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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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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 (EC₅₀ = 0.0012 μ M) although it was toxic (IC₅₀ = 10.0 μ M). The order of anti-HIV potency of pyrimidine analogues was as follows: 5-fluorocytosine (β -isomer) > cytosine (β -isomer) > 5-fluorocytosine $(\alpha$ -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 $(\beta$ -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 $(\alpha$ -isomer) > N⁶-methyladenine (β -isomer). It is interesting to note that the α -5-fluorocytosine analogue exhibited an excellent anti-HIV activity (EC₅₀ = $0.063 \,\mu$ M) without cytotoxicity up to 100 μ M in PBM cell.

Introduction

The anti-HIV activity of (\pm) -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 $(-)-\beta$ -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 (EC₅₀ = 0.3 μ M) without cytotoxicity up to 100 μ M. Recently, we have also reported the comprehensive structure-activity relationships of enantiomerically pure D-(2R)-1,3-dioxolanylpyrimidine⁵ and D-(2R)-1,3-dioxolanylpurine⁶ nucleosides as potential anti-HIV agents.

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Figure 2.

From these studies, (+)- β -D-(2R,4R)-dioxolanylcytosine (Figure 1) was found to exhibit the most potent anti-HIV activity (EC₅₀ = 0.016 and 0.009 μ M in PBM and CEM cells, respectively) among pyrimidine series,⁵ although it was also the most toxic compound in PBM (IC₅₀ = 62.0 μ M) and in CEM cells (IC₅₀ = 12.8 μ M). Among purine series, the (-)- β -D-(2R,4R)-dioxolanylguanine derivative exhibited the most potent anti-HIV activity (EC₅₀ = 0.03 μ M) without toxicity up to 100 μ M in PBM cells.⁶

Our observation that the anti-HIV activity of $(-)-\beta$ -L-(2R,5S)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine (Figure 2) was more potent than that of $(+)-\beta$ -D-(2S,5R)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine (Figure 2)⁷ has prompted us to synthesize the remaining enantiomer [L-isomer (2S)] to discover new anti-HIV nucleosides. Therefore, we have recently synthesized $(+)-\beta$ -L-(2S,4S)dioxolanylthymine and $(-)-\beta$ -L-(2S,4S)-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, $(-)-\beta$ -L-(2S,4S)-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-(2S)-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 CuSO₄/acetone, respectively.¹¹⁻¹³ Oxidation of the anhydro sugar 2 with NaIO₄ and then reduction with NaBH₄ 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/CH₂Cl₂/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 silvlated 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 NH₃/MeOH to give the enantiomerically pure (+)- β -L-(2S,4S)-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. Debenzovlation of 13-24 with $NH_3/MeOH$ afforded the final nucleosides 25–36.

For the preparation of the purine derivatives, silvlated 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 NH₃/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 MeNH₂ 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 NH₃/DME to give 49-52, which were separated by silica gel column chromatography. Compounds 49-52 were deprotected with NH₃/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 NH₃/MeOH to yield 2-chloro-6-aminopurine derivatives 65 and 66, respectively. The reactions of 59 and 60 with NaN₃/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 NH₃/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) NaIO₄, MeOH, H₂O; (ii) NaBH₄; (c) *p*-TsOH, acetone; (d) BzCl, py, CH₂Cl₂; (e) *p*-TsOH, MeOH; (f) NaIO₄, RuO₂, CH₃CN-CCl₄-H₂O (2:2:3); (g) Pb(OAc)₄, THF.

Scheme II^a



 $^{\alpha}$ (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'-H¹⁵ 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 effect¹⁶ 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

Scheme III^a



 $^{\alpha}$ (a) TMSOTf, ClCH_2CH_2Cl, room temperature; (b) NH_3/MeOH, room temperature.

activities. The antiviral results shown in Table II are the average values of at least three separate experiments. Among the L-(2S)-dioxolanylpyrimidines, 5-fluorocytosine derivative 29 was found to exhibit the most potent anti-HIV activity (EC₅₀ = 0.0012 μ M) although it was toxic $(IC_{50} = 10.0 \ \mu M)$. 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) > 5methylcytosine (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, ClCH₂CH₂Cl, reflux; (b) NH₃/MeOH, room temperature; (c) NaOMe, MeOH, room temperature; (d) HOCH₂CH₂SH, NaOCH₃, MeOH, reflux; (e) NH₂CH₃, MeOH, 85 °C.

