Enantiomeric Syntheses of Conformationally Restricted D- and L-2′,3′-Dideoxy-2′,3′-*endo*-methylene Nucleosides from Carbohydrate Chiral Templates

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D- and L-2′,3′-dideoxy-2′,3′-*endo*-methylene nucleosides were synthesized as potential antiviral agents. The key intermediates 5-*O*-*tert*-butyldiphenylsilyl-D- and L-2,3-dideoxy-2,3-*endo*-methylenepentofuranoses (**20** and **33**, respectively) were obtained by selective protection of the D- and L-2,3-dideoxy-2,3-*endo*-methylenepentose derivatives **19** and **32** which were prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol and L-gulonic γ-lactone, respectively, and converted to 5-*O*-*tert*-butyldiphenylsilyl-D- and L-2,3-dideoxy-2,3-*endo*-methylenepentofuranosyl acetates (**21** and **34**, respectively) or the chlorides **22** and **35**. The acetates and chlorides were condensed with pyrimidine and purine bases by Vorbrüggen conditions or S_N2-type condensation. Vorbrüggen conditions using the acetates gave mostly α-isomers. In contrast, S_N2-type condensation using the chlorides greatly improved the β/α ratio. From the synthesis, several D- and L-2′,3′-dideoxy-2′,3′-*endo*-methylene nucleoside analogues have been obtained, and their structures have been elucidated by NMR spectroscopy and X-ray crystallography. The synthesized D- and L-adenine derivatives were tested as substrates of adenosine deaminase, which indicated that the D-adenosine derivative **4a** was a good substrate of a mammalian adenosine deaminase from calf intestinal mucosa (EC 3.5.4.4) while its L-enantiomer **10a** was a poor substrate. Either the D-adenine derivative **4a** or its L-enantiomer **10a** did not serve as an inhibitor of the enzyme.

Introduction

For the past decade, intensive efforts by medicinal chemists to discover potent and selective antiviral agents have resulted in the discovery of many 2′,3′-dideoxynucleoside analogues, some of which exhibited excellent antiviral activities against human immunodeficiency virus type 1 (HIV-1) (AZT,[1] ddC,[2] ddI,[3] d4T,[4] 3TC,[5] Abacavir[6]), herpes virus (Ganciclovir,[7] Famciclovir,[8] and Cidofovir[9]), and hepatitis B virus (HBV) (3TC,[5] FTC,[10] DAPD,[11] L-FMAU,[12] and L-Fd4C[13]). However, the toxicities[14,15] associated with these nucleosides as well as the emergence of resistant viral strains[16,17] prompted nucleoside chemists to search for additional novel and structurally diverse compounds with minimally overlapping resistance and toxicity profiles. Thus, as part of our discovery program in the search of novel antiviral nucleosides, we synthesized a novel class of nucleosides, D-2′,3′-*endo*-methylene nucleosides, where the sugar moieties are conformationally restricted due to the methylene group fused between the 2′ and 3′ positions such that the overall structures are analogous to those of the biologically active 2′,3′-didehydro-2′,3′-dideoxy nucleosides (d4N) such as d4T [4] and d4A[18] (Figure 1). The preliminary syntheses of the D-isomers have previously been reported

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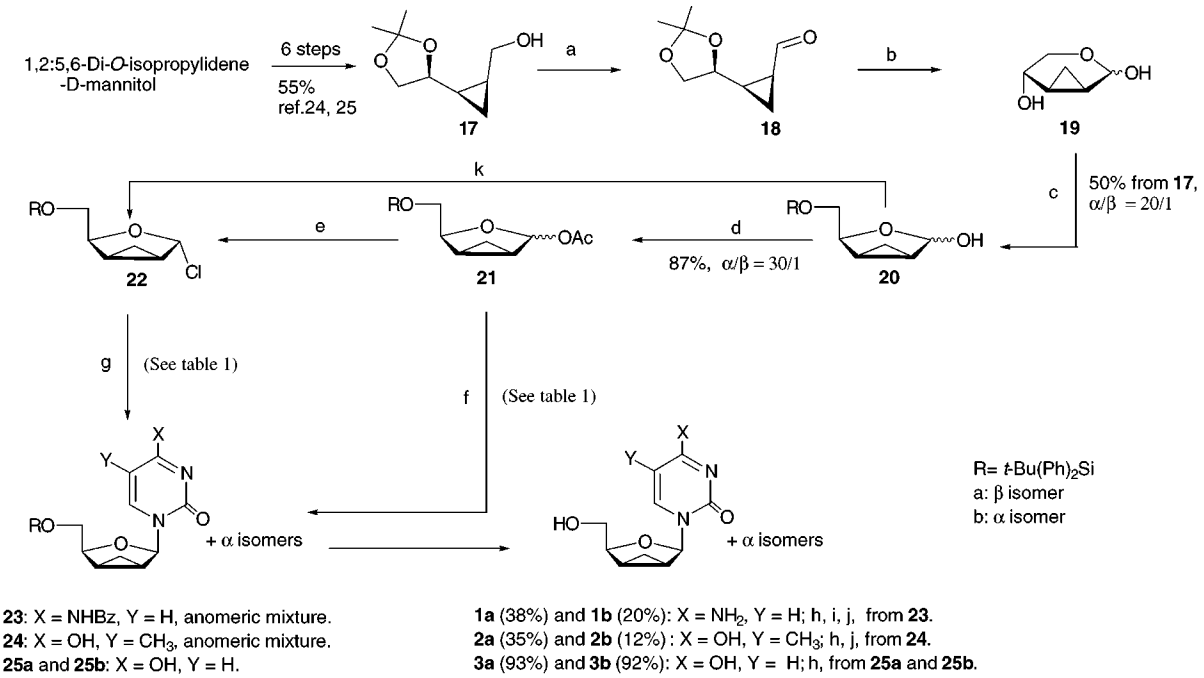
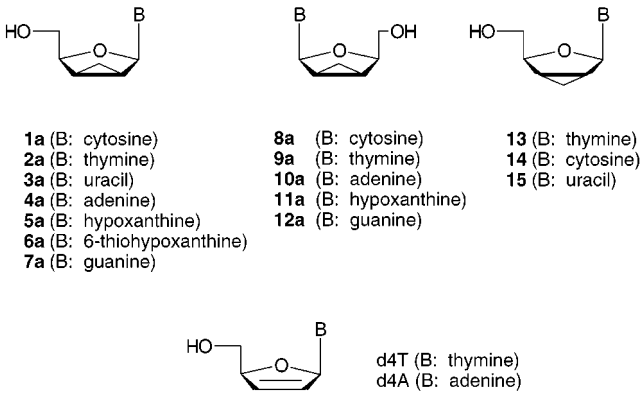
Scheme 1[a]



23: X = NHBz, Y = H, anomeric mixture.
24: X = OH, Y = CH_3, anomeric mixture.
25a and **25b**: X = OH, Y = H.

1a (38%) and **1b** (20%): X = NH_2, Y = H; h, i, j, from **23**.
2a (35%) and **2b** (12%): X = OH, Y = CH_3; h, j, from **24**.
3a (93%) and **3b** (92%): X = OH, Y = H; h, from **25a** and **25b**.

