Asymmetric Synthesis of 1,3-Dioxolane–Pyrimidine Nucleosides and Their Anti-HIV Activity

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In order to study the structure–activity relationships of dioxolane nucleosides as potential anti-HIV agents, various enantiomerically pure dioxolane–pyrimidine nucleosides have been synthesized and evaluated against HIV-1 in human peripheral blood mononuclear cells. The enantiomerically pure key intermediate **8** has been synthesized in nine steps from 1,6-anhydro-D-mannose (**1**), which was condensed with 5-substituted pyrimidines to obtain various dioxolane–pyrimidine nucleosides. Upon evaluation of these compounds, cytosine derivative **19** was found to exhibit the most potent anti-HIV agent although it is the most toxic. The order of anti-HIV potency was as follows: cytosine (β-isomer) > thymine > cytosine (α-isomer) > 5-chlorouracil > 5-bromouracil > 5-fluorouracil derivatives. Uracil, 5-methylcytosine, and 5-iodouracil derivatives were found to be inactive. Interestingly, α-isomer **20** showed good anti-HIV activity without cytotoxicity. As expected, other α-isomers did not exhibit any significant antiviral activity. (−)-Dioxolane-T was 5-fold less effective against AZT-resistant virus than AZT-sensitive virus.

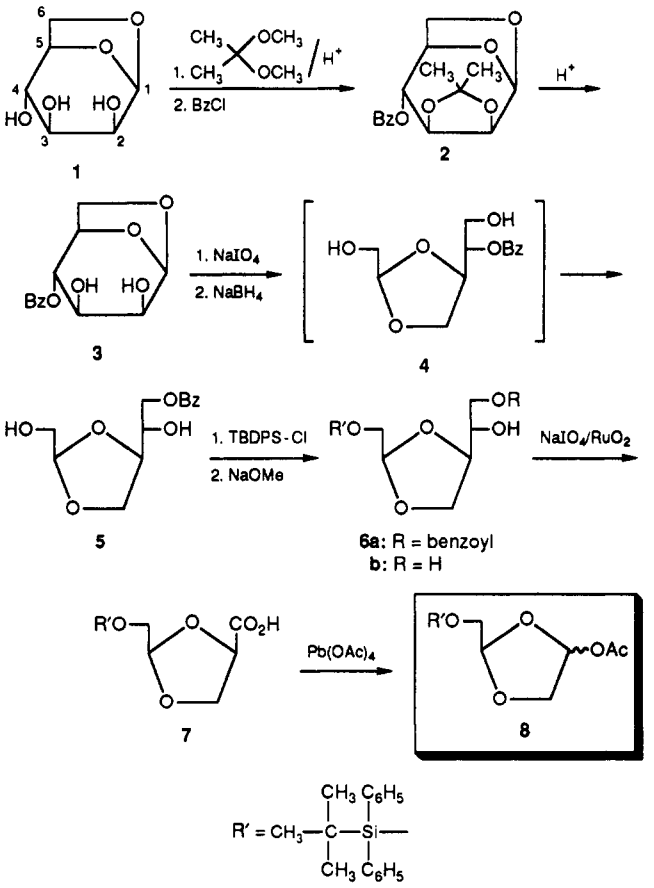
Introduction

Although AZT is a potent inhibitor of HIV in vitro[1] and a clinically useful antiviral agent for patients with AIDS and AIDS-related complex,[2] it is far from being an ideal anti-HIV agent. Furthermore, the drug resistance problem has begun to emerge as an important issue in AIDS chemotherapy.[3] Thus, it is necessary to discover more potent and less toxic agents as well as meet the continuous challenge of drug resistance. A number of nucleosides, including 2′,3′-dideoxyinosine (DDI),[4] 2′,3′-dideoxycytidine (DDC),[5] 2′,3′-dideoxy-2′,3′-didehydrothymidine (D4T),[6] 2′-fluoro-DDC,[7] 3′-azido-2′,3′-dideoxyuridine (AZDU)[8,9] and 2′,3′-dideoxy-3′-thiacytidine (3TC)[10] are undergoing various stages of clinical trials. Additionally, there are several second generation anti-HIV nucleosides in various preclinical stages, which include 3′-azido-2′,3′-dideoxy-5-methylcytidine (CS-92),[11] and 4′-azidothymidine.[12] Several interesting nucleosides, modified at the C3′-position by a heteroatom such as (±)-BCH-189[10] and dioxolanylthymine (dioxolane-T),[10,13] have recently been reported. (±)-BCH-189 exhibits an excellent anti-HIV activity in vitro and one of its enantiomers (3TC) is in clinical trials. Synthesis and anti-HIV activity of racemic dioxolane-T have been reported by Belleau et al.[10a] and Norbeck et al.,[13] which showed a moderate anti-HIV activity in ATH8 cells (EC_{50} = 20 μM) without cytotoxicity up to 200 μM. Therefore, it was of interest to synthesize one of the enantiomers of dioxolane-T and compare the differences in anti-HIV activities between the enantiomer and the racemic mixture. It was of further interest to synthesize various enantiomerically pure dioxolane nucleosides for the structure–activity relationships.

Results and Discussion

Retrosynthetic analysis of dioxolane-T suggests that 1,6-anhydro-D-mannose (**1**) is the chiral template that leads to enantiomerically pure dioxolane-T and that this optical antipode corresponds to the natural configuration for nucleosides. The synthesis of 1,6-anhydro-D-mannose (**1**) has previously been reported by Hudson and co-workers[14] and on a preparative scale more recently by Fraser-Reid and co-workers.[15] The 2,3-diol moiety of **1** was selectively protected as its isopropylidene group by reaction with dimethoxypropane and catalytic amounts of *p*-toluenesulfonic acid followed by the treatment with benzoyl chloride to give the fully protected 1,6-anhydro-D-mannose

Scheme I



6a: R = benzoyl
b: R = H

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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.

(2) Richman, D. D.; Fischl, M. A.; Grieco, M. H.; Gottlieb, M. S.; Volberding, P. A.; Laskin, O. L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Hirsch, M. S.; Jackson, G. G.; Durack, D. T.; Phil, D.; Nusinoff-Lehrman, S.; The AZT Collaborative Working Group. The Toxicity of Azidothymidine (AZT) in The Treatment of Patients with AIDS and AIDS-Related Complex. *N. Engl. J. Med.* **1987**, *317*, 192–197.

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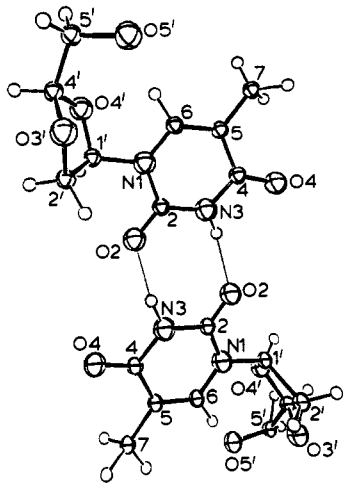
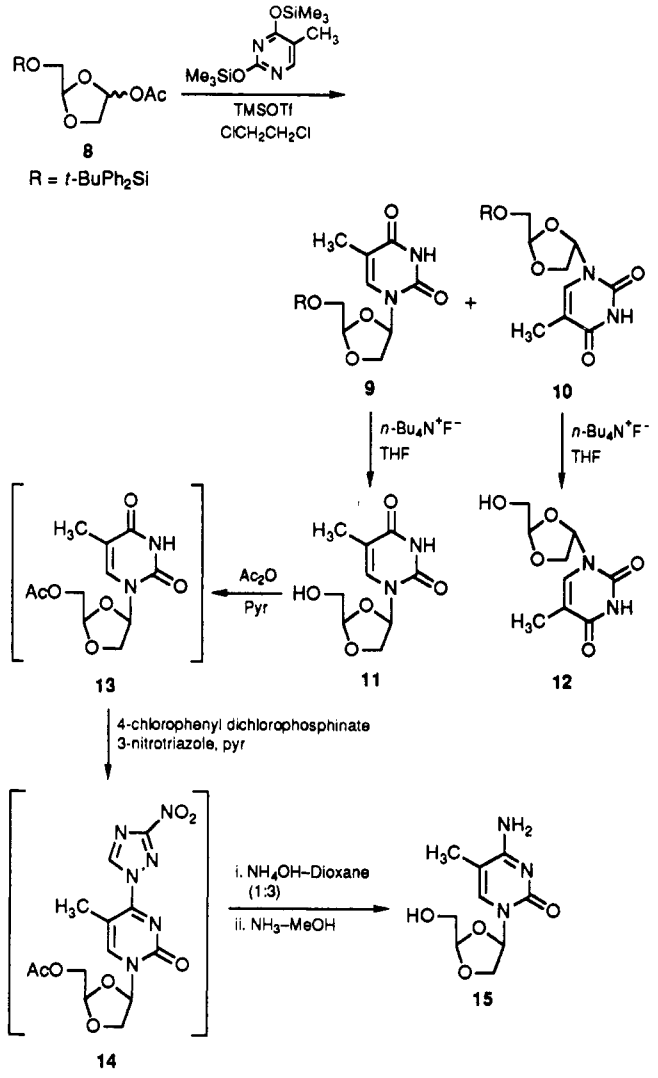


Figure 1. ORTEP drawing of the molecular structure of **11** as determined by X-ray crystallography, shown as a heterodimer. The regular numbering system of nucleoside was used.

(2) in good yield (Scheme I). The isopropylidene group of **2** was then selectively removed by dilute sulfuric acid in 60% aqueous dioxane to give 1,6-anhydro-4-*O*-benzoyl-D-mannose (**3**). Treatment of **3** with $NaIO_4$ fol-

Scheme II



(3) Larder, B. A.; Darby, G.; Richman, D. D. HIV with Reduced Sensitivity to Zidovudine (AZT) Isolated During Prolonged Therapy. *Science* **1989**, *243*, 1731–1734.

(4) Mitsuya, H.; Broder, S. Inhibition of the in vitro Infectivity and Cytopathic effect of human T-lymphotrophic 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, 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. *N. Engl. J. Med.* **1990**, *322*, 1333–1340.

(5) Yarchoan, R.; Thomas, R. V.; Allain, J-P.; McAtee, N.; Dubinsky, R.; Mitsuya, H.; Lawley, T. J.; Safai, B.; Myers, C. E.; Perno, C. F.; Klecker, R. W.; Wills, R. J.; Fischl, M. A.; McNeely, M. C.; Pluda, J. M.; Leuther, M.; Collins, J. M.; Broder, S. Phase I Studies of 2′,3′-Dideoxycytidine in Severe Human Immunodeficiency Virus Infection as a Single Agent and Alternating with Zidovudine (AZT). *Lancet* **1988**, *1*, 76–80.