in size of substituents at the same position diminishes the biological activity in β -analogues (CH₃ < Cl < Br < I). As in the case of D-(2R)-dioxolanyl,⁵ D-(2S)-oxathiolanyl,¹⁸ and L-(2R)-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-(2S)-dioxolanylpurines, 2,6-diamino derivative 67 exhibited the most potent anti-HIV activity (EC₅₀ = 0.014 μ M). 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) > 2-fluoroadenine (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.fludiaminopurine (α -isomer) > N⁶-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 NHCH₃, Cl, or OMe decreased the anti-HIV activity. Despite of moderate anti-HIV activity of $(-)-\beta$ -D-(2R,4R)dioxolanylhypoxanthine (EC₅₀ = 5.0 μ M), the L-(2S,4S)isomer 45 was found to be inactive. In the case of 2,6disubstituted 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-(2R,4R)-guanine derivative (EC₅₀) = $0.3 \,\mu$ M),⁶ L-(2S,4S)-isomer 57 exhibited only moderate anti-HIV activity.

(+)- β -L-(2S,4S)-Dioxolanylthymine 11 (EC₅₀ = 4.8 μ M) was less potent than (-)- β -D-(2R,4R)-dioxolanylthymine (EC₅₀ = 0.39 μ M),⁴ while (-)- β -L-(2S,4S)-dioxolanylcytosine 25 (EC₅₀ = 0.002 μ M) was found to give more potent anti-HIV and anti-HBV activity than (+)- β -D-(2R,4R)dioxolanylcytosine (EC₅₀ = 0.016 μ M).⁵ Other D-(2R,4R)-1,3-dioxolanyl nucleosides exhibited more potent anti-HIV activity than the corresponding L-(2S,4S)-1,3dioxolanyl nucleosides. Therefore, it is interesting to mention that only L-(2S,4S)-cytosine derivative was found to be more potent than that of D-(2R,4R)-cytosine derivative.

In summary, from the study of comprehensive structureactivity relationships, it was found that 5-fluorocytosine derivative 29 showed the most potent anti-HIV activity among the L-(2S)-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 Me₄Si 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.

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, H₂O, MeOH, H₂O, and saturated NaHCO₃ 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, CHCl₃-MeOH, 10:1) to give slightly yellow solid, which was recrystallized from absolute alcohol to yield a colorless solid 2 [$R_f = 0.43$ (CHCl₃-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%): ¹H NMR (DMSO-d₆) 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, $J_{2-OH,2} = 6.59$ Hz, 1 H, 2-OH, exchangeable with D₂O), 4.62 (d, $J_{3-OH,3} = 5.28$ Hz, 1 H, 3-OH, exchangeable with D_2O), 5.07 (d, $J_{4-OH,4} = 4.84$ Hz, 1 H, 4-OH, exchangeable with D_2O), 5.20 (d, $J_{1,2} = 2.19$ Hz, 1 H, H-1).

(-)-(1'S,2S,4S)-4-(1,2-Dihydroxy-1,2-O-isopropylideneethyl)-2-(hydroxymethyl)dioxolane (4). A solution of NaIO₄ (22.4g, 0.1 mol) in H₂O (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. NaBH₄ (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 Scheme VI ^a



 a (a) TMSOTf, CH₂Cl₂, reflux; (b) NaN₃/EtOH, reflux; (c) H₂, 10% Pd–C, EtOH, room temperature; (d) NH₃/MeOH, room temperature.

washed with MeOH (300 mL). The combined filtrate was neutralized by $0.5 \,\mathrm{N}\,\mathrm{HCl}\,(\sim 200 \,\mathrm{mL})$ 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 Et₃N, filtered, and concentrated to dryness. The residue was dissolved in EtOAc (350 mL), washed with H_2O (500 mL \times 2), dried (MgSO₄), 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-CHCl₃, 1-5%) to give 4 [$R_f = 0.82$ (CHCl₃-MeOH, 10: 1), 8.8 g, 61.8%] as a colorless oil: ¹H NMR (DMSO-d₆) δ 1.26 and 1.32 (2 s, 2×3 H, isopropylidene), 3.41 (dd, $J_{CH_{2}OH,OH} = 6.04$ 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, CH₂OH, exchangeable with D_2O), 4.85 (t, $J_{2,CH_2OH} = 3.96$ Hz, 1 H, H-2).

