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Articles

Asymmetric Synthesis and Biological Evaluation of β-L-(2*R*,5*S*)- and α-L-(2*R*,5*R*)-1,3-Oxathiolane–Pyrimidine and –Purine Nucleosides as Potential Anti-HIV Agents

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In order to study the structure–activity relationships of L-oxathiolanyl nucleosides as potential anti-HIV agents, a series of enantiomerically pure L-oxathiolanyl pyrimidine and purine nucleosides were synthesized and evaluated for anti-HIV-1 activity in human peripheral blood mononuclear (PBM) cells. The key intermediate 8 was synthesized starting from L-gulose via 1,6-thioanhydro-L-gulopyranose. The acetate 8 was condensed with thymine, 5-substituted uracils and cytosines, 6-chloropurine, and 6-chloro-2-fluoropurine to give pyrimidine and purine nucleosides. Upon evaluation of these final nucleosides, the 5-fluorocytosine derivative 51 was found to be the most potent compound among those tested. In the case of 5-substituted cytosine analogues, the antiviral potency was found to be in the following decreasing order: cytosine (β-isomer) > 5-iodocytosine (β-isomer) > 5-fluorocytosine (α-isomer) > 5-methylcytosine (α-isomer) > 5-methylcytosine (β-isomer) > 5-bromocytosine (β-isomer) > 5-chlorocytosine (β-isomer). Among the thymine, uracil, and 5-substituted uracil derivatives, thymine (α-isomer) and uracil (β-isomer) derivatives exhibited moderate anti-HIV activity. In the purine series, the antiviral potency is found to be in the following decreasing order: adenine (β-isomer) > 6-chloropurine (β-isomer) > 6-chloropurine (α-isomer) > 2-NH_2-6-Cl-purine (β-isomer) > guanine (β-isomer) > N^6-methyladenine (α-isomer) > N^6-methyladenine (β-isomer). The cytotoxicity was also determined in human PBM cells as well as Vero cells. None of the synthesized nucleosides was toxic up to 100 μM in PBM cells.

Introduction

Since 3′-azido-3′-deoxythymidine (AZT) has been found to be effective against HIV-1,[1] a number of 2′,3′-dideoxynucleosides have been developed as potential anti-HIV agents.[2-8] Among these, AZT, 2′,3′-dideoxyinosine (ddI), and 2′,3′-dideoxycytidine (ddC) have been approved by FDA and are being clinically used for the treatment of AIDS and AIDS-related complex,[2-4] while other 2′,3′-dideoxynucleosides such as 2′,3′-didehydro-3′-deoxythy-

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(1) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. 3′-Azido-3′-deoxythymidine (BW A509U): An antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus *in vitro*. *Proc. Natl. Acad. Sci. U.S.A.* 1985, 82, 7096–7100.

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(3) Mitsuya, H.; Broder, S. Inhibition of the *in vitro* Infectivity and Cytopathic effect on human T- lymphotropic Virus Type III/lymphadenopathy-associated Virus (HTLV-III/LAV) by 2′,3′-dideoxynucleosides. *Proc. Natl. Acad. Sci. U.S.A.* 1986, *83*, 1911–1915. Lambert, J. S.; Seidlin,

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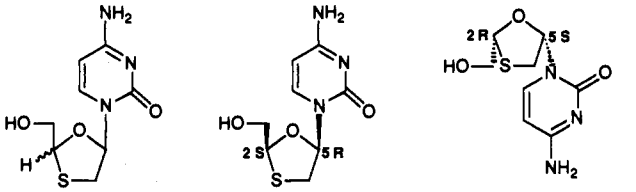
midine (d4T),[5] 3'-azido-2',3'-dideoxyuridine (AZDU),[6,7] and 3'-fluoro-3'-deoxythymidine (FLT)[8] are at various stages of clinical trials. Although FDA-approved drugs extend the life of AIDS patients, bone marrow toxicity and side effects such as peripheral neuropathy and pancreatitis limit the long-term use of these drugs. Furthermore, the emergence of AZT-resistant[9] and ddI-resistant[10] strains from the patients who have received the prolonged AZT and ddI therapies, respectively, has caused significant concern in AIDS chemotherapy. Therefore, it is critical to discover new anti-HIV agents with improved selectivity and activity against resistant strains.

Recently, several unusual classes of nucleosides such as 4'-azidothymidine,[11] (±)-dioxolane-T,[12,13] and 2',3'-dideoxy-3'-thiacytidine (BCH-189)[12,16,17] have been discovered to be active against HIV-1 in vitro. We have first reported the asymmetric synthesis of D-1,3-dioxolane-pyrimidine nucleosides and their anti-HIV activities in human PBM cells.[14,15] From this study, (+)-β-D-dioxolane-cytosine was found to be the most potent compound although it was the most toxic among this series.



BCH-189 (+)-β-D-(2S,5R)-1,3 oxa thiolanyl-cytosine (−)-β-L-(2R,5S)-1,3 oxa thiolanyl-cytosine

Figure 1. Structures of BCH-189, (+)-β-D-(2S,5R)-1,3-oxathiolanylcytosine, and (−)-β-L-(2R,5S)-1,3-oxathiolanylcytosine.

BCH-189 was first reported as a potent anti-HIV agent in vitro by Belleau et al.[12] BCH-189 showed potent anti-HIV activity (EC_{50} = 0.73 μM) in MT-2 cells and no cross-resistance to AZT resistant strains and was 10 times less toxic than AZT in the same cell system.[16] BCH-189 also exhibited potent anti-HIV activity (EC_{50} = 0.02–0.06 μM) in human PBM cells.[17]

More recently, our laboratories have reported the enantiomeric syntheses, anti-HIV, and anti-HBV activities of both (+)-β-D-(2S,5R)-1,3-oxathiolanylcytosine[18,19] and (−)-β-L-(2R,5S)-1,3-oxathiolanylcytosine (3TC)[17,20] (Figure 1). (−)-β-L-(2R,5S)-1,3-oxathiolanylcytosine (EC_{50} = 0.0018 μM in human PBM cells) exhibited more potent anti-HIV activity than the corresponding racemate (EC_{50} = 0.02–0.06 μM in human PBM cells). (−)-β-L-(2R,5S)-1,3-oxathiolanylcytosine was also found to exhibit the most potent anti-HBV activity with the least toxic effects among four possible stereoisomers.[21] Therefore, it was of interest to synthesize enantiomerically pure pyrimidine and purine derivatives to study the structure–activity relationships of these unusual nucleosides series.

Chemistry

The key intermediate 8 was synthesized via 1,6-thioanhydro-L-gulopyranose (4) from L-gulose (1), which can be easily prepared from β,γ-6,3-gulonolactone[22a,b] or

M.; Reichman, R. C.; Plank, C. S.; Laverty, M.; Morse, G. D.; Knupp, C.; McLaren, C.; Pettinelli, C.; Valentine, F. T.; Dolin, R. 2',3'-Dideoxyinosine (ddI) in Patients with the Acquired Immunodeficiency Syndrome or AIDS-Related Complex. *New Engl. J. Med.* 1990, *322*, 1333–1340.

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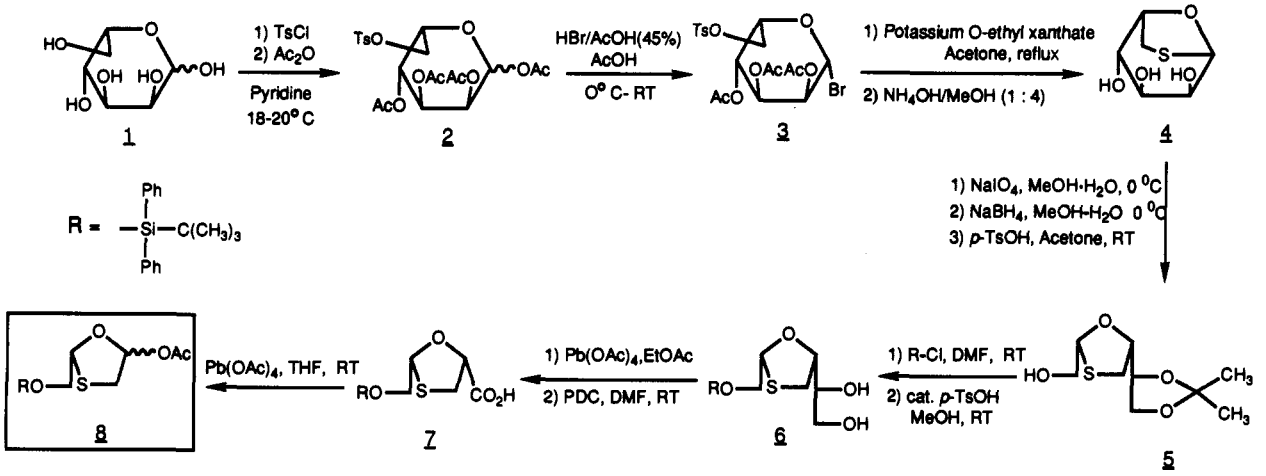
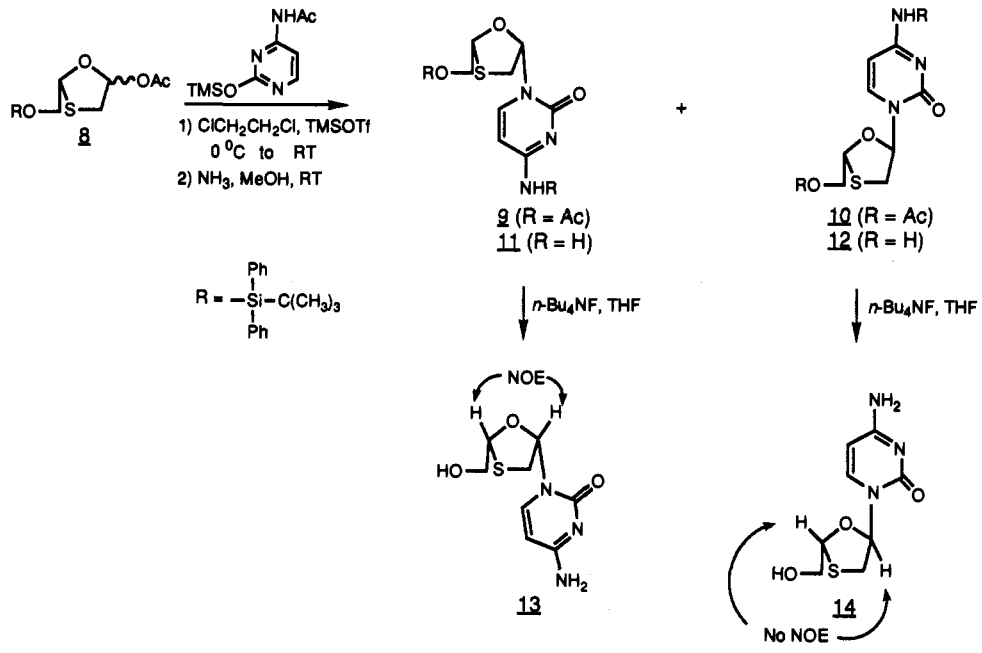
Scheme I

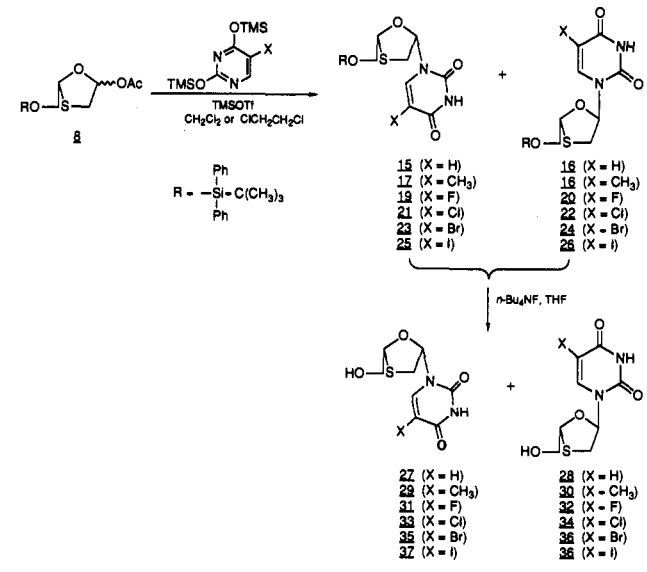


Scheme II



L-ascorbic acid[22c] (Scheme I). The selective tosylation of 1 followed by acetylation gave 2 in 97% yield. The treatment of 2 with 45% HBr in AcOH (v/v) yielded the bromo derivative 3, which was refluxed with potassium

Scheme III



O-ethylxanthate in acetone[18,20a,23] and then deacetylated using NH_4OH in MeOH to obtain the 1,6-thioanhydro-

Rouse, P. L.; Marr, C. L. P.; Reid, P. J.; Boehme, R. E.; Coates, J. A. V.; Penn, C. R.; Cameron, J. M. Cellular Metabolism of (−) Enantiomeric 2′-Deoxy-3′-Thiacytidine. *Biochem. Pharmacol.* **1992**, *43*, 2059–2064. (e) Hart, G. J.; Orr, D. C.; Penn, C. R.; Figueiredo, H. T.; Gray, N. M.; Boehme, R. E.; Cameron, J. M. Effects of (−)-2′-Deoxy-3′-Thiacytidine (3TC) 5′-Triphosphate on Human Immunodeficiency Virus Reverse Transcriptase and Mammalian DNA Polymerase Alpha, Beta, and Gamma. *Antimicrob. Agents Chemother.* **1992**, *36*, 1688–1694. (f) Humber, D. C.; Jones, M. F.; Payne, J. J.; Ramsay, V. J. Expeditious Preparation of (−)-2′-Deoxy-3′-Thiacytidine (3TC). *Tetrahedron Lett.* **1992**, *33*, 4625–4628.

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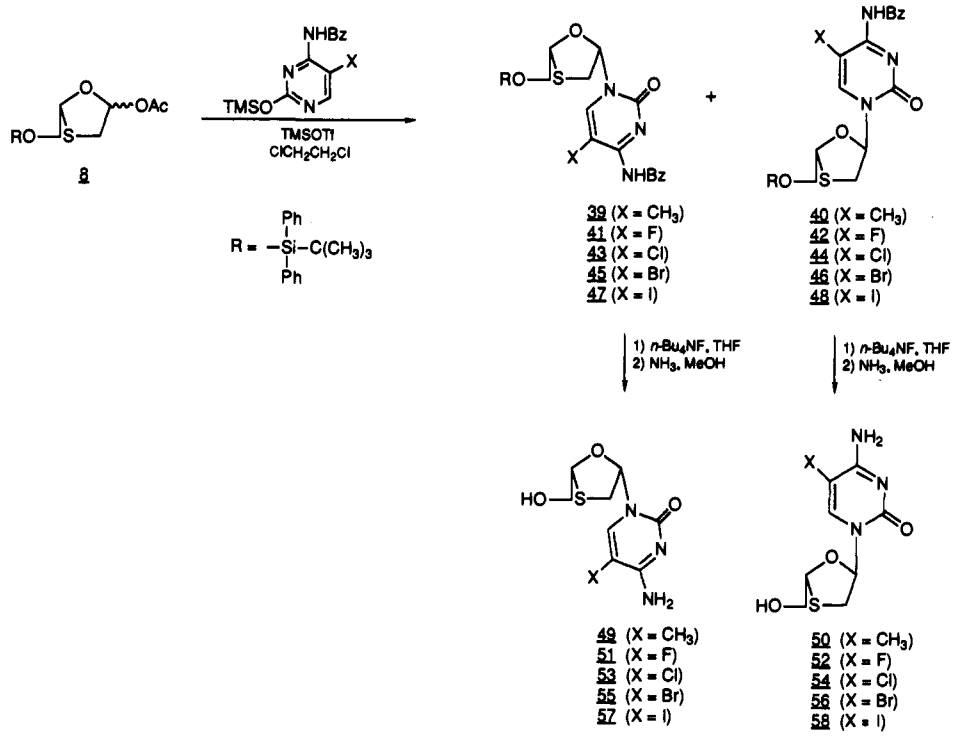
Scheme IV



L-gulopyranose (**4**) after purification by silica gel column chromatography. The selective oxidative cleavage of vicinal *cis*-diol in **4** by $NaIO_4$ to the corresponding aldehyde, reduction with $NaBH_4$ followed by protection of the resulting diol as the acetonide using acetone and *p*-toluenesulfonic acid yielded the 1,3-oxathiolane derivative **5** in 65% yield from **4**. The protection of the hydroxyl group with a *tert*-butyldiphenylsilyl group followed by deprotection of the isopropylidene moiety by catalytic *p*-toluenesulfonic acid in MeOH afforded the protected diol **6** in 70% yield from **5**. The preparation of the key intermediate **8** was accomplished in three steps from diol **6**: The oxidative cleavage of vicinal diol of **6** by $Pb(OAc)_4$ followed by pyridinium dichromate (PDC) oxidation in DMF[24] gave the acid **7**. Without further purification, the treatment of the acid **7** with $Pb(OAc)_4$/pyridine in anhydrous THF afforded acetate **8** (64% yield from **6**), which can be used for the preparation of various L-oxathiolanyl nucleosides.