(6) (a) Lin, T.-S.; Schinazi, R. F.; Prusoff, W. H. Potent and Selective in vitro Activity of 3′-Deoxythymidin-2′-ene (3′-Deoxy-2′,3′-didehydrothymidine) against Human Immunodeficiency Virus. *Biochem. Pharmacol.* **1987**, *36*, 2713–2718. (b) Balzarini, J.; Kang, G.-J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D. G. The Anti-HTLV-III (Anti-HIV) and Cytotoxic Activity of 2′,3′-Didehydro-2′,3′-dideoxyribonucleosides: A Comparison with Their Parental 2′,3′-Dideoxyribonucleosides. *Mol. Pharmacol.* **1987**, *32*, 162–167; Hamamoto, Y.; Nakashima, H.; Matsui, T.; Matsuda, A.; Ueda, T.; Yamamoto, N. Inhibitory Effect of 2′,3′-Didehydro-2′,3′-Dideoxynucleosides on Infectivity, Cytopathic Effects, and Replication of Human Immunodeficiency Virus. *Antimicrob. Agents Chemother.* **1987**, *31*, 907–910.

(7) Martin, T. A.; Bushnell, D. J.; Duncan, I. B.; Dunsdon, S. J.; Hall, M. J.; Machin, P. J.; Merrett, J. H.; Parkes, K. E. B.; Roberts, N. A.; Thomas, G. J.; Galpin, S. A.; Kinchington, D. Synthesis and Antiviral Activity of Monofluoro and Difluoro Analogues of Pyrimidine Deoxyribonucleosides against Human Immunodeficiency Virus (HIV-1). *J. Med. Chem.* **1990**, *133*, 2137–2145. Watanabe, K. A.; Harada, K.; Zeidler, J.; Matulic-Adamic, J.; Takahashi, K.; Ren, W. Y.; Cheng, L. C.; Fox, J. J.; Chou, T. C.; Zhu, Q. Y.; Polsky, B.; Gold, J. W. M.; Armstrong, D. Synthesis and Anti-HIV-1 Activity of 2′-"Up"-Fluoro Analogues of Active Anti-AIDS Nucleosides 3′-Azido-3′-deoxythymidine (AZT) and 2′,3′-Dideoxycytidine (DDC). *J. Med. Chem.* **1990**, *33*, 2145–2150. Sterzychi, R. Z.; Ghazzouli, I.; Brankovan, V.; Martin, J. C.; Mansuri, M. M. Synthesis and Anti-HIV Activity of Several 2′-Fluoro-Containing Pyrimidine Nucleosides. *J. Med. Chem.* **1990**, *33*, 2150–2157.

(8) (a) Chu, C. K.; Schinazi, R. F.; Ahn, M. K.; Ullas, G. V.; Gu, J. P. Structure–Activity Relationships of Pyrimidine Nucleosides as Antiviral Agents for Human Immunodeficiency Virus Type 1 in Peripheral Blood Mononuclear Cells. *J. Med. Chem.* **1989**, *32*, 612–617. (b) Lin, T.-S.; Guo, J.-Y.; Schinazi, R. F.; Chu, C. K.; Xiang, J.-N.; Prusoff, W. H. Synthesis and Antiviral Activity of Various 3′-Azido Analogues of Pyrimidine Deoxyribonucleosides against Human Immunodeficiency Virus (HIV-I, HTLV-III/LAV). *J. Med. Chem.* **1988**, *31*, 336–340.

(9) Eriksson, B. F. H.; Chu, C. K.; Schinazi, R. F. Phosphorylation of 3′-Azido-2′,3′-Dideoxyuridine and Preferential Inhibition of Human and Simian Immunodeficiency Virus Reverse Transcriptase by its 5′-Triphosphate. *Antimicrob. Agents Chemother.* **1989**, *33*, 1729–1734.

(10) (a) Belleau, B.; Dixit, D.; Nguyen-Ga, N.; Kraus, J. L. *International Conference* on AIDS, Montreal, Canada, June 4–9, 1990, paper no. T.C.O.I. (b) Soudeyns, H.; Yao, Q.; Belleau, B.; Kraus, J.-L.; Nguyen-Ba, N.; Spira, B.; Wainberg, M. A. Anti-Human Immunodeficiency Virus Type 1 Activity and In Vitro Toxicity of 2′-Deoxy-3′-Thiacytidine (BCH-189), a Novel Heterocyclic Nucleoside Analog. *Antimicrob. Agents Chemother.* **1991**, *35*, 1386–1390.

(11) Schinazi, R. F.; Chu, C. K.; Eriksson, B. F. H.; Sommadossi, J. P.; Gallo, J. M.; Boudinot, F. D.; Anderson, D.; McClure, H. M. Antiretroviral Activity, Biochemistry, and Pharmacokinetics of 3′-Azido-2′,3′-Dideoxy-5-Methylcytidine. *Ann. N.Y. Acad. Sci.* **1990**, *616*, 385–397.

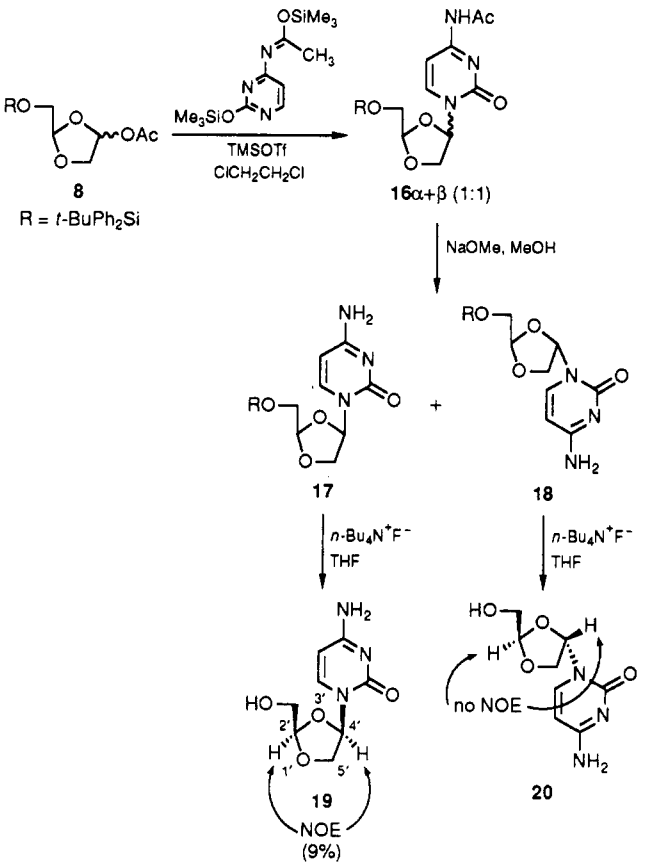
Table I. Physical and Optical Data

no.	mp, °C (solv)[a]	$[\alpha]_D^{25}$, deg	no.	mp, °C (solv)[a]	$[\alpha]_D^{25}$, deg
3	124–125 (b)	−154.7 (c 0.21, MeOH)	24	86–87 (b)	+5.44 (c 1.04, MeOH)
5	46–48 (f)	−18.5 (c 0.20, MeOH)	25	135.136 (c)	+8.22 (c 1.00, MeOH)
6a	oil	−14.2 (c 0.26, MeOH)	26	foam	−0.33 (c, 1.03, MeOH)
6b	oil	−2.4 (c 0.25, MeOH)	27	80–83 (d)	+12.25 (c 0.98, MeOH)
7	foam	+17.23 (c 1.08, MeOH)	28	70–72 (d)	+0.41 (c 0.59, MeOH)
8	oil		29	70–71 (e)	+16.82 (c, 1.00, MeOH)
9	foam	−6.98 (c 0.43, MeOH)	30	64.65 (e)	+6.81 (c 1.00, MeOH)
10	foam	+11.3 (c 0.23, MeOH)	31	180–181 (d)	−14.35 (c, 1.00, MeOH)
11	174–175 (3)	−18.8 (c 0.17, MeOH)	32	120–121 (d)	−0.88 (c, 1.00, MeOH)
12	foam	+10.7 (c 0.15, MeOH)	33	162–164 (d)	−3.7 (c 1.00, MeOH)
15	92–95 (e)	+14.25 (c 1.13, MeOH)	34	128–132 (b)	−5.9 (c 1.02, MeOH)
17	162–163 (b)	+18.08 (c 1.00, MeOH)	35	189–190 (d)	+3.3 (c, 1.0, MeOH)
18	181–183 (b)	−19.92 (c 1.00, MeOH)	36	132–133 (d)	−5.80 (c, 1.02, MeOH)
19	181–183 (b)	+21.00 (c 1.00, MeOH)	37	221–223 (d)	−30.08 (c 1.00, MeOH)
20	185 (c)	−25.22 (c 1.00, MeOH)	38	114–117 (d)	+1.56 (c 0.55, MeOH)
21 + 22	120 (c)		39	225 dec (c)	+4.23 (c 1.00, MeOH)
23	92–95 (b)	+4.61 (c 1.03, MeOH)	40	221 dec (c)	+7.39 (c 1.00, MeOH)

[a] Solvents: b, Hx–CH_2Cl_2; c, MeOH; d, $CHCl_3$–MeOH; e, ether; f, ether–Hx.

lowed by reduction with $NaBH_4$ gave the desired dioxolane derivative **5** in good yield without racemization. Of note was that the secondary benzoyl group in **4** migrated to the primary hydroxyl group in **5** under the reaction conditions. The free primary hydroxyl group of **5** was then selectively protected with *tert*-butyldiphenylsilyl group followed by the removal of the primary benzoyl group using NaOMe to give the diol **6b** in excellent yield. Oxidation of the diol **6b** to the acid **7** was accomplished by $NaIO_4/RuO_2$.[16] Oxidative decarboxylation of **7** with $Pb(OAc)_4$[13,17] afforded the key intermediate **8**. Synthesis of enantiomerically pure form of dioxolane-T **11** and **12** was accomplished from the condensation of the intermediate **8** with silylated thymine to obtain an α,β-mixture of **10** and **9** (1:1.5 ratio) (Scheme II). The mixture was separated by silica gel column chromatography to give the individual isomers **9** and **10**. Desilylation of **9** and **10** afforded the free nucleosides **11** and **12**, respectively. In order to prepare the 5-methylcytosine derivative **15**, silylated 5-methylcytosine and the 4-acetoxy-1,3-dioxlane derivative **8** were reacted under various conditions. However, we were only able to obtain the inseparable anomeric mixture of the desired product by silica gel chromatography. Thus, the desired product was prepared by the amination procedure[18] as shown in

Scheme III



Scheme II.

