionally substituted with a lower alkyl, alkoxy, di(lower alkyl)-amino, or halogen, C_{1-10} haloalkyl, C_{3-10} cycloalkyl, cycloalkyl alkyl, cycloheteroalkyl, aminoacyl, aryl, such as phenyl, heteroaryl, such as, pyridinyl, substituted aryl, or substituted heteroaryl;

(e) R^5 is H, a lower alkyl, CN, vinyl, O-(lower alkyl), hydroxyl lower alkyl, i.e., $-(CH_2)_pOH$, where p is 1 -6, including hydroxyl methyl (CH_2OH), CH_2F, N_3, CH_2CN, CH_2NH_2, CH_2NHCH_3, $CH_2N(CH_3)_2$, alkyne (optionally substituted), or halogen, including F, Cl, Br, or I;

(f) R^6 is H, CH_3, CH_2F, CHF_2, CF_3, F, CN, vinyl, or ethynyl;

(g) R^7 is hydrogen, n-alkyl, branched alkyl, cycloalkyl, alkaryl, or aryl, which includes, but is not limited to, phenyl or naphthyl, where phenyl or naphthyl are optionally substituted with at least one of H, F, Cl, Br, I, OH, $OR^{7'}$, SH, $SR^{7'}$, NH_2, $NHR^{7'}$, $NR^{7'}_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6, lower alkynyl of C_2-C_6, such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, $CO_2R^{7'}$, $CONH_2$, $CONHR^{7'}$, $CONR^{7'}_2$, $CH{=}CHCO_2H$, or $CH{=}CHCO_2R^{7'}$ wherein $R^{7'}$ is an optionally

substituted alkyl, cycloalkyl, alkenyl, alkynyl, or alkoxyalkyl, which includes, but is not limited to, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and C_{1-10} alkoxyalkyl,

(h) X is H, OH, OMe, halogen, CN, NH_2, or N_3;

(i) Y is OH;

(j) Z is N or CR^{10};

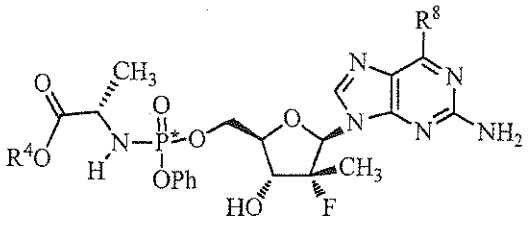
(k) R^8 and R^9 are independently H, F, Cl, Br, I, OH, OR', SH, SR', NH_2, NHR', NR'$_2$, nitrogen heterocycle, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, lower alkenyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$,

and

(l) R^{10} is H, halogen (including F, Cl, Br, I), OH, OR', SH, SR', NH_2, NHR', NR'$_2$, NO_2 lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6, lower alkenyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6 , lower alkynyl of C_2-C_6, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6, halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6, CO_2H, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH=CHCO_2H$, or $CH=CHCO_2R'$;

wherein R' is an optionally substituted alkyl, which includes, but is not limited to, an optionally substituted C_{1-20} alkyl, an optionally substituted C_{1-10} alkyl, an optionally substituted lower alkyl; an optionally substituted cycloalkyl; an alkaryl; an optionally substituted alkynyl of C_2-C_6; an optionally substituted lower alkenyl of C_2-C_6, or optionally substituted acyl, which includes but is not limited to C(O) alkyl, C(O)(C_{1-20} alkyl), C(O)(C_{1-10} alkyl), or a C(O)(lower alkyl).

2. The compound I or salt thereof of claim 1, wherein R^1 is Ph, R^2 is H, R^{3a} is H, R^{3b} is CH_3, R^5 is H, R^6 is CH_3, R^9 is NH_2, X is F, Y is OH, and Z is N, as shown in the following structure:



and wherein R^4 is a lower alkyl or lower cycloalkyl and R^8 is a O(lower alkyl) or O(lower cycloalkyl).

3. The compound **I** or salt thereof of claim 2, wherein R^4 is Me, Et, ^{i}Pr, ^{c}Pr, ^{c}Bu, or ^{c}Pn and R^8 is OMe, OEt, O^{i}Pr, O^{c}Pr, O^{c}Bu, or O^{c}Pn.

