JOURNAL OF
MEDICINAL
CHEMISTRY

Volume 36, Number 5 March 5, 1993

Articles

L-β-(2S,4S)- and L-α-(2S,4R)-Dioxolanyl Nucleosides as Potential Anti-HIV Agents: Asymmetric Synthesis and Structure–Activity Relationships

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Received September 9, 1992

In order to study the structure–activity relationships of L-(2S,4S)- and L-(2S,4R)-dioxolanyl nucleosides as potential anti-HIV agents, various enantiomerically pure L-(2S,4S)- and (2S,4R)-dioxolanylpyrimidine and -purine nucleosides have been synthesized and evaluated against HIV-1 in human peripheral blood mononuclear (PBM) cells. The enantiomerically pure key intermediate **8** has been synthesized in six steps from 1,6-anhydro-β-L-gulose (**2**), and compound **8** was condensed with 5-substituted pyrimidines, 6-chloropurine, and 2,6-disubstituted purine to obtain various dioxolanylpyrimidine and -purine nucleosides, respectively. Among the compound synthesized, 5-fluorocytosine derivative **29** was found to exhibit the most potent anti-HIV activity (EC_{50} = 0.0012 μM) although it was toxic (IC_{50} = 10.0 μM). The order of anti-HIV potency of pyrimidine analogues was as follows: 5-fluorocytosine (β-isomer) > cytosine (β-isomer) > 5-fluorocytosine (α-isomer) > 5-iodocytosine (β-isomer) > cytosine (α-isomer) > 5-bromocytosine (β-isomer) > thymine (β-isomer) > 5-methylcytosine (α-isomer) > 5-iodocytosine (α-isomer) > 5-chlorocytosine (β-isomer). The anti-HIV potency of purine analogues was found to be in the following decreasing order: 2,6-diaminopurine (β-isomer) > 2-chloroadenine (α-isomer) > 2-fluoroadenine (β-isomer) > adenine (β-isomer) > 2-amino-6-chloropurine (α-isomer) > 2-amino-6-chloropurine (β-isomer) > guanine (β-isomer) > 2-fluoroadenine (α-isomer) > adenine (α-isomer) > 2,6-diaminopurine (α-isomer) > N^6-methyladenine (β-isomer). It is interesting to note that the α-5-fluorocytosine analogue exhibited an excellent anti-HIV activity (EC_{50} = 0.063 μM) without cytotoxicity up to 100 μM in PBM cell.

Introduction

The anti-HIV activity of (±)-dioxolanylthymine has been reported by Belleau et al.,[1] and its synthesis has been published by Norbeck et al.[2] and Choi et al.[3] However, the synthesis of this compound has only been reported as a racemic mixture. Therefore, we have recently reported the synthesis of enantiomerically pure (−)-β-D-(2R,4R)-dioxolanylthymine (Figure 1), of which configuration is the naturally occurring D form (2R), and evaluated it against HIV-1 in human peripheral blood mononuclear (PBM) cells.[4] It was found that the (−)-β-D-(2R,4R)-dioxolanylthymine exhibited potent anti-HIV activity (EC_{50} = 0.3 μM) without cytotoxicity up to 100 μM. Recently, we have also reported the comprehensive structure–activity relationships of enantiomerically pure D-(2R)-1,3-dioxolanylpyrimidine[5] and D-(2R)-1,3-dioxolanylpurine[6] nucleosides as potential anti-HIV agents.

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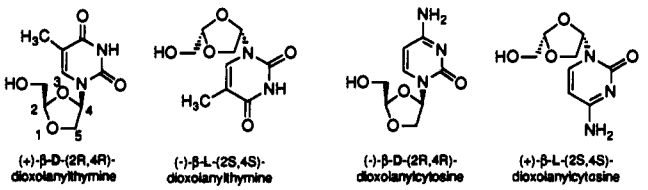


Figure 1.

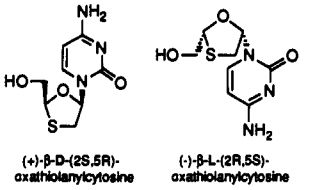


Figure 2.

From these studies, (+)-β-D-(2*R*,4*R*)-dioxolanylcytosine (Figure 1) was found to exhibit the most potent anti-HIV activity (EC_{50} = 0.016 and 0.009 μM in PBM and CEM cells, respectively) among pyrimidine series,[5] although it was also the most toxic compound in PBM (IC_{50} = 62.0 μM) and in CEM cells (IC_{50} = 12.8 μM). Among purine series, the (-)-β-D-(2*R*,4*R*)-dioxolanylguanine derivative exhibited the most potent anti-HIV activity (EC_{50} = 0.03 μM) without toxicity up to 100 μM in PBM cells.[6]

Our observation that the anti-HIV activity of (-)-β-L-(2*R*,5*S*)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine (Figure 2) was more potent than that of (+)-β-D-(2*S*,5*R*)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine (Figure 2)[7] has prompted us to synthesize the remaining enantiomer [L-isomer (2*S*)] to discover new anti-HIV nucleosides. Therefore, we have recently synthesized (+)-β-L-(2*S*,4*S*)-dioxolanylthymine and (-)-β-L-(2*S*,4*S*)-dioxolanylcytosine (Figure 1) from L-gulose via 1,6-anhydro-L-gulopyranose, and these compounds were evaluated against HIV-1 in human PBM cells.[8] As expected, (-)-β-L-(2*S*,4*S*)-dioxolanylcytosine exhibited more potent anti-HIV activity than the corresponding racemate or D-isomer.

In this paper, the synthesis and comprehensive structure–activity relationships of various L-(2*S*)-1,3-dioxolanylpyrimidine and -purine nucleosides are reported.

Chemistry

The synthesis of L-1,3-dioxolanyl nucleosides was accomplished via the key intermediate **8** which was prepared from 2,3:5,6-di-*O*-isopropylidene-L-gulofuranose (**1**)[9,10] (Scheme I). L-1,6-Anhydrogulopyranose (**2**) was prepared by the treatment of 2,3:5,6-di-*O*-isopropylidene-L-gulofuranose (**1**) with 0.5 N HCl, which was prepared from L-gulono-6,3-lactone by reduction and protection using DIBAL/toluene at −78 °C and $CuSO_4$/acetone, respectively.[11-13] Oxidation of the anhydro sugar **2** with $NaIO_4$ and then reduction with $NaBH_4$ gave triol **3**, which, without isolation, was reacted with a catalytic amount of *p*-TsOH in acetone to yield the isopropylidene derivative **4**. After purification on silica gel column, the acetonide **4** was benzoylated by treating with BzCl/CH_2Cl_2/pyridine to give benzoate **5**, which was deprotected to diol derivative **6** using catalytic *p*-TsOH in MeOH. Oxidation of **6** to the acid **7** was accomplished by $NaIO_4/RuO_2$. Oxidative decarboxylation of acid **7** with $Pb(OAc)_4$/pyridine in anhydrous THF afforded the key intermediate **8**.

Condensation of acetate **8** with silylated thymine in dry 1,2-dichloroethane using TMSOTf as the Lewis acid catalyst gave an α,β-mixture of **10** and **9**, which was separated by fractional crystallization from MeOH (Scheme II). Both anomers were individually treated with NH_3/MeOH to give the enantiomerically pure (+)-β-L-(2*S*,4*S*)-dioxolanylthymine (**11**) and its α-isomer **12**, respectively.

The synthesis of L-1,3-dioxolanylcytosine and 5-substituted cytosine nucleosides **25–36** is illustrated in Scheme III. We have first tried the condensation of **8** with unprotected cytosine derivatives, but it resulted in inseparable α/β anomeric mixtures. In order to separate the anomeric mixture, we had to use protected 5-substituted cytosines such as N^4-acetyl or N^4-benzoyl derivatives. Although N^4-acetyl derivatives resulted in good separation of α/β anomer on TLC, the condensed products were too unstable to be purified by silica gel column chromatography. However, the use of N^4-benzoyl derivatives gave the better α/β anomeric separation and stability, compared to N^4-acetyl derivatives. Using N^4-benzoylcytosine and 5-substituted cytosines, fully protected nucleosides **13–24** were prepared by condensation of acetate **8** with silylated bases in dry 1,2-dichloroethane using TMSOTf as the Lewis acid catalyst. Debenzoylation of **13–24** with NH_3/MeOH afforded the final nucleosides **25–36**.

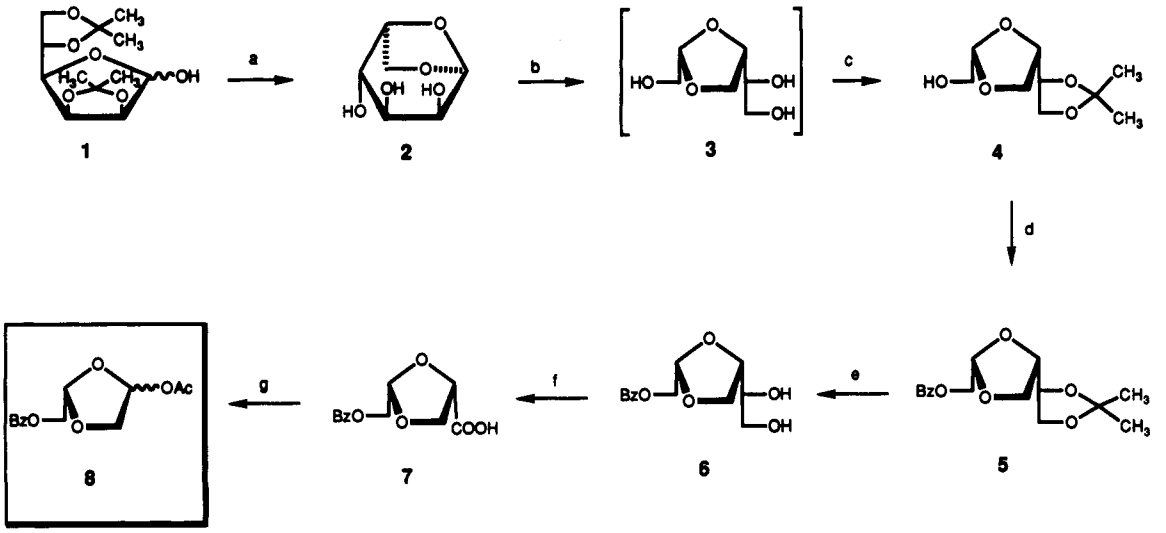
For the preparation of the purine derivatives, silylated 6-chloropurine was condensed with **8** in the presence of TMSOTf to give an α,β-mixture of **38** and **37**, which was separated by silica gel column chromatography (Scheme IV). To obtain debenzoylated product **39**, **37** was treated with NH_3/MeOH, however under the reaction conditions adenine derivative **41**, and an inseparable mixture of 6-chloro derivative **39** and 6-OMe-substituted product **40** were obtained. In order to avoid the formation of the adenine derivative, **37** was treated with NaOMe/MeOH to give an inseparable mixture of **39** and **40**, which was converted to inosine derivative **45** by using 2-mercaptoethanol/NaOMe in MeOH and to N^6-methyl derivative **46** by treating with $MeNH_2$ in MeOH (Scheme IV). During the conversion of the inseparable mixture of **39** and **40** to **45**, **40** was inert to these reaction conditions and could be separated from **39** as **40**. The α-adenine derivative **44** was prepared by a similar method.