Cytosine analogues **17** and **18** have been prepared from the condensation of the intermediate **8** and silylated N^4-acetylcytosine in the presence of TMSOTf in 1,2-dichloroethane to give a 1:1 α,β-mixture **16** which, without separation, was treated with NaOMe to remove the N^4-acetyl group (Scheme III). Silica gel column chromatography was used to separate to an individual **17** and **18** followed by desilylation afforded the corresponding nucleosides **19** and **20**. The structural assignment of the thymine and cytosine analogues was made on the basis of the ^1H NMR studies. For example, the nuclear Overhauser effect (NOE) was observed in **19** (9%) between the 2′-H and 4′-H, indicating the β-configuration (cis-arrangement), while no NOE was detected in the α-isomer **20**, indicating a trans arrangement. Furthermore, the thymine derivative

(12) Prisbe, E. J.; Maag, H.; Verheyden, J. P. H. *Abstracts of Papers*, 201st National Meeting of the American Chemical Society, Atlanta, GA, April 14–19, 1991; American Chemical Society: Washington, DC, 1991; Carbohydrate Division paper 28.
(13) Norbeck, D. W.; Spanton, S.; Broder, S.; Mitsuya, H. (±)-Dioxolane-T ((±)-1-[(2β,4β)-2-(hydroxymethyl)-4-dioxolanyl]-thymine). A New 2′,3′-Dideoxynucleoside Prototype with In Vitro Activity against HIV. *Tetrahedron Lett.* **1989**, *30*, 6263–6266.
(14) Knauf, A. E.; Hann, R. M.; Hudson, C. S. D-Mannosan ⟨1,5⟩-β⟨1,6⟩ or Levomannosan. *J. Am. Chem. Soc.* **1941**, *63*, 1447–1451.
(15) Zottola, M. A.; Alonso, R.; Vite, G. D.; Fraser-Reid, B. A Practical Efficient Large-Scale Synthesis of 1,6-Anhydrohexopyranose. *J. Org. Chem.* **1989**, *54*, 6123–6125.
(16) Nunez, M. T.; Martin, V. S. Efficient Oxidation of Phenyl Group to Carboxylic Acids with Rutenium Tetroxide. A Simple Synthesis of (R)-γ-Caprolactone, the Pheromone of *Trogoderma granarium*. *J. Org. Chem.* **1990**, *55*, 1928–1931.
(17) Dhavale, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. Novel. Synthetic Equivalents of Differentially Protected Tartaric Aldehyde. A Simple Route to Useful C-4 Chiral Synthons. *Tetrahedron Lett.* **1988**, *29*, 6163–6165.
(18) Lin, T.-S.; Chen, M. S.; McLaren, C.; Gao, Y.-S.; Ghazzouli, I.; Prusoff, W. H. Synthesis and Antiviral Activity of Various 3′-Azido, 3′-Amino, 2′,3′-Unsaturated, and 2′,3′-Dideoxy Analogues of Pyrimidine Deoxyribonucleosides against Retroviruses. *J. Med. Chem.* **1987**, *30*, 440–444.