(+)-(1'S,2S,4S)-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-CH₂Cl₂ (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 CH₂Cl₂ (300 mL) and washed with H₂O (100 mL × 2), brine, dried (MgSO₄), 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 O	ptical	Dat
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	mp, °C					mp, °C					
no.	(solv)ª	[α] ²⁵ D	formula	anal.	no.	(solv) ^a	[α] ²⁵ D	formula		an	al.
2	142-145 (b)	-50.011 (c 1.61, MeOH)			32	190-192 (h)	+55.729 (c 0.82, MeOH)	C ₈ H ₁₀ ClN ₃ O ₄	C,	H,	Cl, N
4	oil	-12.48 (c 1.11, CHCl ₃)	$C_9H_{16}O_5$	С, Н	33	195–196 dec	-26.679 (c 0.96, MeOH)	C ₈ H ₁₀ BrN ₃ O ₄ .	С,	Η,	N
5	oil	+10.73 (c 1.75, MeOH)	$C_{16}H_{20}O_6$	С, Н				0.3H ₂ O	_		
6	oil	+9.16 (c 1.01, CHCl ₃)	$C_{13}H_{16}O_{6}$	С, Н	34	199 dec	+35.151 (c 0.95, MeOH)	$C_8H_{10}BrN_3O_4$	C,	Η,	N
8	oil	-12.53 (c 1.11, CHCl ₃)	$C_{13}H_{14}O_6$	С, Н				$0.1C_4H_8O_2$			
9	211-212 (c)	+39.616 (c 0.8, CH ₂ Cl ₂)	$C_{16}H_{16}N_2O_6$	C, H, N	35	171 dec	-16.454 (c 0.75, MeOH)	$C_8H_{10}IN_3O_4$	С,	Η,	I, N
10	124-125 (c)	+4.59 (c 1.95, CHCl ₃)	$C_{16}H_{16}N_2O_6$	as mixture	36	182 dec	+21.385 (c 0.67, MeOH)	$C_8H_{10}IN_3O_4$	С,	Η,	N
				of 9 and 10	37	164.5-165 (i)	+59.063 (c 0.73, CHCl ₃)	$C_{16}H_{13}CIN_4O_4$	С,	Н,	N
11	174-175 (d)	+18.601 (c 0.75, MeOH)	$C_9H_{12}N_2O_5$	C, H, N	38	112–113 (i)	-9.819 (c 0.74, CHCl ₃)	$C_{16}H_{13}CIN_4O_4$	C,	Н,	N
12	foam	-10.011 (c 0.45, MeOH)	$C_9H_{12}N_2O_5$	C, H, N	40	111-112	+31.601 (c 0.82, MeOH)	$C_{10}H_{12}N_4O_4$	C,	H,	N
13	203-205 (e)	-56.45 (c 0.99, CHCl ₃)	$C_{22}H_{19}N_3O_6$	C, H , N				0.3MeOH	~		
			0.35CHCl ₃		41	164-166	+33.142 (c 0.71, MeOH)	$C_9H_{11}N_5O_3$	Ċ,	Η,	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)	$C_9H_{11}N_5O_3$	Ċ,	Н,	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)	$C_9H_{10}N_4O_4$	С,	Н,	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)	$C_{10}H_{13}N_5O_3$	С,	Η,	N