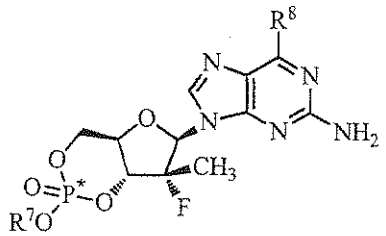
4. A composition comprising the compound or salt thereof of claim 3.

5. A pharmaceutical composition comprising the compound or salt thereof of claim 3.

6. A method of treating a condition caused by a viral agent, which comprises administering to a patient in need thereof a therapeutically effective amount of the compound or salt thereof of claim 3.

7. Use of the compound or salt thereof of claim 3 in the manufacture of a medicament for the treatment of a condition caused by a viral agent.

8. The compound **II** or salt thereof of claim 1, wherein R^5 is H, R^6 is CH_3, R^9 is NH_2, X is F, and Z is N, as shown in the following structure:



where R^7 is a lower alkyl or lower cycloalkyl and R^8 is a O(lower alkyl) or O(lower cycloalkyl).

9. The compound or salt thereof of claim 8, wherein R^4 is Me, Et, ^{i}Pr, ^{c}Pr, ^{c}Bu, or ^{c}Pn and R^8 is OMe, OEt, O^{i}Pr, O^{c}Pr, O^{c}Bu, or O^{c}Pn.

10. A composition comprising the compound or salt thereof of claim 9.

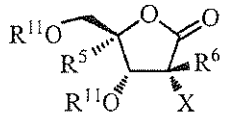
11. A pharmaceutical composition comprising the phosphoramidate nucleoside or salt thereof of claim 9.

12. A method of treating a condition caused by a viral agent, which comprises administering to a patient in need thereof a therapeutically effective amount of the compound or salt thereof of claim 9.

13. Use of the compound or salt thereof of claim 9 in the manufacture of a medicament for the treatment of a condition caused by a viral agent.

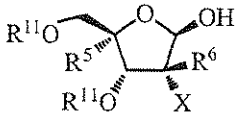
14. A process for preparing the compound **I** or salt thereof or the compound **II** or salt thereof of claim 1, wherein said process comprises:

(a) stereoselective reduction of a protected ribonolactone **III** using a hydride reducing agent



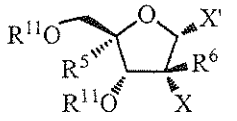
III

to provide a beta-lactol derivative **IV**; and



IV

(b) stereoselective conversion of the lactol derivative **IV** using a reagent to obtain an anomeric alpha-derivative **V**



V ,

wherein R^5, R^6, and X have the meanings as defined above, X' is a leaving group and R^{11} is a protecting group.

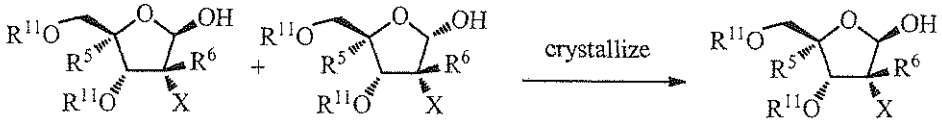
15. A process for preparing the compound **I** or salt thereof or the compound **II** or salt thereof of claim 1, said process comprising stereoselective reduction of a protected ribonolactone **III** using a hydride reducing agent to provide

a mixture comprising a beta-lactol derivative **IV** and an alpha-lactol derivative of the structure **IV-α**:



III **IV** **IV-α**

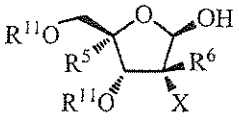
and crystallizing the beta-lactol derivative **IV** from the mixture comprising the beta-lactol derivative and the alpha-lactol derivative



IV **IV-α** **IV**

wherein R^{11} is a protecting group.

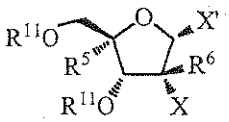
16. A compound **IV**



IV

wherein R^5 is H or N_3, R^6 is CH_3, R^{11} is a protecting group and X is F.

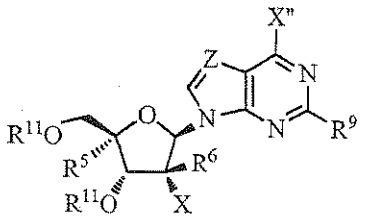
17. A compound **V**



V

wherein R^5 is H or N_3, R^6 is CH_3, R^{11} is a protecting group and X is F. X' is Cl, Br, or I.