Table II. ^{1}H NMR Data

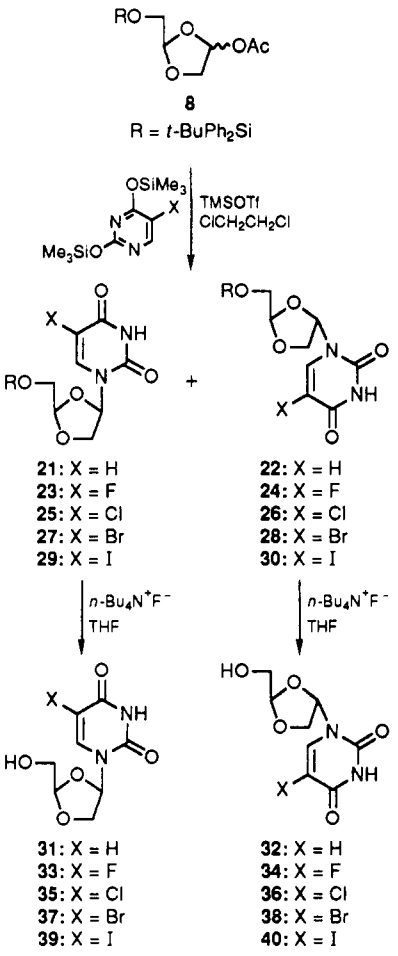
no.	H-1′[d]	H_a-2′	H_b-2′	H-4′	H-5′	other signals
9	6.36 (t, $J_{1',2'}$ = 4.0)	4.14 (d, $J_{2',1'}$ = 4.0)		5.06 (t, $J_{4',5'}$ = 3.2)	3.92 (d, $J_{5',4'}$ = 3.2)	1.08 (s, *t*-Bu), 1.67 (s, CH_3), 7.50 (m, Ar), 9.51 (br s, NH)[b]
10	6.32 (dd, $J_{1',2b}$ = 5.3, $J_{1',2'a}$ = 2.3)	4.01 (dd, $J_{2'a,2'b}$ = 9, 5, $J_{2'a,1'}$ = 2.3)	4.35 (dd, $J_{2'b,2'a}$ = 9.5, $J_{2'b,1'}$ = 5.3)	5.55 (t, $J_{4',5'}$ = 3.2)	3.70 (d, $J_{5',4'}$ = 3.2)	1.08 (s, *t*-Bu), 1.94 (d, $J_{CH3,6}$ = 1.2, CH_3), 7.17 (d, $J_{6,CH3}$ = 1.2, H-6), 7.55 (m, Ar), 9.57 (br s, NH)[b]
11	6.21 (dd, $J_{1',2'a}$ = 5.5, $J_{1',2'b}$ = 2.0)	4.03 (dd, $J_{2'a,2'b}$ = 9.9, $J_{2'a,1'}$ = 5.5)	4.22 (dd, $J_{2'b,2'a}$ = 9.9, $J_{2'b,1'}$ = 2.0)	4.90 (t, $J_{4',5'}$ = 2.6)	3.63 (dd, $J_{5',4'}$ = 2.6, $J_{5',CH}$ = 6.0)	1.75 (d, $J_{CH3,6}$ = 1.2, H-6), 5.16 (t, $J_{CH,6}$ = 6.0, OH), 7.67 (d, $J_{6,CH3}$ = 1.2, H-6), 11.27 (br s, NH)[a]
12	6.17 (dd, $J_{1',2'b}$ = 5.3, $J_{1',2'a}$ = 3.3)	4.20 (dd, $J_{2'a,2'b}$ = 9.5, $J_{2'a,1'}$ = 3.3)	4.28 (dd, $J_{2'b,2'a}$ = 9.5, $J_{2b,1'}$ = 5.3)	5.47 (t, $J_{4',5'}$ = 3.7)	3.43 (dd, $J_{5',OH}$ = 6.0, $J_{5',4'}$ = 3.7)	1.79 (s, CH_3), 5.00 (t, $J_{OH,5'}$ = 6.0, OH), 7.43 (s, H-6), 11.32 (br s, NH)[a]
15	6.22 (dd, $J_{1',2'a}$ = 5.6, $J_{1',2b}$ = 2.1)	4.05 (dd, $J_{2'a,2b}$ = 10.0, $J_{2'a,1'}$ = 5.6)	4.23 (dd, $J_{2'b,2'a}$ = 10.0, $J_{2'b,1'}$ = 2.1)	4.91 (t, $J_{4',5'}$ = 2.6)	3.64 (dd, $J_{5',OH}$ = 6.2, $J_{5',4'}$ = 2.6)	1.76 (d, $J_{CH3,6}$ = 1.2, CH_3), 5.18 (t, $J_{OH,5'}$ = 6.2, OH), 7.68 (d, $J_{6,CH3}$ = 1.2, H-6), 11.28 (br s, NH)[a]
17	6.28 (t, $J_{1',2'}$ = 3.3)	4.18 (d, $J_{2',1'}$ = 3.3)		5.04 (t, $J_{4',5'}$ = 2.6)	3.96 (d, $J_{5',4'}$ = 2.6)	1.08 (s, *t*-Bu), 1.91 (br s, NH_2), 5.36 (d, $J_{5,6}$ = 8.3, H-5), 7.46 (m, Ar), 7.9 (d, $J_{6,5}$ = 7.3, H-6)[b]
18	6.17 (dd, $J_{1',2b}$ = 4.8, $J_{1',2'a}$ = 2.4)	4.01 (dd, $J_{2'a,2'a}$ = 9.5, $J_{2'b,1'}$ = 4.8)	4.42 (dd, $J_{2'b,2'a}$ = 9.5, $J_{2'b,1'}$ = 4.8)	5.48 (t, $J_{4',5'}$ = 3.5)	3.72 (d, $J_{5',4'}$ = 3.5)	1.07 (s, *t*-Bu), 1.81 (br s, NH_2), 5.72 (d, $J_{5,6}$ = 7.5, H-5), 7.40 (m, Ar), 7.64 (d, $J_{6,5}$ = 7.5, H-6), 7.68 (m, Ar)[b]
19	6.20 (t, $J_{1,2'}$ = 3.5)	4.07 (d, $J_{2',1'}$ = 3.5)		4.94 (t, $J_{4',5'}$ = 3.0)	3.65 (dd, $J_{5',OH}$ = 5.0, $J_{5',4'}$ = 3.0)	4.30 (t, $J_{OH,5'}$ = 5.0, OH), 5.78 (d, $J_{5,6}$ = 7.5, H-5), 7.23 (br s, NH_2), 7.82 (d, $J_{6,5}$ = 7.5, H-6)[a]
20	6.10 (dd, $J_{1',2'b}$ = 5.1, $J_{1',2'a}$ = 3.0)	3.90 (dd, $J_{2'a,2'b}$ = 9.3, $J_{2'a,1'}$ = 3.0)	4.25 (dd, $J_{2'b,2'a}$ = 9.3, $J_{2'b,1'}$ = 5.1)	5.41 (t, $J_{4',5'}$ = 3.3)	3.45 (dd, $J_{5',4'}$ = 3.3, $J_{5',OH}$ = 5.0)	4.30 (t, $J_{OH,5'}$ = 5.0, OH), 5.77 (d, $J_{5,6}$ = 7.5, H-5), 7.23 (br s, NH_2), 7.57 (d, $J_{6,5}$ = 7.5)[a]
21	6.34 (aa t, $J_{1',2'}$ = 4.3, 3.1)	4.13 (d, J = 1.5)	4.18 (s)	5.01 (t, $J_{4',5'}$ = 2.8)	3.70 (d, $J_{5',4'}$ = 2.8)	1.08 (s, *t*-Bu, 5.42 (d, $J_{5,6}$ = 8.2, H-5), 7.52 (m, Ar, H-6), 9.73 (br s, NH)[b]
22				5.56 (d, $J_{4',5'}$ = 3.6)	3.95 (d, $J_{5',4'}$ = 3.6)	
23	6.33 (dd, $J_{1',2'}$ = 4.1, 2.6)	4.20 (d, $J_{2',1'}$ = 2.6)		5.03 (t, $J_{4',5'}$ = 2.5)	3.94 (d, $J_{5',4'}$ = 2.5)	1.10 (s, *t*-Bu), 7.45 (m, Ar), 7.7 (m, Ar, H-6), 9.50 (br s, NH)[b]
24	6.13 (dd, $J_{1',2'b}$ = 4.1, $J_{1',2'a}$ = 1.8)	3.90 (dd, $J_{2'a,2'b}$ = 9.7, $J_{2'a,1'}$ = 1.8)	4.25 (dd, $J_{2'a,2'b}$ = 9.7, $J_{2'b,1'}$ = 4.1)	5.41 (aa t, $J_{4',5'}$ = 3.2, 2.7)	3.57 (d, $J_{5',4'}$ = 3.2)	0.94 (s, *t*-Bu), 7.30 (m, Ar, H-6), 9.58 (br s, NH)[b]
25	6.25 (t, $J_{1',2'}$ = 4.0)	4.18 (d, $J_{2',1'}$ = 4.0)		5.06 (t, $J_{4',5'}$ = 3.2)	3.91 (d, $J_{5',4'}$ = 3.2)	1.08 (s, *t*-Bu), 7.50 (m, Ar, H-6), 8.53 (br s, NH)[b]
26	6.24 (dd, $J_{1',2'b}$ = 5.0, $J_{1',2'a}$ = 2.0)	4.10 (dd, $J_{2'a,2'b}$ = 9.8, $J_{2'a,1'}$ = 2.0)	4.40 (dd, $J_{2b,2'a}$ = 9.8, $J_{2'b,1'}$ = 5.0)	5.56 (t, $J_{4',5'}$ = 3.2)	3.72 (d, $J_{5',4'}$ = 3.2)	1.07 (s, *t*-Bu), 7.62 (m, Ar, H-6), 8.49 (br s, NH)[b]
27	6.25 (app t, $J_{1',2'}$ = 4.0, 3.5)	4.18 (d, $J_{2',2'}$ = 4.0)		5.08 (t, $J_{4',5'}$ = 3.4)	3.91 (3, $J_{5',4'}$ = 3.4)	1.09 (s, *t*-Bu), 7.52 (m, Ar, H-6), 8.52 (br s, NH)[b]
28	6.23 (dd, $J_{1',2'a}$ = 2.1)	4.04 (dd, $J_{2'a,2'b}$ = 9.6, $J_{2'a,1'}$ = 2.1)	4.41 (dd, $J_{2'a,2'b}$ = 9.6, $J_{2'b,1'}$ = 5.1)	5.57 (aap t, $J_{4',5'}$ = 3.5, 3.3)	3.72 (d, $J_{5',4'}$ = 3.3)	1.07 (s, *t*-Bu), 7.51 (m, Ar, H-6), 8.41 (br s, NH)[b]
29	6.23 (t, $J_{1',2'}$ = 3.7)	4.17 (d, $J_{2',1'}$ = 2.8)		5.10 (t, $J_{4',5'}$ = 3.7)	3.91 (dd, $J_{5',4'}$ = 3.8, 1.2)	1.09 (s, *t*-Bu), 7.52 (m, Ar), 7.82 (s, H-6), 8.72 (br s, NH)[b]
30	6.23 (t, $J_{1',2'b}$ = 4.9, $J_{1',2'a}$ = 1.9)	4.04 (dd, $J_{2'a,2'b}$ = 9.8, $J_{2'a,1'}$ = 1.9)	4.42 (dd, $J_{2'b,2'a}$ = 9.8, $J_{2'b,1'}$ = 4.9)			8.68 (br s, NH)[b]
31	6.20 (dd, $J_{1',2'a}$ = 5.3, $J_{1',2'b}$ = 1.8)	4.04 (dd, $J_{2'a,2'b}$ = 9.9, $J_{2'a,1'}$ = 5.3)	4.23 (dd, $J_{2'b,2'a}$ = 9.9, $J_{2'b,1'}$ = 1.8)	4.91 (t, $J_{4',5'}$ = 2.6)	3.58 (dd, $J_{5',OH}$ = 5.9, $J_{5',4'}$ = 2.6)	5.60 (d, $J_{5,6}$ = 8.2, H-5), 7.80 (d, $J_{6,5}$ = 8.2, H-6), 5.17 (t, $J_{OH,5'}$ = 5.9, OH), 11.27 (br s, NH)[a]
32	6.16 (dd, $J_{1',2'b}$ = 5.4, $J_{1',2'a}$ = 3.2)	4.03 (dd, $J_{2'a,2'b}$ = 9.4, $J_{2'a,1'}$ = 3.2)	4.26 (dd, $J_{2'b,2'a}$ = 9.4, $J_{2'b,1'}$ = 5.4)	5.44 (t, $J_{4',5'}$ = 3.7)	3.43 (d, $J_{5',4'}$ = 3.7)	5.62 (d, $J_{5,6}$ = 7.9, H-5), 7.57 (d, $J_{6,5}$ = 7.9, H-6), 4.98 (t, $J_{OH,5'}$ = 5.4, OH), 11.30 (br s, NH)[a]
33	6.18 (dd, $J_{1',2'a}$ = 4.5, $J_{1',2'b}$ = 1.5)	4.05 (dd, $J_{2'a,2'b}$ = 10.0, $J_{2'a,1'}$ = 4.5)	4.30 (dd, $J_{2'b,2'a}$ = 10.0, $J_{2'b,1'}$ = 1.5)	4.92 (app t, $J_{4',5'}$ = 2.1, 1.8)	3.68 (s)	8.23 (d, $J_{6,F}$ = 7.2, H-6), 5.32 (app t, J = 3.5, 1.2), 11.80 (br s, NH)[a]
34	6.12 (m)	4.06 (dd, $J_{2'a,2'b}$ = 9.7, $J_{2'a,1'}$ = 3.5)	4.29 (dd, $J_{2'b,2'a}$ = 9.7, $J_{2'b,1'}$ = 5.6)	5.50 (t, $J_{4',5'}$ = 3.5)	3.42 (d, $J_{5',4'}$ = 3.5)	7.87 (d, $J_{6,F}$ = 6.7, H-6), 4.98 (br s, OH), 11.83 (br s, NH)[a]
35	6.18 (dd, $J_{1',2'a}$ = 4.9, $J_{1',2'b}$ = 1.3	4.05 (dd, $J_{2'a,2'b}$ = 10.0, $J_{2'a,1'}$ = 4.9)	4.34 (dd, $J_{2'b,2'a}$ = 10.0, $J_{2'b,1'}$ = 1.3)	4.94 (t, $J_{4',5'}$ = 2.0)	3.68 (dd, $J_{5',OH}$ = 5.6, $J_{5',4'}$ = 2.0)	8.33 (d, $J_{6,Cl}$ = 5.3, H-6), 5.34 (t, $J_{OH,5'}$ = 5.6, OH), 11.75 (br s, NH)[a]
36	6.10 (dd, $J_{1',2'b}$ = 5.4, $J_{1',2'a}$ = 2.6)	4.10 (dd, $J_{2'a,2'b}$ = 9.6, $J_{2'a,1'}$ = 2.6)	4.31 (dd, $J_{2'b,2'a}$ = 9.6, $J_{2'b,1'}$ = 5.4)	5.52 (t, $J_{4',5'}$ = 3.5)	3.43 (dd, $J_{5',4'}$ = 3.7, 1.6)	7.88 (d, $J_{6,Cl}$ = 2.5, H-6), 5.18 (br s, OH), 11.50 (br s, NH)[a]
37	6.17 (dd, $J_{1',2'a}$ = 4.9, $J_{1',2'b}$ = 1.3)	4.05 (dd, $J_{2'a,2'b}$ = 9.8, $J_{2'a,1'}$ = 5.5)	4.33 (dd, $J_{2'b,2'a}$ = 9.8, $J_{2'b,1'}$ = 1.1)	4.93 (t, $J_{4',5'}$ = 1.8)	3.67 (dd, $J_{5',OH}$ = 5.6, $J_{5',4'}$ = 1.8)	8.44 (s, H-6), 5.34 (t, $J_{OH,5'}$ = 5.6, OH), 11.78 (br s, NH)[a]
38	6.09 (dd, $J_{1',2'b}$ = 5.5, $J_{1',2'a}$ = 3.3)	4.10 (dd, $J_{2'a,2'b}$ = 9.6, $J_{2'a,1'}$ = 3.3)	4.30 (dd, $J_{2'b,2'a}$ = 9.6, $J_{2'b,1'}$ = 5.5)	4.42 (t, $J_{4',5'}$ = 3.8, 3.5)	3.31 (s)	7.93 (s, H-6), 4.97 (br s, OH), 11.17 (br s, NH)[a]
39	6.17 (dd, $J_{1',2'a}$ = 5.1, $J_{1',2'b}$ = 1.3)	4.07 (dd, $J_{2'a}m_{a,2'b}$ = 9.8, $J_{2'a,1'}$ = 5.1)	4.30 (dd, $J_{2'b,2'a}$ = 9.8, $J_{2'b,1'}$ = 1.3)	4.93 (t, $J_{4',5'}$ = 2.0)	3.67 (dd, $J_{5',OH}$ = 5,6, $J_{5',4'}$ = 2.0)	8.44 (s, H-6), 5.32 (t, $J_{OH,5'}$ = 5.6, OH), 11.66 (br s, NH)[a]
40	6.09 (dd, $J_{1',2'b}$ = 5.6, $J_{1',2'a}$ = 2.5)	4.05 (dd, $J_{2'a,2'b}$ = 9.3, $J_{2'a,1'}$ = 2.5)	4.34 (dd, $J_{2'b,2'a}$ = 9.3, $J_{2'b,1'}$ = 5.6)	5.47 (t, $J_{4',5'}$ = 3.5)	3.46 (dd, $J_{5',OH}$ = 5.8, $J_{5',4'}$ = 3.5)	7.80 (s, H-6), 4.98 (t, $J_{OH,5'}$ = 5.8, OH), 11.70 (br s, NH)[a]

[a] Me_2SO. [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.