The synthesis of (−)-β-L-(2*R*,5*S*)-1,3-oxathiolanylcytosine (**13**) and its α isomer **14** is outlined in Scheme II. The condensation of **8** with silylated N^4-acetylcytosine in 1,2-dichloroethane in the presence of TMSOTf yielded fully protected nucleosides **9** and **10** (2:1 ratio). The deacetylation of **9** and **10** by methanolic ammonia followed by desilylation by tetra-*n*-butylammonium fluoride gave the desired (−)-β-L-(2*R*,5*S*)-1,3-oxathiolanylcytosine (**13**) and its α isomer **14**, respectively. It is interesting to note that the use of stannic chloride[25] in place of TMSOTf yielded only β isomer, but resulted in racemization, which was characterized by chiral HPLC and optical rotation.[26] The assignments of anomeric configurations of **13** and **14** were based on NOE experiments that upon irradiation of 4′-H in **13** and **14**, enhancement of 1′-H peak, suggesting cis orientation, was observed, while no enhancement was observed in **14**, indicating the trans configuration. Anomeric configurations of other nucleosides were assigned based on the comparison of the ^1H NMR patterns of **13** and **14** and the chemical shifts of the β anomeric protons in the NMR spectra, which were upfield relative to the α anomeric signals. Furthermore, the 4′ proton of the β anomers appeared upfield from that observed for the α anomer and the 5′ protons of the β anomer appeared downfield from those observed for the α anomers.[15]

The general synthetic route to thymidine, uridine, and 5-substituted uridine analogues **27–38** is depicted in Scheme III. The fully protected 1,3-oxathiolanyluracil, -thymine, and -5-halouracil nucleosides **15–26** were prepared as inseparable α,β-anomeric mixtures from the condensation of acetate **8** with silylated uracil, thymine, and 5-halouracils, respectively, using TMSOTf as Lewis acid catalyst. Desilylation of the protected nucleosides **15–26** by tetra-*n*-butylammonium fluoride in THF and purification by silica gel column chromatography yielded the final nucleosides **27–38** in good yields.

The synthesis of 1,3-oxathiolanyl-5-substituted cytosine nucleosides are illustrated in Scheme IV. The intermediate **8** was condensed with silylated 5-substituted cytosines. However, we could only obtain chromatographically inseparable anomeric mixtures of corresponding nucleosides. In order to avoid this problem, N^4-acetyl-5-halocytosines were prepared and condensed with the acetate **8**. Although separations of α,β-anomers were detected on TLC, the individual anomers of N^4-acetyl-

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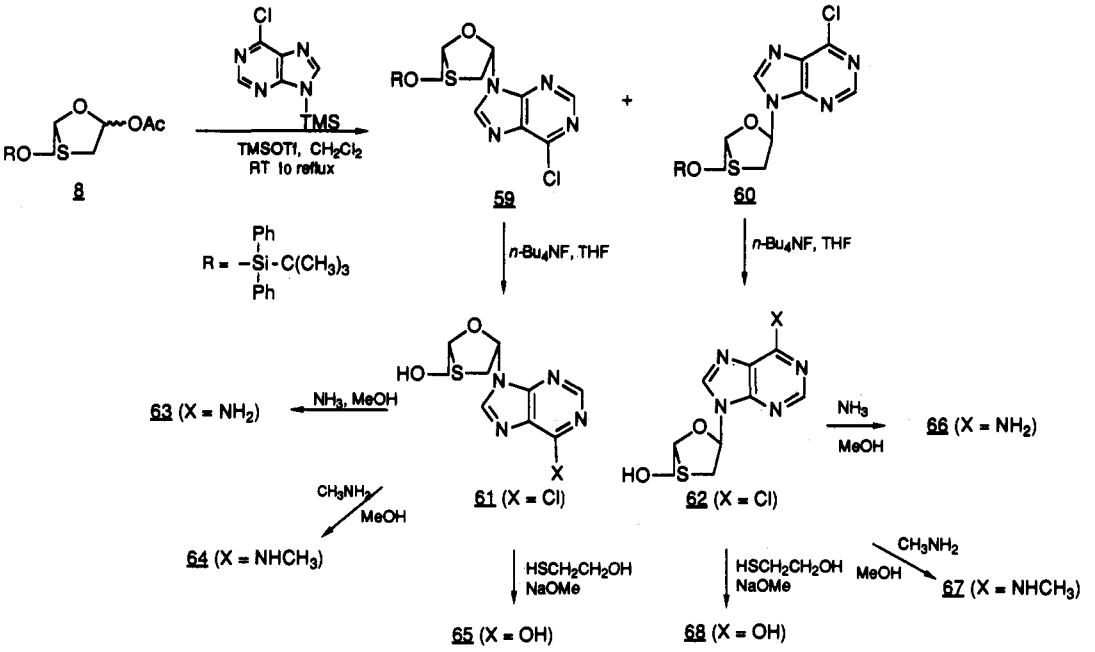
(26) (a) Chiral HPLC was performed on a Cyclobond I Acetylated Column (Astec) using 0.2% (v/v) Triethylamine in Water Adjusted to pH 7.2 with Glacial Acetic Acid and Flow Rate of 1 mL/min. (b) $[\alpha]^{25}_D$ = 0° (*c* 1.0, MeOH).

Scheme V



5-substituted cytosine derivatives were too unstable to be separated by silica gel column chromatography. Therefore, we have prepared N^4-benzoyl-5-substituted cytosines, which were synthesized by treating 5-substituted cytosines[27] with benzoic anhydride at 70–80 °C and then condensed with 8. This method resulted in stable derivatives during the silica gel column chromatography as well as better separation of α,β-anomers on TLC. Therefore, we could obtain fully protected individual α and β anomers **39–48**. Desilylation of compounds **39–48** by tetra-*n*-butylammonium fluoride and then debenzoylation using methanolic ammonia followed by silica gel column chromatography yielded the desired 5-substituted cytosine nuleosides **49–58**.

L-1,3-Oxathiolanyl acetate **8** was also condensed with silylated 6-chloropurine, which was then converted to ddA, ddI, and N^6-MeddA derivatives (Scheme V). The condensation of the acetate **8** with silylated 6-chloropurine yielded protected nucleosides **59** and **60** after silica gel column chromatography. During the condensation, the initially formed possibly N-3 isomers[28] were converted to N-9 isomers on refluxing overnight. Desilylation of **59** and **60** by tetra-*n*-butylammonium fluoride gave the free nucleosides **61** and **62**, respectively. The 6-chloropurine derivative **61** was converted to the ddA derivative **63** by treating with methanolic ammonia at 85–90 °C. N^6-Methyl-ddA analogue **64** was prepared by treating **61** with methylamine in methanol at 85–90 °C. The ddI derivative **65** was also synthesized from **61** by refluxing with sodium methoxide and 2-mercaptoethanol in methanol. The corresponding α-anomers **66–68** were prepared by similar procedures used for **63–65**.

For the syntheses of 2,6-disubstituted purine analogues such as 2′,3′-dideoxyguanosine, the acetate **8** was reacted with 2-fluoro-6-chloropurine[29] to give an inseparable anomeric mixture of **69** and **70** (Scheme VI). As observed with 6-chloropurine, rearrangement of initially formed isomers to N-9 isomers occurred while stirring overnight at room temperature. The treatment of anomeric mixture **69** and **70** with ammonia in DME at room temperature resulted in two pairs of α,β anomer **71–74**. Desilylation of individual anomers by tetra-*n*-butylammonium fluoride gave 6-amino-2-fluoro[30] and 2-amino-6-chloro derivatives **75** and **77** and their α isomers **76** and **78**, respectively. The 2-amino-6-chloro analogues **77** and **78** were treated with sodium methoxide and 2-mercaptoethanol in methanol to give guanine derivatives **79** and **80**, respectively.[31] ^{1}H NMR spectra of all synthesized compounds are summarized in Tables I and II and physicochemical properties such as optical rotations and melting points are shown in Table III.

Anti-HIV Activity

The anti-HIV-1 activity of the synthesized L-(2*R*,5*S*)- and (2*R*,5*R*)-oxathiolanyl pyrimidine and purine nucleosides was determined in human peripheral blood mononuclear (PBM) cells infected with HIV-1 strain LAV (Table IV).[32]

As seen in Table IV, the 5-fluorocytosine derivative **51** was found to be the most potent compound among compounds tested without cytotoxicity up to 100 μM.

In the case of 5-substituted cytosine analogues, the antiviral potency was found to be in the following decreasing order: cytosine (β-isomer) > 5-iodocytosine

(27) 5-Halocytosines (Cl, Br, I) were synthesized by refluxing cytosine with *N*-halosuccinimide (Cl, Br, I) in glacial acetic acid, and 5-fluoro- and 5-methylcytosines were commercially available.

(28) (a) UV (MeOH) λ_{max} 270.5 nm (pH 7), 263.5 (pH 2), 264.5 (pH 11). (b) Prasad, R. N.; Robins, R. K. Potential Purine Antagonists, VIII. The Preparation of Some 7-Methyl Purines. *J. Am. Chem. Soc.* **1957**, *79*, 6401–6407.

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(30) Montgomery, J. A.; Hewson, K. Nucleosides of 2-Fluoroadenine. *J. Med. Chem.* **1969**, *12*, 498–501.

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(32) Schinazi, R. F.; Sommadossi, J.-P.; Saalmann, V.; Cannon, D. L.; Xie, M.-Y.; Hart, G. C.; Smith, G. A.; Hahn, E. F. Activities of 3′-Azido-3′-Deoxythymidine Nucleotide Dimers in Primary Lymphocytes Infected with Human Immunodeficiency Virus Type 1. *Antimicrob. Agents. Chemother.* **1990**, *34*, 1061–1067.