2,6-Disubstituted purine derivatives **53–57** were synthesized by condensation of acetate **8** with silylated 6-chloro-2-fluoropurine, which gave **47** and **48** after silica gel column chromatography (Scheme V).[6] The compounds **47** and **48** were separately treated with NH_3/DME to give **49–52**, which were separated by silica gel column chromatography. Compounds **49–52** were deprotected with NH_3/MeOH to yield the desired nucleosides **53–56**. 6-Chloro-2-amino derivatives **53** and **54** were converted to guanine derivatives **57** and **58** by treating with 2-mercaptoethanol/NaOMe in MeOH.

For the synthesis of 2-chloro-6-amino- and 2,6-diaminopurine derivatives **65–68**, acetate **8** was condensed with silylated 2,6-dichloropurine to give an α/β mixture of **60** and **59** which was separated by silica gel column chromatography (Scheme VI). The compounds **59** and **60** were separately treated with NH_3/MeOH to yield 2-chloro-6-aminopurine derivatives **65** and **66**, respectively. The reactions of **59** and **60** with NaN_3/EtOH gave 2,6-diazidopurine derivatives **61** and **62**, respectively, which were hydrogenated to give **63** and **64**.[14] Debenzoylation of **63** and **64** by NH_3/MeOH gave 2,6-diaminopurine derivatives **67** and **68**.

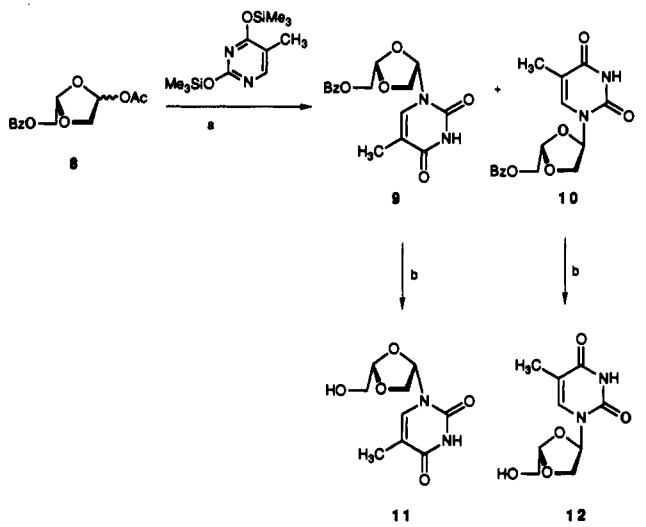
Physical and optical data of synthesized compounds are listed in Table I. The assignments of anomeric

Scheme I [a]



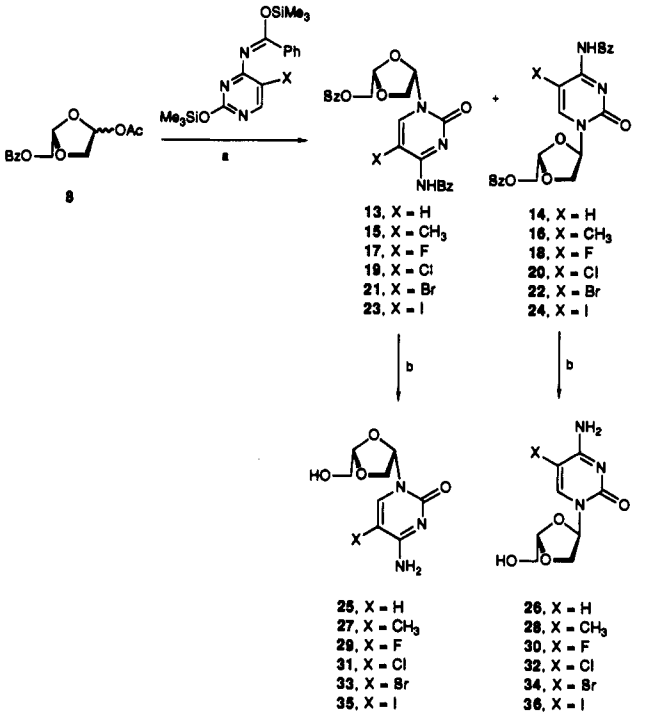
[a] (a) 0.5 N HCl, reflux; (b) (i) $NaIO_4$, MeOH, H_2O; (ii) $NaBH_4$; (c) *p*-TsOH, acetone; (d) BzCl, py, CH_2Cl_2; (e) *p*-TsOH, MeOH; (f) $NaIO_4$, RuO_2, CH_3CN–CCl_4–H_2O (2:2:3); (g) $Pb(OAc)_4$, THF.

Scheme II [a]



[a] (a) TMSOTf, $ClCH_2CH_2Cl$, room temperature; (b) NH_3/MeOH, room temperature.

Scheme III [a]



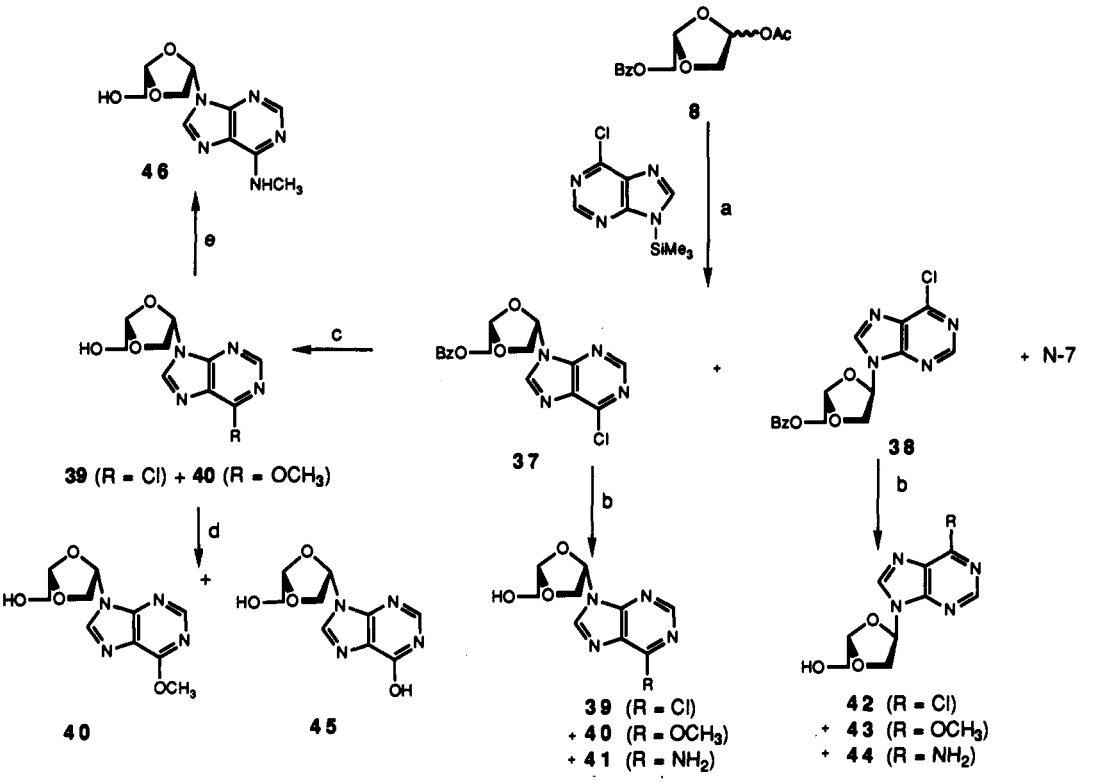
[a] (a) TMSOTf, $ClCH_2CH_2Cl$, room temperature; (b) NH_3/MeOH, room temperature.

configurations of **25** and **26** were based on NOE experiments. When 4′-H[15] of **25** and **26** was irradiated, enhancement of 1′-H peak of **25**, suggesting cis orientation, was observed, while no enhancement of 1′-H peak of **26** was observed, indicating the trans configuration.[5] Anomeric configurations of other nucleosides were assigned based on the comparison of the ^1H NMR patterns of **25** and **26**. Additionally, the chemical shifts of the β-anomeric protons appeared upfield relative to that of the α-anomeric protons and were used for the determination of the anomeric configurations. Furthermore, the 4′ proton of the β-isomers appeared upfield from that observed for the α-isomer because of the deshielding effect[16] by bases, and the 5′ protons of the β-isomer also appeared downfield from those observed for the α-isomer due to the same deshielding effect.[5,6]