11 was conclusively assigned on the basis of the X-ray crystallography (Figure 1), indicating the β-configuration. The structural assignment of the rest of the compounds in this report was based on the above results. Compounds **31–40** have been prepared by a similar method of condensation of **8** with the corresponding heterocycles, separation of the α,β-mixture, and desilylation (Scheme IV and Tables I and II).

In order to gain insight into the molecular mechanism of anti-HIV activity, conformational analysis of various 2′,3′-dideoxynucleosides have been studied by X-ray crystallography.[19–22] The study indicated that most of the

Scheme IV



active anti-HIV nucleosides assume a 3′-exo ($^2T_3$) or similar carbohydrate conformation while inactive compounds prefer to have a 3′-endo ($^3T_2$) conformation. AZT, AZDU, DDA, DDC, DDI, 3′-fluoro-3′-deoxythymidine (FLT), and others have the 3′-exo conformation.[20] Inactive compounds, such as DDU and 3′-allyl-DDU, however, assume 3′-endo conformation in the solid state. Thus, it was of interest to determine the solid-state conformation of dioxolane nucleosides in order to compare their conformation to that of the anti-HIV nucleosides listed above and also to confirm the structure. The conformations of the dioxolane analogues were determined in an effort to examine if these compounds have a similar conformational preference. Figures 1 and 2 show the respective molecular conformations of (1′*R*,4′*R*)-dioxolanylthymine 11 (Figure 1) and (1′*R*,4′*R*)-dioxolanylcytosine 19 (Figure 2). The most important conformational parameters are listed in Table III. The dioxolane ring of both molecules in the

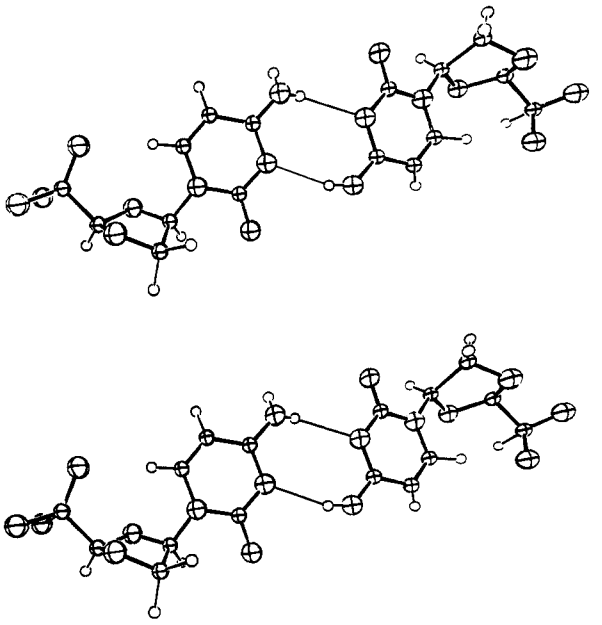


Figure 2. ORTEP drawing of the molecular structure of **19** as determined by X-ray crystallography, shown as a heterodimer.

Table III. Conformational Parameters of (1′*R*,4′*R*)-Dioxolanylthymine (11) and (1′*R*,4′*R*)-Dioxolanylcytosine (19)[a]

parameter	11A	11B	19A	19B
N1–C1′ (Å)	1.483 (6)	1.471 (6)	1.46 (2)	1.47 (2)
χ (deg)	−175 (5)	−133 (6)	−163 (1)	−157 (1)
γ (deg)	49 (6)	64 (9)	61 (2)[1]	53 (2)[1]
			−85 (2)[2]	−78 (2)[2]
			−155 (2)[3]	
P (deg)	9	20	18	13
ν_{max} (deg)	41	36	41	40
dioxolane ring conformation	$^3T_2$	^3E	^3E	$^3T_2$

[a] The letters A and B refer to the two independent molecules in the asymmetric unit. Superscript numbers 1–3 refer to multiple disordered conformations in the same molecule.

structures of 11 and 19 have O3′-endo conformations with primarily +*sc* 5′-hydroxyl group orientations. Previously, Norbeck et al.[13] reported the X-ray structure of (±)-dioxolane-T, which shows $^3T_4$ conformation. In our studies with the enantiomerically pure dioxolanylthymine, it was found that (−)-(*R*,*R*)-dioxolanylthymine 11 has two independent conformations ($^3T_2$ and ^3E) in solid state (Figure 1). Both molecules assume the 3′-endo dioxolane ring conformation, which is similar to that observed for the racemic mixture except that it has been found to have only one conformation ($^3T_4$). The pseudorotational angles (*P*) of (−)-(*R*,*R*)-dioxolanylthymine 11 are 9° and 20° for $^3T_2$ and ^3E conformations, respectively, while 42.4° has been reported for the pseudorotational angle of (±)-dioxolanylthymine.[13] The conformational differences between the anti-HIV nucleosides and dioxolane nucleosides may originate from the greater flexibility of dioxlane ring system.

Anti-HIV-1 activities (Table IV) of the synthesized dioxolane nucleosides have been determined in human peripheral blood mononuclear (PBM) cells infected with HIV-1. The antiviral potency was found to be in the following decreasing order: cytosine derivative (β-isomer) > thymine > cytosine (α-isomer) > 5-chlorouracil > 5-bromouracil > 5-fluorouracil. Uracil, 5-methylcytosine, and 5-iodouracil derivatives were found to be inactive. It is interesting to note that the α-derivative of cytosine **20** showed good anti-HIV activity as has been previously reported.[10] The cell toxicity was also determined in PBM

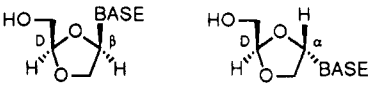
(19) Van Roey, P.; Salerno, J. M.; Duax, W. L.; Chu, C. K.; Ahn, M. K.; Schinazi, R. F. Solid-State Conformation of Anti-Human Immunodeficiency Virus Type-1 Agents: Crystal Structures of Three 3′-Azido-3′-Deoxythymidine Analogues. *J. Am. Chem. Soc.* **1988**, *110*, 2277–2282.

(20) Van Roey, P.; Salerno, J. M.; Chu, C. K.; Schinazi, R. F. Correlation between Prefered Sugar Ring Conformation and Activity of Nucleoside analogues against Human Immunodeficiency Virus. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 3929–3933.

(21) Van Roey, P.; Taylor, E. W.; Chu, C. K.; Schinazi, R. F. Correlation of Molecular Conformation and Activity of Reverse Transcriptase Inhibitors. *Ann. N.Y. Acad. Sci.* **1990**, *616*, 29–40.

(22) Taylor, E. W.; Van Roey, P.; Schinazi, R. F.; Chu, C. K. A Stereochemical Rationale for the Activity of Anti-HIV Nucleosides. *Antiviral Chem. Chemother.* **1990**, *1*, 163–173.

Table IV. Median Effective (EC_{50}) and Inhibitory (IC_{50}) Concentration of Dioxolane–Pyrimidine Nucleosides in PBM Cells and Cytotoxicity in Vero Cells



compd no.	compd base	anomer	EC_{50} (μM)[a] anti-HIV-1 (PBM)	IC_{50} (μM)[a] cytotoxicity (PBM)	IC_{50} (μM)[a] cytotoxicity (Vero)
11	thymine	(−)-β	0.39	>100	>100
12	thymine	(+)-α	>100	>100	>100
15	5-methylcytosine	(+)-β	>100	>100	>100
19	cytosine	(+)-β	0.016	62.0	8.3
20	cytosine	(−)-α	2.4	>100	>100
31	uracil	(−)-β	>100	>100	>100
32	uracil	(−)-α	>100	>100	>100
33	5-fluorouracil	(−)-β	69.6	>100	>100
34	5-fluorouracil	(−)-α	>100	>100	>100
35	5-chlorouracil	(−)-β	6.8	>100	>100
36	5-chlorouracil	(−)-α	>100	>100	>100
37	5-bromouracil	(−)-β	9.3	>100	>100
38	5-bromouracil	(+)-α	>100	>100	>100
39	5-iodouracil	(−)-β	>100	>100	>100
40	5-iodouracil	(+)-α	>100	>100	>100
AZT			0.009	>100	28.0
dioxolane-T		(±)	0.09	>100	>100

[a] Mean values (>10% variability).

Table V. Median Effective (EC_{50}) and EC_{90} of AZT and (−)-Dioxolane-T against AZT-Resistant Strain 9F and AZT-Sensitive Strain 10 HIV-1 in PBM Cells

treatment	AZT-resistant; μM		AZT-sensitive; μM		fold increase for	
	EC_{50}	EC_{90}	EC_{50}	EC_{90}	EC_{50}	EC_{90}
AZT	1.2	19.0	0.0012	0.0065	1000	2923
(−)-dioxolane-T	4.9	39.7	0.2	1.5	25	27

and Vero cells. Previous studies had indicated that rapidly dividing cells such as Vero cells are more useful at predicting toxicity than slow-growing PBM cells.[24] It was found that, although the cytosine derivative **19** was the most potent anti-HIV agent, it was also the most toxic compound among the dioxolane nucleosides tested. As expected, all of the α-isomers, except the cytosine derivative **20**, did not show any significant anti-HIV activity. It is interesting to note that (±)-dioxolane-T is somewhat more potent than the enantiomerically pure form **11**. There may be several explanations for this discrepancy. First of all, higher potency of (±)-dioxolane-T (4.3 times) compared to that of **11** is within the experimental variability since its results presented are mean EC_{50}s obtained using different donor cells. The second possibility may be that the enantiomers of **11** [i.e. (+)-isomer] might be more potent. Synthesis of such an isomer is in progress.

Viral isolates from patients who have been undergoing a long-term AZT therapy have been found to be resistant to against AZT.[3] Thus, it was of interest to verify the report by Lader et al. using primary cells. Furthermore, we wanted to measure antiviral activity of the dioxolane nucleoside against AZT-sensitive as well as AZT-resistant isolates in PBM cells. From the study we were able to reproduce the results of Lader et al. using a pair of AZT-resistant and sensitive viruses in human PBM cells. As can be seen in Table V, there was a 1000-fold increase in the EC_{50} for the two viruses. (−)-Dioxolane-T was only 25-fold more resistant to the pretherapy isolate than the posttherapy resistant virus (Table V). This modest cross-resistance between AZT and (−)-dioxolane-T has not been previously reported and suggests that this compound may act at a similar site as AZT.

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 Fourier transform spectrometer for 90-MHz ^1H NMR spectra 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 from CaH_2.