Table I. NMR Data of 1,3-Oxathiolane–Pyrimidines

compd no.	H-1′ [c,d]	H_a-2′	H_b-2′	H-4′	H-5′	other signals
9[b]	6.35 (dd, $J_{1',2'b}$ = 2.4, $J_{1',2'a}$ = 5.3)	3.56 (dd, $J_{1',2'a}$ = 5.3, $J_{2'a,2'b}$ = 12.5)	3.20 (dd, $J_{1',2'b}$ = 2.4, $J_{2'a,2'b}$ = 12.5)	5.21 (t, $J_{4',5'}$ = 3.5)	4.21 (dd, $J_{5',4'}$ = 3.5, $J_{5'a,5'b}$ = 11.8), 3.95 (dd, $J_{5',4'}$ = 3.5, $J_{5'a,5'b}$ = 11.8)	8.88 (br s, NH), 8.28 (d, $J_{6,5}$ = 7.4, H-6), 7.32–7.80 (m, Ar), 7.21 (d, $J_{5,6}$ = 7.4, H-5), 2.24 (s, $COCH_3$), 1.11 (s, *tert*-butyl)
10[b]	6.35 (d, $J_{1',2'}$ = 4.1)	3.54 (dd, $J_{1',2'a}$ = 4.1, $J_{2'a,2'b}$ = 12.1)	3.14 (dd, $J_{1',2'b}$ = 4.1, $J_{2'a,2'b}$ = 12.1)	5.62 (t, $J_{4',5'}$ = 4.4)	3.74 (d, $J_{5',4'}$ = 4.4)	9.91 (br s, NH), 7.32–7.85 (m, Ar, H-5, and H-6), 2.28 (s, $COCH_3$), 1.07 (s, *tert*-butyl)
11[b]	6.35 (dd, $J_{1',2'b}$ = 3.3, $J_{1',2'a}$ = 5.3)	3.50 (dd, $J_{1',2'a}$ = 5.3, $J_{2'a,2'b}$ = 12.3)	3.13 (dd, $J_{1',2'b}$ = 3.3, $J_{2'a,2'b}$ = 12.3)	5.25 (t, $J_{4',5'}$ = 3.5)	4.16 (dd, $J_{5',4'}$ = 3.5, $J_{5'a,5'b}$ = 12.8)	7.94 (d, $J_{6,5}$ = 7.4, H-6), 7.32–7.83 (m, Ar), 5.92 (br s, NH_2), 5.46 (d, $J_{5,6}$ = 7.4, H-5), 1.09 (s, *tert*-butyl)
12[b]	6.41 (dd, $J_{1',2'b}$ = 1.1, $J_{1',2'a}$ = 4.8)	3.51 (dd, $J_{1',2'a}$ = 4.8, $J_{2'a,2'b}$ = 12.3)	3.12 (dd, $J_{1',2'b}$ = 1.1, $J_{2'a,2'b}$ = 12.3)	5.55 (t, $J_{4',5'}$ = 4.8)	3.73 (d, $J_{5',4'}$ = 4.8)	7.31–7.82 (m, Ar and H-6), 5.97 (br s, NH_2), 5.67 (d, $J_{5,6}$ = 7.4, H-5), 1.06 (s, *tert*-butyl)
13[a]	6.21 (pseudo, t, $J_{1',2'a}$ = 5.3, $J_{1',2'b}$ = 4.4)	3.43 (dd, $J_{1',2'a}$ = 5.3, $J_{2'a,2'b}$ = 11.9)	3.03 (dd, $J_{1',2'b}$ = 4.4, $J_{2'a,2'b}$ = 11.9)	5.22 (t, $J_{4',5'}$ = 4.2)	3.80 (t, $J_{5',4'}$ = 4.2)	7.89 (d, $J_{6,5}$ = 7.5, H-6), 7.19 (br s, NH_2), 5.88 (d, $J_{5,6}$ = 7.5, H-5), 5.31 (t, $J_{OH,5'}$ = 4.6, OH)
14[a]	6.36 (dd, $J_{1',2'b'}$ = 3.3, $J_{1',2'a}$ = 5.1)	3.46 (dd, $J_{1',2'a}$ = 5.1, $J_{2'a,2'b}$ = 12.1)	3.08 (dd, $J_{1',2'b}$ = 3.3, $J_{2'a,2'b}$ = 12.1)	5.53 (t, $J_{4',5'}$ = 5.1)	3.54 (t, $J_{5',4'}$ = 5.1)	7.63 (d, $J_{6,5}$ = 7.5, H-6), 7.16 (br s, NH_2), 5.83 (d, $J_{5,6}$ = 7.5, H-5), 5.16 (t, $J_{OH,5'}$ = 5.7, OH)
15/16[b]	6.40 (dd, $J_{1',2'b}$ = 1.8, $J_{1',2'a}$ = 5.3), 6.33 (dd, $J_{1',2'b}$ = 5.3, $J_{1',2'a}$ = 3.6)	3.52 (m)	3.11 (m)	5.73 (dd, $J_{4',5'a}$ = 3.7, $J_{5'a,5'b}$ = 9.8), 5.24 (t, $J_{4',5'}$ = 3.3)	4.15 (dd, $J_{5',4'}$ = 3.3, $J_{5'a,5'b}$ = 11.6), 3.93 (dd, $J_{5',4'}$ = 3.7, $J_{5'a,5'b}$ = 12.1), 3.72 (m)	8.81 (br s, NH), 7.91 (d, $J_{6,5}$ = 8.7, H-6), 7.38–7.71 (m, Ar), 5.56 (d, $J_{5,6}$ = 4.5, H-5), 1.09 (s, *tert*-butyl), 1.07 (s, *tert*-butyl)
17/18[b]	6.43 (dd, $J_{1',2'b}$ = 2.6, $J_{1',2'a}$ = 5.3), 6.35 (t, $J_{1',2'}$ = 6.0)	3.49 (m)	3.05 (m)	5.56 (t, $J_{4',5'}$ = 4.5), 5.27 (t, $J_{4',5'}$ = 3.7)	4.03 (dd, $J_{5',4'}$ = 3.7, $J_{5'a,5'b}$ = 11.3), 3.95 (dd, $J_{5',4'}$ = 4.5, $J_{5'a,5'b}$ = 11.4)	9.01 (br s, NH), 7.21–7.69 (m, Ar and H-6), 1.78 (s, CH_3), 1.77 (s, CH_3) 1.24 (s, *tert*-butyl), 1.07 (s, *tert*-butyl)
19/20[b]	6.37 (m), 6.30 (m)	3.50 (m)	3.12 (m)	5.58 (t, $J_{4',5'}$ = 4.5), 5.23 (t, $J_{4',5'}$ = 4.0)	4.10 (dd, $J_{5',4'}$ = 4.0, $J_{5'a,5'b}$ = 12.0), 3.91 (dd, $J_{5',4'}$ = 4.5, $J_{5'a,5'b}$ = 11.3)	9.06 (br s, NH), 7.94 (d, $J_{F,6}$ = 6.4, H-6), 7.38–7.70 (m, Ar), 1.09 (s, *tert*-butyl), 1.07 (s, *tert*-butyl)
21/22[b]	6.36 (m), 6.28 (m)	3.48 (dd, $J_{1',2'a}$ = 5.7, $J_{2'a,2'b}$ = 12.0)	3.07 (dd, $J_{1',2'b}$ = 3.4, $J_{2'a,2'b}$ = 12.0)	5.59 (t, $J_{4',5'}$ = 4.5), 5.25 (t, $J_{4',5'}$ = 3.9)	3.99 (t, $J_{5',4'}$ = 3.9), 3.76 (d, $J_{5',4'}$ = 4.5)	8.65 (br s, NH), 7.33–7.71 (m, Ar), 7.88 (s, H-6), 1.09 (s, *tert*-butyl), 1.07 (s, *tert*-butyl)
23/24[b]	6.36 (m), 6.28 (m)	3.56 (m)	3.07 (m)	5.59 (t, $J_{4',5'}$ = 4.6), 5.25 (t, $J_{4',5'}$ = 4.2)	3.99 (dd, $J_{5',4'}$ = 4.2 $J_{5'a,5'b}$ = 3.7), 3.76 (d, $J_{5',4'}$ = 4.6)	8.67 (br s, NH), 7.95 (s, H-6), 7.38–7.77 (m, Ar), 1.09 (s, *tert*-butyl), 1.07 (s, *tert*-butyl)
25/26[b]	6.35 (m), 6.27 (m)	3.55 (m)	3.06 (m)	5.58 (t, $J_{4',5'}$ = 4.6), 5.27 (t, $J_{4',5'}$ = 4.2)	3.99 (dd, $J_{5',4'}$ = 4.2 $J_{5'a,5'b}$ = 3.8), 3.76 (d, $J_{5',4'}$ = 4.6)	8.70 (br s, NH), 7.96 (s, H-6), 7.35–7.77 (m, Ar), 1.09 (s, *tert*-butyl), 1.07 (s, *tert*-butyl)
27[a]	6.20 (t, $J_{1',2'}$ = 5.0)	3.44 (dd, $J_{2'a,2'b}$ = 11.5, $J_{2'a,1'}$ = 5.0)	3.20 (dd, $J_{2'b,2'a}$ = 11.5, $J_{2'b,1'}$ = 5.0)	5.19 (t, $J_{4',5'}$ = 4.4)	3.73 (d, $J_{5',4'}$ = 4.4)	11.4 (br s, NH), 7.91 (d, $J_{6,5}$ = 7.9, H-6), 5.64 (d, $J_{5,6}$ = 7.9, H-5), 5.36 (br s, OH)
28[a]	6.35 (dd, $J_{1',2'b}$ = 3.0, $J_{1',2'a}$ = 5.4)	3.49 (dd, $J_{2'a,2'b}$ = 11.8, $J_{2'a,1'}$ = 5.4)	3.20 (dd, $J_{2'b,2'a}$ = 11.8, $J_{2'b,1'}$ = 3.0)	5.52 (t, $J_{4',5'}$ = 5.3)	3.49 (m)	11.4 (br s, NH), 7.66 (d, $J_{6,5}$ = 7.9, H-6), 5.64 (d, $J_{5,6}$ = 7.9, H-5), 5.36 (br s, OH)
29[a]	6.19 (t, $J_{1',2'}$ = 5.3)	3.39 (dd, $J_{2'a,2'b}$ = 11.6, $J_{2'a,1'}$ = 5.3)	3.19 (dd, $J_{2'b,2'a}$ = 11.6, $J_{2'b,1'}$ = 5.3)	5.17 (t, $J_{4',5'}$ = 4.6)	3.72 (m)	11.4 (br s, NH), 7.75 (s, H-6), 5.34 (t, $J_{OH,5'}$ = 5.9, OH), 1.78 (s, CH_3)
30[a]	6.35 (pseudo t, $J_{1',2'a}$ = 3.9, $J_{1',2'b}$ = 2.6)	3.52 (dd, $J_{2'a,2'b}$ = 11.5, $J_{2'a,1'}$ = 3.9)	3.24 (dd, $J_{2'b,2'a}$ = 11.5, $J_{2'b,1'}$ = 2.6)	5.53 (t, $J_{4',5'}$ = 4.6)	3.52 (m)	11.3 (br s, NH), 7.54 (s, H-6), 5.21 (t, $J_{OH,5'}$ = 5.5, OH), 1.79 (s, CH_3)
31[a]	6.17 (m)	3.45 (dd, $J_{2'a,2'b}$ = 12.2, $J_{2'a,1'}$ = 5.5)	3.28 (dd, $J_{2'b,2'a}$ = 12.2, $J_{2'b,1'}$ = 4.3)	5.21 (t, $J_{4',5'}$ = 3.8)	3.77 (m)	11.9 (br s, NH), 8.36 (d, $J_{6,5}$ = 7.6, H-6), 5.48 (t, $J_{OH,5'}$ = 5.5, OH)
32[a]	6.32 (m)	3.52 (dd, $J_{2'b,2'a}$ = 12.2, $J_{2'a,1'}$ = 4.0)	3.27 (dd, $J_{2'b,2'a}$ = 12.2, $J_{2'b,1'}$ = 3.0)	5.62 (t, $J_{4',5'}$ = 5.2)	3.52 (m)	11.9 (br s, NH), 7.98 (d, $J_{6,5}$ = 7.0, H-6), 5.21 (t, $J_{OH,5'}$ = 5.9, OH)
33[a]	6.18 (t, $J_{1',2'}$ = 4.8)	3.50 (dd, $J_{2'b,2'a}$ = 11.9, $J_{2'a,1'}$ = 4.8)	3.35 (dd, $J_{2'b,2'a}$ = 11.9, $J_{2'b,1'}$ = 4.8)	5.22 (t, $J_{4',5'}$ = 3.8)	3.79 (m)	11.9 (br s, NH), 8.45 (s, H-6), 5.50 (t, $J_{OH,5'}$ = 5.4, OH)
34[a]	6.32 (dd, $J_{1',2'b}$ = 2.8, $J_{1',2'a}$ = 6.5)	3.53 (dd, $J_{2'b,2'a}$ = 11.9, $J_{2'a,1'}$ = 6.5)	3.32 (dd, $J_{2'b,2'a}$ = 11.9, $J_{2'b,1'}$ = 2.8)	5.63 (t, $J_{4',5'}$ = 6.0)	3.53 (m)	11.4 (br s, NH), 7.96 (s, H-6), 5.20 (br s, OH)
35[a]	6.17 (t, $J_{1',2'}$ = 4.9)	3.47 (dd, $J_{2'b,2'a}$ = 11.9, $J_{2'a,1'}$ = 4.9)	3.30 (dd, $J_{2'b,2'a}$ = 11.9, $J_{2'b,1'}$ = 4.9)	5.21 (t, $J_{4',5'}$ = 3.4)	3.79 (m)	11.9 (br s, NH), 8.52 (s, H-6), 5.50 (t, $J_{OH,5'}$ = 5.7, OH)
36[a]	6.32 (dd, $J_{1',2'b}$ = 2.7, $J_{1',2'a}$ = 6.6)	3.50 (dd, $J_{2'b,2'a}$ = 11.9, $J_{2'a,1'}$ = 6.6)	3.31 (dd, $J_{2'b,2'a}$ = 11.9, $J_{2'b,1'}$ = 2.7)	5.62 (t, $J_{4',5'}$ = 6.0)	3.50 (m)	11.7 (br s, NH), 8.01 (s, H-6), 5.20 (br s, OH)
37[a]	6.16 (dd, $J_{1',2'b}$ = 3.2, $J_{1',2'a}$ = 5.3)	3.50 (dd, $J_{2'a,2'b}$ = 12.1, $J_{2'a,1'}$ = 5.3)	3.11 (dd, $J_{2'a,2'b}$ = 12.1, $J_{2'b,1'}$ = 3.2)	5.20 (t, $J_{4',5'}$ = 3.2)	3.80 (m)	11.8 (br s, NH), 8.51 (s, H-6), 5.50 (t, $J_{OH,5'}$ = 5.4, OH)
38[a]	6.30 (dd, $J_{1',2'b}$ = 3.8, $J_{1',2'a}$ = 5.9)	3.46 (dd, $J_{2'b,2'a}$ = 12.1, $J_{2'a,1'}$ = 5.9)	3.31 (dd, $J_{2'b,2'a}$ = 12.1, $J_{2'b,1'}$ = 5.9)	5.51 (t, $J_{4',5'}$ = 5.4)	3.50 (m)	11.8 (br s, NH), 8.01 (s, H-6), 5.10 (t, $J_{OH,5'}$ = 5.4, OH)

Table I (Continued)