17	163-164	+1.926 (c 0.94, CHCl ₃)	C ₂₂ H ₁₈ FN ₃ O ₆	C, H, N	47	139–140 (e)	+40.71 (c 0.63, CHCl ₃)	$C_{16}H_{12}CIFN_4O_4$ 0.1C ₂ H ₁₄	C,	H,	Cl, N
10	109-190	±49.291 (a 1.09 CHCL)	C.H. FN.O.	CHN	48	145–146 (e)	-7.32 (c 0.54, CHCla)	C12H12CIFN.O	C.	H.	CL N
10	169 (a)	$\pm 2650 (2081 \text{ CHCl})$	$C_{22} M_{18} M_{3} O_{6}$	C H N	53	204 dec (e)	+65.29 (c 0.25, MeOH +	010-1202 11404	Ξ,	,	01, 11
20	162 (e) 169 (g)	$\pm 49.868 (a 0.87 CHCl_{o})$	$C_{22}II_{18}OII_{3}O_{6}$	CHN			NHLOH)	CoH10ClNsO2	C.	H.	N
40 91	100 (g) 159 (a)	-6.052 (a 0.02) CUC(1)	C., H., B , N.O.	CHN	54	146–147 (i)	-20.56 (c 0.50, MeOH)	C ₀ H ₁₀ ClN ₁ O ₂	Č.	H.	CL N
41	103 (6)	-0.003 (C 0.92, CHCI3)	02211181114306	O , H , N	55	240-241 dec (e)	+46.19 (c 0.25, MeOH +	C ₆ H ₁₀ FN ₁ O ₂	Č.	H.	N
22	176–177 (e)	+37.075 (c.0.83, CHCla)	CooH10BrNaOe	C. H. N			NH.OH)	0910	Ο,	,	••
	110 111 (0)		0.42(CoHe)oO	0,11,11	56	263-264 dec (e)	insoluble	CoH10FN5O2	C.	H.	N
23	162	+1.541 (c 0.79, CHCl ₂)	C ₁₀ H ₁₀ IN ₂ O ₆	C. H. N	57	280 dec (e)	insoluble	CoH11NsO4	Č.	H.	N
24	179-181	+31.491 (c 0.93, CHCl ₂)	C ₂₂ H ₁ eIN ₂ O ₆	C. H. N	58	259-260 (k)	-101.57 (c 0.25, H ₂ O +	CoH11N5O4	Ĉ.	H.	N
25	176-177 (f)	-38.33 (c 0.43, MeOH)*	C ₄ H ₁₁ N ₂ O ₄	C. H. N		• •	NH ₄ OH)	$0.5H_2O$	-,	,	
26	192-193 (f)	+66.14 (c 0.50, MeOH)*	C ₆ H ₁₁ N ₂ O ₄	C. H. N	59	foam	+49.54 (c 0.38, MeOH)	$C_{16}H_{12}Cl_2N_4O_4$	С,	H,	Cl, N
27	144-145	-23.403 (c 0.61, MeOH)	C ₀ H ₁₉ N ₂ O ₄	C. H. N	60	144-145	+73.04 (c 0.29, MeOH)	$C_{16}H_{12}Cl_2N_4O_4$	С,	H,	CI, N
28	191-193	+39.133 (c 0.32, MeOH)	C ₉ H ₁₃ N ₃ O ₄	C. H. N	65	235-236 (e)	+29.32 (c 0.24, MeOH)	$C_9H_{10}ClN_5O_3$	C,	H,	CI, N
29	181-182	-53.283 (c 0.86, MeOH)	C ₈ H ₁₀ FN ₃ O ₄	C, H, N	66	21 9 -220 (e)	-9.16 (c 0.22, MeOH)	$C_9H_{10}CIN_5O_3$	C,	H,	Cl, N
30	153-155	+64.801 (c 0.98, MeOH)	C ₈ H ₁₀ FN ₃ O ₄	C, H, N	67	176–178 (l)	+29.40 (c 0.32, MeOH)	$C_9H_{12}N_6O_3$	С,	H,	N
31	200-201 (h)	-18.881 (c 0.95, MeOH)	CaH10CIN3O4	C, H, Cl, N	68	148-149 (i)	-24.24 (c 0.26, MeOH)	$C_9H_{12}N_6O_3$.	C,	H,	N
		. ,,						$0.25H_2O$			