(−)-1,6-Anhydro-4-*O*-benzoyl-2,3-isopropylidene-β-D-mannopyranose (2). A mixture of 1,6-anhydro-D-mannose, prepared from D-mannose (150 g, 0.83 mol) according to the procedure of Zottola et al.,[15] acetone (1.2 L), dimethoxypropane (450 mL), and *p*-toluenesulfonic acid (8.0 g, 0.03 mol) was stirred at room temperature for 24 h. The reaction mixture was adjusted to pH 8 by adding triethylamine and the resulting white solid was removed by filtration. The filtrate was evaporated in vacuo to give a solid which was extracted with ethyl acetate (4 × 350 mL). The combined extracts were evaporated to dryness to yield a solid which was recrystallized from ethyl acetate to give 2,3-acetonide as colorless needles (66 g, 39.2% from D-mannose), mp 159–160 °C (lit.[14] mp 161–162 °C).

Benzoyl chloride (11.21 mL, 0.096 mol) was added dropwise to a solution of 2,3-acetonide (15 g, 0.07 mol) in pyridine (120 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 45 min. After the reaction was quenched by adding ice and stirring for

(23) Chu, C. K.; Ahn, S. K.; Kim, H. O.; Beach, J. W.; Alves, A. J.; Jeong, L. S.; Islam, Q.; Van Roey, P.; Schinazi, R. F. Asymmetric Synthesis of Enantiomerically Pure (−)-β-D-Dioxolane-thymine and its Anti-HIV Activity. *Tetrahedron Lett.* **1991**, 3791–3794.

(24) 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.

15 min, the solvent was evaporated to dryness in vacuo and the residue was dissolved in ethyl acetate (150 mL). The organic layer was washed with saturated $NaHCO_3$ and brine and dried (anhydrous $MgSO_4$). After filtration and evaporation of the solvent, a pale yellow solid was obtained. Recrystallization from ethanol gave **2** (22.32 g, 98.2%) as colorless crystals, mp 129–131 °C (lit.[14] mp 134–135 °C from methanol).

(−)-1,6-Anhydro-4-*O*-benzoyl-β-D-mannopyranose (3). A solution of **2** (10.0 g, 32.6 mmol) and concentrated H_2SO_4 (3.36 mL) in 60% aqueous dioxane (820 mL) was stirred at 70–80 °C for 15 h. The reaction mixture was cooled in an ice bath and neutralized with saturated $NaHCO_3$ solution. The mixture was concentrated to half of the original volume and the residue was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with saturated $NaHCO_3$ and water, dried (anhydrous $MgSO_4$), and filtered. The filtrate was evaporated to dryness in vacuo to obtain **3** as a white solid: ^{1}H NMR (DMSO-d_6) δ 3.56–4.61 (m, 5 H, H-2, -3, -5, and -6), 4.82 (d, J = 8.1 Hz, 1 H, OH, exchangeable with D_2O), 5.02 (s, 1 H, H-4), 5.09 (d, J = 3.7 Hz, 1 H, OH, exchangable with D_2O), 5.28 (s, 1 H, H-1), 7.46–8.05 (m, 5 H, Ph); IR (KBr) 3410, 1710 cm^{-1}. Anal. ($C_{13}H_{14}O_6$) C, H.

(−)-(2*R*,4*R*,1′*S*)-4-(2-*O*-Benzoyl-1-hydroxyethyl)-2-(hydroxymethyl)dioxolane (5). A solution of $NaIO_4$ (6.54 g, 30.7 mmol) in water (200 mL) was added to a solution of **3** (7.4 g, 27.8 mmol) in 95% EtOH (200 mL) and the mixture was stirred at room temperature for 1 h. After the complete conversion of diol to aldehyde, the reaction mixture was concentrated to half of its original volume and cooled to 5 °C. $NaBH_4$ (4.2 g, 111.0 mmol) was then added portionwise to the mixture over a period of 5 min and the reaction mixture was stirred for 10 min. The resulting mixture was neutralized with glacial HOAc and concentrated to dryness to give crude **5** as a yellow oil, which was purified by silica gel column chromatography to yield **5** as a colorless oil, which was crystallized from Et_2O–*n*-hexane to yield **5** (6.12 g, 82%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 3.47 (dd, J = 5.9 and 3.7 Hz, 2 H, CH_2OH), 3.72–4.14 (m, 4 H, H-4, -5 and C*H*OH), 4.27–4.95 (m, 2 H, CH_2OBz), 4.81–4.95 (m, 2 H, H-2 and CH$_2$O*H*), 5.43 (d, J = 5.5 Hz, 1 H, CHO*H*, exchangable with D_2O), 7.43–8.09 (m, 5 H, Ph). Anal. ($C_{13}H_{16}O_6$) C, H.

(−)-(2*R*,4*R*,1′*S*)-4-(2-*O*-Benzoyl-1-hydroxyethyl)-2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]dioxolane (6a). To a solution of **5** (2.8 g, 10.4 mmol) and imidazole (2.04 g, 30.0 mmol) in DMF (40 mL), *tert*-butyldiphenylsilyl chloride (3 mL, 11.5 mmol) was added and the mixture was stirred at room temperature for 2 h. The reaction mixture was evaporated to yield a yellow oil, which was purified by silica gel column chromatography (hexane–ethyl acetate, 1:2) to yield **6a** (4.48 g, 85%) as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 1.00 (s, 9 H, t-Bu), 3.68–3.87 (m, 3 H, CH_2OTBDPS and C*H*OH), 3.98–4.16 (m, 3 H, H-4 and -5), 4.20–4.55 (m, 2 H, CH_2OBz), 5.07 (t, J = 3.3 Hz, 1 H, H-2), 5.47 (d, J = 5.7 Hz, 1 H, OH, exchangable with D_2O), 7.40–8.33 (m, 10 H, Ph). Anal. ($C_{29}H_{34}O_6Si$) C, H.

(−)-(2*R*,4*R*,1′*S*)-2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-4-(1,2-dihydroxyethyl)dioxolane (6b). To a solution of **6a** (2.52 g, 5.0 mmol) in MeOH (40 mL), was added NaOMe (0.078 M, 7.3 mL) in MeOH, and the mixture was stirred at room temperature for 2 h. The mixture was neutralized with HOAc and concentrated. The residue was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated $NaHCO_3$ solution, dried (anhydrous $MgSO_4$), evaporated, and then purified by silica gel column chromatography (hexane–ethyl acetate, 5:1) to yield **6b** (1.9 g, 95%) as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 1.00 (s, 9 H, *t*-Bu), 3.40–3.52 (m, 3 H, H-4 and -5), 4.49 (t, J = 5.3 Hz, 1 H, H-2), 7.36–7.71 (m, 10 H, Ph_2). Anal. ($C_{22}H_{30}O_5Si$) C, H.

(+)-(2*R*,4*R*)-2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]dioxolane-4-carboxylic Acid (7). To a biphasic solution of **6b** (1.6 g, 4.0 mmol) in acetonitrile (8 mL), CCl_4 (8 mL), and water (12 mL) were added $NaIO_4$ (3.59 g, 16.8 mmol) and RuO_2 (8.5 mg), and the mixture was vigorously stirred at room temperature for 5 h. After adding methylene chloride (40 mL), the mixture was separated and the aqueous layer was extracted with methylene chloride. The combined organic layer was washed with water, filtered through a Celite pad, and concentrated to yield crude **7** [R_f = 0.08 (hexane–ethyl acetate, 1:1), 1.2 g, 77.4%] as a brown oil, which was used in the next reaction without further purification. For an analytical sample, crude **7** was purified by silica gel column chromatography (hexane–ethyl acetate, 1:5) to yield **7** as a white foam: ^{1}H NMR (DMSO-d_6) δ 0.99 (s, 9 H, *t*-Bu), 3.43–4.05 (m, 4 H, H-5 and CH_2OTBDPS), 4.25 (t, J = 6.8 Hz, 1 H, H-4), 5.04 (dd, J = 5.1 and 3.7 Hz, 1 H, H-2), 7.38–7.72 (m, 10 H, Ph_2).

For the identification of **7**, crude **7** was converted to its methyl ester: To a solution of **7** (2.0 g, 5.15 mmol) and K_2CO_3 (2.0 g) in acetone (30 mL), was added dimethyl sulfate (0.47 mL, 5.15 mmol), and the reaction mixture was stirred at room temperature for 3 h. The solid was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in ethyl acetate (30 mL), washed with water and brine, dried (anhydrous $MgSO_4$), and evaporated to dryness to yield an oil, which was purified by silica gel column chromatograpy (hexane–ethyl acetate, 2:3) to give methyl ester of **7** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9 H, *t*-Bu), 3.69 (s, 3 H, OCH_3), 3.81 (m, 2 H, CH_2OTBDPS), 4.13 (m, 2 H, H-5), 4.60 (m, 1 H, H-4), 5.18 (pseudo t, J = 4.4 and 3.7 Hz, 1 H, H-2), 7.33, 7.70 (m, 10 H, Ph_2). Anal. ($C_{22}H_{28}O_5Si$) C, H.

(2*R*,4*S*)- and (2*R*,4*R*)-4-Acetoxy-2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]dioxolane (8). To a solution of **7** (0.46 g, 1.14 mmol) in ethyl acetate (10 mL) was added pyridine (0.09 mL, 1.25 mmol) and $Pb(OAc)_4$ (0.66 g, 1.49 mmol), and the mixture was stirred at room temperature for 15 h under nitrogen. The mixture was filtered through a Celite pad, concentrated, and purified by silica gel column chromatography (hexane–ethyl acetate, 2:1) to yield **8** [R_f = 0.92 (hexane–ethyl acetate, 1:1), 0.29 g, 63.5%] as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.06, 1.10 (s, 9 H, *t*-Bu), 1.92, 2.06 (s, 1 H, CH_3), 3.71–4.24 (m, 4 H, H-5 and CH_2OTBDPS), 5.25, 5.38 (t, J = 4.3 and 3.3 Hz each, 1 H, H-2), 6.27–6.41 (m, 1 H, H-4), 7.20–7.72 (m, 10 H, Ph_2); IR (KBr) 3400, 1620 cm^{-1}. Anal. ($C_{22}H_{28}O_5Si$) C, H.