Anti-HIV-1 Activity

Antiviral activities of the synthesized dioxolanyl nucleosides were evaluated in human PBM cells infected with HIV-1 strain LAV.[17] As shown in Table II, most of the compounds exhibited good to excellent anti-HIV-1 activities. The antiviral results shown in Table II are the average values of at least three separate experiments. Among the L-(2*S*)-dioxolanylpyrimidines, 5-fluorocytosine derivative **29** was found to exhibit the most potent anti-HIV activity (EC_{50} = 0.0012 μM) although it was toxic (IC_{50} = 10.0 μM). The order of anti-HIV potency of pyrimidine analogues was as follows: 5-fluorocytosine (β-isomer) > cytosine (β-isomer) > 5-fluorocytosine (α-isomer) > 5-iodocytosine (β-isomer) > cytosine (α-isomer) > 5-bromocytosine (β-isomer) > thymine (β-isomer) > 5-methylcytosine (α-isomer) > 5-iodocytosine (α-isomer) > 5-chlorocytosine (β-isomer). The α-isomers of thymine and 5-chloro- and 5-bromocytosine were found to be inactive. It appears that a small size substituent (F) with strong electron-withdrawing effect at the 5-position of cytosine enhances the anti-HIV activity, while the decrease

Scheme IV [a]



[a] (a) TMSOTf, $ClCH_2CH_2Cl$, reflux; (b) NH_3/MeOH, room temperature; (c) NaOMe, MeOH, room temperature; (d) $HOCH_2CH_2SH$, $NaOCH_3$, MeOH, reflux; (e) NH_2CH_3, MeOH, 85 °C.

in size of substituents at the same position diminishes the biological activity in β-analogues (CH_3 < Cl < Br < I). As in the case of D-(2*R*)-dioxolanyl,[5] D-(2*S*)-oxathiolanyl,[18] and L-(2*R*)-1,3-oxathiolanyl nucleosides,[7] some α-isomers **26, 28, 30, 36, 44, 54, 56, 66** exhibited not only good anti-HIV activity but also better activity than their corresponding β-isomer. These unexpected findings require further investigation, which is in progress in our laboratories.

Among the L-(2*S*)-dioxolanylpurines, 2,6-diamino derivative **67** exhibited the most potent anti-HIV activity (EC_{50} = 0.014 μM). The anti-HIV potency of purine analogues was found to be in the following decreasing order: 2,6-diaminopurine (β-isomer) > 2-chloroadenine (α-isomer) > 2-fluoroadenine (β-isomer) > adenine (β-isomer) > 2-amino-6-chloropurine (α-isomer) > 2-amino-6-chloropurine (β-isomer) > guanine (β-isomer) > 2-fluoroadenine (α-isomer) > adenine (α-isomer) > 2,6-diaminopurine (α-isomer) > N^6-methyladenine (β-isomer).

In the case of 6-substituted purine derivatives, compounds with amino group at 6-position exhibited good anti-HIV activity, but other bulky substituents such as $NHCH_3$, Cl, or OMe decreased the anti-HIV activity. Despite of moderate anti-HIV activity of (−)-β-D-(2*R*,4*R*)-dioxolanylhypoxanthine (EC_{50} = 5.0 μM), the L-(2*S*,4*S*)-isomer **45** was found to be inactive. In the case of 2,6-disubstituted purine derivatives, the amino substituent (**55** and **67**) at the 6-position also showed good anti-HIV activity, while the introduction of OH (**57**) or Cl (**53**) at the 6-position decreased the activity. The 2-position of purine also seemed to prefer the amino group to exhibit good anti-HIV activity, showing 2,6-diamino derivative (β-isomer) **67** was the most potent anti-HIV agent among purine series. Unlike D-(2*R*,4*R*)-guanine derivative (EC_{50} = 0.3 μM),[6] L-(2*S*,4*S*)-isomer **57** exhibited only moderate anti-HIV activity.

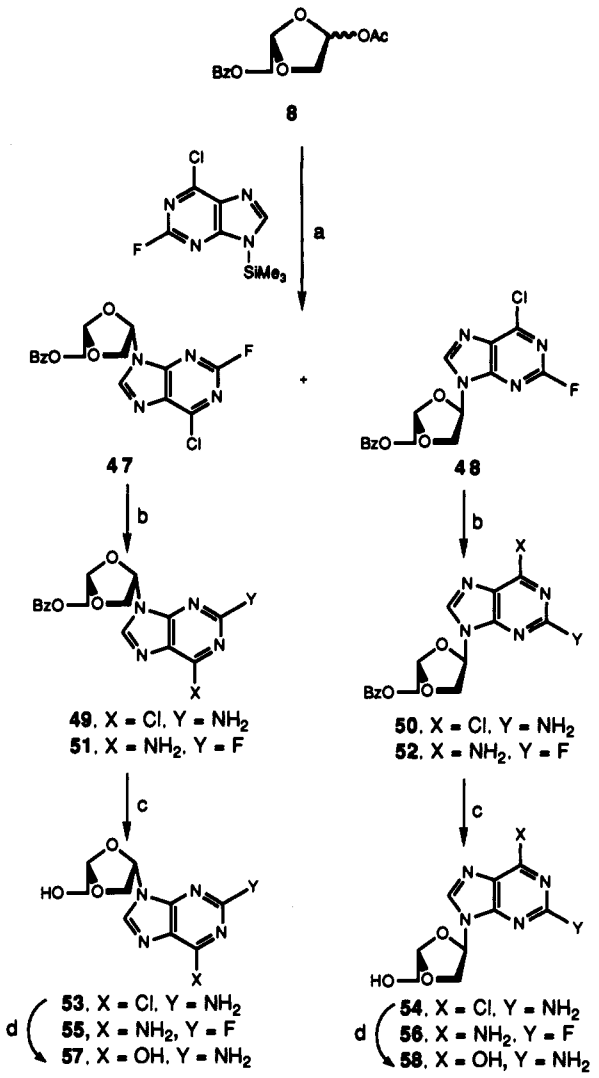
(+)-β-L-(2*S*,4*S*)-Dioxolanylthymine **11** (EC_{50} = 4.8 μM) was less potent than (−)-β-D-(2*R*,4*R*)-dioxolanylthymine (EC_{50} = 0.39 μM),[4] while (−)-β-L-(2*S*,4*S*)-dioxolanylcytosine **25** (EC_{50} = 0.002 μM) was found to give more potent anti-HIV and anti-HBV activity than (+)-β-D-(2*R*,4*R*)-dioxolanylcytosine (EC_{50} = 0.016 μM).[5] Other D-(2*R*,4*R*)-1,3-dioxolanyl nucleosides exhibited more potent anti-HIV activity than the corresponding L-(2*S*,4*S*)-1,3-dioxolanyl nucleosides. Therefore, it is interesting to mention that only L-(2*S*,4*S*)-cytosine derivative was found to be more potent than that of D-(2*R*,4*R*)-cytosine derivative.

In summary, from the study of comprehensive structure–activity relationships, it was found that 5-fluorocytosine derivative **29** showed the most potent anti-HIV activity among the L-(2*S*)-dioxolanylpyrimidines and -purines. Further virological and biochemical studies with those active compounds are warranted in order to determine their usefulness as anti-HIV agents for the treatment of AIDS. Conformational studies of the above reported L-nucleosides with respect to the antiviral activities is in progress in our laboratories.

Experimental Section

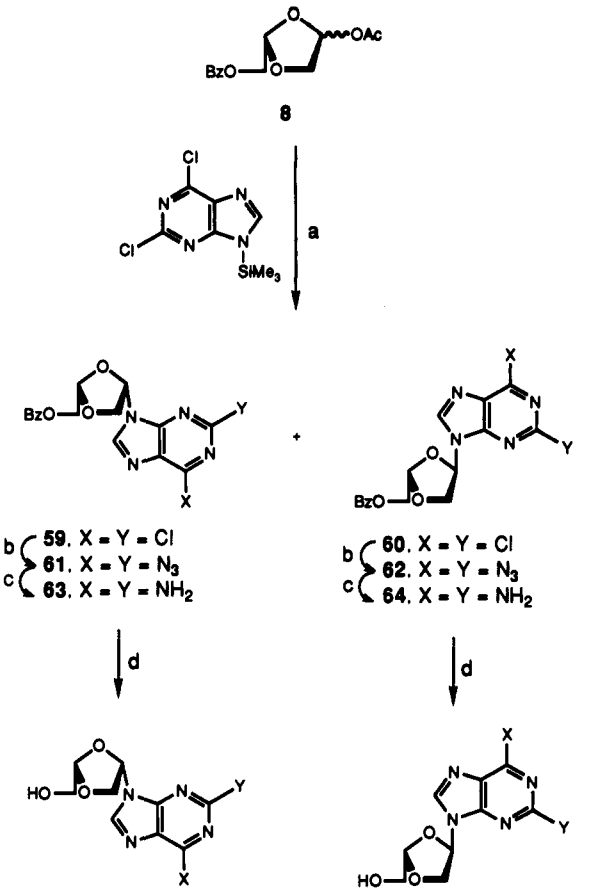
Melting points were determined on a Mel-temp II laboratory device and are uncorrected. ^1H NMR spectra were recorded on a JEOL FX 90Q or Bruker 300 fourier transform spectrometer for 90- or 300-MHz ^1H NMR spectra, respectively, with Me_4Si as internal standard; chemical shifts are reported in parts per million (δ), and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). UV spectra were obtained on a Beckman DU-7 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA, or Galbraith Laboratories, Inc., Knoxville, TN. Dry 1,2-dichloroethane and methylene chloride were obtained

Scheme V [a]



[a] (a) TMSOTf, $ClCH_2CH_2Cl$, reflux; (b) NH_3/DME; (c) NH_3/MeOH, room temperature; (d) $HSCH_2CH_2OH$, NaOMe, MeOH.

Scheme VI [a]



[a] (a) TMSOTf, CH_2Cl_2, reflux; (b) NaN_3/EtOH, reflux; (c) H_2, 10% Pd–C, EtOH, room temperature; (d) NH_3/MeOH, room temperature.

by distillation from CaH_2 prior to use. Dry THF was obtained by distillation from Na and benzophenone prior to use.