^a Solvents: b, ethanol; c, hexanes-ether; d, ether-MeOH; e, MeOH; f, hexanes-CH₂Cl₂; g, EtOAc; h, 2-propanol-hexanes; i, ether; j, ethanolether; 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: ¹H NMR (CDCl₃) 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, CH₂OBz), 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,2S,4S)-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 Et₃N and the solvent was evaporated to dryness. The residue was purified by silica gel column chromatography (hexanes-EtOAc, 10-33%) to give 6 [R/ = 0.15 (hexanes-EtOAc, 1:1), 4.9 g, 99.2%] as a colorless syrup: ¹H NMR (DMSO-d₆) 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, CH₂OBz), 4.60 (t, J = 5.72 Hz, 2'-OH, exchangeable with D₂O), 5.23 (t, J = 3.96 Hz, 1 H, H-2), 7.45-7.7, 7.93-8.04 (m, 3 H, 2H, OBz).

(-)-(2S,4S)- and (-)-(2S,4R)-4-Acetoxy-2-[(benzoyloxy)methyl]dioxolane (8). A solution of NaIO₄ (10.2 g, 48.0 mmol) in H₂O (120 mL) was added to a solution of 6 (3.1 g, 11.0 mmol) in CCl₄-CH₃CN (1:1, 160 mL) and then RuO₂-H₂O (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 CH₂Cl₂ (100 mL), and the H₂O layer was extracted with CH₂Cl₂ (100 mL × 2). The combined organic layer was washed with brine (50 mL), dried (MgSO₄), 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 N₂ 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: ¹H NMR (CDCl₃) 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, CH₂OBz), 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).

(-)-(2S,4S)-1-[2-[(Benzoyloxy)methyl]-1,3-dioxolan-4-yl]thymine (9) and (+)-(2S,4R)-1-[2-[(Benzoyloxy)methyl]-1,3dioxolan-4-yl]thymine (10). A mixture of thymine (0.25g, 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 NaHCO₃ (10 mL) and CHCl₃, 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 \times 3). The combined organic layer was washed with saturated $NaHCO_3$ and H_2O and dried (anhydrous MgSO₄). 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 (CHCl₃-MeOH, 20:1) of crude 10. 9: UV (MeOH) λ_{max} 265.0 nm. 10: UV (MeOH) λ_{max} 265.0 nm.

(+)-(2S,4S)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]thymine (11). A mixture of 9 (140 mg, 0.43 mmol) in NH₃/ MeOH (50 mL) was stirred at room temperature for 2 days. After the mixture was concentrated, the residue was purified by preparative TLC (CHCl₃-MeOH, 15:1) to yield 11 (75 mg, 75.8%) as a white solid; UV (H₂O) λ_{max} 266.0 (ϵ 10 760) (pH 7), 266.5 (ϵ 9890) (pH 2), 266.3 nm (ϵ 8400) (pH 11).

(-)-(2S,4R)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-y]]-

Table II. Median Effective (EC₅₀) and Inhibitory (IC₅₀) Concentration of L-(2S)-Dioxolanyl Nucleosides in PBM Cells and Cytotoxicity in Vero Cells



compd no.	base	anomer	EC ₅₀ (μM) ^α 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	$\mathbf{n.d.}^{b}$	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 EC₅₀ 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 NH₃/MeOH was stirred at room temperature for 2 days. After the mixture was concentrated, the residue was purified by preparative TLC (CHCl₃-MeOH, 15:1) to yield 12 (0.13 g, 95.6%) as a white foam: UV (H₂O) 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 N⁴-benzoylcytosine, which was prepared from N⁴-benzoylcytosine (4.56 g, 21.2 mmol), hexamethyldisilazane (50 mL), and ammonium sulfate (catalytic amount) by refluxing for 2.5 h, in dry 1,2dichloroethane (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 NaHCO₃(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.

(-)-(2S,4S)-N⁴-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]cytosine (13) and (+)-(2S,4R)-N⁴-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.

(+)-(2S,4S)-N^a-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-methylcytosine (15) and (+)-(2S,4R)-N^a-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5methylcytosine (16). N^a-Benzoyl-5-methylcytosine (0.72g, 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/CHCl₃) to yield 15 [R_f = 0.56 (CHCl₃-MeOH, 50:1), 0.39 g, 39.8%] and 16 (R_f = 0.67, 0.32 g, 32.0%) as white solids. 15: UV (CHCl₃) λ_{max} 328.7 nm. 16: UV (CHCl₃) λ_{max} 328.7 nm.

(+)-(25,45)-M-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-fluorocytosine (17) and (+)-(25,4R)-M-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-fluorocytosine (18). N⁴-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-CHCl₃, 500:1), 230-400 mesh] to yield 17 [$R_f = 0.26$ (CHCl₃-MeOH, 50:1), 0.38 g, 49.0%] and 18 ($R_f =$ 0.32, 0.38 g, 48.0%) as white solids. 17: UV (CHCl₃) λ_{max} 328.2 nm. 18: UV (CHCl₃) λ_{max} 328.7 nm.