(−)-(2*R*,4*R*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]thymine (9) and (+)-(2*R*,4*S*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]thymine (10). A mixture of thymine (0.15 g, 1.2 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 thymine as colorless oil. To a solution of silylated thymine in dry 1,2-dichloroethane (5 mL) were added a solution of **8** (0.24 g, 0.6 mmol) in dry 1,2-dichloroethane (5 mL) and TMSOTf (0.23 mL, 1.2 mmol) at 5 °C, and the reaction mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was quenched by saturated $NaHCO_3$ (10 mL) and stirred for an additional 30 min at room temperature. The organic layer was separated and the aqueous layer was extracted with methylene chloride (30 mL × 3). The combined organic layer was washed with saturated $NaHCO_3$ and water and dried (anhydrous $MgSO_4$). After filtration, the filtrate was concentrated and the residue was separated by silica gel column chromatography (chloroform–methanol, 20:1) to yield **9** [R_f = 0.27 (hexane–ethyl acetate, 1:1), 0.13 g, 44.6%] and **10** [R_f = 0.36 (hexane–ethyl acetate, 1:1), 0.08 g, 28.6%] as white foams. **9**: UV (MeOH) λ_{max} 265.0 nm (pH 7), 265.0 (pH 2), 264.5 (pH 11). Anal. $C_{25}H_{30}N_2O_5Si$ C, H, N. **10**: UV (MeOH) λ_{max} 265.0 nm (pH 7,) 265.0 (pH 2), 264.5 (pH 11). Anal. ($C_{25}H_{30}N_2O_5Si$) C, H, N.

(−)-(2*R*,4*R*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]thymine (11). A mixture of **9** (93.3 mg, 0.2 mmol) and 1.0 M tetra-*n*-butylammonium fluoride in THF (0.24 mL, 0.24 mmol) in THF (3 mL) was stirred at room temperature for 1 h. After the mixture was concentrated, the residue was purified by silica gel column chromatography (chloroform–methanol, 20:1) to yield **11** (42 mg, 92.1%) as a white solid: UV (H_2O) λ_{max} 266.0 nm (ε 10760) (pH 7), 266.5 (ε 9890) (pH 2), 266.3 (ε 8400) (pH 11). Anal. ($C_9H_{12}N_2O_5$) C, H, N.

(+)-(2*R*,4*S*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]thymine (12). A mixture of **10** (60 mg, 0.13 mmol) and 1.0 M tetra-*n*-butylammonium fluoride in THF (0.15 mL, 0.15 mmol) in THF (3 mL) was stirred at room temperature for 1 h. After the mixture was concentrated, the residue was purified by silica gel column chromatography (chloroform–methanol, 20:1) to yield **12** (26 mg, 87.6%) as a white foam: UV (H_2O) λ_{max} 266.5 nm (ε

9450) (pH 7), 266.5 (ε 9200) (pH 2), 266.3 (ε 6930) (pH 11). Anal. ($C_9H_{12}N_2O_5$) C, H, N.

(+)-(2*R*,4*R*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-methylcytosine (15). A mixture of **11** (0.113 g, 0.50 mmol) and acetic anhydride (0.24 mL, 2.48 mmol) in pyridine (10 mL) was stirred at 0 °C for 3 h and refrigerated overnight. After completion of the reaction, the reaction mixture was concentrated in vacuo to dryness, the residue was dissolved in pyridine (10 mL), and 4-chlorophenyl dichlorophosphinate (0.18 g, 0.73 mmol) and 3-nitrotriazole (0.17 g, 1.49 mmol) were added. The mixture was stirred for 3 days and concentrated to dryness in vacuo. The residue was dissolved in chloroform (20 mL) and washed with water, saturated $NaHCO_3$, and brine. After drying (anhydrous $MgSO_4$) and filtering, the filtrate was evaporated under reduced pressure to yield crude **14** as yellowish syrup (UV (MeOH) λ_{max} 335.0 nm). A solution of **14** in a mixture of NH_4OH and 1,4-dioxane (1:3, 20 mL) was stirred for 5 h at room temperature. The reaction mixture was concentrated under reduced pressure and saturated methanolic ammonia (20 mL) was added. After stirring for 20 h, volatile materials were evaporated, and the residue was purified by silica gel column chromatography (chloroform–methanol, 10:1) to yield **15** (95 mg, 84% from **11**) as a white solid. In order to remove contaminated 3-nitrotriazole (byproduct), **15** was reacted with acetic anhydride (0.1 mL) and pyridine (10 mL), and the mixture was stirred for 2.5 h at room temperature. After evaporation of pyridine in vacuo, the residue was separated by silica gel column chromatography (chloroform–methanol, 10:1) to yield 0.095 g of acetate which was deacetylated using NaOMe (1 equiv) in MeOH to give pure **15** [R_f = 0.125 (chloroform–methanol, 10:1), 0.13 g, 60% from **11**] which was crystallized from Et_2O: UV λ_{max} 277.0 nm (ε 7940) (pH 7), 285.3 (ε 12100) (pH 2), 277.0 (ε 8020) (pH 11). Anal. ($C_9H_{13}N_3O_4 \cdot H_2O \cdot 0.2C_4H_{10}O$) C, H, N.

(+)-(2*R*,4*R*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]cytosine (17) and (−)-(2*R*,4*S*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]cytosine (18). A mixture of N^4-acetylcytosine (0.76 g, 4.96 mmol), ammonium sulfate (catalytic amount), and hexamethyldisilazane (20 mL) was refluxed for 4 h under nitrogen. After evaporation of HMDS under anhydrous conditions, a mixture of the silylated *N*-acetylcytosine in dry 1,2-dichloroethane (15 mL), a solution of acetate **8** (1 g, 2.5 mmol) in dry 1,2-dichloroethane (15 mL), and TMSOTf (0.96 mL, 5 mmol) was stirred for 45 min under nitrogen, aqueous $NaHCO_3$ (1 mL) was added, and the mixture was stirred for an additional 30 min. The resulting solid was filtered off through Celite pad and the filtrate was dried (anhydrous $MgSO_4$). The mixture was concentrated to dryness in vacuo and the residue was purified by silica gel column chromatography (chloroform–methanol, 20:1) to yield **16α** [R_f = 0.72 (chloroform–methanol, 20:1), 480 mg, 39%] and **16β** [R_f = 0.63 (chloroform–methanol, 20:1), 485 mg, 39%]: UV (MeOH) 298.5 nm. Both **16α** and **16β** were separately treated with NaOMe (12.6 mg of Na in 12.6 mL of MeOH) in MeOH (10 mL) at room temperature for 1.5 h. The mixture was neutralized with acetic acid and concentrated to dryness under reduced pressure. After deacetylation, TLC showed the transposition of both compounds. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 1:1) to give **17** (quantitative yield, white crystals, mp 162–164 °C) and **18** (quantitative yield, white solid, mp 181–183 °C). **17**: UV (MeOH) λ_{max} 272.8 nm (ε 7890). Anal. ($C_{24}H_{29}N_3O_4Si$) C, H, N. **18**: UV (MeOH) λ_{max} 272.8 nm (ε 9800). Anal. ($C_{24}H_{29}N_3O_4Si$) C, H, N.

(+)-(2*R*,4*R*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]cytosine (19). A mixture of **17** (0.107 g, 0.24 mmol) and 1.0 M tetra-*n*-butylammonium fluoride (0.26 mL, 0.26 mmol) in THF (5 mL) was stirred for 30 min at room temperature and the solvent was concentrated to dryness under reduced pressure. The syrupy residue was purified by silica gel column chromatography (chloroform–methanol, 10:1) to yield **19** (0.04 g, 79.2%), which was crystallized from hexane–methylene chloride; UV λ_{max} 270.0 nm (ε 8880) (pH 7), 277.8 (ε 13430) (pH 2), 270.00 (ε 9120) (pH 11). Anal. ($C_8H_{11}N_3O_4 \cdot 0.35H_2O$) C, H, N.

(−)-(2*R*,4*S*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]cytosine (20). A mixture of **18** (0.107 g, 0.24 mmol) and 1.0M tetra-*n*-butylammonium fluoride (0.26 mL, 0.26 mmol) in THF (5 mL) was stirred for 30 min at room temperature. The mixture was concentrated under reduced pressure to dryness and the syrupy residue was purified by silica gel column chromatography (chloroform–methanol, 10:1) to yield **20** (0.04 g, 79.2%) as a white solid: UV λ_{max} 270.5 nm (ε 7930) (pH 7), 278.5 (ε 11960) (pH 2), 270.5 (ε 7720) (pH 11). Anal. ($C_8H_{11}N_3O_4$) C, H, N.

(±)-(2*R*,4*SR*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]uracil (21 and 22). Silylated uracil, which was prepared from uracil (0.62 g, 5.54 mmol) and HMDS (20 mL), was treated with **8** (0.23 g, 0.56 mmol) in 1,2-dichloroethane (15 mL) and TMSOTf (0.22 mL, 1.13 mmol) at room temperature for 2 h under nitrogen, 1,2-dichloroethane (5 mL) and saturated $NaHCO_3$ (5 mL) were added, and the mixture was 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 $CHCl_3$ (50 mL × 4), and the combined organic extracts were washed with saturated $NaHCO_3$, dried (anhydrous $MgSO_4$), and evaporated under reduced pressure to give a yellow oil residue, which was purified by silica gel column chromatography (chloroform–methanol, 33:1) to yield a mixture of **21** and **22** (0.76 g, 60%): UV (MeOH) λ_{max} 262.0 nm. Anal. ($C_{24}H_{28}N_2O_5Si$) C, H, N.

(+)-(2*R*,4*R*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-5-fluorouracil (23) and (+)-(2*R*,4*S*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-5-fluorouracil (24). A mixture of silylated 5-fluorouracil [prepared from 0.39 g (3.0 mmol) of 5-fluorouracil and 20 mL of HMDS], **8** (0.6 g, 1.5 mmol), and TMSOTf (0.58 mL, 3.0 mmol) in 20 mL of 1,2-dichloroethane was stirred for 30 min at room temperature under argon. After workup similar to that for **21** and **22**, the purification by silica gel chromatography (hexane–ethyl acetate, 2:1) gave **23** (R_f = 0.18 (hexane–ethyl acetate, 1:1), 0.294 g, 41.7%) and **24** (R_f: 0.28, 0.196 g, 27.8%). **23**: UV (MeOH) λ_{max} 266.0 nm (ε 8200). Anal. ($C_{24}H_{27}FN_2O_5Si$) C, H, N. **24**: UV (MeOH) λ_{max} 266.0 nm (ε 9000). Anal. ($C_{24}H_{27}FN_2O_5Si$) C, H, N.