[a] Conditions: (a) Swern oxidation. (b) 1% HCl/1,4-dioxane (1:1), rt, 4 h. (c) TBDPSCl, py, CH_2Cl_2, 0 °C, 24 h. (d) Ac_2O, py, 30 min, (e) HCl/ether −10 °C, 10 min. (f) Silylated pyrimidines, TMSOTf, CH_3CN, 0 °C to rt, 3 h. (g) Silylated pyrimidines, $CHCl_3$ or THF, 0 °C to rt, 3 h. (h) TBAF, THF, rt, 20 min. (i) NH_3, MeOH, rt, 8 h. (j) HPLC separation. (k) Ph_3P, CCl_4, THF, 50 °C, 3 h.



1a (B: cytosine)
2a (B: thymine)
3a (B: uracil)
4a (B: adenine)
5a (B: hypoxanthine)
6a (B: 6-thiohypoxanthine)
7a (B: guanine)

8a (B: cytosine)
9a (B: thymine)
10a (B: adenine)
11a (B: hypoxanthine)
12a (B: guanine)

13 (B: thymine)
14 (B: cytosine)
15 (B: uracil)

d4T (B: thymine)
d4A (B: adenine)

Figure 1. Newly synthesized 2′,3′-dideoxy-2′,3′-*endo*-methylene nucleosides **1a**−**12a**, reported 2′,3′-dideoxy-2′,3′-*exo*-methylene nucleosides **13**−**15**, and bioactive 2′,3′-didehydro-2′,3′-dideoxynucleosides (d4Ns).

by our laboratory.[19] Recently, much attention has been given to L-nucleosides since some of the L-enantiomers have been shown to possess improved biological profiles.[12,13b,20] For example, L-FMAU showed greater potency against HBV and lower toxicity than that of D-FMAU.[12] On the basis of these observations, it was of interest to synthesize the L-enantiomers as well as the D-enantiomers (**1a**−**12a** in Figure 1) to compare their biological properties. Although several 2′,3′-*exo*-methylene counterparts have been reported (**13**−**15** in Figure 1),[21−23] the 2′,3′-*endo*-methylene nucleosides have not been reported other than our preliminary report.[19] Furthermore, the synthesis of the target compounds may not be readily achievable by other published methods due to the high steric hindrance imposed on the *β*-face of the *endo*-methylene sugar moiety. Herein we describe the full accounts of the syntheses of D- and L-2′,3′-dideoxy-*endo*-methylene nucleoside as well as our preliminary enzymatic studies with adenosine deaminase to determine the enantioselectivity of the enzyme.

Results and Discussion

To synthesize the target compounds D-2′,3′-dideoxy-2′,3′-*endo*-methylene nucleosides, 1,2:5,6-di-*O*-isopropylidene-D-mannitol was used as the starting material, which was readily converted to cyclopropyl intermediate **17** in 55% yield (Scheme 1).[24,25] The alcohol **17** was oxidized to aldehyde **18** by Swern oxidation in high yield, which was deprotected to give lactol **19**. Selective protection of the primary hydroxy group of **19** with TBDPSCl afforded the desired bicyclic furanose **20** (α/*β* = 20/1, determined by NMR) (Scheme 1). Treatment of **20** with acetic anhydride gave acetate **21** (α/*β* = 30/1, determined by NMR). The unusual high α/*β* ratios in **20** and **21** may be due to both anomeric [26] and steric effects. The acetate **21** was condensed with silylated N^4-benzoylcytosine and thymine under Vorbrüggen conditions,[27] which gave mainly the undesired α-isomers in 89% and 82% yields, respectively (Table 1). In particular, condensation with

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Table 1. β/α Ratio of the Glycosylation Reactions

heterocycle[a]	sugar[b]	solvent[c]	β/α	yield (%)[d]	product
N^4-Bz-cytosine	**21**	CH_3CN	1/6	89	**23**
	22	$CHCl_3$	2/1	68	**23**
thymine	**21**	CH_3CN	1/3	82	**24**
	22	$CHCl_3$	3/1	63	**24**
	22	THF	1/1	65	**24**
uracil	**22**	CH_2Cl_2	2/1	61	**25**
N^6-Bz-adenine	**21**	CH_3CN	only α	75	ref 19
	22	CH_3CN	2.5/1	35	ref 19
6-Cl-purine	**22**	CH_3CN	3/1	68	**26**
	22	DMF	5/1	65	**26**
	22[e]	DMF/THF	6/1	66[f]	**26**
2-NH_2-6-Cl-purine	**22**	DMF	9/1	40	**28**

[a] Silylated pyrimidine bases were used in the glycosylation reactions. Silylated purine bases were used for Vorbrüggen-type condensation, and sodium salts of purines were used for S_N2-type ondensation. [b] Acetate **21** was used for Vorbrüggen-type condensation and chloride **22** for S_N2-type condensation. [c] The sugars were added to the solutions of heterocycles in the indicated solvents at 0 °C, and the resulting mixtures were stirred at room temperature for 3 h. [d] Yields from **21**. [e] **22** was prepared directly from **20** using Ph_3P and CCl_4 in THF. [f] Yield from **20**.

a bulky base, N^6-benzoyladenine, gave exclusively the α-isomer due to the high steric hindrance on the β face of the sugar (Table 1).[19] To overcome the undesired stereoselectivity, an alternative approach was tried using the chloride **22**, which was easily obtainable as mainly the α-isomer by treating the acetate **21** with HCl in ether at low temperature. S_N2-type condensations of the chloride **22** with the sodium salt of purines or silylated pyrimidines[28] gave mainly the β-anomers as major isomers in 40−68% yields along with the α-anomers, in contrast to the Vorbrüggen-type condensation with the acetate **21**, which gave exclusively the α-isomers[19] (Table 1). The chloride **22** was also prepared directly from the protected lactol **20** by treatment with Ph_3P and CCl_4 in THF at 50 °C,[29] which was also used for the S_N2-type condensation. The S_N2-type condensations, however, were not completely stereospecific as previously reported. Hildebrand et al. postulated that the α-chlorosugar epimerizes during the reaction.[30] Results of the glycosylation reactions are summarized in Table 1. In the S_N2-type condensation, sodium salts of purine bases gave higher β/α ratios than silylated pyrimidine bases. In the condensation of **22** with silylated thymine, $CHCl_3$ provides higher stereoselectivity than a polar solvent such as THF,[31] whereas in the condensations of **22** with sodium salts of purines the more polar solvent gave the higher β/α ratio (Table 1).