(+)-(2S,4S)-N⁴-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-chlorocytosine (19) and (+)-(2S,4R)-N^a-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-chlorocytosine (20). N⁴-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 (CHCl₃) λ_{max} 332.2 nm. 20: UV (CHCl₃) λ_{max} 331.7 nm.

(-)-(2S,4S)-N⁴-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-bromocytosine (21) and (+)-(2S,4R)-N⁴-Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5bromocytosine (22). N⁴-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 (CHCl₃) λ_{max} 333.2 nm. 22: UV (CHCl₃) λ_{max} 332.7 nm.

(+)-(2S,4S)- N^4 -Benzoyl-1-[2-[(benzoyloxy)methyl]-1,3-dioxolan-4-yl]-5-iodocytosine (23) and (+)-(2S,4R)-N-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 (CHCl₃-MeOH, 50:1) to give 23 [$R_f = 0.35$ (CHCl₃-MeOH, 50:1), 0.36 g, 43.8%] and 24 ($R_f =$ 0.43, 0.32 g, 38.9%) as white solids. 23: UV (CHCl₃) λ_{max} 338.2 nm. 24: UV (CHCl₃) 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%).

(-)-(2S,4S)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]cytosine (25): UV (H₂O) λ_{max} 270.0 (ϵ 7770) (pH 7), 278.0 (ϵ 11 970) (pH 2), 269.0 nm (ϵ 8380) (pH 11).

(+)-(2S,4R)-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 (CHCl₃-MeOH, 5:1) to give an oil, which was crystallized from CH₂Cl₂/ hexanes to yield 26 (0.14 g, 64.3%) as a white solid: UV (H₂O) λ_{max} 270.0 (ϵ 8780) (pH 7), 278.0 (ϵ 13 240) (pH 2), 269.0 nm (ϵ 9070) (pH 11).

(-)-(2S,4S)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5methylcytosine (27). 15 (0.25 g, 0.57 mmol) was debenzoylated, and the crude product was purified by preparative TLC (CHCl₃-MeOH, 10:1) to give 27 (0.11 g, 82.7%) as a white solid: UV (H₂O) λ_{max} 277.0 (ϵ 8320) (pH 7), 285.8 (ϵ 13 860) (pH 2), 276.8 nm (ϵ 9440) (pH 11).

(+)-(2S,4R)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5methylcytosine (28). 16 (200 mg, 0.46 mmol) was debenzoylated, and the crude product was purified by preparative TLC (CHCl₃-MeOH, 10:1) to give an oil. This was crystallized from MeOHether to yield 28 (88 mg, 84.0%) as a white solid: UV (H₂O) λ_{max} 277.0 (ϵ 9150) (pH 7), 286.3 (ϵ 14 580) (pH 2), 276.8 nm (ϵ 10 080) (pH 11).

(-)-(2S,4S)-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 (CHCl₃-MeOH, 10:1) to give 29 (63 mg, 60.0%) as a white solid: UV (H₂O) λ_{max} 279.5 (ϵ 9020) (pH 7), 286.3 (ϵ 12 020) (pH 2), 279.5 nm (ϵ 9380) (pH 11).

(+)-(2S,4R)-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 (CHCl₃-MeOH, 10:1) to give 30 (127 mg, 83.0%) as a white solid: UV (H₂O) λ_{max} 279.5 (ϵ 9060) (pH 7), 285.8 (ϵ 11 380) (pH 2), 279.8 nm (ϵ 9100) (pH 11).

(-)-($2\overline{S}$,4S)-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 (CHCl₃-MeOH, 10:1) to give 31 (82 mg, 64.6%) as a white solid after trituration with 2-propanol-hexanes: UV (H₂O) λ_{max} 285.0 (ϵ 7210) (pH 7), 294.0 (ϵ 11 420) (pH 2), 285.0 nm (ϵ 8260) (pH 11).

(+)-(2S,4R)-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 (CHCl₃-MeOH, 10:1) to give 32 (74 mg, 75.7%) as a white solid after trituration with 2-propanol-hexanes: UV (H₂O) λ_{max} 285.5 (ϵ 11 340) (pH 7), 293.5 (ϵ 15 020) (pH 2), 285.5 nm (ϵ 11 540) (pH 11).