(+)-(2*R*,4*R*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-5-chlorouracil (25) and (−)-(2*R*,4*S*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-5-chlorouracil (26). A mixture of silylated 5-chlorouracil [prepared from 0.73 g (5 mmol) of 5-chlorouracil and 45 mL of HMDS], **8** (1.0 g, 2.5 mmol), and TMSOTf (0.97 mL, 5.02 mmol) in 23 mL of 1,2-dichloroethane was stirred for 1 h under nitrogen. After workup similar to that for **21** and **22**, the purification by silica gel column chromatography (hexane–ethyl acetate, 1:1) gave **25** [R_f = 0.65 (chloroform–methanol, 20:1), 0.36 g, 29.6%] as a white solid and **26** [R_f = 0.65 (chloroform–methanol, 20:1), 0.33 g, 27.1%] (0.33 g, 27.1%) as a colorless foam, respectively. **25**: UV (MeOH) λ_{max} 272.0 nm (ε 7580). Anal. ($C_{24}H_{27}ClN_2O_5Si$) C, H, N. **26**: UV (MeOH) λ_{max} 272.0 nm (ε 8960). Anal. ($C_{24}H_{27}ClN_2O_5Si$) C, H, N.

(+)-(2*R*,4*R*)-5-Bromo-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]uracil (27) and (+)-(2*R*,4*S*)-5-Bromo-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]uracil (28). A mixture of silylated 5-bromouracil [prepared from 0.477 g (2.46 mmol) of 5-bromouracil and 20 mL of HMDS], **8** (0.5 g, 1.25 mmol), and TMSOTf (0.48 mL, 2.46 mmol) in 5 mL of 1,2-dichloroethane was stirred for 1 h at room temperature. After workup similar to that for **21** and **22**, purification by silica gel column chromatography (hexane–ethyl acetate, 2:1) yielded **27** (R_f = 0.48 (hexane–ethyl acetate, 1:1), 0.23 g, 34.7%) and **28** (R_f = 0.58, 0.2 g, 30.2%). **27**: UV (MeOH) λ_{max} 278.0 nm (ε 8860). Anal. ($C_{24}H_{27}BrN_2O_5Si$) C, H, Br, N. **28**: UV (MeOH) λ_{max} 278.0 nm (ε 9960). Anal. ($C_{24}H_{27}BrN_2O_5Si$) C, H, Br, N.

(+)-(2*R*,4*R*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-5-iodouracil (29) and (+)-(2*R*,4*S*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-5-iodouracil (30). A mixture of silylated 5-iodouracil [prepared from 1.2 g (5 mmol) of 5-iodouracil and 20 mL of HMDS], **8** (1 g, 2.5 mmol), and TMSOTf (1.1 mL, 5.7 mmol) in 15 mL of 1,2-dichloroethane (15 mL) was stirred at room temperature for 1 h under nitrogen. After workup similar to that for **21** and **22**, purification by silica gel column chromatography (chloroform–methanol, 200:1) yielded **29** (R_f = 0.33, 0.41 g, 17.2%) and **30** (R_f = 0.39, 0.43 g, 17.9%) which was crystallized from Et_2O. **29**: UV (MeOH) λ_{max} 285.0 nm. Anal. ($C_{24}H_{27}IN_2O_5Si$) C, H,

I, N. **30**: UV (MeOH) λ_{max} 285.0 nm. Anal. ($C_{24}H_{27}IN_2O_5Si \cdot 0.25C_4H_{10}O$) C, H, I, N.

(−)-(2*R*,4*R*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]uracil (31) and (−)-(2*R*,4*S*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]uracil (32). An α,β mixture of **21** and **22** (0.13 g, 0.28 mmol) in THF (5 mL) was treated with 1.0 M tetra-*n*-butylammonium fluoride in THF (0.3 mL, 0.3 mmol) for 1 h at room temperature and the solvent was evaporated to dryness under reduced pressure. The residue was purified by preparative TLC (chloroform–methanol, 20:1) to yield **31** (27 mg, 45.7%, R_f = 0.39) and **32** (23 mg, 38.9%, R_f = 0.33) as white solids. **31**: UV λ_{max} 261.0 nm (ε 7780) (pH 7), 261.0 (ε 7665) (pH 2), 260.5 (ε 5814) (pH 11). Anal. ($C_8H_{10}N_2O_5$) C, H, N. **32**: UV λ_{max} 261.5 nm (ε 9975) (pH 7), 261.5 (ε 9565) (pH 2), 260.5 (ε 7667) (pH 11). Anal. ($C_8H_{10}N_2O_5$) C, H, N.

(−)-(2*R*,4*R*)-5-Fluoro-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]uracil (33). A solution of **23** (0.28 g, 0.6 mmol) and 1.0 M tetra-*n*-butylammonium fluoride in THF (0.66 mL, 0.66 mmol) in THF (5 mL) was stirred for 1 h at room temperature. After evaporation of solvent, the residue was purified by silica gel column chromatography (chloroform–methanol, 20:1) to give **33** [R_f = 0.09 (chloroform–methanol, 20:1), 0.13 g, 94.2%] (0.13 g, 94.2%) as a white solid: UV λ_{max} 268.0 nm (ε 7970) (pH 7), 268.0 (ε 8540) (pH 2), 267.5 (ε 6340) (pH 11). Anal. ($C_8H_9FN_2O_5$) C, H, N.

(−)-(2*R*,4*S*)-5-Fluoro-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]uracil (34). Compound **24** (0.14 g, 0.3 mmol) was treated according to the same procedure for **33** to give **34** (0.055 g, 79.7%) as a white solid which was crystallized from hexane–methylene chloride: UV λ_{max} 268.0 nm (ε 9980) (pH 7), 268.3 (ε 10980) (pH 2), 268.0 (ε 8890) (pH 11). Anal. ($C_8H_9FN_2O_5 \cdot 0.04C_6H_{14}$) C, H, N.

(+)-(2*R*,4*R*)-5-Chloro-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]uracil (35). Compound **25** (0.28 g, 0.57 mmol) was treated according to the procedure for **33** to give **35** (0.11 g, 77%) as a white solid: UV (H_2O) λ_{max} 275.50 nm (ε 7730) (pH 7), 275.5 (ε 8630) (pH 2), 274.5 (ε 6150) (pH 11). Anal. ($C_8H_9ClN_2O_5$) C, H, Cl, N.

(−)-(2*R*,4*S*)-5-Chloro-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]uracil (36). Compound **26** (0.217 g, 0.45 mmol) was treated according to the procedure for **33** to give **36** (0.078 g, 69%) as a white solid: UV (H_2O) λ_{max} 276.0 nm (ε 8230) (pH 7), 276.0 nm (ε 8880) (pH 2), 274.5 nm (ε 6960) (pH 11). Anal. ($C_8H_9ClN_2O_5$) C, H, Cl, N.

(−)-(2*R*,4*R*)-5-Bromo-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]uracil (37). Compound **27** (0.19 g, 0.36 mmol) was treated according to the procedure for **33** to give **37** (0.109 g, 99%) as a white solid: UV λ_{max} 278.5 nm (ε 7420) (pH 7), 270.0 nm (ε 9120) (pH 2), 276.00 (ε 4710) (pH 11). Anal. ($C_8H_9BrN_2O_5$) C, H, N.

(+)-(2*R*,4*S*)-5-Bromo-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]uracil (38). Compound **28** (0.2 g, 0.38 mmol) was treated according to the procedure for **33** to give **38** (0.104 g, 94.5%) as a white solid: UV λ_{max} 278.5 nm (ε 9320) (pH 7), 270.0 nm (ε 9040) (pH 2), 276.0 nm (ε 5520) (pH 11). Anal. ($C_8H_9BrN_2O_5$) C, H, Br, N.

(+)-(2*R*,4*R*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-iodouracil (39). Compound **29** (84 mg, 0.24 mmol) was treated according to the procedure for **33** to give **39** as a white solid (27 mg, 45.7%): UV λ_{max} 287.0 nm (ε 6760) (pH 7) 287.0 (ε 6610) (pH 2), 277.5 (ε 5380) (pH 11). Anal. ($C_8H_9IN_2O_5$) C, H, I, N.

(+)-(2*R*,4*S*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-iodouracil (40). Compound **30** (85 mg, 0.25 mmol) was treated according to the procedure for **33** to give **40** (23 mg, 38.9%) as a white solid which was recrystallized from methanol: UV λ_{max} 287.5 nm (ε 5687) (pH 7), 287.5 (ε 6435) (pH 2), 278.5 (ε 4759) (pH 11). Anal. ($C_8H_9IN_2O_5 \cdot 0.5MeOH$) C, H, I, N.

Antiviral Assays. HIV-1 (strain LAV-1) was obtained from Dr. P. Feorino (Emory University, Atlanta, GA). The virus was propagated in human PBM cells using RPMI 1640 medium. Virus obtained from cell-free culture supernatant was titrated and stored in aliquots at −70 °C until use. AZT-resistant and -sensitive viruses strain 9F (G910-6) and 10 (H112-2) were obtained through the NIH AIDS Research and Reference Program and propagated in PBM cells. The procedures for the antiviral assays in human PBM cells have been published previously.[24] Briefly, uninfected phytohemagglutinin-stimulated human PBM cells were infected with HIV [about 63000 disintegrations per minute of reverse transcriptase activity per 10^7 cells per 10 mL of medium which is equivalent to a multiplicity of infection (MOI) of 0.1]. The drugs were then added to duplicate to triplicate cultures. Virus yield in the supernatant was determined on day 6 after infection by a reverse transcriptase assay. AZT was used as a positive control for all the virological assays.

PBM and Vero Cells Proliferation Assay. The drugs were evaluated for their potential toxic effects on uninfected PHA-stimulated human PBM and in Vero cells. The cells were cultured with and without drug for 6 or 3 days at which time aliquots were counted for cell viability and proliferation, as described previously.[27]

Median-Effect Method. EC_{50} and IC_{50} values were obtained by analysis of the data using median-effect method.[218] The EC_{90} values were determined from the EC_{50} and the slope of the dose–response curve.

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Supplementary Material Available: Atomic coordinates and anisotropic thermal parameters for compounds **11** and **19** (4 pages). Ordering information is given on any current masthead page.

(25) Pearlman, D. A.; Kim. S. H. Conformational Studies of Nucleic Acids II. The Conformational Energetics of Commonly Occurring Nucleosides. *J. Biomol. Struct. Dyn.* **1985**, *3*, 99–125.
(26) Sanger, W. *Principles of Nucleic Acid Structure*; Springer: New York, 1984; pp 9–104.
(27) Schinazi, R. F.; Peters, J.; Williams, C. C.; Chance, D.; Nahmias, A. J. Effect of Combinations of Acyclovir with Vidarabine or Its 5′-Monophosphate on Herpes Simplex Viruses in Cell Culture and in Mice. *Antimicrob. Agents. Chemother.* **1982**, *22*, 499–507.
(28) Chou, T.-C.; Talalay, P. Quantitative Analysis of Dose–Effect Relationships: The Combined Effects of Multiple Drugs or Enzyme Inhibitors. *Adv. Enzyme Regul.* **1984**, *22*, 27–55.