Anomeric mixtures of cytosine and thymine derivatives **23** and **24** were deprotected by sequential treatment with TBAF and NH_3/MeOH and separated by reversed-phase HPLC to give cytosine derivatives **1a** (38%) and **1b** (23%), and thymine derivatives **2a** (35%) and **2b** (12%), respectively. An anomeric mixture of uracil derivative **25** was separated by silica gel column chromatography to **25a** (43%) and **25b** (18%), and following deprotection with TBAF gave **3a** and **3b** in quantitative yields (Scheme 1). An anomeric mixture of the 6-chloropurine derivative **26** was separated to **26a** and **26b** by silica gel column chromatography followed by deprotection with TBAF to give **27a** and **27b**. The purine nucleosides **4a**−**6b** were obtained from the common intermediates **27a** and **27b**. The adenine derivatives **4a** and **4b** were prepared by treating **27a** and **27b** with NH_3/MeOH in a steel bomb at 90 °C in 65% yields. The hypoxanthine derivatives **5a** and **5b** were obtained by treating **27a** and **27b** with 2-mercaptoethanol and $NaOCH_3$ in refluxing MeOH in 54% and 52% yield, respectively. The 6-thiohypoxanthine derivatives **6a** and **6b** were obtained by treating **27a** and **27b** with H_2S and $NaOCH_3$ in refluxing MeOH in 61% and 62% yield, respectively.[32] For the preparation of the guanine derivative **7a**, an anomeric mixture of the 2-amino-6-chloropurine derivative **28** was first deprotected with TBAF to give **29**, which was treated with 2-mercaptoethanol and $NaOCH_3$ in refluxing MeOH, and subsequent separation by reversed-phase HPLC afforded the guanine derivative **7a** in 29% yield (Scheme 2). To obtain the L-counterparts, cyclopropyl intermediate **30** was prepared from L-gulonic γ-lactone in 61% yield,[33,34] which was converted to free sugar **32** by Swern oxidation followed by acidic deprotection (Scheme 3). Selective protection of compound **32** with TBDPSCl gave protected lactol **33**, which was acetylated with Ac_2O and subsequently chlorinated with HCl in ether at low temperature to obtain chloride derivative **35**. The chloride **35** was condensed with silylated pyrimidine bases or sodium salts of purine bases, as described in the preparation of the D-isomers, to afford L-2′,3′-*endo*-methylene nucleosides (**8a**−**12a**).

Stereochemical assignments of the final compounds were made on the basis of 1D and 2D NMR spectroscopy and X-ray crystallography. The configuration of the anomeric center was assigned mainly by ^{1}H NMR data, in which the anomers with H4′ appearing at lower field were assigned as the α-anomers and the ones at higher field were assigned as the β-anomers on the basis of the deshielding effect of the base moiety (Table 2). This assignment was further confirmed by the NOESY experiment of **26a** and **26b** (Figure 2) as well as X-ray crystallography[35] of **4a** (Figure 3) and **1b** (Figure 4). An additional characteristic of the ^{1}H NMR spectra was that the $J_{1',2'}$ of the β-isomer (average 2.6 Hz) was larger than that of the α-isomer (Table 2). These small coupling constants between the *anti*-vicinal H1′ and H2′ of the α-isomer suggest that the H1′−C1′ bond is nearly or-

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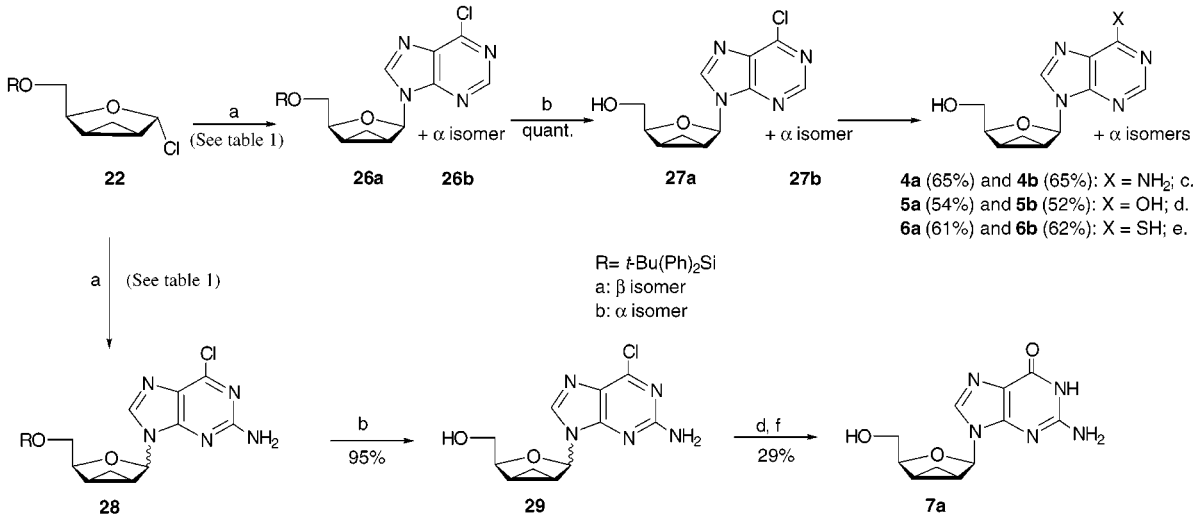
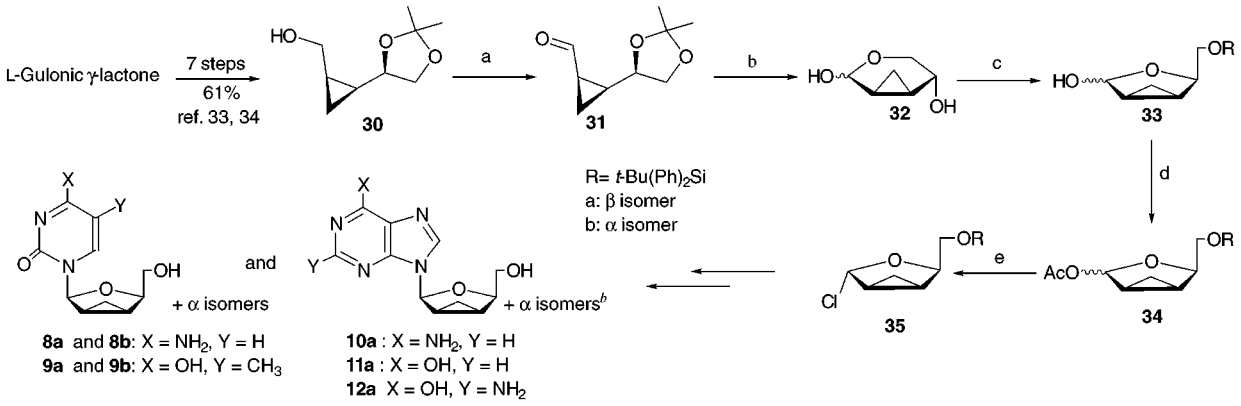
Scheme 2[a]



[a] Conditions: (a) Sodium salts of purines, CH_3CN or DMF or DMF/THF, 0 °C to rt, 3 h. (b) TBAF, THF, rt, 20 min. (c) NH_3, MeOH, 90 °C, 16 h. (d) 2-Mercaptoethanol, NaOMe, MeOH, reflux, 5 h for **5a** and **5b**, 16 h for **7a**. (e) H_2S, NaOMe, MeOH, reflux, 1 h. (f) HPLC separation.

Scheme 3[a]



[a] Conditions: (a) Swern oxidation. (b) 1% HCl/1,4-dioxane (1:1), rt, 4 h. (c) TBDPSCl, py, CH_2Cl_2, 0 °C, 24 h. (d) Ac_2O, py, rt 30 min. (e) HCl/ether, −10 °C, min. [b] Not characterized.