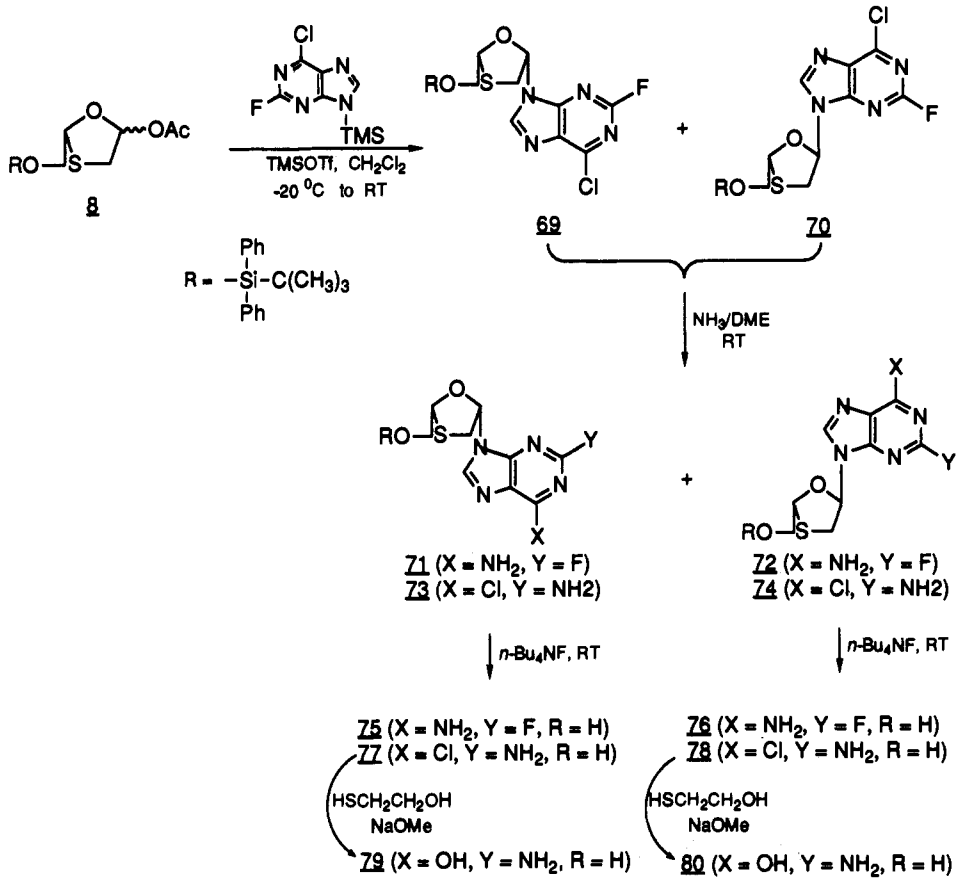
compd no.	H-1′ [c,d]	H_a-2′	H_b-2′	H-4′	H-5′	other signals
39[b]	6.37 (t, $J_{1'2'}$ = 5.3)	3.49 (dd, $J_{2'a,2'b}$ = 12.4, $J_{2'a,1'}$ = 5.3)	3.11 (dd, $J_{2'a,2'b}$ = 12.4, $J_{2'b,1'}$ = 5.3)	5.30 (t, $J_{4',5'}$ = 4.5)	4.08 (dd, $J_{5'a,5'b}$ = 12.9, $J_{5'b,4'}$ = 4.5), 3.97 (dd, $J_{5'a,5'b}$ = 12.9, $J_{5'a,4'}$ = 4.5)	9.40 (br s, NH), 8.31 (d, J = 7.4, Ar), 7.39–7.72 (m, Ar and H-6), 1.93 (s, CH_3), 1.10 (s, *tert*-butyl)
40[b]	6.42 (dd, $J_{1'2'b}$ = 2.5, $J_{1'2'a}$ = 5.4)	3.56 (dd, $J_{2'a,2'b}$ = 12.0, $J_{2'a,1'}$ = 5.4)	3.12 (dd, $J_{2'a,2'b}$ = 12.1, $J_{2'b,1'}$ = 2.5)	5.61 (t, $J_{4',5'}$ = 4.5)	3.76 (dd, $J_{5',4'}$ = 4.5, $J_{5'b,5'a}$ = 11.8)	9.41 (br s, NH), 8.31 (d, J = 7.2, Ar) 7.38–7.71 (m, Ar and H-6), 2.14 (s, CH_3), 1.08 (s, *tert*-butyl)
41[b]	6.32 (m)	3.53 (dd, $J_{2'a,2'b}$ = 12.2, $J_{2'a,1'}$ = 5.4)	3.20 (dd, $J_{2'a,2'b}$ = 12.2, $J_{2'b,1'}$ = 3.2)	5.25 (t, $J_{4',5'}$ = 3.5)	4.15 (dd, $J_{5'a,5'b}$ = 11.7, $J_{5'b,4'}$ = 3.0), 3.92 (dd, $J_{5'a,5'b}$ = 11.9, $J_{5'a,4'}$ = 3.8)	13.5 (br s, NH), 8.27 (d, J = 7.5 Ar), 8.12 (d, $J_{6,F}$ = 6.1, H-6), 7.39–7.72 (m, Ar), 1.08 (s, *tert*-butyl)
42[b]	6.37 (d, $J_{1'2'}$ = 5.1)	3.81 (dd, $J_{2'a,2'b}$ = 11.1, $J_{2'a,1'}$ = 5.1)	3.74 (dd, $J_{2'a,2'b}$ = 11.1, $J_{2'b,1'}$ = 5.1)	5.62 (t, $J_{4',5'}$ = 4.6)	3.59 (dd, $J_{5'a,5'b}$ = 12.4, $J_{5'b,4'}$ = 4.6), 3.16 (dd, $J_{5'a,5'b}$ = 12.4, $J_{5'a,4'}$ = 4.6)	13.2 (br s, NH), 8.28 (d, J = 6.9, Ar), 7.38–7.71 (m, Ar and H-6), 1.08 (s, *tert*-butyl)
43[b]	6.30 (dd, $J_{1'2'b}$ = 4.4, $J_{1'2'a}$ = 5.5)	3.51 (dd, $J_{2'a,2'b}$ = 12.3, $J_{2'a,1'}$ = 5.5)	3.11 (dd, $J_{2'a,2'b}$ = 12.3, $J_{2'b,1'}$ = 4.4)	5.27 (t, $J_{4',5'}$ = 4.4)	4.21 (dd, $J_{5'a,5'b}$ = 12.8, $J_{5'a,4'}$ = 4.4), 3.95 (dd, $J_{5'a,5'}$ = 12.8, $J_{5'b,4'}$ = 4.4)	9.53 (br s, NH), 8.31 (d, J = 7.2, Ar), 8.01 (s, H-6), 7.30–7.82 (m, Ar), 1.07 (s, *tert*-butyl)
44[b]	6.38 (dd, $J_{1'2'b}$ = 1.8, $J_{1'2'a}$ = 5.1)	3.58 (dd, $J_{2'a,2'b}$ = 12.5, $J_{2'a,1'}$ = 5.1)	3.11 (dd, $J_{2'a,2'b}$ = 12.5, $J_{2'b,1'}$ = 1.8)	5.63 (t, $J_{4',5'}$ = 4.6)	3.77 (d, $J_{5',4'}$ = 4.6)	9.50 (br s, NH), 8.31 (d, J = 7.4, Ar), 7.91 (s, H-6), 7.31–7.72 (m, Ar) 1.09 (s, *tert*-butyl)
45[b]	6.30 (pseudo, t, $J_{1'2'b}$ = 5.5, $J_{1'2'a}$ = 4.6)	3.51 (dd, $J_{2'a,2'b}$ = 12.3, $J_{2'a,1'}$ = 4.6)	3.14 (dd, $J_{2'a,2'b}$ = 12.2, $J_{2'b,1'}$ = 5.5)	5.28 (t, $J_{4',5'}$ = 4.0)	4.08 (dd, $J_{5'a,5'b}$ = 11.6, $J_{5'a,4'}$ = 4.0), 3.97 (dd, $J_{5'a,5'}$ = 11.6, $J_{5'b,4'}$ = 4.0)	13.2 (br s, NH), 8.34 (d, J = 7.3, Ar), 8.09 (s, H-6), 7.39–7.73 (m, Ar), 1.08 (s, *tert*-butyl)
46[b]	6.36 (dd, $J_{1'2'b}$ = 1.3, $J_{1'2'a}$ = 5.0)	3.59 (dd, $J_{2'a,2'b}$ = 12.4, $J_{2'a,1'}$ = 5.0)	3.16 (dd, $J_{2'a,2'b}$ = 12.4, $J_{2'b,1'}$ = 1.3)	5.65 (t, $J_{4',5'}$ = 4.4)	3.81 (dd, $J_{5'a,5'b}$ = 11.3, $J_{5'a,4'}$ = 4.4), 3.73 (dd, $J_{5'a,5'}$ = 11.1, $J_{5'b,4'}$ = 4.4)	13.0 (br s, NH), 8.34 (d, J = 7.1, Ar), 7.82 (s, H-6), 7.39–7.71 (m, Ar), 1.08 (s, *tert*-butyl)
47[b]	6.38 (pseudo, t, $J_{1'2'b}$ = 5.5, $J_{1'a,2'a}$ = 5.1)	3.50 (dd, $J_{2'a,2'b}$ = 12.8, $J_{2'a,1'}$ = 5.1)	3.08 (dd, $J_{2'a,2'b}$ = 12.8, $J_{2'b,1'}$ = 5.5)	5.28 (t, $J_{4',5'}$ = 4.4)	4.00 (d, $J_{5',4'}$ = 4.4)	12.5 (br s, NH), 8.35 (d, J = 7.4, Ar), 8.10 (s, H-6), 7.18–7.30 (m, Ar), 1.10 (s, *tert*-butyl)
48[b]	6.35 (dd, $J_{1'2'b}$ = 2.0, $J_{1'2'a}$ = 5.0)	3.45 (dd, $J_{2'a,2'b}$ = 12.8, $J_{2'a,1'}$ = 5.0)	3.10 (dd, $J_{2'a,2'b}$ = 12.8, $J_{2'b,1'}$ = 2.0)	5.62 (t, $J_{4',5'}$ = 4.7)	3.75 (d, $J_{5',4'}$ = 4.7)	12.8 (br s, NH), 8.34 (d, J = 7.3, Ar), 7.90 (s, H-6), 7.39–7.80 (m, Ar), 1.08 (s, *tert*-butyl)
49[a]	6.20 (pseudo t, $J_{1'2'b}$ = 5.9, $J_{1'2'a}$ = 5.5)	3.35 (dd, $J_{2'a,2'b}$ = 11.5, $J_{2'a,1'}$ = 5.5)	3.03 (dd, $J_{2'a,2'b}$ = 11.5, $J_{2'b,1'}$ = 5.9)	5.16 (t, $J_{4',5'}$ = 4.5)	3.73 (m)	7.65 (s, H-6), 7.39 (br s, 4-NH_a), 6.88 (br s, 4-NH_b), 5.32 (t, $J_{OH,5}$ = 5.7, OH), 1.84 (s, CH_3)
50[a]	6.34 (dd, $J_{1'2'b}$ = 3.4, $J_{1'2'a}$ = 5.5)	3.45 (dd, $J_{2'a,2'b}$ = 12.1, $J_{2'a,1'}$ = 5.5)	3.09 (dd, $J_{2'a,2'b}$ = 12.1, $J_{2'b,1'}$ = 3.4)	5.52 (t, $J_{4',5'}$ = 5.2)	3.48 (m)	7.42 (s, H-6), 7.33 (br s, 4-NH_a), 6.84 (br s, 4-NH_b), 5.19 (t, $J_{OH,5'}$ = 5.8, OH), 1.85 (s, CH_3)
51[a]	6.14 (m)	3.42 (dd, $J_{2'a,2'b}$ = 11.8, $J_{2'a,1'}$ = 5.5)	3.12 (dd, $J_{2'a,2'b}$ = 11.8, $J_{2'b,1'}$ = 4.3)	5.18 (t, $J_{4',5'}$ = 3.9)	3.74 (m)	8.20 (d, $J_{6,F}$ = 7.3, H-6), 7.82 (br s, 4-NH_a), 7.58 (br s, 4-NH_b), 5.42 (t, $J_{OH,5'}$ = 5.7, OH)
52[a]	6.28 (m)	3.40 (dd, $J_{2'a,2'b}$ = 12.1, $J_{2'a,1'}$ = 5.6)	3.15 (dd, $J_{2'a,2'b}$ = 12.1, $J_{2'b,1'}$ = 4.4)	5.60 (t, $J_{4',5'}$ = 5.3)	3.40 (m)	7.86 (d, $J_{6,F}$ = 7.0, H-6), 7.80 (br s, 4-NH_a), 7.60 (br s, 4-NH_b), 5.32 (br s, OH)
53[a]	6.15 (pseudo t, $J_{1'2'}$ = 3.6, $J_{1'2'a}$ = 5.5)	3.45 (dd, $J_{2'a,2'b}$ = 11.8, $J_{2'a,1'}$ = 5.5)	3.16 (dd, $J_{2'a,2'b}$ = 11.8, $J_{2'b,1'}$ = 3.6)	5.21 (t, $J_{4',5'}$ = 3.5)	3.75 (m)	8.32 (s, H-6), 7.91 (br s, 4-NH_a), 7.29 (br s, 4-NH_b), 5.10 (t, $J_{OH,5'}$ = 5.6, OH)
54[a]	6.30 (dd, $J_{1'2'b}$ = 2.5, $J_{1'2'a}$ = 5.7)	3.47 (dd, $J_{2'a,2'b}$ = 12.1, $J_{2'a,1'}$ = 5.7)	3.18 (dd, $J_{2'a,2'b}$ = 12.1, $J_{2'b,1'}$ = 2.5)	5.60 (t, $J_{4',5'}$ = 5.5)	3.50 (m)	7.90 (br s, 4-NH_a), 7.84 (s, H-6), 7.29 (br s, 4-NH_b), 5.10 (t, $J_{OH,5'}$ = 5.6, OH)
55[a]	6.15 (dd, $J_{1'2'b}$ = 3.7, $J_{1'2'a}$ = 5.2)	3.44 (dd, $J_{2'b,2'a}$ = 12.1, $J_{2'a,1}$ = 5.2)	3.17 (dd, $J_{2'a,2'b}$ = 12.1, $J_{2'b,1'}$ = 3.7)	5.20 (t, $J_{4',5'}$ = 3.5)	3.75 (m)	8.39 (s, H-6), 7.92 (br s, 4-NH_a), 7.07 (br s, 4-NH_b), 5.49 (t, $J_{OH,5'}$ = 5.6, OH)
56[a]	6.30 (dd, $J_{1'2'b}$ = 5.3, $J_{1'2'a}$ = 2.7)	3.51 (dd, $J_{2'b,2'a}$ = 11.1, $J_{2'a,1}$ = 2.7)	3.19 (dd, $J_{2'a,2'b}$ = 11.1, $J_{2'b,1'}$ = 5.3	5.62 (t, $J_{4',5'}$ = 4.9)	3.51 (m)	7.93 (br s, 4-NH_a), 7.89 (s, H-6), 7.09 (br s, 4-NH_a), 5.19 (t, $J_{OH,5'}$ = 5.9, OH)
57[a]	6.16 (pseudo t, $J_{1'2'b}$ = 3.8, $J_{1'2'a}$ = 5.5)	3.43 (dd, $J_{2'b,2'a}$ = 11.8, $J_{2'a,1}$ = 5.5)	3.15 (dd, $J_{2'a,2'b}$ = 11.8, $J_{2'b,1'}$ = 3.8)	5.19 (t, $J_{4',5'}$ = 3.6)	3.75 (m)	8.37 (s, H-6), 7.88 (br s, 4-NH_a), 6.88 (br s, 4-NH_b), 5.46 (br s, OH)
58[a]	6.30 (dd, $J_{1'2'b}$ = 2.8, $J_{1'2'a}$ = 5.1)	3.46 (dd, $J_{2'b,2'a}$ = 11.8, $J_{2'a,1}$ = 5.1)	3.17 (dd, $J_{2'a,2'b}$ = 11.8, $J_{2'b,1'}$ = 2.8)	5.58 (t, $J_{4',5'}$ = 5.0)	3.50 (m)	7.90 (br s, 4-NH_a), 7.88 (s, H-6), 6.70 (br s, 4-NH_b), 5.58 (t, $J_{OH,5'}$ = 5.0, OH)

[a] DMSO-d_6. [b] $CDCl_3$. [c] Parts per million downfield from TMS. [d] In order to avoid complications the furanose numbering system was used for interpretation of the NMR data.

(β-isomer) > 5-fluorocytosine (α-isomer) > 5-methylcytosine (α-isomer) > 5-methylcytosine (β-isomer) > 5-bromocytosine (β-isomer) > 5-chlorocytosine (β-isomer). It is not surprising that some α-isomers exhibited good anti-HIV activity because α-isomer of dioxolanylcytosine have been reported to be very potent compound.[12,15] Furthermore, it was interesting to note that α-isomer of 5-methylcytosine derivative was found to be more potent than β-isomer of 5-methylcytosine derivative. This may be due to the substrate specificity for deoxycytidine deaminase, which deaminates the β-isomer of the 5-methylcytosine derivative to less active β-thymine analogue. Other α-isomers in this series were found to be inactive.

Among thymine, uracil, and 5-substituted uracil derivatives, most of the compounds did not show any significant anti-HIV-1 activity except thymine (α-isomer) and uracil (β-isomer) derivatives, which exhibited mod-

Scheme VI



erate anti-HIV activity. The α-isomer of thymine analogue was also found to be more potent than the corresponding β-isomer.

In purine series, adenine derivative (β-isomer) **63** was found to be the most potent compound. The antiviral potency of other purine nucleosides is indicated as the following: 6-chloropurine (β-isomer) derivative > 6-chloropurine (α-isomer) > 2-NH_2-6-Cl-purine (β-isomer) > guanine (β-isomer) > N^6-methyladenine (α-isomer) > N^6-methyladenine (β-isomer) > 2-fluoroadenine (α and β isomers). As in 5-methylcytosine and thymine derivatives, α-isomers of N^6-methyladenine and 2-fluoroadenine were more potent than β-isomers of N^6-methyladenine and 2-fluoroadenine. This may be in part related to the greater overall cell toxicity of the compound **76** than the compound **75**, which produced a low multiplicity of the virus. These unexpected findings require further investigation, which is in progress in our laboratories. Inosine derivatives and other α-nucleosides did not show any significant activity against HIV-1. The cell toxicity was also determined in human PBM cells as well as in Vero cells. None of the synthesized nucleosides was toxic up to 100 μM in PBM cells, while 2-fluoroadenine (α-isomer) was very toxic in rapidly dividing Vero cells.

Experimental Section

Melting points were determined on a Mel-temp II, laboratory device and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL FX 90Q Fourier transform spectrometer or Bruker AM 300 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 Microlabs Inc., Norcross, GA or Galbraith Laboratories, Inc., Knoxville, TN. Dry 1,2-dichloroethane and methylene chloride were obtained by distillation immediately from CaH_2 prior to use.

1,2,3,4-Tetra-*O*-acetyl-6-*O*-tosyl-L-gulopyranoside (2). A solution of *p*-toluenesulfonyl chloride (77.1 g, 0.405 mol, 1.5 equiv) in pyridine (300 mL) was added dropwise to a suspension of L-gulose (1) (48.7 g, 0.27 mol) in dry pyridine (450 mL). The internal temperature was maintained between 18–20 °C during the addition using an ice bath. Upon completion of addition, the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was cooled and acetic anhydride (142 mL, 1.29 mol, 4.8 equiv) was added dropwise, maintaining the internal temperature between 18–20 °C. Upon completion of addition, the reaction mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was washed with 1% aqueous H_2SO_4 (400 mL × 2), H_2O, and saturated $NaHCO_3$ solution (× 2), dried ($MgSO_4$), filtered, and concentrated. The residue was dried under high vacuum to give **2** (135.84 g, 96.7%) as a foam, which was used in the next step without further purification.

2,3,4-Tri-*O*-acetyl-1-bromo-6-*O*-tosyl-α-L-gulopyranoside (3). HBr in acetic acid (45% w/v, 136 mL, 3 equiv) was added to a 1-L round-bottom flask containing **2** (132 g, 0.25 mol) in acetic acid, cooled in an ice–water bath. The flask was fitted with a $CaCl_2$ tube and stirred in the ice bath for 30 min and then at room temperature for 15 h. The solvent was removed under reduced pressure and the residue partitioned between ethyl ether and cold water. The organic layer was washed twice with cold water and twice with cold saturated $NaHCO_3$ solution, dried ($MgSO_4$), filtered, and concentrated. The residue was dried under high vacuum to give **3** (136.6 g, 99%) as a hygroscopic foam which was used without further purification.

(−)-1,6-Dideoxy-1,6-thioanhydro-L-gulose (4). Potassium *O*-ethylxanthate (134 g, 0.835 mol, 3.2 equiv) was added to a solution of **3** (136.6 g, 0.261 mol) in acetone (1 L), and the reaction mixture was refluxed for 3 h at which time TLC indicated