(−)-1,6-Anhydro-β-L-gulopyranose (2). A mixture of 1 (33.0 g, 0.127 mol) and 0.5 N HCl (330 mL, 0.165 mol) was refluxed for 20 h, and the mixture was cooled and neutralized to pH 6 by resin (Dowex-2, HCO_3^- form) with air bubbling. The resin was recycled by washing with 10% HCl, H_2O, MeOH, H_2O, and saturated $NaHCO_3$ solution. The reaction mixture was filtered, and the resin was washed with H_2O (500 mL). The combined filtrates were concentrated to dryness and dried in vacuo overnight. The residue was purified over column (5-cm depth, silica gel, TLC grade, $CHCl_3$–MeOH, 10:1) to give slightly yellow solid, which was recrystallized from absolute alcohol to yield a colorless solid 2 [R_f = 0.43 ($CHCl_3$–MeOH, 5:1), 7.3 g, 35.5%]. The L-gulose (R_f = 0.07, 11.0 g) obtained from the column was recycled to give 2 (5.0 g, total yield 60.0%): ^{1}H NMR (DMSO-d_6) δ 3.22–3.68 (m, 4 H, H-2, -3, -4, and -6a), 3.83 (d, $J_{6b,6a}$ = 7.25 Hz, 1 H, H_b-6), 4.22 (pseudo t, $J_{5,6a}$ = 4.61 and 4.18 Hz, 1 H, H-5), 4.46 (d, $J_{2\text{-}OH,2}$ = 6.59 Hz, 1 H, 2-OH, exchangeable with D_2O), 4.62 (d, $J_{3\text{-}OH,3}$ = 5.28 Hz, 1 H, 3-OH, exchangeable with D_2O), 5.07 (d, $J_{4\text{-}OH,4}$ = 4.84 Hz, 1 H, 4-OH, exchangeable with D_2O), 5.20 (d, $J_{1,2}$ = 2.19 Hz, 1 H, H-1).

(−)-(1′*S*,2*S*,4*S*)-4-(1,2-Dihydroxy-1,2-*O*-isopropylideneethyl)-2-(hydroxymethyl)dioxolane (4). A solution of $NaIO_4$ (22.4 g, 0.1 mol) in H_2O (300 mL) was added dropwise to a solution of 2 (11.3 g, 0.07 mol) in MeOH (350 mL) for 10 min at 0 °C, and the mixture was stirred mechanically for 15 min. $NaBH_4$ (7.9 g, 0.21 mol) was added, and the reaction mixture was stirred for 10 min at 0 °C. The white solid was filtered off, and the solid was washed with MeOH (300 mL). The combined filtrate was neutralized by 0.5 N HCl (~200 mL) and concentrated to dryness. The residue was dried in vacuo overnight to give crude 3. The syrupy residue of 3 was triturated with MeOH–acetone (1:5, 1200 mL) using a mechanical stirrer (5 h), and the white solid was filtered off. The filtrate was concentrated to dryness, and the residue was dissolved in acetone (500 mL) and followed by the addition of *p*-TsOH (6.6 g, 0.035 mol). After stirring for 6 h, the mixture was neutralized by Et_3N, filtered, and concentrated to dryness. The residue was dissolved in EtOAc (350 mL), washed with H_2O (500 mL × 2), dried ($MgSO_4$), filtered, and evaporated to give crude 4 (3.6 g) as a yellowish syrup. The dried H_2O layer was recycled using 10% MeOH–acetone (900 mL), *p*-TsOH (16.0 g, 0.084 mol) by 1 h stirring to yield crude 4 (5.6 g). The crude products obtained were purified by dry column over silica gel (MeOH–$CHCl_3$, 1–5%) to give 4 [R_f = 0.82 ($CHCl_3$–MeOH, 10:1), 8.8 g, 61.8%] as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 1.26 and 1.32 (2 s, 2 × 3 H, isopropylidene), 3.41 (dd, $J_{CH_2OH,OH}$ = 6.04 Hz, $J_{CH_2OH,2}$ = 3.96 Hz, 2 H, CH_2OH), 3.56–4.16 (m, 6 H, H-4, -5, -1′, and -2′), 4.82 (t, J_{OH,CH_2} = 6.0 Hz, 1 H, CH_2OH, exchangeable with D_2O), 4.85 (t, J_{2,CH_2OH} = 3.96 Hz, 1 H, H-2).

(+)-(1′*S*,2*S*,4*S*)-4-(1,2-Dihydroxy-1,2-*O*-isopropylideneethyl)-2-[(benzoyloxy)methyl]dioxolane (5). Benzoyl chloride (6.5 mL, 56.0 mmol) was added dropwise to a solution of 4 (8.5 g, 42.0 mmol) in pyridine–CH_2Cl_2 (1:2, 120 mL) at 0 °C and the temperature raised to room temperature. After stirring for 2 h, the reaction was quenched with MeOH (10 mL) and the mixture was concentrated to dryness in vacuo. The residue was dissolved in CH_2Cl_2 (300 mL) and washed with H_2O (100 mL × 2), brine, dried ($MgSO_4$), filtered, and evaporated to give a yellowish syrup, which was purified by silica gel column chromatography (EtOAc–hexanes, 4–30%) to yield 5 [R_f = 0.45

Table I. Physical and Optical Data

no.	mp, °C (solv)[a]	$[\alpha]^{25}_D$	formula	anal.	no.	mp, °C (solv)[a]	$[\alpha]^{25}_D$	formula	anal.
2	142–145 (b)	−50.011 (c 1.61, MeOH)			32	190–192 (h)	+55.729 (c 0.82, MeOH)	$C_8H_{10}ClN_3O_4$	C, H, Cl, N
4	oil	−12.48 (c 1.11, $CHCl_3$)	$C_8H_{16}O_5$	C, H	33	195–196 dec	−26.679 (c 0.96, MeOH)	$C_8H_{10}BrN_3O_4 \cdot 0.3H_2O$	C, H, N
5	oil	+10.73 (c 1.75, MeOH)	$C_{18}H_{20}O_6$	C, H	34	199 dec	+35.151 (c 0.95, MeOH)	$C_8H_{10}BrN_3O_4 \cdot 0.1C_4H_8O_2$	C, H, N
6	oil	+9.16 (c 1.01, $CHCl_3$)	$C_{13}H_{16}O_6$	C, H					
8	oil	−12.53 (c 1.11, $CHCl_3$)	$C_{13}H_{14}O_6$	C, H					
9	211–212 (c)	+39.616 (c 0.8, CH_2Cl_2)	$C_{18}H_{16}N_2O_6$	C, H, N	35	171 dec	−16.454 (c 0.75, MeOH)	$C_8H_{10}IN_3O_4$	C, H, I, N
10	124–125 (c)	+4.59 (c 1.95, $CHCl_3$)	$C_{18}H_{16}N_2O_6$	as mixture of 9 and 10	36	182 dec	+21.385 (c 0.67, MeOH)	$C_8H_{10}IN_3O_4$	C, H, N
					37	164.5–165 (i)	+59.063 (c 0.73, $CHCl_3$)	$C_{18}H_{13}ClN_4O_4$	C, H, N
11	174–175 (d)	+18.601 (c 0.75, MeOH)	$C_8H_{12}N_2O_5$	C, H, N	38	112–113 (i)	−9.819 (c 0.74, $CHCl_3$)	$C_{18}H_{13}ClN_4O_4$	C, H, N
12	foam	−10.011 (c 0.45, MeOH)	$C_8H_{12}N_2O_5$	C, H, N	40	111–112	+31.601 (c 0.82, MeOH)	$C_{10}H_{12}N_4O_4 \cdot 0.3MeOH$	C, H, N
13	203–205 (e)	−56.45 (c 0.99, $CHCl_3$)	$C_{22}H_{19}N_3O_6 \cdot 0.35CHCl_3$	C, H, N	41	164–166	+33.142 (c 0.71, MeOH)	$C_9H_{11}N_5O_3$	C, H, N
14	138–140 (g)	+78.11 (c 1.02, $CHCl_3$)	$C_{22}H_{19}N_3O_6$	C, H, N	44	178–179	−35.694 (c 0.76, MeOH)	$C_8H_{11}N_5O_3$	C, H, N
15	159	+14.479 (c 0.93, $CHCl_3$)	$C_{23}H_{21}N_3O_6$	C, H, N	45	207–208	+19.726 (c 0.28, MeOH)	$C_9H_{10}N_4O_4$	C, H, N
16	111	+32.298 (c 0.97, $CHCl_3$)	$C_{23}H_{21}N_3O_6$	C, H, N	46	140–141	+25.973 (c 0.82, MeOH)	$C_{10}H_{13}N_5O_3$	C, H, N
17	163–164	+1.926 (c 0.94, $CHCl_3$)	$C_{22}H_{18}FN_3O_6 \cdot 0.7H_2O$	C, H, N	47	139–140 (e)	+40.71 (c 0.63, $CHCl_3$)	$C_{18}H_{12}ClFN_4O_4 \cdot 0.1C_6H_{14}$	C, H, Cl, N
18	128–129	+48.381 (c 1.08, $CHCl_3$)	$C_{22}H_{18}FN_3O_6$	C, H, N	48	145–146 (e)	−7.32 (c 0.54, $CHCl_3$)	$C_{16}H_{12}ClFN_4O_4$	C, H, Cl, N
19	162 (e)	+3.650 (c 0.81, $CHCl_3$)	$C_{22}H_{18}ClN_3O_6$	C, H, N	53	204 dec (e)	+65.29 (c 0.25, MeOH + NH_4OH)	$C_8H_{10}ClN_5O_3$	C, H, N
20	168 (g)	+49.868 (c 0.87, $CHCl_3$)	$C_{22}H_{18}ClN_3O_6$	C, H, N	54	146–147 (j)	−20.56 (c 0.50, MeOH)	$C_8H_{10}ClN_5O_3$	C, H, Cl, N
21	153 (e)	−6.053 (c 0.92, $CHCl_3$)	$C_{22}H_{18}BrN_3O_6$	C, H, N	55	240–241 dec (e)	+46.19 (c 0.25, MeOH + NH_4OH)	$C_9H_{10}FN_5O_3$	C, H, N
22	176–177 (e)	+37.075 (c 0.83, $CHCl_3$)	$C_{22}H_{18}BrN_3O_6 \cdot 0.42(C_2H_5)_2O$	C, H, N	56	263–264 dec (e)	insoluble	$C_8H_{10}FN_5O_3$	C, H, N
					57	280 dec (e)	insoluble	$C_8H_{11}N_5O_4$	C, H, N
23	162	+1.541 (c 0.79, $CHCl_3$)	$C_{22}H_{18}IN_3O_6$	C, H, N	58	259–260 (k)	−101.57 (c 0.25, H_2O + NH_4OH)	$C_8H_{11}N_5O_4 \cdot 0.5H_2O$	C, H, N
24	179–181	+31.491 (c 0.93, $CHCl_3$)	$C_{22}H_{18}IN_3O_6$	C, H, N					
25	176–177 (f)	−38.33 (c 0.43, MeOH)*	$C_8H_{11}N_3O_4$	C, H, N	59	foam	+49.54 (c 0.38, MeOH)	$C_{16}H_{12}Cl_2N_4O_4$	C, H, Cl, N
26	192–193 (f)	+66.14 (c 0.50, MeOH)*	$C_8H_{11}N_3O_4$	C, H, N	60	144–145	+73.04 (c 0.29, MeOH)	$C_{18}H_{12}Cl_2N_4O_4$	C, H, Cl, N
27	144–145	−23.403 (c 0.61, MeOH)	$C_8H_{13}N_3O_4$	C, H, N	65	235–236 (e)	+29.32 (c 0.24, MeOH)	$C_8H_{10}ClN_5O_3$	C, H, Cl, N
28	191–193	+39.133 (c 0.32, MeOH)	$C_9H_{13}N_3O_4$	C, H, N	66	219–220 (e)	−9.16 (c 0.22, MeOH)	$C_9H_{10}ClN_5O_3$	C, H, Cl, N
29	181–182	−53.283 (c 0.86, MeOH)	$C_8H_{10}FN_3O_4$	C, H, N	67	176–178 (l)	+29.40 (c 0.32, MeOH)	$C_9H_{12}N_6O_3$	C, H, N
30	153–155	+64.801 (c 0.98, MeOH)	$C_8H_{10}FN_3O_4$	C, H, N	68	148–149 (i)	−24.24 (c 0.26, MeOH)	$C_8H_{12}N_6O_3 \cdot 0.25H_2O$	C, H, N
31	200–201 (h)	−18.881 (c 0.95, MeOH)	$C_8H_{10}ClN_3O_4$	C, H, Cl, N					