(-)-(2S,4S)-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 (CHCl₃-MeOH, 10:1) to give 33 (129 mg, 88.3%) as a white solid: UV (H₂O) λ_{max} 287.0 (ϵ 6720) (pH 7), 297.0 (ϵ 10 960) (pH 2), 287.0 nm (ϵ 8270) (pH 11).

(+)-(2S,4R)-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 (CHCl₃-MeOH, 10:1) to give 34 (103 mg, 70.6%) as a white solid: UV (H₂O) λ_{max} 287.0 (ϵ 6330) (pH 7), 296.5 (ϵ 10 600) (pH 2), 287.0 nm (ϵ 7740) (pH 11).

(-)-(2S,4S)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5iodocytosine (35). 23 (240 mg, 0.44 mmol) was debenzoylated, and the crude product was purified by silica gel column chromatography (CHCl₃-MeOH, 10:1) to give 35 (123 mg, 83.1%) as a white solid: UV (H₂O) λ_{max} 293.0 (ϵ 3450) (pH 7), 307.0 (ϵ 8130) (pH 2), 293.0 nm (ϵ 5540) (pH 11).

(+)-(2S,4R)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5iodocytosine (36). 24 (285 mg, 0.52 mmol) was debenzoylated, and the crude product was purified by silica gel column chromatography (CHCl₃-MeOH, 10:1) to give 36 (124 mg, 70.5%) as a white solid: UV (H₂O) λ_{max} 293.5 (ϵ 4150) (pH 7), 307.0 (ϵ 8920) (pH 2), 293.0 nm (ϵ 6240) (pH 11).

(+)-(2S,4S)-9-[2-[(Benzoyloxy)methyl]-1,3-dioxolan-4-yl]-6-chloropurine (37) and (-)-(2S,4R)-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 CH₂Cl₂ (40 mL), and a solution of 8 (1.50 g, 5.63 mmol) in dry CH₂Cl₂ (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 N2. 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 NaHCO3 solution (20 mL), stirred for 15 min, and filtered through a Celite pad. The organic layer was washed with saturated NaHCO₃ 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.

(+)-(2S,4S)-6-Chloro-9-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]purine (39) and (+)-(2S,4S)-9-[2-(Hydroxymethyl)-1,3dioxolan-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 CHCl₃-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.

(+)-(2S,4S)-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 CHCl₃-MeOH (40:1) as the eluent to give a mixture of 39 and 40 [$R_f = 0.26$ (CHCl₃-MeOH, 20:1), 172 mg, 71.0%] and 41 ($R_f = 0.06$, 79 mg, 36.0%) as white solids: UV (H₂O) λ_{max} 258.9 (ϵ 16 980) (pH 7), 257.0 (ϵ 16 820) (pH 2), 258.0 nm (ϵ 17 050) (pH 11).

(-)-(2S,4R)-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 CHCl₃-MeOH (40:1) as the eluent to give a mixture of 42 and 43 [$R_f = 0.26$ (CHCl₃-MeOH), 320 mg, 80.0%] and 44 ($R_f = 0.07, 79$ mg, 21.0%) as white solids: UV (H₂O) λ_{max} 258.9 (ϵ 17 410) (pH 7), 256.5 (ϵ 17 170) (pH 2), 258.9 nm (ϵ 17 930) (pH 11).

(+)-(2S,4S)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-6methoxypurine (40) and (+)-(2S,4S)-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 N₂. The mixture was cooled, neutralized with glacial HOAc, and evaporated to dryness under vacuum. The residue was separated by silica gel column chromatography (CHCl₃-MeOH, 10:1) to give 40 [$R_f = 0.46$ (CHCl₃-MeOH, 10:1), 120 mg, 53.1%] and 45 (R_f = 0.07, 50 mg, 23.5%) as white solids. 40: UV (H₂O) λ_{max} 249.9 (ϵ 11 770) (pH 7), 250.5 (ϵ 12 610) (pH 2), 249.9 nm (ϵ 11 310) (pH 1). 45: UV (H₂O) λ_{max} 248.5 (ϵ 5920) (pH 7), 248.5 (ϵ 5910) (pH 2), 252.9 nm (ϵ 6420) (pH 11).