Table II. ^{1}H NMR Data of 1,3-Oxathiolane–Purines

compd no.	H-1′ [c,d]	H-2′	H-4′	H-5′	other signals
59[b]	6.61 (dd, $J_{1',2'b}$ = 4.0, $J_{1',2'a}$ = 8.8)	3.53 (dd, $J_{1',2'a}$ = 8.8, $J_{1',2'b}$ = 4.0)	5.42 (t, $J_{4',5'}$ = 4.6)	3.97 (d, $J_{5',4'}$ = 4.6)	8.72 (s, H-8), 8.50 (s, H-2), 7.26–7.74 (m, Ar), 1.08 (s, *tert*-butyl)
60[b]	6.75 (dd, $J_{1',2'b}$ = 2.2, $J_{1',2'a}$ = 4.8)	3.56 (dd, $J_{1',2'a}$ = 4.8, $J_{1',2'b}$ = 2.2)	5.54 (t, $J_{4',5'}$ = 4.6)	3.85 (d, $J_{5',4'}$ = 4.6)	8.75 (s, H-8), 8.50 (s, H-2), 7.27–7.75 (m, Ar), 1.08 (s, *tert*-butyl)
61[a]	6.62 (t, $J_{1',2'}$ = 4.9)	3.70 (dd, $J_{1',2'}$ = 4.9, $J_{2'a,2'b}$ = 11.8)	5.35 (t, $J_{4',5'}$ = 4.5)	3.70 (m)	8.98 (s, H-8), 8.96 (s, H-2), 5.35 (t, $J_{OH,5'}$ = 6.0, OH)
62[a]	6.86 (dd, $J_{1',2'b}$ = 2.5, $J_{1',2'a}$ = 5.2)	3.65 (dd, $J_{1',2'a}$ = 5.2, $J_{1',2'b}$ = 2.5)	5.53 (t, $J_{4',5'}$ = 4.8)	3.65 (m)	8.86 (s, H-8), 8.84 (s, H-2), 5.26 (t, $J_{OH,5'}$ = 6.0, OH)
63[a]	6.42 (t, $J_{1',2'}$ = 5.4)	3.65 (dd, $J_{1',2'}$ = 5.4, $J_{2'a,2'b}$ = 12.0)	5.28 (t, $J_{4',5'}$ = 4.7)	3.70 (m)	8.42 (s, H-8), 8.32 (s, H-2), 7.35 (br s, NH_2), 5.37 (t, $J_{OH,5'}$ = 6.0, OH)
64[a]	6.43 (t, $J_{1',2'}$ = 5.4)	3.63 (dd, $J_{1',2'}$ = 5.4, $J_{2'a,2'b}$ = 11.9)	5.28 (t, $J_{4',5'}$ = 5.1)	3.70 (m)	8.41 (s, H-8), 8.26 (s, H-2), 7.83 (br s, NH), 5.34 (t, $J_{OH,5'}$ = 5.9, OH), 2.95 (br d, NCH_3)
65[a]	6.40 (t, $J_{1',2'}$ = 5.3)	3.65 (dd, $J_{1',2'}$ = 5.3, $J_{2'a,2'b}$ = 11.9)	5.28 (t, $J_{4',5'}$ = 4.4)	3.71 (m)	13.2 (br s, NH), 8.38 (s, H-8), 8.09 (s, H-2), 5.34 (t, $J_{OH,5'}$ = 5.9, OH)
66[a]	6.69 (dd, $J_{1',2'b}$ = 3.0, $J_{1',2'a}$ = 5.6)	3.53 (dd, $J_{1',2'a}$ = 3.0, $J_{1',2'b}$ = 5.6)	5.40 (t, $J_{4',5'}$ = 5.1)	3.65 (m)	8.31 (s, H-8), 8.17 (s, H-2), 5.22 (t, $J_{OH,5'}$ = 5.9, OH)
67[a]	6.70 (dd, $J_{1',2'b}$ = 3.1, $J_{1',2'a}$ = 5.6)	3.66 (dd, $J_{1',2'a}$ = 5.6, $J_{1',2'b}$ = 3.1)	5.40 (t, $J_{4',5'}$ = 5.1)	3.57 (m)	8.31 (s, H-8), 8.26 (s, H-2), 7.80 (br s, NH), 5.22 (t, $J_{OH,5'}$ = 6.0, OH), 2.95 (br s, NCH_3)
68[a]	6.67 (pseudo t, $J_{1',2'b}$ = 3.8, $J_{1',2'a}$ = 4.4)	3.53 (dd, $J_{1',2'a}$ = 4.4, $J_{1',2'b}$ = 3.8)	5.41 (t, $J_{4',5'}$ = 4.9)	3.60 (m)	8.25 (s, H-8), 8.09 (s, H-2), 5.23 (br s, OH)
69/70[b]	6.66 (dd, $J_{1',2'b}$ = 2.5, $J_{1',2'a}$ = 5.0) 6.53 (dd, $J_{1',2'b}$ = 2.5, $J_{1',2'a}$ = 5.0)	3.65 (m), 3.43 (m)	5.55 (t, $J_{4',5'}$ = 5.0), 5.39 (t, $J_{4',5'}$ = 2.5).	3.40 (dd, $J_{5'a,4'}$ = 2.0, $J_{5'b,4'}$ = 2.5), 3.85 (dd, $J_{5'a,4'}$ = 2.5, $J_{5'b,4'}$ = 5.0)	8.42 (s, H-8), 7.34–7.70 (m, Ar), 1.08 (s, *tert*-butyl) 8.52 (s, H-8), 7.34–7.70 (m, Ar), 1.07 (s, *tert*-butyl)
71[b]	6.45 (pseudo t, $J_{1',2'b}$ = 3.9, $J_{1',2'a}$ = 5.3)	3.58 (dd, $J_{2'a,1'}$ = 5.3, $J_{2'a,2'b}$ = 11.9), 3.37 (dd, $J_{2'b,1'}$ = 3.9, $J_{2'a,2'b}$ = 11.9)	5.37 (t, $J_{4',5'}$ = 5.0)	3.98 (dd, $J_{5',4'}$ = 5.0)	8.17 (s, H-8), 7.37–7.71 (m, Ar), 6.02 (br s, NH_2), 1.08 (s, *tert*-butyl)
72[b]	6.72 (dd, $J_{1',2'b}$ = 1.7, $J_{1',2'a}$ = 5.3)	3.72 (dd, $J_{2'a,1'}$ = 5.3, $J_{2'a,2'b}$ = 12.1), 3.53 (dd, $J_{2'b,1'}$ = 1.7, $J_{2'a,2'b}$ = 12.1)	5.62 (t, $J_{4',5'}$ = 5.0)	3.94 (dd, $J_{5',4'}$ = 5.0)	8.21 (s, H-8), 7.47–7.81 (m, Ar), 6.20 (br s, NH_2), 1.17 (s, *tert*-butyl)
73[b]	6.39 (pseudo t, $J_{1',2'b}$ = 4.7, $J_{1',2'a}$ = 4.8)	3.54 (dd, $J_{2'a,1'}$ = 4.8, $J_{2'a,2'b}$ = 10.0), 3.42 (dd, $J_{2'b,1'}$ = 4.7, $J_{2'a,2'b}$ = 10.0)	5.39 (t, $J_{4',5'}$ = 5.0)	3.93 (t, $J_{5',4'}$ = 5.0)	8.11 (s, H-8), 7.26–7.68 (m, Ar), 5.10 (br s, NH_2), 1.07 (s, *tert*-butyl)
74[b]	6.56 (dd, $J_{1',2'b}$ = 1.9, $J_{1',2'a}$ = 2.1)	3.85 (dd, $J_{1',2'b}$ = 1.9, $J_{2'a,2'b}$ = 12.0), 3.44 (dd, $J_{1',2'a}$ = 2.1, $J_{2'a,2'b}$ = 12.0)	5.47 (t, $J_{4',5'}$ = 5.0)	3.85 (d, $J_{5',4'}$ = 5.0)	8.13 (s, H-8), 7.35–7.70 (m, Ar), 1.07 (s, *tert*-butyl)
75[a]	6.31 (t, $J_{1',2'}$ = 6.0)	3.58 (dd, $J_{1',2'b}$ = 6.0, $J_{2'a,2'b}$ = 12.1), 3.43 (dd, $J_{1',2'a}$ = 6.0, $J_{2'a,2'b}$ = 12.1)	5.30 (t, $J_{4',5'}$ = 6.0)	3.58 (m)	8.39 (s, H-8), 7.87 (br s, NH_2), 5.29 (t, $J_{OH,5'}$ = 6.0)
76[a]	6.56 (dd, $J_{1',2'b}$ = 2.1, $J_{1',2'a}$ = 3.2)	3.58 (dd, $J_{1',2'b}$ = 3.2, $J_{2'a,2'b}$ = 11.0), 3.49 (dd, $J_{1',2'a}$ = 2.1, $J_{2'a,2'b}$ = 11.0)	5.38 (t, $J_{4',5'}$ = 3.0)	3.58 (m)	8.27 (s, H-8), 7.87 (br s, NH_2), 5.21 (t, $J_{OH,5'}$ = 6.0)
77[b]	6.24 (dd, $J_{1',2'b}$ = 4.4, $J_{1',2'a}$ = 4.4)	3.78 (dd, $J_{1',2'b}$ = 4.4, $J_{2'a,2'b}$ = 12.0) 3.36 (dd, $J_{1',2'a}$ = 4.4, $J_{2'a,2'b}$ = 12.0)	5.37 (t, $J_{4',5'}$ = 6.0)	3.78 (m)	7.99 (s, H-8), 5.23 (br s, NH_2), 4.48 (m, OH)
78[a]	6.54 (pseudo t, $J_{1',2'b}$ = 4.8, $J_{1',2'a}$ = 4.9)	3.59 (dd, $J_{1',2'b}$ = 4.8, $J_{2'a,2'b}$ = 11.8) 3.36 (dd, $J_{1',2'a}$ = 4.9, $J_{2'a,2'b}$ = 11.8)	5.43 (t, $J_{4',5'}$ = 5.0)	3.59 (d, $J_{5',4'}$ = 5.0)	8.27 (s, H-8), 7.03 (br s, NH_2) 5.21 (t, $J_{OH,5'}$ = 5.7)
79[a]	6.13 (pseudo t, $J_{1',2'b}$ = 6.0, $J_{1',2'a}$ = 5.1)	3.56 (dd, $J_{1',2'b}$ = 6.0, $J_{2'a,2'b}$ = 12.3) 3.36 (dd, $J_{1',2'a}$ = 5.1, $J_{2'a,2'b}$ = 12.3)	5.24 (t, $J_{4',5'}$ = 5.3)	3.75 (m)	10.8 (br s, NH), 7.83 (s, H-8), 7.00 (br s, NH_2), 5.44 (t, $J_{OH,5'}$ = 6.0, OH)
80[a]	6.43 (pseudo t, $J_{1',2'b}$ = 6.0, $J_{1',2'a}$ = 5.5)	3.54 (dd, $J_{1',2'b}$ = 6.0, $J_{2'a,2'b}$ = 12.3) 3.36 (dd, $J_{1',2'a}$ = 5.5, $J_{2'a,2'b}$ = 12.3)	5.32 (t, $J_{4',5'}$ = 3.2)	3.56 (m)	10.9 (br s, NH), 7.84 (s, H-8), 6.94 (br s, NH_2), 5.25 (t, $J_{OH,5'}$ = 5.8, OH)

[a] DMSO-d_6. [b] $CDCl_3$. [c] Parts per million downfield from TMS. [d] In order to avoid complications the furanose numbering system was used for interpretation of the NMR data.

complete disappearance of starting material and the formation of the thioanhydro triacetate. The reaction mixture was cooled and the solid filtered. The filtrate was concentrated and the residue partitioned between water and chloroform. The chloroform layer was washed with water, saturated $NaHCO_3$ solution, and brine, dried, filtered, and concentrated. The residue was dissolved in methanol and treated with concentrated ammonium hydroxide solution (4:1) and allowed to stir overnight. The reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (7% MeOH in chloroform) as eluant to give 4 (33.4 g, 72%) as a crystalline solid from 2-propanol: ^{1}H NMR (DMSO-d_6) δ 2.81 (dd, J = 6.6 and 10.1 Hz,

Table III. Optical Data, Melting Points and Elemental Analyses

compound	mp, °C (solv)[a]	$[\alpha]^{25}_D$, deg	formula	anal.
4	142–144 (A)	−79.2 (c 1.06, MeOH)	$C_8H_{10}O_4S$	C, H, S
5	oil	−12.1 (c 0.75, MeOH)	$C_8H_{16}O_4S$	C, H, S
6	oil	19.06 (c 0.64, MeOH)	$C_{22}H_{30}O_4SSi$	C, H, S
8	oil	16.28 (c 0.52, MeOH)	$C_{22}H_{30}O_4SSi$	C, H, S
13	143–145 (B)	−121.6 (c 1.1, MeOH)	$C_6H_{11}N_3O_3S$	C, H, N, S
14	150–153 (B)	146.6 (c 0.55, MeOH)	$C_6H_{11}N_3O_3S$	C, H, N, S
15/16	foam	mixture	$C_{24}H_{28}N_2O_4SSi$	C, H, N, S
17/18	foam	mixture	$C_{25}H_{30}N_2O_4SSi$	C, H, N, S
19/20	foam	mixture	$C_{24}FH_{27}N_2O_4SSi\cdot0.4H_2O$	C, H, N, S
21/22	foam	mixture	$C_{24}ClH_{27}N_2O_4SSi$	C, H, N, S
23/24	foam	mixture	$C_{24}BrH_{27}N_2O_4SSi$	C, H, N, S
25/26	foam	mixture	$C_{24}H_{27}IN_2O_4SSi\cdot0.5C_6H_6$	C, H, N, S
27	130–133 (B)	−76.55 (c 1.0, MeOH)	$C_6H_{10}N_2O_4S$	C, H, N, S
28	foam	101.28 (c 0.52, MeOH)	$C_6H_{10}N_2O_4S$	C, H, N, S
29	124–128 (C)	−64.29 (c 0.50, MeOH)	$C_9H_{12}N_2O_4S$	C, H, N, S
30	foam	69.66 (c 0.45, MeOH)	$C_6H_{12}N_2O_4S$	C, H, N, S
31	187–190 (C)	−64.37 (c 0.34, MeOH)	$C_8FH_9N_2O_4S$	C, H, N, S
32	150–153 (C)	92.51 (c 0.30, MeOH)	$C_8FH_9N_2O_4S$	C, H, N, S
33	183–184 (C)	−75.55 (c 0.50, MeOH)	$C_8ClH_9N_2O_4S$	C, Cl, H, N, S
34	130–132 (C)	96.08 (c 0.50, MeOH)	$C_8ClH_9N_2O_4S\cdot0.1C_4H_{10}O$	C, Cl, H, N, S
35	174–175 (C)	−59.48 (c 0.50, MeOH)	$C_8BrH_9N_2O_4S$	C, Br, H, N, S
36	152–153 (C)	84.01 (c 0.50, MeOH)	$C_8BrH_9N_2O_4S$	C, Br, H, N, S
37	127–129 (B)	−45.14 (c 1.29, MeOH)	$C_6H_{27}IN_2O_4S\cdot0.1C_4H_{10}O$	C, H, I, N, S
38	140–142 (B)	64.77 (c 1.29, MeOH)	$C_6H_{27}IN_2O_4S$	C, H, I, N, S
39	foam	−72.11 (c 0.75, $CHCl_3$)	$C_{32}H_{35}N_3O_4SSi$	C, H, N, S
40	foam	101.02 (c 0.71, $CHCl_3$)	$C_{32}H_{35}N_3O_4SSi$	C, H, N, S
41	foam	−105.35 (c 0.60, $CHCl_3$)	$C_{31}FH_{32}N_3O_4SSi$	C, H, N, S
42	foam	98.13 (c 0.63, $CHCl_3$)	$C_{31}FH_{32}N_3O_4SSi$	C, H, N, S
43	foam	−82.87 (c 1.03, MeOH)	$C_{31}ClH_{32}N_3O_4SSi\cdot0.3C_6H_{14}$	C, Cl, H, N, S
44	foam	102.69 (c 0.69, MeOH)	$C_{31}ClH_{32}N_3O_4SSi\cdot0.3C_6H_{14}$	C, Cl, H, N, S
45	foam	−79.35 (c 0.50, $CHCl_3$)	$C_{31}BrH_{32}N_3O_4SSi\cdot0.5C_4H_{10}O$	C, H, N, S
46	foam	93.95 (c 0.60, $CHCl_3$)	$C_{31}BrH_{32}N_3O_4SSi\cdot0.4C_4H_{10}O$	C, H, N, S
47	foam	−67.08 (c 0.63, MeOH)	$C_{31}H_{32}IN_3O_4SSi\cdot0.4C_6H_{14}$	C, H, I, N, S
48	foam	83.16 (c 0.65, MeOH)	$C_{31}H_{32}IN_3O_4SSi\cdot0.4C_6H_{14}$	C, H, I, N, S
49	68–72 (B)	−99.14 (c 0.84, MeOH)	$C_9H_{13}N_3O_3S$	C, H, N, S
50	162–164 (B)	135.31 (c 0.74, MeOH)	$C_9H_{13}N_3O_3S$	C, H, N, S
51	136–140 (B)	−133.60 (c 0.23, MeOH)	$C_9FH_{10}N_3O_3S$	C, H, N, S
52	150–153 (B)	78.53 (c 0.34, MeOH)	$C_9FH_{10}N_3O_3S$	C, H, N, S
53	149–151 (B)	−100.16 (c 0.74, MeOH)	$C_9ClH_{10}N_3O_3S\cdot0.4C_4H_{10}O$	C, Cl, H, N, S
54	162–164 (B)	155.47 (c 0.65, MeOH)	$C_9ClH_{10}N_3O_3S$	C, Cl, H, N, S
55	170–173 (B)	−99.48 (c 0.66, MeOH)	$C_9BrH_{10}N_3O_3S$	C, Br, H, N, S
56	157–160 (B)	115.78 (c 0.48, MeOH)	$C_9BrH_{10}N_3O_3S$	C, Br, H, N, S
57	161–162 (B)	−67.67 (c 0.78, MeOH)	$C_9H_{10}IN_3O_3S\cdot0.2H_2O$	C, H, I, N, S
58	192–193 (B)	94.31 (c 0.78, MeOH)	$C_9H_{10}IN_3O_3S$	C, H, I, N, S
59	119–122 (D)	4.88 (c, 1.90, $CHCl_3$)	$C_{25}ClH_{27}N_4O_2SSi$	C, Cl, H, N, S
60	foam	14.0 (c 0.70, $CHCl_3$)	$C_{25}ClH_{27}N_4O_2SSi$	C, Cl, H, N, S
61	112–115 (C)	11.9 (c 0.74, MeOH)	$C_9ClH_9N_4O_2S$	C, Cl, H, N, S
62	114–116 (C)	11.0 (c 1.1, MeOH)	$C_9ClH_9N_4O_2S$	C, Cl, H, N, S
63	170–172 (C)	7.53 (c 0.51, MeOH)	$C_9H_{11}N_5O_2S$	C, H, N, S
64	112–114 (C)	4.91 (c 0.53, MeOH)	$C_{10}H_{13}N_5O_2S$	C, H, N, S
65	>170 dec (C)	6.01 (c 0.50, MeOH)	$C_9H_{10}N_4O_3S$	C, H, N, S
66	191–194 (B)	6.11 (c 0.37, MeOH)	$C_9H_{11}N_5O_2S$	C, H, N, S
67	144–148 (E)	6.99 (c 0.40, MeOH)	$C_{10}H_{13}N_5O_2S$	C, H, N, S
68	>210 dec	12.51 (c 0.23, MeOH)	$C_9H_{10}N_4O_3S$	C, H, N, S
69/70	104–107 (G)	mixture	$C_{25}ClFH_{26}N_4O_2SSi$	C, Cl, H, N, S
71	166–167 (F)	4.31 (c 0.24, $CHCl_3$)	$C_{25}FH_{28}N_5O_2SSi$	C, F, H, N, S
72	164–166 (F)	13.44 (c 0.41, $CHCl_3$)	$C_{25}FH_{28}N_5O_2SSi$	C, F, H, N, S
73	67–69 (F)	23.13 (c 0.40, $CHCl_3$)	$C_{25}ClH_{28}N_5O_2SSi$	C, Cl, H, N, S
74	59–61 (F)	−9.24 (c 0.25, $CHCl_3$)	$C_{25}ClH_{28}N_5O_2SSi$	C, Cl, H, N, S
75	214–215 (F)	25.97 (c 0.28, H_2O)	$C_9FH_{10}N_5O_2S$	C, F, H, N, S
76	262–263 (D)	9.76 (c 0.25, MeOH)	$C_9FH_{10}N_5O_2S$	C, F, H, N, S
77	69–70 (F)	−29.2 (c 0.23, MeOH)	$C_9ClH_{10}N_5O_2S$	C, Cl, H, N, S
78	102–103 (F)	12.2 (c 0.21, MeOH)	$C_9ClH_{10}N_5O_2S\cdot0.1H_2O$	C, Cl, H, N, S
79	>220 dec (B)	48.1 (c 0.30, H_2O)	$C_9H_{11}N_5O_3S$	C, H, N, S
80	>300 (D)	−29.5 (c 0.20, H_2O)	$C_9H_{11}N_5O_3S$	C, H, N, S

[a] Crystallized or silica gel column solvents: A, 2-propanol; B, ether–methanol; C, ether; D, methanol; E, hexane–methylene chloride; F, chloroform–methanol; G, hexanes–ethyl acetate.