Table 2. Some Selected ^{1}H NMR Data of the Synthesized Nucleosides

compd no.	H1′ $J_{1',2'}$(Hz)	H4′ δ (ppm)	compd no.	H1′ $J_{1',2'}$(Hz)	H4′ δ (ppm)
1a	2.6	4.11	**4a**	2.7	4.03
b	<0.5	4.19	**b**	<0.5	4.25
2a	2.7	4.09	**5a**	2.5	4.12
b	<0.5	4.29	**b**	1.7	4.22
3a	2.6	4.11	**6a**	2.7	4.19
b	<0.5	4.29	**b**	<0.5	4.25

thogonal with respect to the H2′−C2′ bond, as predicted by Karplus correlation,[36] which is also consistent with a reported example.[37] This structural feature is shown in the X-ray structure of the α-isomer **1b**, where the

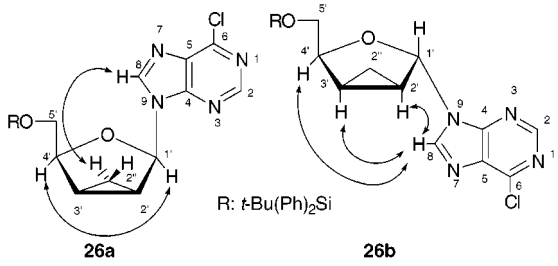


Figure 2. NOE correlations from NOESY spectra of **26a** and **26b**.

dihedral angle of the two bonds is 80.1° while that of the β-isomer **4a** is 55.8° (Figures 3 and 4).

The X-ray structure of **4a** reveals that the conformation around the glycosylic bond is highly *anti* with a χ value of −73° (torsion angle of C4−N9−C1′−O4′) and the conformation around the C4′−C5′ bond is *trans* with a γ value of 177° (torsion angle of O5′−C5′−C4′−C3′), which are similar to those of 2′,3′-didehydro-2′,3′-dideoxyadenosine (d4A)[18] (Table 3). However, the furanoid ring adopts an O4′-*endo* conformation with a pseudorotational angle *P* of 91.7° and a relatively large puckering degree

(35) (a) X-ray data for compound **4a**: crystal dimensions, 0.50 × 0.30 × 0.30 mm; colorless crystals, prism; empirical formula $C_{11}H_{13}N_5O_2$; formula weight 247.26; crystal system monoclinic; lattice parameters a = 5.231 Å, b = 8.050 Å, c = 13.577 Å; space group $P2_1$(no. 4); Z = 2. (b) X-ray data for compound **1b**: crystal dimensions 0.20 × 0.30 × 0.50 mm; colorless crystals, rock; empirical formula $C_{10}H_{15}N_3O_4$; formula weight 241.25; crystal system orthorhombic; lattice parameters a = 8.469 Å, b = 9.417 Å, c = 14.50 Å; space group $P2_12_12_1$(no. 19); Z = 4.

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Table 3. Some Conformational Parameters from X-ray Crystallographic of 4a and Reported Reference Nucleosides

param	**4a**	**15**[38]	d4A[18]	ddA[18]
P^a	91.7° (O4′-*endo*)	273.3° (O4′-*exo*)	243.9° (O4′-*exo*)	193.5° (C2′-*endo*/C3′-*exo*)
χ^b	−73.0°	−106.9°	−100.2°	−96.1°
γ^c	177.0°	−174.7°	179.8°	−179.9°
$\nu_m{}^d$	34.5°	8.8°	7.5°	36.7°
d^e	4.6 Å (5.1 Å)[f]	3.9 Å (4.6 Å)[f]	3.9 Å (4.6 Å)[f]	3.9 Å (4.5 Å)[f]

[a] Pseudorotation angle of the sugar moiety. [b] Torsion angle of C2−N1−C1′−O4′ (pyrimidine nucleosides) or C4−N9−Cl′−O4′ (purine nucleosides). [c] Torsion angle of C3′−C4′−C5′−O5′. [d] Maximum amplitude of puckering. [e] Distance between C5′ and N9 (N1 for pyrimidine nucleosides). [f] Distance between O5′ and N9 (N1 for pyrimidine nucleosides).

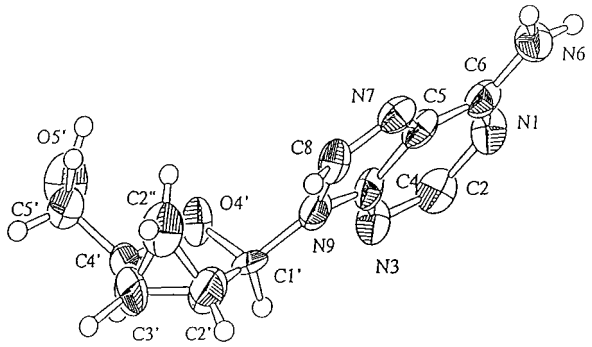

Figure 3. ORTEP drawing of the X-ray crystallographic structure of **4a**.

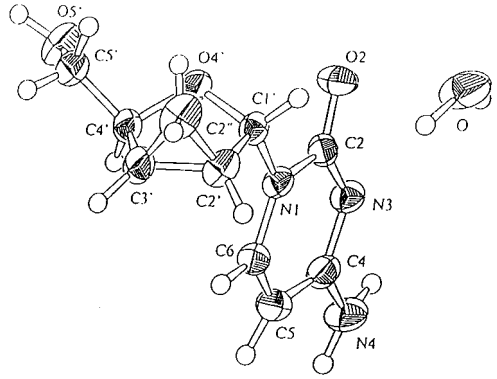

Figure 4. ORTEP drawing of the X-ray crystallographic structure of **1b**.

ν_m of 34.5°, which are quite different from those of 2′,3′-*exo*-methylene uridine (**15**)[38] as well as from those of d4N such as d4A,[18] which adopts a nearly planar sugar conformation (small ν_m) (Table 3). As a result, the distance between C5′ and N9 (N1 for pyrimidine nucleoside), one of the critical elements for the recognition by nucleoside kinases,[39] was increased in comparison with those of anti-HIV active nucleosides such as d4A and ddA[18] (Figure 5 and Table 3). This conformational feature results from the steric crowdedness of the β face of the sugar moiety. The unfavorable steric interactions among the substituents on the β face may be reduced by adopting the O4′-*endo* conformation with a relatively high degree of puckering.

Anti-HIV activities and cytotoxicities of the synthesized D-nucleosides have been evaluated in human PBM cells and other cell lines. None of the synthesized nucleosides showed any significant anti-HIV activity up to 100 μM

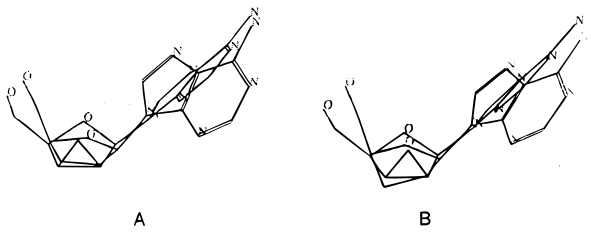

Figure 5. Overlaps of X-ray structures: **4a**−d4A (A) and **4a**−ddA (B).

Table 4. Kinetic Parameters of the Enzymatic Studies on the Adenosine Deaminase

compd	$K_m{}^a$ (μM)	$V_{max}{}^b$ (μmol/unit·min)	$V_{max}/K_m{}^c$	$t_{1/2}$
4a (D)	113	272	2.4	90 s
10a (L)	ND[d]	ND[d]	ND[d]	22 h
adenosine	24	409	17.0	30 s

[a] Michaelis constant. [b] Maximum rate. [c] Substrate efficiency. [d] Not determined.

in PBM cells. The unusual conformation of the new nucleosides, as described above, may potentially be the reason for their biological inactivity against HIV.