[a] Solvents: b, ethanol; c, hexanes–ether; d, ether–MeOH; e, MeOH; f, hexanes–CH_2Cl_2; g, EtOAc; h, 2-propanol–hexanes; i, ether; j, ethanol–ether; k, water; l, 2-propanol. * Optical rotation data published in ref 5 were in error. New data for the optical isomers of **25** and **26** are $[\alpha]_D^{25}$ = +43.332 (c 0.8, MeOH) and −63.743 (c 0.82, MeOH), respectively.

(hexanes–EtOAc, 3:1), 10.7 g, 83.4%] as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.35 and 1.44 (2 s, 2 × 3 H, isopropylidene), 3.3–4.35 (m, 6 H, H-4, -5, -1′, and -2′), 4.44 (d, J = 3.96 Hz, 2 H, CH_2OBz), 5.29 (t, J = 3.74 Hz, 1 H, H-2), 7.3–7.64, 8.02–8.18 (m, 3 H, 2 H, OBz).

(+)-(1′*S*,2*S*,4*S*)-4-(1,2-Dihydroxyethyl)-2-[(benzoyloxy)methyl]dioxolane (6). The mixture of **5** (5.7 g, 18.0 mmol) and *p*-TsOH (1.1 g, 5.5 mmol) in MeOH (70 mL) was stirred at room temperature for 2 h. Due to incompletion of the reaction, solvents were evaporated to half volume, and MeOH (50 mL) and *p*-TsOH (0.7 g, 3.7 mmol) were added. After stirring for another 1 h, the reaction mixture was neutralized by Et_3N and the solvent was evaporated to dryness. The residue was purified by silica gel column chromatography (hexanes–EtOAc, 10–33%) to give **6** [R_f = 0.15 (hexanes–EtOAc, 1:1), 4.9 g, 99.2%] as a colorless syrup: ^{1}H NMR (DMSO-d_6) δ 3.43 (m, 2 H, H-2′), 3.67–4.1 (m, 4 H, H-4, -5, and -1′), 4.32 (d, J = 3.73 Hz, 2 H, CH_2OBz), 4.60 (t, J = 5.72 Hz, 2′-OH, exchangeable with D_2O), 5.23 (t, J = 3.96 Hz, 1 H, H-2), 7.45–7.7, 7.93–8.04 (m, 3 H, 2H, OBz).

(−)-(2*S*,4*S*)- and (−)-(2*S*,4*R*)-4-Acetoxy-2-[(benzoyloxy)methyl]dioxolane (8). A solution of $NaIO_4$ (10.2 g, 48.0 mmol) in H_2O (120 mL) was added to a solution of **6** (3.1 g, 11.0 mmol) in CCl_4–CH_3CN (1:1, 160 mL) and then $RuO_2 \cdot H_2O$ (0.02 g). After the reaction mixture was stirred for 5 h, the solid was removed by filtration over Celite and the filtrate was evaporated to 1/3 volume. The residue was dissolved in CH_2Cl_2 (100 mL), and the H_2O layer was extracted with CH_2Cl_2 (100 mL × 2). The combined organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered, evaporated to dryness, and dried in vacuo for 16 h to give crude **7** (2.6 g, 91%).

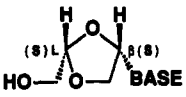
To a solution of crude **7** (2.6 g, 10 mmol) in dry THF (60 mL) were added $Pb(OAc)_4$ (5.48 g, 12.4 mmol) and pyridine (0.83 mL, 10.3 mmol) under N_2 atmosphere. The mixture was stirred for 45 min, and the solid was removed by filtration. Then the solid was washed with EtOAc (60 mL), and the combined organic layer was evaporated to dryness. The residue was purified by silica gel column chromatography (hexanes–EtOAc, 2:1) to yield anomeric mixture of **8** [R_f = 0.73 and 0.79 (hexanes–EtOAc, 2:1), 1.90 g, 69.3%] as colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.998, 2.11 (2 s, 3 H, OAc), 3.93–4.33 (m, 2 H, H-5), 4.43, 4.48 (2 d, J = 3.73, 3.74 Hz, 2 H, CH_2OBz), 5.46, 5.55 (2 t, J = 4.18, 3.63 Hz, 1 H, H-2), 6.42 (m, 1 H, H-4), 7.33–7.59, 8.00–8.15 (m, 3 H, 2 H, -OBz).

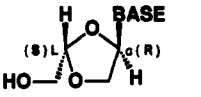
(−)-(2*S*,4*S*)-1-[2-[(Benzoyloxy)methyl]-1,3-dioxolan-4-yl]thymine (9) and (+)-(2*S*,4*R*)-1-[2-[(Benzoyloxy)methyl]-1,3-dioxolan-4-yl]thymine (10). A mixture of thymine (0.25 g, 1.98 mmol) in hexamethyldisilazane (15 mL) and ammonium sulfate (catalytic amount) was refluxed for 12 h. The resulting clear solution was concentrated in vacuo under anhydrous condition to yield silylated thymine as colorless oil. To a solution of silylated thymine in dry 1,2-dichloroethane (5 mL) were added a solution of **8** (0.35 g, 1.31 mmol) in dry 1,2-dichloroethane (15 mL) and TMSOTf (0.5 mL, 2.63 mmol), and the reaction mixture was stirred at room temperature for 2 h under nitrogen. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ (10 mL) and $CHCl_3$, and it was stirred for an additional 30 min at room temperature. The organic layer was separated, and the aqueous layer was extracted with methylene chloride (50 mL × 3). The combined organic layer was washed with saturated $NaHCO_3$ and H_2O and dried (anhydrous $MgSO_4$). After filtration, the filtrate was concentrated, the residue was boiled with MeOH, the white solid was filtered to yield **9** [R_f = 0.11 (hexanes–EtOAc, 1:1), 0.19 g, 42.3%], and the filtrate was evaporated to give crude **10** [R_f = 0.19 (hexanes–EtOAc, 1:1), 0.20 g, 45.7%] as a white foam. An analytical sample of **10** was obtained from preparative TLC ($CHCl_3$–MeOH, 20:1) of crude **10**. **9**: UV (MeOH) λ_{max} 265.0 nm. **10**: UV (MeOH) λ_{max} 265.0 nm.

(+)-(2*S*,4*S*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]thymine (11). A mixture of **9** (140 mg, 0.43 mmol) in NH_3/MeOH (50 mL) was stirred at room temperature for 2 days. After the mixture was concentrated, the residue was purified by preparative TLC ($CHCl_3$–MeOH, 15:1) to yield **11** (75 mg, 75.8%) as a white solid; UV (H_2O) λ_{max} 266.0 (ε 10 760) (pH 7), 266.5 (ε 9890) (pH 2), 266.3 nm (ε 8400) (pH 11).