1 H, 6-H_a), 3.12 (d, J = 10.1 Hz, 1 H, 6-H_b), 3.41–3.83 (m, 3 H, 2-H, 3-H, 4-H), 4.52 (d, J = 5.0 Hz, 1 H, OH), 4.55 (dd, J = 5.94 and 6.37 Hz, 1 H, 5-H), 4.82 (d, J = 4.6 Hz, 1 H, OH), 5.12 (d, J = 4.4 Hz, 1 H, OH), 5.35 (d, J = 2.2 Hz, 1 H, 1-H).

(−)-(1′*S*,2*R*,5*R*)-2-(Hydroxymethyl)-5-[1′,2′-(isopropylidenedioxy)ethyl]-1,3-oxathiolane (5). An aqueous solution (30 mL) of $NaIO_4$ (29.9 g, 0.142 mol) was added dropwise to a solution of 4 (18 g, 0.101 mol) in MeOH (150 mL) at 0 °C over 20 min, and the mixture was stirred at 0 °C for 10 min. $NaBH_4$ (15.3 g, 0.404 mol) was added and the mixture was further stirred at 0 °C for 10 min. After filtration, the filtrate was neutralized with 1 N HCl at 0 °C and solvents were evaporated. The residue was dried overnight under high vacuum, treated with acetone (500 mL) and p-TsOH·H_2O (9.62 g, 0.05 mol), and stirred at room temperature for 1 h. The mixture was neutralized with triethylamine, filtered, and evaporated. The residue was dissolved in ethyl acetate (350 mL), washed with H_2O and brine, dried ($MgSO_4$), and evaporated to give a crude residue, which was

Table IV. Median Effective (EC_{50}) and Inhibitory (IC_{50}) Concentration of β-L-(2R,5S)- and α-L-(2R,5R)-Oxathiolane–Pyrimidine and -Purine Nucleosides in PBM Cells and Vero Cells

compd no.	base	anomer	anti-HIV-1 in PBM cells EC_{50} (μM)[a]	cytotoxicity in PBM cells IC_{50} (μM)[a]	cytotoxicity in Vero cells IC_{50} (μM)[a]
13	cytosine	(−)-β	0.0018	>100	>100
14	cytosine	(+)-α	10.1	>100	>100
27	uracil	(−)-β	11.7	>100	>100
28	uracil	(+)-α	32.8	>100	>100
29	thymine	(−)-β	34.3	>100	>100
30	thymine	(+)-α	4.4	>100	>100
31	5-fluorouracil	(−)-β	>100	>100	>100
32	5-fluorouracil	(+)-α	>100	>100	>100
33	5-chlorouracil	(−)-β	>100	>100	>100
34	5-chlorouracil	(+)-α	>100	>100	>100
35	5-bromouracil	(−)-β	>100	>100	>100
36	5-bromouracil	(+)-α	121.0	>100	>100
37	5-iodouracil	(−)-β	92.9	>100	>100
38	5-iodouracil	(+)-α	157	>100	>100
49	5-methylcytosine	(−)-β	1.90	>100	>100
50	5-methylcytosine	(+)-α	0.45	>100	>100
51	5-fluorocytosine	(−)-β	0.0013	>100	>100
52	5-fluorocytosine	(+)-α	0.43	>100	>100
53	5-chlorocytosine	(−)-β	31.8	>100	>100
54	5-chlorocytosine	(+)-α	>100	>100	31.1
55	5-bromocytosine	(−)-β	2.51	>100	>100
56	5-bromocytosine	(+)-α	>100	>100	>100
57	5-iodocytosine	(−)-β	0.14	>100	>100
58	5-iodocytosine	(+)-α	>100	>100	>100
61	6-chloropurine	(+)-β	1.44	>100	20.2
62	6-chloropurine	(+)-α	2.75	>100	32.7
63	adenine	(+)-β	1.01	>100	>100
64	*N*-methyladenine	(+)-β	15.0	>100	>100
65	inosine	(+)-β	>100	>100	>100
66	adenine	(+)-α	78.9	>100	>100
67	*N*-methyladenine	(+)-α	13.0	>100	>100
68	inosine	(+)-α	>100	>100	>100
75	2-fluoroadenine	(+)-β	16.3	>100	>100
76	2-fluoroadenine	(+)-α	15.8	>100	<1.0
77	2-amino-6-chloropurine	(−)-β	9.8	>100	48.5
78	2-amino-6-chloropurine	(+)-α	42.1	>100	>100
79	guanine	(+)-β	10.2	>100	>100
80	guanine	(−)-α	>100	>100	>100
AZT			0.004	>100	>100
BCH-189		(±)	0.02–0.06[17]	>100	>100
(2*S*,5*R*)-BCH-189		(+)-β	0.21[20]	>100	>100

[a] Mean of triplicate values.

purified by silica gel column chromatography (hexanes–ethyl acetate = 1:1) to yield isopropylidene derivative **5** (14.68 g, 66%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.38 and 1.45 (2 × s, 6 H, isopropyl), 2.35 (br s, 1 H, O*H*), 2.83 (dd, *J* = 10.2 and 5.5 Hz, 1 H, 4-H_a), 2.98 (pseudo t, *J* = 9.2 and 10.2 Hz, 1 H, 4-H_b), 3.85–3.88 (m, 1 H, CH_2OH), 4.04 (dd, *J* = 6.4 and 1.1 Hz, 2 H, 2′-CH_2O), 4.15–4.30 (m, 2 H, 5-H and 1′-C*H*), 5.33 (dd, *J* = 3.5 and 4.0 Hz, 1 H, 2-H).

(+)-(1′*S*,2*R*,5*R*)-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5-(1′,2′-dihydroxyethyl)-1,3-oxathiolane (6). Imidazole (9.28 g, 0.136 mol) and *tert*-butyldiphenylsilyl chloride (26.6 mL, 0.102 mol) were added to a solution of **5** (15 g, 0.0682 mol) in DMF (20 mL) and the mixture was stirred at room temperature for 1 h. DMF was evaporated and the residue was dissolved in EtOAc (500 mL), washed with H_2O and brine, dried ($MgSO_4$), and evaporated to give a crude residue which, without further purification, was treated with *p*-TsOH·H_2O (1.30 g, 6.82 mmol) in MeOH (30 mL) at room temperature and stirred for 30 min. The mixture was neutralized with triethylamine, diluted with EtOAc (200 mL), and separated. The aqueous layer was extracted with EtOAc (300 mL × 2), and the combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated to give a residue which was purified by silica gel column chromatography (hexanes–ethyl acetate, 10:1) to give protected diol **6** (18 g, 63.4%) as a colorless syrup: ^{1}H NMR (DMSO-d_6) δ 1.00 (s, 9 H, *tert*-butyl), 2.82 (pseudo t, *J* = 3.8 and 7.5 Hz, 1 H, 4-H_a), 2.98 (dd, *J* = 2.1 and 7.5 Hz, 1 H, 4-H_b), 3.45 (dd, *J* = 5.5 and 11.0 Hz, 2 H, 2-CH_2OSi), 3.73 (dd, *J* = 3.5 and 9.5 Hz, 1 H, 2′-CH_aOH), 3.87–4.02 (m, 2 H, 2′-CH_bOH and 5-H), 4.07 (m, 1 H, 1′-C*H*OH), 4.58 (t, *J* = 5.27 Hz, 1 H, 2′-CH$_2$O*H*), 4.77 (d, *J* = 5.49 Hz, 1 H, 1′-CHO*H*), 5.22 (t, *J* = 5.5 Hz, 1 H, 2-H), 7.37–7.72 (m, 10 H, 2 × C_6H_5).

(+)-(2*R*,5*RS*)-5-Acetoxy-2-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-1,3-oxathiolane (8). $Pb(OAc)_4$ (9.5 g, 0.215 mol) was added to a solution of **6** (9.0 g, 0.215 mol) in EtOAc (200 mL) and the mixture was stirred at room temperature for 10 min under N_2. The mixture was filtered through a Celite pad and washed with EtOAc successively. The organic layer was washed with saturated $NaHCO_3$ (200 mL × 3), H_2O and brine, dried with $MgSO_4$, and evaporated. The crude aldehyde was dissolved in DMF (200 mL) followed by pyridinium dichromate (20.1 g, 0.538 mol), and the mixture was stirred at room temperature for 8 h. The reaction mixture was poured into H_2O (300 mL) and extracted with ether (500 mL × 3). The combined organic layers were washed with H_2O and brine, dried with $MgSO_4$, and evaporated to give crude acid **7** (8.4 g). After drying overnight under high vacuum, crude acid **7** was dissolved in anhydrous THF (30 mL) followed by $Pb(OAc)_4$ (11 g, 0.258 mol) and pyridine (1.88 mL, 0.258 mol), and the mixture was stirred at room temperature for 30 min under N_2. The reaction mixture was filtered through a Celite pad and washed with THF successively. After removal of solvent, the residue was purified by silica gel column chroma-

tography (hexanes–ethyl acetate = 5:1) to give acetate 8 (5.9 g, 66% from 6) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.06 and 1.09 (2 × s, 9 H, *tert*-butyl), 1.88 and 2.09 (s, 3 H, OCOCH_3), 3.01–3.38 (m, 2 H, 4-H), 3.66–4.25 (m, 2 H, CH_2OSi), 5.38–5.53 (m, 1 H, 2-H), 7.31–7.77 (m, 10 H, 2 × C_6H_5).

(2*R*,5*S*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*^{4}-acetylcytosine (9) and (2*R*,5*R*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-*N*^{4}-acetylcytosine (10). A stirred suspension of N^4-acetylcytosine (0.653 g, 3.47 mmol, 1.5 equiv) and $(NH_4)_2SO_4$ (10 mg, 0.075 mmol) in hexamethyldisilazane (HMDS, 25 mL) was heated to reflux under argon until a clear solution was obtained (3 h). The solution was allowed to cool to room temperature and the HMDS removed under reduced pressure using anhydrous conditions. To the solid obtained was added 1,2-dichloroethane (dried over CaH_2 and distilled; 40 mL) followed by the acetate 8 (0.965 g, 2.314 mmol) in 1,2-dichloroethane (30 mL). This suspension was cooled in an ice–water bath to 5 °C and treated with trimethylsilyl triflate (0.7 mL, 3.47 mmol, 1.5 equiv). The reaction mixture became a solution and was allowed to warm to room temperature and stir for 1.5 h at which time the reaction was judged complete by TLC. The reaction mixture was poured in ethyl acetate (300 mL) and 5% $NaHCO_3$ solution (50 mL) and stirred for 20 min. The ethyl acetate layer was separated, washed once with saturated $NaHCO_3$ solution and twice with H_2O, dried, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 1:1) to give 9 (R_f = 0.30, 0.53 g, 44.5%) and 10 (R_f = 0.35, 0.27 g, 22.2%). 9 (β isomer): UV (MeOH) λ_{max} 297 nm (pH 7), 311 nm (pH 2). 10 (α isomer): UV (MeOH) λ_{max} 297 nm (pH 7), 311 nm (pH 2).

(2*R*,5*S*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]cytosine (11). A solution of the β anomer 9 (0.15 g, 0.294 mmol) in MeOH (10 mL) was treated with NH_3–MeOH (saturated solution, 0.5 mL) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue purified by preparative TLC using MeOH–$CHCl_3$–0.5NH_4OH (5/94.5/0.5) as eluant. The material obtained from the plate gave 11 (0.10 g, 73%) as a solid on trituration with hexane and Et_2O: UV (MeOH) λ_{max} 271.5 nm (pH 7), 283.5 nm (pH 2).

(2*R*,5*R*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]cytosine (12). A solution of the α anomer 10 (0.10 g, 0.196 mmol) in MeOH (10 mL) was treated with NH_3–MeOH (saturated solution, 0.5 mL) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then concentrated and the residue crystallized from hexane–CH_2Cl_2 to give 12 (0.07 g, 76%) as a white crystalline solid: UV (MeOH) λ_{max} 271 nm (pH 7), 283 nm (pH 2).

(−)-(2*R*,5*S*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (13). To a solution of the β anomer 11 (0.15 g, 0.32 mmol) in THF (25 mL) was added 1 M tetra-*n*-butylammonium fluoride in THF (0.35 mL, 0.35 mmol, 1.1 equiv) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure and the residue purified by preparative TLC (12% MeOH–$CHCl_3$) to give 13 (0.055 g, 75%) as a white crystalline solid, which was crystallized with ether–MeOH (trace): $[\alpha]^{23}_D$ = −121.6° (*c* 1.1, MeOH) (for the *S*,*R* isomer $[\alpha]^{23}_D$ = 120.96° (*c* 1.06, MeOH)); UV (H_2O) λ_{max} 270.1 nm (ϵ 9300) (pH 7), 270.0 (ϵ 12150) (pH 2), 270.0 (ϵ 9950) (pH 11).

(+)-(2*R*,5*R*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]-cytosine (14). To a solution of the α anomer 12 (0.10 g, 0.213 mmol) in THF (20 mL) was added 1 M tetra-*n*-butylammonium fluoride in THF (0.24 mL, 0.24 mmol, 1.1 equiv) and the reaction mixture was stirred at room temperature 30 min. The reaction mixture was concentrated under reduced pressure and the residue purified by preparative TLC using 12% MeOH–$CHCl_3$ as development solvent to give 14 (0.036 g, 76%) as a white solid: $[\alpha]^{23}_D$ = 146.6° (*c* 0.55, MeOH) (for *S*,*S* isomer $[\alpha]^{23}_D$ = −143.18° (*c* 0.62, MeOH)); UV (H_2O) λ_{max} 270.1 nm (ϵ 9850) (pH 7), 270.0 (ϵ 13750) (pH 2), 270.0 (ϵ 9970) (pH 11).

(2*R*,5*SR*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]uracil (15 and 16). A mixture of uracil (0.323 g, 2.88 mmol) in hexamethyldisilazane (15 mL) and ammonium sulfate (catalytic amount) was refluxed for 3 h. The resulting clear solution was concentrated in vacuo under anhydrous condition to yield silylated uracil as colorless oil. TMSOTf (0.56 mL, 2.88 mmol) was added at 5 °C to a mixture of silylated uracil and 8 (0.60 g, 1.44 mmol) in dry CH_2Cl_2 (25 mL) and the reaction mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was quenched by saturated $NaHCO_3$ (20 mL) and stirred for an additional 30 min at room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL), water (20 mL), and dried (anhydrous $MgSO_4$). After filtration, the filtrate was concentrated and the residue was purified by silica gel column chromatography (chloroform–methanol, 20:1) to yield an inseparable mixture of anomers 15 and 16 (R_f = 0.62, chloroform–methanol, 20:1, 0.51 g, 75.6%) as a white foam: UV (MeOH) λ_{max} 261.0 nm.

(2*R*,5*SR*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]thymine (17 and 18). Silylated thymine, which was prepared from thymine (0.364 g, 2.88 mmol) and HMDS (20 mL), was treated with 8 (0.60 g, 1.44 mmol) in dry CH_2Cl_2 (15 mL) and TMSOTf (0.56 mL, 2.88 mmol) at room temperature for 2 h under nitrogen. After workup similar to that of 15 and 16, the purification by silica gel column chromatography (chloroform–methanol, 20:1) gave an inseparable anomeric mixture of 17 and 18 (R_f = 0.65, chloroform–methanol, 20:1, 0.50 g, 71.9%) as a white foam: UV (MeOH) λ_{max} 265.0 nm.