As part of the evaluation for metabolic stability, the D- and L-adenosine derivatives **4a** and **10a** were treated with a mammalian adenosine deaminase from calf intestinal mucosa (EC 3.5.4.4.). D-Enantiomer **4a** was found to be the better substrate of adenosine deaminase with a $t_{1/2}$ of 90 s than its L-enantiomer **10a**, which was a poor substrate of the adenosine deaminase with a $t_{1/2}$ of 22 h, although **4a** was a less favorable substrate with lower substrate efficiency (V_{max}/K_m) than the natural substrate adenosine (Table 4). Resistance to the adenosine deaminase of the L-adenosine analogue **10a** would be advantageous for its biological activity since many biologically active adenosine analogues are deactivated by the enzyme.[40] None of them served as inhibitors of the adenosine deaminase.

In summary, we have developed a synthetic method for a novel class of nucleosides, D- and L-2′,3′-dideoxy-2′,3′-*endo*-methylene nucleosides from 1,2:5,6-di-*O*-isopropylidene-D-mannitol and L-gulonic γ-lactone, respectively. Structure, conformation, and biochemical activity of the new nucleosides have been investigated.

Experimental Section

Melting points (mp) are uncorrected. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) in the indicated solvents.

***α/β*-5-*O*-*tert*-Butyldiphenylsilyl-D-2,3-dideoxy-2,3-*endo*-methylenepentofuranose (20).** DMSO (6 mL, 84.55 mmol)

(38) Koole, L. H.; Neidle, S.; Crawford, M. D.; Krayevsky, A. A.; Gurskaya. G. V.; Sandström, A.; Wu, J.-C.; Tong, W.; Chattopadhyaya, J. *J. Org. Chem.* **1991**, *56*, 6884.

(39) Taylor, E. W.; Van Roey, P.; Schinazi, R. F.; Chu, C. K. *Antiviral Chem. Chemother.* **1990**, *1*, 163.

(40) Pèlicano, H.; Pierra, C.; Eriksson, S.; Gosselin, G.; Imbach, J.-L.; Maury, G. *J. Med. Chem.* **1997**, *40*, 3969.

was added to a solution of oxalic chloride (3.2 mL, 36.68 mmol) in CH_2Cl_2 (70 mL) at −78 °C over 5 min, and the resulting solution was stirred for 10 min at −78 °C. Compound **17**[24,25] (5.4 g, 31.36 mmol) in CH_2Cl_2 (26 mL) was added to the above solution over 5 min. The reaction mixture was stirred at −78 °C for an additional 15 min, treated with Et_3N (28 mL), washed with water (20 mL × 2), and evaporated to give compound **18** as a syrup, which was dissolved in dioxane−0.1 N HCl (1:1, 60 mL). The resulting reaction mixture was stirred at room temperature for 4 h, neutralized with K_2CO_3 powder, and evaporated to dryness. The residue was partitioned between ether (50 mL) and water (100 mL), and the water layer was evaporated to a residue. The residue was dissolved in CH_2Cl_2 (100 mL), and the insoluble salts were removed by filtration. The filtrate was evaporated to give compound **19** as a syrup, which was dissolved in CH_2Cl_2 (80 mL), treated with TBDPSCl (5.4 mL) and pyridine (10 mL) at 0 °C, and kept at room temperature for 24 h. After removal of the solvent, the residue was purified by silica gel column chromatography (hexanes:EtOAc = 1:1) to give compound **20** (5.80 g, 50% from **17**) as a syrup (α/*β* = 20/1 determined by NMR): ^{1}H NMR[41] ($CDCl_3$) *δ* 7.30−7.50 (m, 4H), 7.19−7.21 (m, 6H), 5.15 (d, 1H, *J* = 4.0 Hz), 4.37 (m, 1H), 3.70 (dd, 1H, *J* = 3.7, 8.2 Hz), 3.53 (dd, 1H, *J* = 4.0, 8.2 Hz), 1.68−1.57 (m, 2H), 0.95 (s, 9H), 0.36 (m, 1H), 0.19 (m, 1H); FABMS (*m*/*z*) 351 (M + 1 − H_2O)$^+$.

α/*β*-5-*O*-*tert*-Butyldiphenylsilyl-D-2,3-dideoxy-2,3-*endo*-methylenepentofuranosyl Acetate (21). A mixture of compound **20** (2.8 g, 7.60 mmol) and Ac_2O (10 mL) in pyridine (40 mL) was stirred for 30 min. After removal of volatile materials, the residue was purified by silica gel column chromatography (hexanes:EtOAc = 60:1) to give compound **21** (2.7 g, 87%) as a syrup (α/*β* = 30/1 determined by NMR): ^{1}H NMR[41] ($CDCl_3$) *δ* 7.67 (m, 4H), 7.39 (m, 6H), 6.06 (s, 1H), 4.43 (m, 1H), 3.84 (m, 1H), 3.57 (m, 1H), 2.05 (s, 3H), 1.81(m, 1H), 1.70 (m, 1H), 1.01 (s, 9H), 0.52 (m, 1H), 0.32 (m, 1H); FABMS (*m*/*z*) 351 (M + 1 − AcOH)$^+$.

α-5-*O*-*tert*-Butyldiphenylsilyl-D-2,3-dideoxy-2,3-*endo*-methylenepentofuranosyl Chloride (22). Method 1: To a solution of the acetate **21** (460 mg, 1.12 mmol) in anhydrous ether (10 mL) was bubbled HCl gas for 10 min at −10 °C. The solvent and acid were removed under reduced pressure, and the residue was used in the next reaction without further purification. Method 2: To a solution of the lactol **20** (340 mg, 0.92 mmol) and Ph_3P (484 mg, 1.85 mmol) in dry THF (10 mL) was added CCl_4 (1 mL). The mixture was heated at 50 °C for 3 h and used for the next reaction without removal of solvent (see method 2 for the preparation of compound **26**). A small amount of the chloride **22** was taken from the residue for characterization. ^{1}H NMR showed exclusively an α-isomer: ^{1}H NMR ($CDCl_3$) *δ* 7.69 (m, 4H), 7.39 (m, 6H), 5.14 (s, 1H), 4.35 (m, 1H), 3.80 (dd, 1H, *J* = 5.3, 10.1 Hz), 3.61 (dd, 1H, *J* = 6.7, 10.1 Hz), 1.73 (m, 1H), 1.63 (m, 1H), 0.99 (s, 9H), 0.44 (m, 1H), 0.27 (m, 1H); FABMS (*m*/*z*) 351 (M + 1 − HCl)$^+$.