(−)-(2*S*,4*R*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-

Table II. Median Effective (EC_{50}) and Inhibitory (IC_{50}) Concentration of L-(2*S*)-Dioxolanyl Nucleosides in PBM Cells and Cytotoxicity in Vero Cells





compd no.	base	anomer	EC_{50} (μM)[a] anti-HIV-1 (PBM)	IC_{50} (μM) cytotoxicity (PBM)	IC_{50} (μM) cytotoxicity (Vero)
11	thymine	(+)-β	4.8	>100	>100
12	thymine	(−)-α	>100	>100	>100
25	cytosine	(−)-β	0.002	>10	0.1
26	cytosine	(+)-α	1.3	>10	16.8
27	5-Me-cytosine	(−)-β	45.9	>100	>100
28	5-Me-cytosine	(+)-α	18.9	>100	>100
29	5-F-cytosine	(−)-β	0.0012	10.0	<1.0
30	5-F-cytosine	(+)-α	0.063	>100	49.10
31	5-Cl-cytosine	(−)-β	34.3	>100	>100
32	5-Cl-cytosine	(+)-α	>100	>100	>100
33	5-Br-cytosine	(−)-β	1.8	>100	>100
34	5-Br-cytosine	(+)-α	>100	>100	>100
35	5-I-cytosine	(−)-β	0.41	56.4	22.9
36	5-I-cytosine	(+)-α	28.8	>100	>100
40	6-OMe-purine	(+)-β	>100	>100	>100
41	adenine	(+)-β	3.8	>100	>100
44	adenine	(−)-α	29.0	>100	>100
45	hypoxanthine	(+)-β	>100	>100	>100
46	N^6-Me-adenine	(+)-β	62.6	>100	>100
53	2-NH_2-6-Cl-purine	(+)-β	13.4	>100	>100
54	2-NH_2-6-Cl-purine	(−)-α	8.1	>100	≥100
55	2-F-adenine	(+)-β	1.6	>100	>100
56	2-F-adenine	(−)-α	23.7	>100	≥100
57	guanine	(+)-β	17.5	>100	>100
58	guanine	(−)-α	101.9	>100	>100
65	2-Cl-adenine	(+)-β	34.7	n.d.[b]	n.d.
66	2-Cl-adenine	(−)-α	1.27	n.d.	n.d.
67	2,6-diaminopurine	(+)-β	0.014	n.d.	n.d.
68	2.6-diaminopurine	(−)-α	42.12	n.d.	n.d.
	AZT		0.004	>100	28.0

[a] EC_{50} values are for inhibition of virus production as indicated by supernatant RT levels. [b] n.d., not determined.

thymine (12). A mixture of **10** (0.20 g, 0.6 mmol) in NH_3/MeOH was stirred at room temperature for 2 days. After the mixture was concentrated, the residue was purified by preparative TLC ($CHCl_3$–MeOH, 15:1) to yield **12** (0.13 g, 95.6%) as a white foam: UV (H_2O) λ_{max} 266.5 (ε 9450) (pH 7), 266.5 (ε 9200) (pH 2), 266.3 nm (ε 6930) (pH 11).

General Procedure for Condensation of Acetate 8 with 5-Substituted Cytosines. A mixture of silylated N^4-benzoylcytosine, which was prepared from N^4-benzoylcytosine (4.56 g, 21.2 mmol), hexamethyldisilazane (50 mL), and ammonium sulfate (catalytic amount) by refluxing for 2.5 h, in dry 1,2-dichloroethane (20 mL) was treated with a solution of **8** (3.75 g, 14.1 mmol) in dry 1,2-dichloroethane (40 mL) and TMSOTf (5.44 mL, 28.1 mmol) at room temperature for 1.5 h. Saturated $NaHCO_3$ (10 mL) was added, and the reaction mixture was stirred another 15 min. After similar workup as **9** and **10**, the residue was dissolved in hot MeOH and kept standing in a hood overnight. The white crystals were filtered to give **13** (2.6 g, 43.8%), the filtrate was concentrated to dryness, and the resulting solid was recrystallized from EtOAc to yield **14** (2.2 g, 37.1%) as a white solid.

(−)-(2*S*,4*S*)-N^4-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]cytosine (13) and (+)-(2*S*,4*R*)-N^4-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]cytosine (14). **13**: UV (MeOH) λ_{max} 302.5 nm. **14**: UV (MeOH) λ_{max} 302.5 nm.

(+)-(2*S*,4*S*)-N^4-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-methylcytosine (15) and (+)-(2*S*,4*R*)-N^4-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-methylcytosine (16). N^4-Benzoyl-5-methylcytosine (0.72 g, 3.38 mmol) and **8** (0.60 g, 2.25 mmol) were reacted for 2 h to give a mixture of **15** and **16**, which were separated by silica gel column chromatography (1–5% MeOH/$CHCl_3$) to yield **15** [R_f = 0.56 ($CHCl_3$–MeOH, 50:1), 0.39 g, 39.8%] and **16** (R_f = 0.67, 0.32 g, 32.0%) as white solids. **15**: UV ($CHCl_3$) λ_{max} 328.7 nm. **16**: UV ($CHCl_3$) λ_{max} 328.7 nm.

(+)-(2*S*,4*S*)-N^4-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-fluorocytosine (17) and (+)-(2*S*,4*R*)-N^4-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-fluorocytosine (18). N^4-Benzoyl-5-fluorocytosine (0.58 g, 2.67 mmol) and **8** (0.47 g, 1.77 mmol) were reacted for 1.5 h to give a mixture of **17** and **18**, which were separated by silica gel column chromatography [(MeOH–$CHCl_3$, 500:1), 230–400 mesh] to yield **17** [R_f = 0.26 ($CHCl_3$–MeOH, 50:1), 0.38 g, 49.0%] and **18** (R_f = 0.32, 0.38 g, 48.0%) as white solids. **17**: UV ($CHCl_3$) λ_{max} 328.2 nm. **18**: UV ($CHCl_3$) λ_{max} 328.7 nm.

(+)-(2*S*,4*S*)-N^4-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-chlorocytosine (19) and (+)-(2*S*,4*R*)-N^4-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-chlorocytosine (20). N^4-Benzoyl-5-chlorocytosine (0.66 g, 2.82 mmol) and **8** (0.50 g, 1.88 mmol) were reacted for 2 h to give a mixture of **19** and **20**, which were separated by silica gel column chromatography (hexanes–EtOAc, 10:1) to yield **19** [R_f = 0.11 (hexanes–EtOAc, 4:1), 0.38 g, 44.4%] as a white foam, which was crystallized from MeOH, and **20** (R_f = 0.18, 0.34 g, 39.7%) as a white foam, which was crystallized from EtOAc. **19**: UV ($CHCl_3$) λ_{max} 332.2 nm. **20**: UV ($CHCl_3$) λ_{max} 331.7 nm.

(−)-(2*S*,4*S*)-N^4-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-bromocytosine (21) and (+)-(2*S*,4*R*)-N^4-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-bromocytosine (22). N^4-Benzoyl-5-bromocytosine (0.70 g, 2.52 mmol) and **8** (0.45 g, 1.69 mmol) were reacted for 2 h to give a mixture of **21** and **22** and fractional crystallization from MeOH gave **21** [R_f = 0.23 (hexanes–EtOAc, 1:1), 0.37 g, 43.8%] as a white solid and **22** (R_f = 0.33, 0.34 g, 40.2%) as a white solid. **21**: UV ($CHCl_3$) λ_{max} 333.2 nm. **22**: UV ($CHCl_3$) λ_{max} 332.7 nm.

(+)-(2*S*,4*S*)-N^4-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-iodocytosine (23) and (+)-(2*S*,4*R*)-N^4-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-iodocytosine (24). N^4-Benzoyl-5-iodocytosine (0.78 g, 2.78 mmol) and **8** (0.41 g, 1.52 mmol) yielded a mixture of **23** and **24**, which were separated by preparative TLC ($CHCl_3$–MeOH, 50:1) to give **23** [R_f = 0.35 ($CHCl_3$–MeOH, 50:1), 0.36 g, 43.8%] and **24** (R_f = 0.43, 0.32 g, 38.9%) as white solids. **23**: UV ($CHCl_3$) λ_{max} 338.2 nm. **24**: UV ($CHCl_3$) λ_{max} 338.3 nm.

General Procedure for Debenzoylation. A mixture of **13** (2.5 g, 5.93 mmol) in NH_3/MeOH (70 mL, saturated at 0 °C) was stirred for 3 days at room temperature. After the mixture was concentrated to dryness, the residue was crystallized from ether–MeOH to give colorless crystalline **25** (1.1 g, 87.3%).

(−)-(2*S*,4*S*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]cytosine (25): UV (H_2O) λ_{max} 270.0 (ε 7770) (pH 7), 278.0 (ε 11 970) (pH 2), 269.0 nm (ε 8380) (pH 11).

(+)-(2*S*,4*R*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]cytosine (26). **14** (0.35 g, 0.99 mmol) was debenzoylated, and the crude product was purified by preparative TLC ($CHCl_3$–MeOH, 5:1) to give an oil, which was crystallized from CH_2Cl_2/hexanes to yield **26** (0.14 g, 64.3%) as a white solid: UV (H_2O) λ_{max} 270.0 (ε 8780) (pH 7), 278.0 (ε 13 240) (pH 2), 269.0 nm (ε 9070) (pH 11).

(−)-(2*S*,4*S*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-methylcytosine (27). **15** (0.25 g, 0.57 mmol) was debenzoylated, and the crude product was purified by preparative TLC ($CHCl_3$–MeOH, 10:1) to give **27** (0.11 g, 82.7%) as a white solid: UV (H_2O) λ_{max} 277.0 (ε 8320) (pH 7), 285.8 (ε 13 860) (pH 2), 276.8 nm (ε 9440) (pH 11).

(+)-(2*S*,4*R*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-methylcytosine (28). **16** (200 mg, 0.46 mmol) was debenzoylated, and the crude product was purified by preparative TLC ($CHCl_3$–MeOH, 10:1) to give an oil. This was crystallized from MeOH–ether to yield **28** (88 mg, 84.0%) as a white solid: UV (H_2O) λ_{max} 277.0 (ε 9150) (pH 7), 286.3 (ε 14 580) (pH 2), 276.8 nm (ε 10 080) (pH 11).

(−)-(2*S*,4*S*)-5-Fluoro-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]cytosine (29). **17** (200 mg, 0.46 mmol) was debenzoylated, and the crude product was purified by silica gel column chromatography ($CHCl_3$–MeOH, 10:1) to give **29** (63 mg, 60.0%) as a white solid: UV (H_2O) λ_{max} 279.5 (ε 9020) (pH 7), 286.3 (ε 12 020) (pH 2), 279.5 nm (ε 9380) (pH 11).

(+)-(2*S*,4*R*)-5-Fluoro-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]cytosine (30). **18** (290 mg, 0.66 mmol) was debenzoylated, and the crude product was purified by silica gel column chromatography ($CHCl_3$–MeOH, 10:1) to give **30** (127 mg, 83.0%) as a white solid: UV (H_2O) λ_{max} 279.5 (ε 9060) (pH 7), 285.8 (ε 11 380) (pH 2), 279.8 nm (ε 9100) (pH 11).