(2*R*,5*SR*)-5-Fluoro-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-1,3-oxathiolan-5-yl]uracil (19 and 20). A mixture of silylated 5-fluorouracil, prepared from 0.44 g (3.05 mmol) of 5-fluorouracil and 20 mL of HMDS, 8 (0.634 g, 1.52 mmol), and TMSOTf (0.589 mL, 3.05 mmol) in dry CH_2Cl_2 (20 mL) was stirred for 2 h at room temperature under argon. After workup similar to that of 15 and 16, purification by silica gel chromatography (chloroform–methanol, 20:1) gave an inseparable mixture of anomers 19 and 20 (R_f = 0.64, chloroform–methanol, 20:1, 0.66 g, 92.7%) as a white foam: UV (MeOH) λ_{max} 266.0 nm.

(2*R*,5*SR*)-5-Chloro-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]-methyl]-1,3-oxathiolan-5-yl]uracil (21 and 22). A mixture of silylated 5-chlorouracil, prepared from 0.28 g (1.92 mmol) of 5-chlorouracil and 20 mL of HMDS, 8 (0.40 g, 0.96 mmol), and TMSOTf (0.37 mL, 1.95 mmol) in dry 1,2-$ClCH_2CH_2Cl$ (20 mL) was stirred at room temperature for 2 h under nitrogen. After workup similar to that of 15 and 16, purification by silica gel column chromatography (chloroform–methanol, 20:1) gave an inseparable mixture of anomers 21 and 22 (R_f = 0.65, chloroform–methanol, 20:1, 0.28 g, 58.4%) as a white foam: UV (MeOH) λ_{max} 272.0 nm.

(2*R*,5*SR*)-5-Bromo-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-1,3-oxathiolan-5-yl]uracil (23 and 24). A mixture of silylated 5-bromouracil, prepared from 0.37 g (1.97 mmol) of 5-bromouracil and 20 mL of HMDS, 8 (0.41 g, 0.98 mmol), and TMSOTf (0.38 mL, 2.0 mmol) in dry 1,2-$ClCH_2CH_2Cl$ (20 mL) was stirred for 2 h at room temperature. After workup similar to that of 15 and 16, purification by silica gel column chromatography (chloroform–methanol, 20:1) gave an inseparable mixture of anomers 23 and 24 (R_f = 0.64, chloroform–methanol, 20:1, 0.287 g, 53.3%) as a white foam: UV (MeOH) λ_{max} 278.0 nm.

(2*R*,5*SR*)-5-Iodo-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]uracil (25 and 26). A mixture of silylated 5-iodouracil, prepared from 0.343 g (1.44 mmol) of 5-iodouracil and 20 mL of HMDS, 8 (0.40 g, 0.96 mmol), and TMSOTf (0.28 mL, 1.44 mmol) in dry 1,2-$ClCH_2CH_2Cl$ (20 mL) was stirred for 2 h at room temperature. After workup similar to that of 15 and 16, purification by silica gel column chromatography (chloroform–methanol, 20:1) gave an inseparable mixture of anomers 25 and 26 (R_f = 0.67, chloroform–methanol, 20:1, 0.50 g, 87.7%) as a white foam: UV (MeOH) λ_{max} 283.0 nm.

(−)-(2*R*,5*S*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]-uracil (27) and (+)-(2*R*,5*R*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (28). An α,β-mixture of 15 and 16 (0.63 g, 1.35 mmol) in THF (10 mL) was treated with 1.0 M tetra-*n*-butylammonium fluoride in THF (1.35 mL, 1.35 mmol) for 1 h at room temperature. The solvent was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (chloroform–methanol, 10:1) to yield 27 (0.13 g, 41.9% R_f = 0.55) as a white solid and 28 (0.081 g, 26.1%, R_f = 0.51) as a white foam. 27: UV (H_2O) λ_{max} 261.3 nm

(ε 14020) (pH 7), 261.3 (ε 13530) (pH 2), 260.8 (ε 10690) (pH 11). **28**: UV (H_2O) λ_{max} 262.3 nm (ε 14180) (pH 7), 262.3 (ε 14080) (pH 2), 261.3 (ε 11380) (pH 11).

(−)-(2*R*,5*S*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]thymine (29) and (+)-(2*R*,5*R*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]thymine (30). An α,β-mixture of **17** and **18** (0.46 g, 0.95 mmol) in THF (20 mL) was treated with 1.0 M tetra-*n*-butylammonium fluoride in THF (0.95 mL, 0.95 mmol) for 1 h at room temperature. The solvent was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (chloroform–methanol, 10:1) to yield **29** (0.10 g, 45.0% R_f = 0.58) as a white solid and **30** (0.09 g, 38.6%, R_f = 0.53) as a white foam. **29**: UV (H_2O) λ_{max} 266.8 nm (ε 14520) (pH 7), 266.8 (ε 14290) (pH 2), 265.8 (ε 11800) (pH 11). **30**: UV (H_2O) λ_{max} 267.3 nm (ε 11480) (pH 7), 267.3 (ε 11470) (pH 2), 266.8 (ε 8980) (pH 11).

(−)-(2*R*,5*S*)-5-Fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (31) and (+)-(2*R*,5*R*)-5-Fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (32). An α,β-mixture of **19** and **20** (0.62 g, 1.33 mmol) in THF (20 mL) was treated with 1.0 M tetra-*n*-butylammonium fluoride in THF (1.33 mL, 1.33 mmol) for 1 h at room temperature. The solvent was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (chloroform–methanol, 10:1) to yield **31** (0.15 g, 46.9%, R_f = 0.60) as a white solid and **32** (0.10 g, 30.4%, R_f = 0.57) as a white solid. **31**: UV (H_2O) λ_{max} 268.5 nm (ε 9980) (pH 7), 268.8 (ε 10970) (pH 2), 267.8 (ε 10860) (pH 11). **32**: UV (H_2O) λ_{max} 268.8 nm (ε 12620) (pH 7), 269.3 (ε 13090) (pH 2), 268.3 (ε 10310) (pH 11).

(−)-(2*R*,5*S*)-5-Chloro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (33) and (+)-(2*R*,5*R*)-5-Chloro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (34). An α,β-mixture of **21** and **22** (0.278 g, 0.552 mmol) in THF (20 mL) was treated with 1.0 M tetra-*n*-butylammonium fluoride in THF (0.552 mL, 0.552 mmol) for 1 h at room temperature. The solvent was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (chloroform–methanol, 10:1) to yield **33** (0.06 g, 41%, R_f = 0.35) as a white solid and **34** (0.07 g, 47.9%, R_f = 0.31) as a white solid. **33**: UV (H_2O) λ_{max} 276.0 nm (ε 9870) (pH 7), 276.0 (ε 9390) (pH 2); 274.0 (ε 6980) (pH 11). **34**: UV (H_2O) λ_{max} 277.0 nm (ε 9170) (pH 7), 277.0 (ε 9830) (pH 2), 274.0 (ε 6980) (pH 11).

(−)-(2*R*,5*S*)-5-Bromo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (35) and (+)-(2*R*,5*R*)-5-Bromo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (36). An α,β-mixture of **23** and **24** (0.287 g, 0.524 mmol) in THF (20 mL) was treated with 1.0 M tetra-*n*-butylammonium fluoride in THF (0.287 mL, 0.524 mmol) for 1 h at room temperature. The solvent was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (chloroform–methanol, 10:1) to yield **35** (0.055 g, 33.9% R_f = 0.37) as a white solid and **36** (0.063 g, 38.8%, R_f = 0.32) as a white solid. **35**: UV (H_2O) λ_{max} 279.0 nm (ε 8900) (pH 7), 279.0 (ε 8500), (pH 2), 276.0 (ε 6710) (pH 11). **36**: UV (H_2O) λ_{max} 279.0 nm (ε 8590) (pH 7), 279.0 (ε 8570) (pH 2), 276.0 (ε 6970) (pH 11).

(−)-(2*R*,5*S*)-5-Iodo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (37) and (+)-(2*R*,5*R*)-5-Iodo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (38). An α,β-mixture of **25** and **26** (0.45 g, 0.756 mmol) in THF (20 mL) was treated with 1.0 M tetra-*n*-butylammonium fluoride in THF (0.756 mL, 0.756 mmol) for 1 h at room temperature. The solvent was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (chloroform–methanol, 10:1) to yield **37** (0.086 g, 32.0%, R_f = 0.46) as a white solid and **38** (0.074 g, 27.5%, R_f = 0.42) as a white solid. **37**: UV (H_2O) λ_{max} 287.5 nm (ε 8320) (pH 7) 288.0 (ε 8200) (pH 2), 278.5 (ε 6700) (pH 11). **38**: UV (H_2O) λ_{max} 287.5 nm (ε 12020) (pH 7), 288.0 (ε 11690) (pH 2), 279.0 (ε 8930) (pH 11).

(−)-(2*R*,5*S*)-5-Methyl-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-N^4-benzoylcytosine (39) and (+)-(2*R*,5*R*)-5-Methyl-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-N^4-benzoylcytosine (40). Silylated N^4-benzoyl-5-methylcytosine, prepared from N^4-benzoyl-5-methylcytosine (0.63 g, 2.96 mmol) and HMDS (30 mL), was treated with **8** (0.615 g, 1.48 mmol) in dry 1,2-$ClCH_2CH_2Cl$ (15 mL) and TMSOTf (0.56 mL, 2.88 mmol) at room temperature for 2 h under nitrogen. $CHCl_3$ (10 mL) and saturated $NaHCO_3$ (20 mL) were added and the mixture stirred for an additional 30 min. The reaction mixture was filtered through a Celite pad and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL × 4) and combined organic layers were washed with saturated $NaHCO_3$ (20 mL × 2) and dried (anhydrous $MgSO_4$). The solvents were evaporated under reduced pressure to give a yellow residue, which was purified by silica gel column chromatography (hexanes–ethyl acetate, 5:1) to yield **39** (R_f = 0.25, hexanes–ethyl acetate, 5:1, 0.31 g, 34.9%) as a white foam and **40** (R_f = 0.29, hexanes–ethyl acetate, 5:1, 0.25 g, 28.1%) as a white foam. **39**: UV ($CHCl_3$) λ_{max} 330.0 nm. **40**: UV ($CHCl_3$) λ_{max} 330.2 nm.

(−)-(2*R*,5*S*)-5-Fluoro-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-N^4-benzoylcytosine (41) and (+)-(2*R*,5*R*)-5-Fluoro-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-N^4-benzoylcytosine (42). A mixture of silylated N^4-benzoyl-5-fluorocytosine, prepared from 0.44 g (3.05 mmol) of N^4-benzoyl-5-fluorocytosine and 20 mL of HMDS, **8** (0.634 g, 1.52 mmol), and TMSOTf (0.589 mL, 3.05 mmol) in dry 1,2-$ClCH_2CH_2Cl$ (20 mL) was stirred for 2 h at room temperature under argon. After similar workup as for **39** and **40**, purification by silica gel column chromatography (hexanes–ethyl acetate, 3:1) gave **41** (R_f = 0.13, hexanes–ethyl acetate, 4:1, 0.35 g, 42.4%) as a white foam and **42** (R_f = 0.20, hexanes–ethyl acetate, 4:1, 0.26 g, 31.5%) as a white foam. **41**: UV ($CHCl_3$) λ_{max} 330.7 nm. **42**: UV ($CHCl_3$) λ_{max} 331.2 nm.

(−)-(2*R*,5*S*)-5-Chloro-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-N^4-benzoylcytosine (43) and (+)-(2*R*,5*R*)-5-Chloro-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-N^4-benzoylcytosine (44). A mixture of silylated N^4-benzoyl-5-chlorocytosine, prepared from 0.56 g (2.24 mmol) of N^4-benzoyl-5-chlorocytosine and 30 mL of HMDS, **8** (0.62 g, 1.49 mmol), and TMSOTf (0.43 mL, 2.24 mmol) in dry 1,2-$ClCH_2CH_2Cl$ (20 mL) was stirred for 2 h under nitrogen. After similar workup as for **39** and **40**, purification by silica gel column chromatography (hexanes–ethyl acetate, 4:1) gave **43** (R_f = 0.21, hexanes–ethyl acetate, 4:1, 0.27 g, 30.0%) as a white foam and **44** (R_f = 0.28, hexanes–ethyl acetate, 4:1, 0.40 g, 44.4%) as a white foam. **43**: UV (2-propanol) λ_{max} 333.2 nm. **44**: UV (2-propanol) λ_{max} 333.1 nm.

(−)-(2*R*,5*S*)-5-Bromo-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-N^4-benzoylcytosine (45) and (+)-(2*R*,5*R*)-5-Bromo-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-N^4-benzoylcytosine (46). A mixture of silylated N^4-benzoyl-5-bromocytosine, prepared from 0.68 g (2.31 mmol) of N^4-benzoyl-5-bromocytosine and 20 mL of HMDS, **8** (0.64 g, 1.54 mmol), and TMSOTf (0.446 mL, 2.31 mmol) in dry 1,2-$ClCH_2CH_2Cl$ (20 mL) was stirred for 1.5 h at room temperature. After workup similar to that of **39** and **40**, purification by silica gel column chromatography (hexanes–ethyl acetate, 3:1) gave **45** (R_f = 0.44, hexanes–ethyl acetate, 3:1, 0.45 g, 45.0%) as a white foam and **46** (R_f = 0.50, hexanes–ethyl acetate, 3:1, 0.35 g, 35.0%) as a white foam. **45**: UV ($CHCl_3$) λ_{max} 334.7 nm. **46**: UV ($CHCl_3$) λ_{max} 333.7 nm.

(−)-(2*R*,5*S*)-5-Iodo-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-N^4-benzoylcytosine (47) and (+)-(2*R*,5*R*)-5-Iodo-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]-N^4-benzoylcytosine (48). A mixture of silylated N^4-benzoyl-5-iodocytosine, prepared from 0.785 g (2.31 mmol) of N^4-benzoyl-5-iodocytosine and 20 mL of HMDS, **8** (0.64 g, 1.54 mmol), and TMSOTf (0.60 mL, 2.31 mmol) in dry 1,2-$ClCH_2CH_2Cl$ (20 mL) was stirred for 1 h at room temperature. After similar workup to **39** and **40**, purification by silica gel column chromatography (hexanes–ethyl acetate, 4:1) gave **47** (R_f = 0.31, hexanes–ethyl acetate, 4:1, 0.39 g, 36.4%) as a white foam and **48** (R_f = 0.38, hexanes–ethyl acetate, 4:1, 0.26 g, 24.3%) as a white foam. **47**: UV ($CHCl_3$) λ_{max} 339.7 nm. **48**: UV ($CHCl_3$) λ_{max} 340.1 nm.

(−)-(2*R*,5*S*)-5-Methyl-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (49). To a solution of **39** (0.45 g, 0.75 mmol) in THF (20 mL) was added 1.0 M tetra-*n*-butylammonium fluoride in THF (0.75 mL, 0.75 mmol) and the mixture was stirred at room temperature for 4 h. The solvent was evaporated to dryness under reduced pressure to give a yellow residue which, without purification, was treated with saturated methanolic ammonia

and stirred at room temperature overnight. The solvent was evaporated and the residue was purified by silica gel column chromatography (chloroform–methanol, 10:1) to yield **49** (R_f = 0.31, 0.17 g, 94.0%) as a white solid, which was triturated with ether and methanol: UV (H_2O) λ_{max} 277.0 nm (ϵ 9690) (pH 7), 286.8 (ϵ 13370) (pH 2), 276.8 (ϵ 9360) (pH 11).

(+)-(2*R*,5*R*)-5-Methyl-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (50). To a solution of **40** (0.40 g, 0.615 mmol) in THF (20 mL) was added 1.0 M tetra-*n*-butylammonium fluoride in THF (0.62 mL, 0.62 mmol), and the mixture was stirred at room temperature for 3 h. The solvent was evaporated to dryness under reduced pressure to give a yellow residue which, without purification, was treated with saturated methanolic ammonia and stirred at room temperature overnight. The solvent was evaporated and the residue was purified by silica gel column chromatography (chloroform–methanol, 10:1) to yield **50** (R_f = 0.31, 0.14 g, 84.6%) as a white solid, which was triturated with ether and methanol: UV (H_2O) λ_{max} 277.5 nm (ϵ 9690) (pH 7), 286.8 (ϵ 13620) (pH 2), 276.8 (ϵ 9470) (pH 11).

(−)-(2*R*,5*S*)-5-Fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (51). Compound **41** (0.4 g, 0.698 mmol) was treated according to the procedure used in the preparation of compound **49** to give **51** (R_f = 0.29, 0.135 g, 78.5%) as a white solid, which was triturated with ether and methanol: UV (H_2O) λ_{max} 280.0 nm (ϵ 11090) (pH 7), 287.8 (ϵ 14210) (pH 2), 279.8 (ϵ 11810) (pH 11).