***N*^{4}-Benzoyl-1-(5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-2,3-*endo*-methylene-α/*β*-D-pentofuranosyl)cytosine (23).** Method 1: A mixture of *N*^{4}-benzoylcytosine (200 mg, 0.93 mmol), anhydrous HMDS (10 mL), and $(NH_4)_2SO_4$ (12 mg, 0.09 mmol) was refluxed under N_2 until a clear solution was obtained (ca. 18 h), and the solvent was removed under reduced pressure to give a colorless syrup, which was dissolved in anhydrous CH_3CN (10 mL). To the solution of silylated *N*^{4}-benzoyl cytosine in anhydrous CH_3CN were added acetate **21** (171 mg, 0.42 mmol) in anhydrous CH_3CN (10 mL) and TMSOTf (0.11 mL, 0.56 mmol) at 0 °C, and the resulting mixture was stirred for 3 h at rt. Saturated $NaHCO_3$ (50 mL) was added to the reaction mixture, which was then extracted with CH_2Cl_2 (10 mL). The combined organic layer was evaporated under reduced pressure to a residue, which was purified by silica gel column chromatography ($CHCl_3$:MeOH = 20:1) to give compound **23** (171 mg, 89%) as a syrup (*β*/α = 1/6 determined by NMR). Method 2: Silylated *N*^{4}-benzoylcytosine was prepared from *N*^{4}-benzoylcytosine (200 mg, 0.93 mmol) as described in method 1. To an ice-cooled solution of silylated *N*^{4}-benzoylcytosine in anhydrous $CHCl_3$ (6 mL) was added a solution of the chloride **22** in anhydrous $CHCl_3$ (6 mL) which was prepared from the acetate **21** (171 mg, 0.42 mmol) as previously described. The resulting mixture was stirred for 3 h at rt and diluted with $CHCl_3$ (20 mL). After removal of insoluble materials by filtration, the filtrate was evaporated under reduced pressure to a residue, which was purified by silica gel column chromatography ($CHCl_3$:MeOH = 20:1) to give compound **23** (162 mg, 68%) as a syrup (*β*/α = 2/1 determined by NMR): UV (MeOH) λ_{max} 259.5, 308.0 nm; ^{1}H NMR ($CDCl_3$) *δ* 8.95 (s, 1H), 7.95−7.35 (m, 16H), 6.10 (d, 0.67H, *J* = 2.9 Hz), 5.92 (s, 1H), 5.73 (s, 0.33H), 4.49 (m, 1H), 3.90−3.70 (m, 2H), 2.4 (m, 0.67H), 2.15 (m, 0.33H), 1.92−1.82 (m, 1H), 1.21 (s, 9H), 0.75 (m, 1H), 0.56−0.45 (m, 1H); FABMS (*m*/*z*) 566 (M + 1)$^+$.

1-(2,3-Dideoxy-2,3-*endo*-methylene-*β*-D-pentofuranosyl)-cytosine (1a) and 1-(2,3-Dideoxy-2,3-*endo*-methylene-α-D-pentofuranosyl)cytosine (1b). Compound **23** (300 mg, 0.53 mmol) in THF (10 mL) was treated with TBAF (0.7 mL, 1 M solution in THF), and the resulting solution was stirred for 20 min. After removal of the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 30:1) to give a crude desilylated cytosine derivative, which was dissolved in MeOH saturated with NH_3 (20 mL), and the resulting reaction mixture was stirred for 8 h. After removal of the volatile materials, the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 10:1) as an anomeric mixture and separated by reversed-phase HPLC (2% MeOH in water, C-18 column) to **1a** (45 mg, 38%) and **1b** (23 mg, 20%) as white solids. Data for compound **1a**: mp 201−3 °C; $[\alpha]^{25}_D$ +152.4° (*c* 0.4, MeOH); UV (H_2O) λ_{max} 271.0 nm (*ϵ* 8430, pH 7), 271.5 nm (*ϵ* 8830, pH 11), 277.5 nm (*ϵ* 11 320, pH 2); ^{1}H NMR (DMSO-d_6) *δ* 7.66 (d, 1H, *J* = 7.4 Hz), 7.16 (2s, 2H), 5.92 (d, 1H, *J* = 2.6 Hz), 5.70 (d, 1H, *J* = 7.4 Hz), 4.81 (t, 1H, *J* = 5.6 Hz), 4.11 (t, 1H, *J* = 3.0 Hz), 3.50 (m, 2H), 1.91 (m, 1H), 1.72 (m, 1H), 0.66 (m, 1H), 0.41 (m, 1H); ^{13}C NMR (DMSO-d_6) *δ* 166.8, 157.5, 141.6, 94.3, 87.1, 80.2, 62.7, 19.4, 18.5, 1.6; FABMS (*m*/*z*) 224 (M + 1)$^+$. Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.86; N, 18.82. Found: C, 53.82; H, 5.86; N, 18.75. Data for compound **1b**: mp 199−201 °C; $[\alpha]^{25}_D$ +6.9° (*c* 0.5, MeOH); UV (H_2O) λ_{max} 271.0 nm (*ϵ* 8940, pH 7), 270.5 nm (*ϵ* 8130, pH 11), 276.5 nm (*ϵ* 13 320, pH 2); ^{1}H NMR (DMSO-d_6) *δ* 7.62 (d, 1H, *J* = 7.4 Hz), 7.18 (2s, 2H), 5.90 (s, 1H), 5.72 (d, 1H, *J* = 7.4 Hz), 4.80 (t, 1H, *J* = 5.6 Hz), 4.19 (t, 1H, *J* = 3.0 Hz), 3.38 (m, 2H), 1.91 (m, 1H), 1.71 (m, 1H), 0.64 (m, 1H), 0.41 (m, 1H);^{13}C NMR (DMSO-d_6) *δ* 166.8, 157.8, 141.7, 95.1, 87.9, 80.6, 63.0, 20.7, 18.9, 5.4; FABMS (*m*/*z*) 224 (M + 1)$^+$. Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.86; N,-18.82. Found: C, 53.87; H, 5.88; N, 18.95.

1-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-dideoxy-2,3-*endo*-methylene-α/*β*-D-pentofuranosyl)thymine (24). Compound **24** was prepared from thymine (277 mg, 2.2 mmol) and acetate **21** (451 mg, 1.1 mmol) using methods 1 and 2 used in the preparation of compound **23**. Two different solvents, $CHCl_3$ and THF, were used in method 2. The obtained residue was purified by silica gel column chromatography (hexanes:EtOAc = 3:1) to give compound **24** as a syrup [method 1, 430 mg, 82%, *β*/α = 1/3 (CH_3CN); meth*o*d 2, 330 mg, 63%, *β*/α = 3/1 ($CHCl_3$); 340 mg, 65%, *β*/α = 1/1 (THF), determined by NMR]: UV (MeOH) λ_{max} 266.5 nm; ^{1}H NMR ($CDCl_3$)[42] *δ* 9.02 (s, 0.75H), 8.98 (s, 0.25H), 7.85−7.41 (m, 11H), 6.04 (d, 0.75H, *J* = 2.6 Hz), 5.96 (s, 0.25H), 4.47−4.32 (m, 1H), 3.81 (m, 1.5H), 3.61 (m, 0.5H), 2.05−2.01 (m, 1H), 1.84−1.76 (m, 4H), 1.11 (s, 9H), 0.72 (m, 0.75H), 0.57 (m, 0.75H), 0.49−0.44 (m, 0.5H); FABMS (*m*/*z*) 477 (M + 1)$^+$.

1-(2,3-Dideoxy-2,3-*endo*-methylene-*β*-D-pentofuranosyl)-thymine (2a) and 1-(2,3-Dideoxy-2,3-*endo*-methylene-α-D-pentofuranosyl)thymine (2b). Compound **24** (400 mg, 0.84 mmol) was desilylated, as described in the preparation of compounds **1a** and **1b**, to give compound **2** (186 mg, 93%) as an anomeric mixture, which was separated by reversed-

(41) ^{1}H NMR data of α isomer.