(−)-(2*S*,4*S*)-5-Chloro-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]cytosine (31). **19** (235 mg, 0.52 mmol) was debenzoylated, and the crude product was purified by silica gel column chromatography ($CHCl_3$–MeOH, 10:1) to give **31** (82 mg, 64.6%) as a white solid after trituration with 2-propanol–hexanes: UV (H_2O) λ_{max} 285.0 (ε 7210) (pH 7), 294.0 (ε 11 420) (pH 2), 285.0 nm (ε 8260) (pH 11).

(+)-(2*S*,4*R*)-5-Chloro-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]cytosine (32). **20** (180 mg, 0.39 mmol) was debenzoylated, and the crude product was purified by preparative TLC ($CHCl_3$–MeOH, 10:1) to give **32** (74 mg, 75.7%) as a white solid after trituration with 2-propanol–hexanes: UV (H_2O) λ_{max} 285.5 (ε 11 340) (pH 7), 293.5 (ε 15 020) (pH 2), 285.5 nm (ε 11 540) (pH 11).

(−)-(2*S*,4*S*)-5-Bromo-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]cytosine (33). **21** (250 mg, 0.50 mmol) was debenzoylated, and the crude product was purified by silica gel column chromatography ($CHCl_3$–MeOH, 10:1) to give **33** (129 mg, 88.3%) as a white solid: UV (H_2O) λ_{max} 287.0 (ε 6720) (pH 7), 297.0 (ε 10 960) (pH 2), 287.0 nm (ε 8270) (pH 11).

(+)-(2*S*,4*R*)-5-Bromo-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]cytosine (34). **22** (250 mg, 0.50 mmol) was debenzoylated, and the crude product was purified by silica gel column chromatography ($CHCl_3$–MeOH, 10:1) to give **34** (103 mg, 70.6%) as a white solid: UV (H_2O) λ_{max} 287.0 (ε 6330) (pH 7), 296.5 (ε 10 600) (pH 2), 287.0 nm (ε 7740) (pH 11).

(−)-(2*S*,4*S*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-iodocytosine (35). **23** (240 mg, 0.44 mmol) was debenzoylated, and the crude product was purified by silica gel column chromatography ($CHCl_3$–MeOH, 10:1) to give **35** (123 mg, 83.1%) as a white solid: UV (H_2O) λ_{max} 293.0 (ε 3450) (pH 7), 307.0 (ε 8130) (pH 2), 293.0 nm (ε 5540) (pH 11).

(+)-(2*S*,4*R*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-iodocytosine (36). **24** (285 mg, 0.52 mmol) was debenzoylated, and the crude product was purified by silica gel column chromatography ($CHCl_3$–MeOH, 10:1) to give **36** (124 mg, 70.5%) as a white solid: UV (H_2O) λ_{max} 293.5 (ε 4150) (pH 7), 307.0 (ε 8920) (pH 2), 293.0 nm (ε 6240) (pH 11).

(+)-(2*S*,4*S*)-9-[2-[(Benzoyloxy)methyl]-1,3-dioxolan-4-yl]-6-chloropurine (37) and (−)-(2*S*,4*R*)-9-[2-[(Benzoyloxy)methyl]-1,3-dioxolan-4-yl]-6-chloropurine (38). A mixture of 6-chloropurine (1.74 g, 11.0 mmol), hexamethyldisilazane (30 mL), and ammonium sulfate (catalytic amount) was refluxed for 4 h under N_2. The clear solution obtained was concentrated in vacuo, the residue was dissolved in dry CH_2Cl_2 (40 mL), and a solution of **8** (1.50 g, 5.63 mmol) in dry CH_2Cl_2 (60 mL) and TMSOTf (2.2 mL, 11 mmol) were added at room temperature. The reaction mixture was stirred for 30 min at room temperature and refluxed for 22 h under N_2. During reflux, the initially formed N-3 condensed product was converted to the N-9 isomer. The resulting solution was poured into an ice-cold mixture of CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ solution (20 mL), stirred for 15 min, and filtered through a Celite pad. The organic layer was washed with saturated $NaHCO_3$ solution and brine and dried ($MgSO_4$). The solvents were removed by distillation under reduced pressure, and the residue was separated by silica gel column chromatography to give **37** [R_f = 0.30 (hexanes–EtOAc, 1:2), 0.81 g, 40.0%] and **38** (R_f = 0.41, 0.83 g, 41.1%) as a syrup, which was crystallized from ether. **37**: UV (MeOH) λ_{max} 264 nm. **38**: UV (MeOH) λ_{max} 264 nm.

(+)-(2*S*,4*S*)-6-Chloro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (39) and (+)-(2*S*,4*S*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-6-methoxypurine (40). A solution of **37** (550 mg, 1.53 mmol) in MeOH (20 mL) containing NaOMe (1.26 mmol, prepared by dissolving 29 mg of Na in MeOH) was stirred for 2 h at room temperature, and the reaction mixture was neutralized by glacial AcOH. After removal of the solvent, the residue was purified by column chromatography using $CHCl_3$–MeOH (50:1) as the eluent to give an inseparable mixture of **39** and **40** (R_f = 0.26, 380 mg, 96.7%), which was crystallized from hexanes.

(+)-(2*S*,4*S*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]adenine (41). **37** (340 mg, 0.94 mmol) was debenzoylated, and the crude product was purified by column chromatography using $CHCl_3$–MeOH (40:1) as the eluent to give a mixture of **39** and **40** [R_f = 0.26 ($CHCl_3$–MeOH, 20:1), 172 mg, 71.0%] and **41** (R_f = 0.06, 79 mg, 36.0%) as white solids: UV (H_2O) λ_{max} 258.9 (ε 16 980) (pH 7), 257.0 (ε 16 820) (pH 2), 258.0 nm (ε 17 050) (pH 11).

(−)-(2*S*,4*R*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]adenine (44). **38** (560 mg, 1.55 mmol) was debenzoylated and the crude product purified by column chromatography using $CHCl_3$–MeOH (40:1) as the eluent to give a mixture of **42** and **43** [R_f = 0.26 ($CHCl_3$–MeOH), 320 mg, 80.0%] and **44** (R_f = 0.07, 79 mg, 21.0%) as white solids: UV (H_2O) λ_{max} 258.9 (ε 17 410) (pH 7), 256.5 (ε 17 170) (pH 2), 258.9 nm (ε 17 930) (pH 11).

(+)-(2*S*,4*S*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-6-methoxypurine (40) and (+)-(2*S*,4*S*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]hypoxanthine (45). A mixture of **39** and **40** (230 mg, 0.9 mmol), 2-mercaptoethanol (0.235 mL, 3.6 mmol), and NaOMe (3.56 mmol, prepared by dissolving 82 mg of Na in MeOH) in MeOH (20 mL) was refluxed for 18 h under N_2. The mixture was cooled, neutralized with glacial HOAc, and evaporated to dryness under vacuum. The residue was separated by silica gel column chromatography ($CHCl_3$–MeOH, 10:1) to give **40** [R_f = 0.46 ($CHCl_3$–MeOH, 10:1), 120 mg, 53.1%] and **45** (R_f = 0.07, 50 mg, 23.5%) as white solids. **40**: UV (H_2O) λ_{max} 249.9 (ε 11 770) (pH 7), 250.5 (ε 12 610) (pH 2), 249.9 nm (ε 11 310) (pH 11). **45**: UV (H_2O) λ_{max} 248.5 (ε 5920) (pH 7), 248.5 (ε 5910) (pH 2), 252.9 nm (ε 6420) (pH 11).

(+)-(2*S*,4*S*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-N^6-methyladenine (46). A solution of **39** and **40** (160 mg, 0.63 mmol) and methylamine (40 wt % solution in H_2O, 8.4 mL) in MeOH (10 mL) was heated at 80 °C in a steel bomb for 16 h. After cooling, the solvents were removed by distillation under vacuum. The residual syrup was purified by column chromatography using $CHCl_3$–MeOH (10:1) as the eluent to give **46** as white solid [R_f = 0.35 ($CHCl_3$–MeOH, 10:1), 130 mg, 83.0%]: UV (H_2O) λ_{max} 265.3 (ε 16 370) (pH 7), 261.8 (ε 17 900) (pH 2), 265.3 nm (ε 16 980) (pH 11).

(+)-(2*S*,4*S*)-6-Chloro-2-fluoro-9-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]purine (47) and (−)-(2*S*,4*R*)-6-Chloro-2-fluoro-9-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]pu-

rine (48). A mixture of 6-chloro-2-fluoropurine (0.73 g, 4.20 mmol) in dry dichloroethane (20 mL), hexamethyldisilazane (15 mL), and ammonium sulfate (catalytic amount) was refluxed for 3 h under nitrogen atmosphere. The resulting clear solution was cooled to 0 °C. To this cooled silylated 6-chloro-2-fluoropurine were added a solution of 8 (1.0 g, 3.76 mmol) in dry dichloroethane (10 mL) and TMSOTf (0.8 mL, 4.20 mmol), and the mixture was stirred for 10 min. Then the temperature was brought up to room temperature, and the reaction mixture was stirred overnight. TLC indicated the presence of the N-3 isomer. So the reaction mixture was refluxed for further 1 h at 80 °C (until all the N-3 isomer converted into the N-9 isomer). After the reaction mixture was cooled, saturated $NaHCO_3$ (10 mL) was added and the mixture was stirred for 15 min. The solvent was evaporated, and the solid was dissolved in EtOAc. It was washed with H_2O and brine, dried (anhydrous $MgSO_4$), filtered, and evaporated to give the crude product, which was purified on a silica column (50% EtOAc/hexanes) to yield a pure β, α mixture of 47 and 48 (1.01 g, 71.2%). This mixture was separated on a long silica column (40% EtOAc/hexanes) to give 37 (0.51 g, 35.9%) and 38 (0.39 g, 27.5%) as white solids after trituration with MeOH. 47: UV (MeOH) λ_{max} 269.0 nm. 48: UV (MeOH) λ_{max} 269.0 nm.