18. A compound **VI** or salt thereof



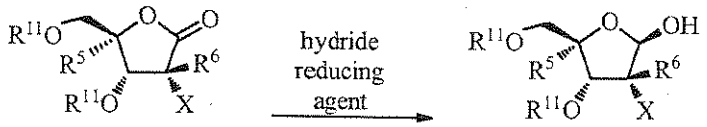
VI

wherein R^5, R^6, R^9, and Z have the meanings as recited in claim 1, X" is a leaving group, and R^{11} is a protecting group.

19. The compound **VI** or salt thereof of claim 18, wherein R^5 is H, R^6 is CH_3, R^9 is NH_2, R^{11} is 4-chloro-benzoyl, X is F, X" is Cl, and Z is N.

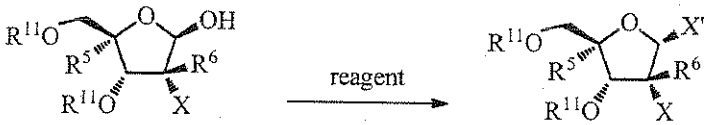
20. A process for preparing compound **VI** of claim 18, wherein said process comprises:

(a) stereoselective reduction of a protected ribonolactone **III** using a hydride reducing agent to provide a beta-lactol derivative **IV**;



III IV

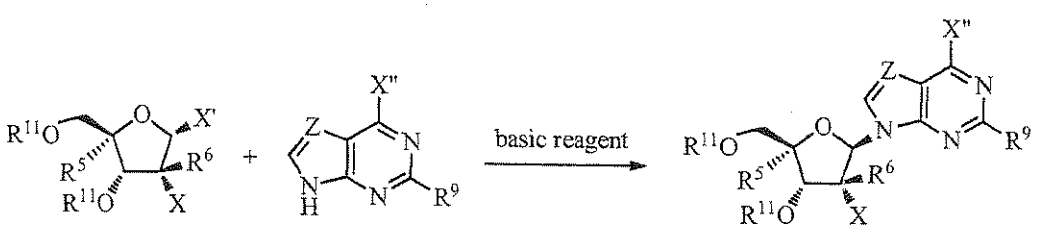
(b) stereoselective conversion of the lactol derivative using a reagent to obtain an anomeric alpha-derivative **V**



IV V

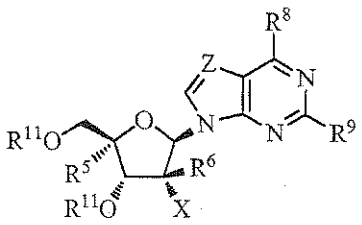
wherein X' is a leaving group, and

(c) stereoselective coupling of an alpha- derivative **V** with a purine or a derivatized purine base using a basic reagent to produce a beta-nucleoside **VI**



V VI

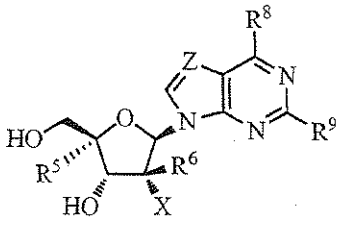
21. A compound **VII** or salt thereof



VII

wherein R^5 is H or N_3, R^6 is CH_3, R^8 is –O(lower alkyl) or –O(lower cycloalkyl), R^9 is NH_2, R^{11} is a protecting group, X is F, and Z is N.

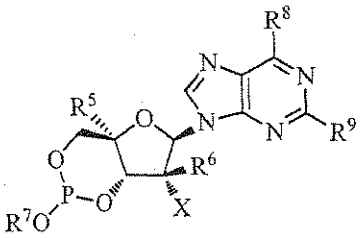
22. A compound **VIII** or salt thereof



VIII

wherein R^5 is H or N_3, R^6 is CH_3, R^8 is –O(lower alkyl) or –O(lower cycloalkyl), R^9 is NH_2, X is F, and Z is N.

23. A compound or salt thereof represented by the following structure:



wherein R^5 is H or N_3, R^6 is CH_3, R^8 is –O(lower alkyl) or –O(lower cycloalkyl), R^9 is NH_2, and X is F.

24. Crystalline R_P-**17**.

25. Crystalline R_P-**17** having having an XRD 2θ-reflections (°) at about 12.2.

26. Orthorhombic crystalline R_P-17.

27. Crystalline R_P-17 having an FT-IR peak at about 999 cm^{-1}.