(42) ^{1}H NMR data of compound **24** with a *β*/α ratio of 3/1.

phase HPLC (2% MeOH in water, C-18 column) to **2a** (70 mg, 35%) and **2b** (24 mg, 12%) as white solids. Data for compound **2a**: mp 158−160 °C; $[\alpha]^{25}_D$ +104.2° (*c* 0.66, MeOH); UV (H_2O) λ_{max} 266.5 nm (ϵ 11 590, pH 7), 263.5 nm (ϵ 11 790, pH 11), 267.0 nm (ϵ 11 910, pH 2); ^{1}H NMR (DMSO-d_6) δ 11.38 (s, 1H), 7.55 (d, 1H, J = 1.2 Hz), 5.93 (d, 1H, J = 2.7 Hz), 4.82 (t, 1H, J = 3.0 Hz), 4.09 (m, 1H), 3.52 (m, 2H), 1.84 (m, 1H), 1.82 (s, 3H), 1.75 (m, 1H), 0.90 (m, 1H), 0.55 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 167.3, 154.0, 139.5, 112.1, 87.6, 82.3, 65.0, 21.6, 21.2, 15.6, 5.7; FABMS (*m*/*z*) 239 (M + 1)$^+$. Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.75. Found: C, 55.52; H, 5.91; N, 11.65. Data for compound **2b**: mp 148−150 °C; $[\alpha]^{25}_D$ +33.2° (*c* 0.5, MeOH); UV (H_2O) λ_{max} 266.5 nm (ϵ 11 230, pH 7), 264.0 nm (ϵ 11 650, pH 11), 266.5 nm (ϵ 11 230, pH 2); ^{1}H NMR (DMSO-d_6) δ 11.34 (s, 1H), 7.53 (s, 1H), 5.90 (s, 1H), 4.82 (t, 1H, J = 5.6 Hz), 4.29 (m, 1H), 3.40 (m, 2H), 2.05 (m, 1H), 1.80−1.78 (m, 4H), 0.75 (m, 1H), 0.41 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 167.1, 154.1, 139.8, 112.8, 88.3, 83.0, 65.3, 22.7, 15.5, 8.6; FABMS (*m*/*z*) 239 (M + 1)$^+$. Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.75. Found: C, 55.17; H, 6.04; N, 11.62.

1-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-dideoxy-2,3-*endo*-methylene-*β*-D-pentofuranosyl]uracil (25a) and 1-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-dideoxy-2,3-*endo*-methylene-α-D-pentofuranosyl)uracil (25b). An anomeric mixture of **25** (β/α = 2/1 determined by NMR) was prepared from uracil (912 mg, 8.14 mmol) and the acetate **21** (1.5 g, 3.65 mmol) using method 2 used for compound **23**, and was separated by silica gel chromatography (hexanes:EtOAc = 3:1) to give **25a** (720 mg, 43%) and **25b** (310 mg, 18%) as syrups. Data for compound **25a**: UV (MeOH) λ_{max} 262.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 7.65 (m, 4H), 7.41−7.35 (m, 7H), 6.01 (d, 1H, J = 2.5 Hz), 5.59 (d, 1H, J = 8.1 Hz), 4.36 (m, 1H), 3.80 (m, 2H), 2.07 (m, 1H), 1.85 (m, 1H), 1.05 (s, 9H), 0.64 (m, 1H), 0.56 (m, 1H); FABMS (*m*/*z*) 463 (M + 1)$^+$. Data for compound **25b**: UV (MeOH) λ_{max} 262.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.71 (s, 1H), 7.67 (m, 4H), 7.46−7.36 (m, 7H), 5.95 (s, 1H), 5.73 (d, 1H, J = 8.0 Hz), 4.38 (m, 1H), 3.81 (dd, 1H, J = 5.0, 10.3 Hz), 3.59 (dd, 1H, J = 6.8, 10.3 Hz), 2.02 (m, 1H), 1.83 (m, 1H), 1.04 (s, 9H), 0.74 (m, 1H), 0.51 (m, 1H); FABMS (*m*/*z*) 463 (M + 1)$^+$.

1-(2,3-Dideoxy-2,3-*endo*-methylene-*β*-D-pentofuranosyl)uracil (3a). Compound **25a** (400 mg, 0.86 mmol) was desilylated as described in the preparation of compound **1a**, purified by silica gel column chromatography ($CHCl_3$:MeOH = 10:1), and crystallized from EtOAc−MeOH (6:1) to give compound **3a** (180 mg, 93%) as a white solid: mp 147−149 °C; $[\alpha]^{25}_D$ +88.5° (*c* 0.20, MeOH); UV (H_2O) λ_{max} 261.5 nm (ϵ 13 870, pH 7), 260.5 nm (ϵ 7900, pH 11), 261.5 nm (ϵ 10 600, pH 2); ^{1}H NMR (DMSO-d_6) δ 11.37 (s, 1H), 7.73 (d, 1H, J = 8.1 Hz), 5.90 (d, 1H, J = 2.6), 5.57 (d, 1H, J = 8.0 Hz), 4.81 (t, 1H, J = 5.7 Hz), 4.11 (m, 1H), 3.49 (m, 2H), 1.87 (m, 1H), 1.75 (m, 1H), 0.77 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 171.2, 157.0, 147.2, 105.8, 91.0, 83.9, 66.5, 22.3, 21.9, 7.1; FABMS (*m*/*z*) 225 (M + 1)$^+$. Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.50; H, 5.42; N, 12.41.

1-(2,3-Dideoxy-2,3-*endo*-methylene-α-D-pentofuranosyl)uracil (3b). Compound **3b** (91 mg, 92%) was prepared as a white solid from **25b** (200 mg, 0.43 mmol) using the same conditions as for compound **3a**: mp 149−150 °C; $[\alpha]^{25}_D$ +18.0° (*c* 0.20, MeOH); UV (H_2O) λ_{max} 262.0 nm (ϵ 13 230, pH 7), 260.5 nm (ϵ 7260, pH 11), 262.0 nm (ϵ 10 230, pH 2); ^{1}H NMR (DMSO-d_6) δ 11.40 (s, 1H), 7.71 (d, 1H, J = 7.9 Hz), 5.88 (s, 1H), 5.60 (d, 1H, J = 7.9 Hz), 4.82 (t, 1H, J = 5.6 Hz), 4.22 (m, 1H), 3.39 (m, 2H), 1.99 (m, 1H), 1.81 (m, 1H), 0.70 (m, 1H), 0.46 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 166.7, 154.3, 144.7, 105.1, 88.7, 83.3, 65.4, 22.9, 22.6, 8.7; FABMS (*m*/*z*) 225 (M + 1)$^+$. Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.35; H, 5.40; N 12.32.