(+)-(2S,4S)-9-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]- N^{s} methyladenine (46). A solution of 39 and 40 (160 mg, 0.63 mmol) and methylamine (40 wt % solution in H₂O, 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 CHCl₃-MeOH (10:1) as the eluent to give 46 as white solid [$R_f = 0.35$ (CHCl₃-MeOH, 10:1), 130 mg, 83.0%): UV (H₂O) λ_{max} 265.3 (ϵ 16 370) (pH 7), 261.8 (ϵ 17 900) (pH 2), 265.3 nm (ϵ 16 980) (pH 11).

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

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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 silvlated 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 NaHCO3 (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 MgSO₄), 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.

(+)-(2S,4S)-2-Amino-6-chloro-9-[2-(hydroxymethyl)-1,3dioxolan-4-yl]purine (53) and (+)-(2S,4S)-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-CH₂Cl₂, 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 (H₂O) λ_{max} 307.0 (ε 5450) (pH 7), 307.0 (ε 7080) (pH 2), 307.0 nm (ϵ 7180) (pH 11). 55: UV (H₂O) λ_{max} 261.0 (ϵ 1400) (pH 7), 261.0 (e 13 990) (pH 2), 261.0 nm (e 1390) (pH 11).

(-)-(2S,4R)-2-Amino-6-chloro-9-[2-(hydroxymethyl)-1,3dioxolan-4-yl]purine (54) and (-)-(2S,4R)-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 NH₃/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 $(H_2O) \lambda_{max} 307.5 \ (\epsilon \ 8120) \ (pH \ 7), \ 307.5 \ (\epsilon \ 8040) \ (pH \ 2), \ 307.0 \ nm$ (ϵ 8150) (pH 11). 56: UV (H₂O) λ_{max} 261.0 (ϵ 15 450) (pH 7), 261.0 (e 15 820) (pH 2), 261.0 nm (e 15 350) (pH 11).

(2S,4S)-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.

(2S,4R)-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 CHCl₃ and concentrated to dryness. The crude was recrystallized from water to give 58 (52 mg, 70.0%) as white crystals: UV (H₂O) 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 CH₂Cl₂ (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 N₂, cooled, and stirred with saturated NaHCO3 solution (10 mL). The residue after evaporation under reduced pressure was extracted with EtOAc. The organic layer was washed with H₂O and brine and dried (Na₂SO₄). 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.

(+)-(2S,4S)-6-Amino-2-chloro-9-[2-(hydroxymethyl)-1,3dioxolan-4-yl]purine (65). A steel bomb charged with 59 (230 mg, 0.58 mmol) and MeOH (15 mL) saturated with NH₃ 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 (H₂O) λ_{max} 263.5 (ϵ 16 880) (pH 7), 263.5 (ϵ 15 450) (pH 2), 263.8 nm (ϵ 17 010) (pH 11).

(-)-(2S,4R)-6-Amino-2-chloro-9-[2-(hydroxymethyl)-1,3dioxolan-4-yl]purine (66). Compound 60 (195 mg, 0.49 mmol) was converted to 66 (96 mg, 71.6%) by treatment with NH₃/ MeOH (30 mL) according to the procedure described for 65: UV (H₂O) λ_{max} 264.0 (ϵ 18 250) (pH 7), 264.0 (ϵ 16 380) (pH 2), 263.8 nm (ϵ 18 750) (pH 11).

(+)-(2S,4S)-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 NaN₃ (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 CHCl₃ (50 mL), washed with water and brine, dried (Na₂SO₄), 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 CHCl₃ to dissolve any precipitated product. The combined organic layers were evaporated to dryness to give 63 (62 mg, 88.8%): UV (H₂O) λ_{max} 281, 257 nm. Compound 63 was treated with NH₃/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 (e 12 360) (pH 7), 252.5 (e 11 470), 290.5 (e 10 130) (pH 2), 255.5 (e 9850), 278.8 nm (e 10 800) (pH 11).

(-)-(2S,4R)-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 NaN₃ (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 H₂/10% 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 NH₃/MeOH (10 mL) to afford 68 (16 mg, 55%) as a white solid: UV (H₂O) 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 hlue

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

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

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