(+)-(2*R*,5*R*)-5-Fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (52). Compound **42** (0.4 g, 0.698 mmol) was treated according to the procedure used in the preparation of compound **49** to give **52** (R_f = 0.29, 0.135 g, 78.5%) as a white solid, which was triturated with ether and methanol: UV (H_2O) λ_{max} 280.5 nm (ϵ 12060) (pH 7), 287.8 (ϵ 14450) (pH 2), 279.8 (ϵ 11450) (pH 11).

(−)-(2*R*,5*S*)-5-Chloro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (53). Compound **43** (0.209 g, 0.34 mmol) was treated according to the procedure used in the preparation of compound **49** to give **53** (R_f = 0.30, 0.073 g, 80.0%) as a white solid, which was triturated with ether and methanol: UV (H_2O) λ_{max} 285.5 nm (ϵ 12190) (pH 7), 295.5 (ϵ 15520) (pH 2), 285.3 (ϵ 12040) (pH 11).

(+)-(2*R*,5*R*)-5-Chloro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (54). Compound **44** (0.13 g, 0.21 mmol) was treated according to the procedure used in the preparation of compound **49** to give **54** (R_f = 0.30, 0.045 g, 80.0%) as a white solid, which was triturated with ether and methanol: UV (H_2O) λ_{max} 286.0 nm (ϵ 10900) (pH 7), 295.5 (ϵ 13550) (pH 2), 285.3 (ϵ 10960) (pH 11).

(−)-(2*R*,5*R*)-5-Bromo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (55). Compound **45** (0.315 g, 0.486 mmol) was treated according to the procedure used in the preparation of compound **49** to give **55** (R_f = 0.32, 0.115 g, 81.0%) as a white solid, which was triturated with ether and methanol: UV (H_2O) λ_{max} 287.5 nm (ϵ 7690) (pH 7), 298.0 (ϵ 12400) (pH 2), 287.0 (ϵ 9430) (pH 11).

(+)-(2*R*,5*R*)-5-Bromo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (56). Compound **46** (0.320 g, 0.493 mmol) was treated according to the procedure used in the preparation of compound **49** to give **56** (R_f = 0.32, 0.125 g, 86.8%) as a white solid, which was triturated with ether and methanol: UV (H_2O) λ_{max} 287.5 nm (ϵ 6160) (pH 7), 298.0 (ϵ 10340) (pH 2), 287.5 (ϵ 7620) (pH 11).

(−)-(2*R*,5*S*)-5-Iodo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (57). Compound **47** (0.40 g, 0.57 mmol) was treated according to the procedure used in the preparation of compound **49** to give **57** (R_f = 0.33, 0.13 g, 64.0%) as a white solid, which was triturated with ether and methanol: UV (H_2O) λ_{max} 293.0 nm (ϵ 7890) (pH 7), 308.0 (ϵ 10950) (pH 2), 293.5 (ϵ 8140) (pH 11).

(+)-(2*R*,5*R*)-5-Iodo-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (58). Compound **48** (0.20 g, 0.29 mmol) was treated according to the procedure used in the preparation of compound **49** to give **58** (R_f = 0.33, 0.073 g, 71.6%) as a white solid, which was triturated with ether and methanol: UV (H_2O) λ_{max} 293.5 nm (ϵ 5530) (pH 7), 308.0 (ϵ 8120) (pH 2), 293.5 (ϵ 6050) (pH 11).

(+)-(2*R*,5*S*)-6-Chloro-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (59) and (+)-(2*R*,5*R*)-6-Chloro-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (60). A mixture of 6-chloropurine (1.48 g, 9.61 mmol), hexamethyldisilazane (50 mL) and ammonium sulfate (catalytic amount) was refluxed for 2 h under N_2. The clear solution obtained was concentrated in vacuo and the residue was dissolved in dry CH_2Cl_2 (20 mL). Trimethylsilyl triflate (1.86 mL, 9.612 mmol) and a solution of **8** (2.0 g, 4.81 mmol) in dry CH_2Cl_2 (30 mL) were added at room temperature. After stirring the reaction mixture for 30 min at room temperature, it was refluxed for 14 h under N_2. During reflux, initially formed isomers were converted to N-9 condensed product. The reaction solution was then poured into an ice-cold mixture of CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ solution (20 mL), stirred for 30 min, and filtered through a Celite pad. The organic layer was washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL) and dried ($MgSO_4$). The solvents were removed under reduced pressure, and the residue was separated by silica gel column chromatography to give **59** (R_f = 0.64, hexanes–ethyl acetate, 1:1, 0.86 g, 35%) as a white solid and **60** (R_f = 0.74, 0.74 g, 30.1%) as a white foam. **59**: UV (MeOH) λ_{max} 265.0 nm. **60**: UV (MeOH) λ_{max} 265.0 nm.

(+)-(2*R*,5*S*)-6-Chloro-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]purine (61). A solution of **59** (0.6 g, 1.17 mmol) in THF (20 mL) was treated with 1 M *n*-Bu_4NF–THF (1.3 mL, 1.3 mmol). After evaporation of the solvent, the residue was chromatographed on silica gel (230–400 mesh) using chloroform–methanol (20:1) as the eluent to give pure **61** (0.24 g, 75.0%) as a white solid, which was triturated with ether: UV (H_2O) λ_{max} 265.0 nm (ϵ 11430) (pH 7), 264.5 (ϵ 11430) (pH 2), 264.3 (ϵ 11800) (pH 11).

(+)-(2*R*,5*R*)-6-Chloro-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]purine (62). A solution of **60** (0.6 g, 1.17 mmol) in THF (20 mL) was desilylated with 1 M *n*-Bu_4NF–THF (1.5 mL, 1.5 mmol). After evaporation of the solvent, the residue was chromatographed on silica gel (230–400 mesh) using chloroform–methanol (20:1) as the eluent to give pure **62** (R_f = 0.23 g, 71.9%) as a white solid: UV (H_2O) λ_{max} 264.5 nm (ϵ 11220) (pH 7), 264.5 (ϵ 11750) (pH 2), 264.3 (ϵ 10530) (pH 11).

(+)-(2*R*,5*S*)-9-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]-adenine (63). A solution of **61** (0.08 g, 0.293 mmol) and NH_3–MeOH (20 mL) was heated at 90 °C in a steel bomb for 24 h. After cooling, the solvent was removed under vacuum and the residual syrup was purified by column chromatography (silica gel 230–400 mesh) using chloroform–methanol (10:1) as the eluent to give **63** (R_f = 0.2, 0.051 g, 68.6%) as a white solid: UV (H_2O) λ_{max} 259.0 nm (ϵ 17730) (pH 7), 258.0 (ϵ 17380) (pH 2), 259.4 (ϵ 18380) (pH 11).

(+)-(2*R*,5*S*)-N^6-Methyl-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]adenine (64). A solution of **61** (0.07 g, 0.256 mmol) and methylamine (40 wt% solution in H_2O, 10 mL) in MeOH (10 mL) was heated at 90 °C in a steel bomb for 15 h. After cooling, the solvents were removed under vacuum. The residual syrup was purified by column chromatography (silica gel 230–400 mesh) using chloroform–methanol (10:1) as the eluent to give **64** (R_f = 0.21, 0.054 g, 78.8%) as a white solid: UV (H_2O) λ_{max} 265.8 nm (ϵ 19990) (pH 7), 262.3 (ϵ 22050) (pH 2), 265.3 (ϵ 20110) (pH 11).

(+)-(2*R*,5*S*)-9-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]-hypoxanthine (65). A mixture of **61** (0.1 g, 0.367 mmol), 2-mercaptoethanol (0.1 mL, 1.47 mmol), and NaOMe (0.079 g, 1.47 mmol) in MeOH (20 mL) was refluxed for 4 h under N_2. The mixture was cooled, neutralized with glacial AcOH, and evaporated to dryness under vacuum. The residue was purified by silica gel column chromatography (chloroform–methanol, 10:1) to give **65** (R_f = 0.15, 0.06 g, 64.5%) as a white leaflet, which was triturated with ether: UV (H_2O) λ_{max} 248.5 nm (ϵ 11390) (pH 7), 249.0 (ϵ 11440) (pH 2), 252.9 (ϵ 12290) (pH 11).

(+)-(2*R*,5*S*)-9-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]-adenine (66). A solution of **62** (0.07 g, 0.257 mmol) and NH_3–MeOH (10 mL) was heated at 90 °C in a steel bomb for 20 h. After cooling, the solvent was removed under vacuum and the residual syrup was purified by column chromatography (silica gel 230–400 mesh) using chloroform–methanol (10:1) as the eluent to give **66** (R_f = 0.2, 0.045 g, 69.2%) as a white solid, which was triturated with ether–methanol: UV (H_2O) λ_{max} 258.9 nm (ϵ 20500) (pH 7), 257.5 (ϵ 20780) (pH 2), 259.4 (ϵ 21090) (pH 11).

(+)-(2*R*,5*S*)-N^6-Methyl-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]adenine (67). A solution of **62** (0.07 g, 0.257 mmol)

and methylamine (40 wt% solution in H_2O, 10 mL) in MeOH (10 mL) was heated at 90 °C in a steel bomb for 15 h. After cooling, the solvents were removed under vacuum. The residual syrup was purified by column chromatography (silica gel 230–400 mesh) using chloroform–methanol (10:1) as the eluent to give **67** (R_f = 0.20, 0.042 g, 61.2%) as a white solid, which was triturated with hexanes–methylene chloride: UV (H_2O) λ_{max} 265.8 nm (ϵ 18840) (pH 7), 262.8 (ϵ 19470) (pH 2), 265.8 (ϵ 19500) (pH 11).

(+)-(2*R*,5*S*)-9-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]hypoxanthine (68). A mixture of **62** (0.07 g, 0.257 mmol), 2-mercaptoethanol (0.07 mL, 1.03 mmol), and NaOMe (0.066 g, 1.03 mmol) in MeOH (10 mL) was refluxed for 3 h under N_2. The mixture was cooled, neutralized with glacial AcOH, and evaporated to dryness under vacuum. The residue was purified by silica gel column chromatography (chloroform–methanol, 10:1) to give **68** (R_f = 0.14, 0.040 g, 61.5%) as a white solid: UV (H_2O) λ_{max} 248.9 nm (ϵ 15620) (pH 7), 249.0 (ϵ 15630) (pH 2), 253.4 (ϵ 17030) (pH 11).

(2*R*,5*SR*)-2-Fluoro-6-chloro-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (69 and 70). A mixture of 2-fluoro-6-chloropurine (0.49 g, 2.84 mmol) in hexamethyldisilazane (20 mL) and ammonium sulfate (catalytic amount) was refluxed for 1 h. The resulting solution was concentrated under anhydrous conditions to yield silylated 2-fluoro-6-chloropurine as a white solid. TMSOTf (0.39 mL, 2.01 mmol) was added to a cooled (−20 °C) and stirred solution of silylated 2-fluoro-6-chloropurine and **8** (0.97 g, 2.33 mmol) in dry methylene chloride (30 mL). The reaction mixture was warmed to room temperature and stirred for 16 h, during which time all the initially formed isomers were converted to N-9 isomers. The reaction mixture was quenched with saturated $NaHCO_3$ solution (5 mL) and stirred for additional 20 min at room temperature. The solvent was evaporated to dryness under reduced pressure and the residue was dissolved in EtOAc (200 mL), washed with water and brine, dried (anhydrous Na_2SO_4), filtered, and evaporated to give a solid residue, which was purified by silica gel column chromatography (20% EtOAc in hexanes) to afford a mixture of β-anomer **69** and α-anomer **70** (0.46:0.53; β/α) as a white crystalline solid (0.66 g, 60.0%), which was used in the next step without separation: UV (MeOH) λ_{max} 269.0 nm.

(+)-(2*R*,5*S*)-2-Fluoro-6-amino-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (71), (+)-(2*R*,5*R*)-2-Fluoro-6-amino-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (72), (+)-(2*R*,5*S*)-2-Amino-6-chloro-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (73), and (−)-(2*R*,5*R*)-2-Amino-6-chloro-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl]purine (74). Dry ammonia gas was bubbled into a stirred solution of **69** and **70** (0.741 g, 1.40 mmol) in DME (40 mL) at room temperature overnight. The salts were removed by filtration and the filtrate evaporated under reduced pressure. The residue was purified by preparative TLC (30% hexanes in diethyl ether) to give four compounds. **71** (R_f = 0.22, 0.053 g, 7.43%) as colorless needles: UV (MeOH) λ_{max} 261.0, 268.0 (sh) nm. **72** (R_f = 0.29, 0.090 g, 12.6%) as a micro-crystalline solid: UV (MeOH) λ_{max} 261.0, 269.0 (sh) nm. **73** (R_f = 0.64, 0.172 g, 23.4%) as a white crystalline solid: UV (MeOH) λ_{max} 310.0 nm. **74** (R_f = 0.62, 0.116 g, 15.8%) as a white crystalline solid: UV (MeOH) λ_{max} 309.5 nm.

(+)-(2*R*,5*S*)-2-Fluoro-6-amino-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]purine (75). A solution of **71** (0.05 g, 0.1 mmol) in THF (5 mL) was treated with 1 M *n*-Bu_4NF–THF (0.152 mL, 0.152 mmol) to give **75** (0.023 g, 85%) as a white crystalline solid, which was recrystallized from MeOH: UV (H_2O) λ_{max} 261.0 (ϵ 13840), 269.0 (sh) nm (ϵ 10820) (pH 7), 261.5 (ϵ 14380), 269.5 (sh) (ϵ 11370) (pH 2), 260.8 (ϵ 14110), 268.5 (sh) (ϵ 12470) (pH 11).

(+)-(2*R*,5*R*)-2-Fluoro-6-amino-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]purine (76). A solution of **72** (0.07 g, 0.14 mmol) in dry THF (5 mL) was treated with 1 M *n*-Bu_4NF–THF (0.219 mL, 0.219 mmol) to give **76** (0.033 g, 89.0%) as a white crystalline solid, which was recrystallized from MeOH: UV (H_2O) λ_{max} 261.0 (ϵ 15750), 269.0 (sh) nm (ϵ 12470) (pH 7), 261.5 (ϵ 12330), 268.5 (sh) (ϵ 10000) (pH 2), 261.0 (ϵ 14380), 268.5 (sh) (ϵ 11500) (pH 11).

(−)-(2*R*,5*S*)-2-Amino-6-chloro-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]purine (77). A solution of **73** (0.152 g, 0.268 mmol) in THF (5 mL) was treated with 1 M *n*-Bu_4NF–THF (0.38 mL, 0.38 mmol). After the reaction mixture was stirred for 30 min, the solution was evaporated in vacuo to dryness and the solid residue was purified by preparative TLC (7% methanol in chloroform) to give **77** (0.062 g, 74.7%) as a crystalline solid: UV (H_2O) λ_{max} 307.5 nm (ϵ 8370) (pH 7), 308.0 nm (ϵ 8140) (pH 2), 307.5 (ϵ 8850) (pH 11).

(+)-(2*R*,5*R*)-2-Amino-6-chloro-9-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]purine (78). A solution of **74** (0.05 g, 0.095 mmol) in THF (5 mL) was treated with 1 M *n*-Bu_4NF–THF (0.123 mL, 0.123 mmol) to give **78** (0.021 g, 74%) as a crystalline solid, which was purified by preparative TLC (5% methanol in chloroform): UV (H_2O) λ_{max} 308.0 nm (ϵ 5070) (pH 7), 308.0 (ϵ 5610) (pH 2), 308.0 (ϵ 5360) (pH 11).

(+)-(2*R*,5*S*)-9-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]guanine (79). A mixture of **77** (0.07 g, 0.243 mmol), 2-mercaptoethanol (0.10 mL, 0.972 mmol), and NaOMe (0.026 g, 0.486 mmol) in MeOH (10 mL) was refluxed for 7 h under N_2. The mixture was cooled, neutralized with glacial AcOH, and evaporated to dryness under vacuum. The residue was purified by preparative TLC (chloroform–methanol, 7:1) to give **79** (R_f = 0.14, 0.040 g, 61.5%) as a white solid: UV (MeOH) λ_{max} 254.0 nm.

(−)-(2*R*,5*R*)-9-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]guanine (80). A mixture of **78** (0.07 g, 0.243 mmol), 2-mercaptoethanol (0.10 mL, 0.972 mmol), and NaOMe (0.026 g, 0.486 mmol) in MeOH (10 mL) was refluxed for 10 h under N_2. The mixture was cooled, neutralized with glacial HOAc, and evaporated to dryness under vacuum. The residue was filtered from hot methanol to give **80** (R_f = 0.14, 0.045 g, 69.0%) as a white solid: UV (MeOH) λ_{max} 254.0 nm.

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.[32] 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.[32] The drugs were also evaluated for their potential toxic effects on uninfected PHA-stimulated human PBM and Vero cells as described previously.[32] 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.[33]

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