(+)-(2*S*,4*S*)-2-Amino-6-chloro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (53) and (+)-(2*S*,4*S*)-6-Amino-2-fluoro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (55). Dry ammonia gas was bubbled into a stirred solution of 47 (470 mg, 1.23 mmol) in DME (50 mL) at room temperature for 15 h. The solvent was evaporated under reduced pressure, and the residue was separated on a silica column (EtOAc–CH_2Cl_2, 1:1) to yield 49 (270 mg, 58.0%) and 51 (100 mg, 23.0%). Both 49 (260 mg, 0.70 mmol) and 51 (90 mg, 26 mmol) were separately treated with NH_3/MeOH (25 mL, saturated at 0 °C) at room temperature overnight. Solvent was evaporated under reduced pressure, and the residue was dissolved in boiling MeOH, cooled, and filtered to give pure 53 (160 mg, 85.8%) and 55 (50 mg, 74.6%) as white solids. 53: UV (H_2O) λ_{max} 307.0 (ϵ 5450) (pH 7), 307.0 (ϵ 7080) (pH 2), 307.0 nm (ϵ 7180) (pH 11). 55: UV (H_2O) λ_{max} 261.0 (ϵ 1400) (pH 7), 261.0 (ϵ 13 990) (pH 2), 261.0 nm (ϵ 1390) (pH 11).

(−)-(2*S*,4*R*)-2-Amino-6-chloro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (54) and (−)-(2*S*,4*R*)-6-Amino-2-fluoro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (56). Dry ammonia gas was bubbled into a stirred solution of 48 (340 mg, 0.91 mmol) in DME (50 mL) at room temperature for 15 h. The solvent was evaporated under reduced pressure, 52 was crystallized out in MeOH as pure white solid (90 mg, 27.6%), and the mother liquor was concentrated to give 50 (240 mg, 70.3%) as a foam. Both 50 (200 mg, 0.53 mmol) and 52 (870 mg, 0.24 mmol) were separatedly treated with NH_3/MeOH (25 mL, saturated at 0 °C) at room temperature overnight. Solvent was evaporated under reduced pressure, and the crude 54 was purified on preparative TLC and crystallized from ether–MeOH to give pure 54 (140 mg, 97.0%). Crude 56 was redissolved in boiling MeOH, cooled, and filtered to give pure 56 (45 mg, 73.8%). 54: UV (H_2O) λ_{max} 307.5 (ϵ 8120) (pH 7), 307.5 (ϵ 8040) (pH 2), 307.0 nm (ϵ 8150) (pH 11). 56: UV (H_2O) λ_{max} 261.0 (ϵ 15 450) (pH 7), 261.0 (ϵ 15 820) (pH 2), 261.0 nm (ϵ 15 350) (pH 11).

(2*S*,4*S*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]guanine (57). A mixture of 53 (75 mg, 0.27 mmol), 2-mercaptoethanol (0.1 mL, 1.38 mmol), and 1.0 M NaOMe/MeOH (2.2 mL) in MeOH (15 mL) was refluxed for 3 h. The reaction mixture was cooled and neutralized with glacial AcOH. The solution was evaporated to dryness, and then the residue was boiled in water and filtered to give 57 (50 mg, 72.0%) as a white solid: UV (MeOH) λ_{max} 254.0 nm.

(2*S*,4*R*)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]guanine (58). A mixture of 54 (80 mg, 0.29 mmol), 2-mercaptoethanol (0.11 mL, 1.47 mmol), and 1.0 M NaOMe/MeOH (2.38 mL) in MeOH (15 mL) was refluxed for 3 h. The reaction mixture was cooled and neutralized with glacial AcOH. The solution was washed with $CHCl_3$ and concentrated to dryness. The crude was recrystallized from water to give 58 (52 mg, 70.0%) as white crystals: UV (H_2O) λ_{max} 252.0 (ϵ 14 850) (pH 7), 255.0 (ϵ 12 790) (pH 2), 261.0 nm (ϵ 12 154) (pH 11).

(+)-(2*S*,4*S*)-9-[2-[(Benzoyloxy)methyl]-1,3-dioxolan-4-yl]-2,6-dichloropurine (59) and (−)-(2*S*,4*R*)-9-[2-[(Benzoyloxy)-methyl]-1,3-dioxolan-4-yl]-2,6-dichloropurine (60). A mixture of 2,6-dichloropurine (1.66 g, 8.78 mmol), hexamethyldisilazane (30 mL), and ammonium sulfate (catalytic amount) was refluxed for 2 h under Ar. The clear solution obtained was concentrated in vacuo, the residue was dissolved in dry CH_2Cl_2 (50 mL), and a solution of 8 (1.56 g, 5.87 mmol) in dry CH_2Cl_2 (30 mL) and TMSOTf (1.69 mL, 8.77 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature overnight, refluxed for 30 min under N_2, cooled, and stirred with saturated $NaHCO_3$ solution (10 mL). The residue after evaporation under reduced pressure was extracted with EtOAc. The organic layer was washed with H_2O and brine and dried (Na_2SO_4). Solvent removal after filtration gave a 1:1 mixture (1.85 g, 80%) of 59 and 60, which were separated by silica gel column chromatography to give 59 [R_f = 0.60 (30% EtOAc in hexanes), 0.90 g, 38.96%] as a foam and 60 (R_f = 0.63, 0.89 g, 38.5%) as a white crystalline solid. 59: UV (MeOH) λ_{max} 273.5 nm. 60: UV (MeOH) λ_{max} 273.5 nm.

(+)-(2*S*,4*S*)-6-Amino-2-chloro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (65). A steel bomb charged with 59 (230 mg, 0.58 mmol) and MeOH (15 mL) saturated with NH_3 was heated at 90 °C for 6 h. After cooling and evaporation of the volatiles, the crude product obtained was recrystallized from MeOH to give 65 (139 mg, 87.9%) as a white crystalline solid: UV (H_2O) λ_{max} 263.5 (ϵ 16 880) (pH 7), 263.5 (ϵ 15 450) (pH 2), 263.8 nm (ϵ 17 010) (pH 11).

(−)-(2*S*,4*R*)-6-Amino-2-chloro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (66). Compound 60 (195 mg, 0.49 mmol) was converted to 66 (96 mg, 71.6%) by treatment with NH_3/MeOH (30 mL) according to the procedure described for 65: UV (H_2O) λ_{max} 264.0 (ϵ 18 250) (pH 7), 264.0 (ϵ 16 380) (pH 2), 263.8 nm (ϵ 18 750) (pH 11).

(+)-(2*S*,4*S*)-2,6-Diamino-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (67). To a stirred solution of 59 (84 mg, 0.21 mmol) in EtOH (30 mL) was added NaN_3 (40 mg, 0.62 mmol) dissolved in minimum amount of H_2O and refluxed for 45 min. After cooling and evaporation of the solvents under reduced pressure, the residue was taken up in $CHCl_3$ (50 mL), washed with water and brine, dried (Na_2SO_4), filtered, and evaporated to give the diazido derivative 61 (80 mg, 93%): UV (MeOH) λ_{max} 296.5 nm. Compound 61 was hydrogenated in EtOH (10 mL) under H_2 and the catalyst of 10% Pd–C (10 mg) at atmospheric pressure for 2 h. The catalyst was removed by filtration and washed with $CHCl_3$ to dissolve any precipitated product. The combined organic layers were evaporated to dryness to give 63 (62 mg, 88.8%): UV (H_2O) λ_{max} 281, 257 nm. Compound 63 was treated with NH_3/MeOH (10 mL) at room temperature for 16 h. After removal of the volatiles, the crude product obtained was recrystallized from 2-propanol to give 67 (35 mg, 85.3%) as a white crystalline compound: UV (MeOH) λ_{max} 255.5 (ϵ 11 330), 280 (ϵ 12 360) (pH 7), 252.5 (ϵ 11 470), 290.5 (ϵ 10 130) (pH 2), 255.5 (ϵ 9850), 278.8 nm (ϵ 10 800) (pH 11).

(−)-(2*S*,4*R*)-2,6-Diamino-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (68). A mixture of compound 60 (40 mg, 0.10 mmol) in EtOH (40 mL) and aqueous NaN_3 (19 mg, 0.29 mmol) was refluxed for 2.5 h. After workup as described for 61, the product 62 [37 mg, 90.2%, UV (MeOH) λ_{max} 296.0 nm] obtained was hydrogenated in EtOH (20 mL) by treatment with H_2/10% Pd–C (10 mg) at atmospheric pressure for 2 h. After workup as described for 63, the crude diamino compound 64 [30 mg, 93.7%, UV (MeOH) λ_{max} 281.0, 257.0 nm] was subjected to debenzoylation by treatment with NH_3/MeOH (10 mL) to afford 68 (16 mg, 55%) as a white solid: UV (H_2O) λ_{max} 255.5 (ϵ 10 630), 279.5 (ϵ 22 910) (pH 7), 253.0 (ϵ 11 960), 291.5 (ϵ 10 290) (pH 2), 255.5 (ϵ 8730), 279.3 nm (ϵ 9490) (pH 11).

Antiviral and Cytotoxicity Assays. Antiviral studies with HIV-1 were performed in mitogen stimulated human peripheral blood mononuclear (PBM) cells infected with strain LAV, as described previously.[17] A multiplicity of infection (MOI) of 0.1, as determined by a limiting dilution method in PBM cells, was selected for the assays. Stock solutions (40 mM) of the compounds were prepared in DMSO and then diluted in the medium to give the desired concentration. The maximal final concentration of DMSO in the solutions was less than 0.25%, which is not antiviral or cytotoxic to the cells. The compounds were added about 45 min after infection. The procedure for culturing the virus and the determination of supernatant RT levels has been described

previously.[17] The drugs were also evaluated for their potential toxic effects on uninfected PHA-stimulated human PBM, Vero, and CEM cells as described previously.[10] These cells were cultured with and without drug for 6, 3, and 6 days, respectively, at which time aliquots were counted in the presence of trypan blue.

Data Analysis. The median effective concentration (EC_{50}) and inhibitory concentration (IC_{50}) values were derived from the computer-generated median effect plot of the dose–effect data, as described previously.[19]

Acknowledgment. This research was supported by the U.S. Public Health Service Research grants (AI 25899 and AI 32351, AI 33655), from the National Institutes of Health, and the Department of Veterans Affairs.

Supplementary Material Available: ^{1}H NMR spectroscopy data for synthesized nucleosides (7 pages). Ordering information is given on any current masthead page.

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