9-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-dideoxy-2,3-*endo*-methylene-*β*-D-pentofuranosyl)-6-chloro-9*H*-purine (26a) and 9-(5-*O*-*tert*-Butyldiphenylsilyl-2,3-dideoxy-2,3-*endo*-methylene-α-D-pentofuranosyl)-6-chloro-9*H*-purine (26b). Method 1: A mixture of 6-chloropurine (1.88 g, 12.16 mmol) and NaH (60% in oil, 0.48 g, 12.00 mmol) in anhydrous CH_3-CN (70 mL) or DMF (40 mL) was stirred under a nitrogen atmosphere for 30 min at room temperature. To the suspension of the sodium salt of the base was added the chloride **22** in anhydrous CH_3CN (20 mL) or DMF (10 mL), which was prepared from the acetate **21** (2.23 g, 5.43 mmol) as previously described, over 20 min at 0 °C. The mixture was stirred for 3 h at rt. After removal of the solvent under reduced pressure, the resulting residue was dissolved in CH_2Cl_2 (100 mL), washed with water (20 mL), and dried on $MgSO_4$. After removal of the drying agent by filtration, the filtrate was evaporated to give a residue, which was purified by silica gel column chromatography (EtOAc:hexanes = 5:1) to give compound **26** as an anomeric mixture [1.87 g, 68% from **21**, β/α = 3/1 (CH_3CN); 1.79 g, 65% from **21**, β/α = 5/1 (DMF), determined by NMR]. Compound **26** was separated by silica gel column chromatography (cyclohexane:ether = 3:1 to 1:1) to give compounds **26a** and **26b** as syrups. Method 2: To a solution of the lactol **20** (340 mg, 0.92 mmol) and Ph_3P (484 mg, 1.85 mmol) in dry THF (10 mL) was added CCl_4 (1 mL). The mixture was heated at 50 °C for 3 h, during which a white solid was precipitated and cooled to rt. The clear supernatant was transferred by syringe, over 15 min at 0 °C, to a solution of the sodium salt of 6-chloropurine in DMF (10 mL) which was prepared from 6-chloropurine (280 mg, 1.84 mmol) and 60% NaH (73 mg, 1.84 mmol) as described in method 1. The mixture was stirred at rt for 3 h. The same workup and purification used in method 1 afforded compound **26** (306 mg, 66% from **20**) with a β/α ratio of 6/1. Data for compound **26a**: UV (MeOH) λ_{max} 264.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.76 (s, 1H), 8.30 (s, 1H), 7.69−7.66 (m, 4H), 7.46−7.35 (m, 6H), 6.39 (d, 1H, J = 2.7 Hz), 4.47 (m, 1H), 3.88 (dd, 1H, J = 5.1, 10.5 Hz), 3.75 (dd, 1H, J = 6.0, 10.5 Hz), 2.20 (m, 1H), 2.02 (m, 1H), 1.05 (s, 9H), 0.87 (m, 1H), 0.72 (m, 1H); FABMS (*m*/*z*) 505 (M + 1)$^+$. Data for compound **26b**: UV (MeOH) λ_{max} 264.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.77 (s, 1H), 8.27 (s, 1H), 7.68−7.64 (m, 4H), 7.45−7.35 (m, 6H), 6.24 (s, 1H), 4.41 (m, 1H), 3.83 (dd, 1H, J = 5.1, 10.4 Hz), 3.75 (dd, 1H, J = 6.5, 10.3 Hz), 2.18−2.08 (m, 2H), 1.08 (s, 9H), 0.81 (m, 1H), 0.67 (m, 1H); FABMS (*m*/*z*) 505 (M + 1)$^+$.

9-(2,3-Dideoxy-2,3-*endo*-methylene-*β*-D-pentofuranosyl)-6-chloro-9*H*-purine (27a). Compound **26a** (430 mg, 0.85 mmol) was desilylated as described in the preparation of compounds **1a** and **1b**, and purified by silica gel column chromatography ($CHCl_3$:MeOH = 60:1) to give compound **27a** as a syrup (204 mg, 90%): UV (MeOH) λ_{max} 266.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.78 (s, 1H), 8.42 (s, 1H), 6.43 (d, 1H, J = 2.87 Hz), 4.47 (m, 1H), 3.84 (m, 2H), 2.21 (m, 1H), 1.97 (m, 1H), 1.10 (m, 1H), 0.95 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 152.2, 142.7, 134.8, 129.7, 127.7, 84.9, 79.7, 63.3, 26.5 19.2, 3.9; FABMS (*m*/*z*) 267 (M + 1)$^+$.

9-(2,3-Dideoxy-2,3-*endo*-methylene-α-D-pentofuranosyl)-6-chloro-9*H*-purine (27b). Compound **27b** (97 mg, 91%) was prepared as a syrup from compound **26b** (200 mg, 0.40 mmol) using the same conditions as for compound **27a**: UV (MeOH) λ_{max} 266.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.83 (s, 1H), 8.33 (s, 1H), 6.26 (s, 1H), 4.83 (t, 1H, J = 5.6 Hz), 4.32 (m, 1H), 3.45 (m, 2H), 2.19 (m, 1H), 2.10 (m, 1H), 0.81 (m, 1H), 0.61 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 152.3, 142.9, 135.6, 130.1, 127.5, 85.2, 80.1, 63.4, 25.1, 18.6, 5.9; FABMS (*m*/*z*) 267 (M + 1)$^+$.

9-(2,3-Dideoxy-2,3-*endo*-methylene-*β*-D-pentofuranosyl)adenine (4a). Compound **27a** (177 mg, 0.66 mmol) was dissolved in MeOH saturated with NH_3 (20 mL), and the resulting solution was stirred for 16 h at 90 °C in a steel bomb. After removal of the solvent, the yellow residue was triturated with EtOAc to give a white solid, which was recrystallized from MeOH to give compound **4a** as a white crystal (106 mg, 65%): mp 192−5 °C; $[\alpha]^{25}_D$ +29.2° (*c* 0.22, MeOH); UV (H_2O) λ_{max} 259.0 nm (ϵ 17 030, pH 7), 258.0 nm (ϵ 17 230, pH 11), 257.5 nm (ϵ 17 010, pH 2); ^{1}H NMR (DMSO-d_6) δ 8.16 (s, 1H), 8.00 (s, 1H), 7.15 (s, 2H), 6.07 (d, 1H, J = 2.7 Hz), 4.67 (t, 1H, J = 5.5 Hz), 4.03 (m, 1H), 3.36 (m, 2H), 1.91 (m, 1H), 1.70 (m, 1H), 0.93 (m, 1H), 0.51 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 159.0, 155.7, 152.6, 141.6, 121.9, 86.5, 82.5, 64.9, 22.2, 22.0, 6.3; FABMS (*m*/*z*) 248 (M + 1)$^+$. Anal. Calcd for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.29; N, 28.32. Found: C, 53.52; H, 5.43; N, 28.09.

9-(2,3-Dideoxy-2,3-*endo*-methylene-α-D-pentofuranos-

yl)adenine (4b). Compound **4b** (30 mg, 65%) was prepared as a white solid from compound **27b** (50 mg, 0.19 mmol) using the same conditions as for compound **4a**: mp 200−2 °C; [α]$^{25}_{D}$ +13.3° (*c* 0.22, MeOH); UV (H_2O) λ_{max} 259.5 nm (ϵ 17 010, pH 7), 258.0 nm (ϵ 17 130, pH 11), 257.5 nm (ϵ 16 430, pH 2); ^{1}H NMR (DMSO-d_6) δ 8.32 (s, 1H), 8.17 (s, 1H), 7.31 (s, 2H), 6.10 (s, 1H), 4.81 (s, 1H), 4.25 (m, 1H), 3.46 (m, 2H), 2.51 (m, 1H), 2.07 (m, 1H), 0.75 (m, 1H) 0.58 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 159.5, 156.3, 152.6, 142.4, 122.4, 86.8, 82.8, 65.2, 23.2, 22.4, 8.7; FABMS (*m*/*z*) 248 (M + 1)$^+$. Anal. Calcd for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.29; N, 28.32. Found: C, 53.71; H, 5.42; N, 28.09.

9-(2,3-Dideoxy-2,3-*endo*-methylene-*β*-D-pentofuranosyl)-hypoxanthine (5a). A mixture of compound **27a** (200 mg, 0.75 mmol), 2-mercaptoethanol (0.11 mL), and 0.5 N NaOMe (2.22 mL) in MeOH (50 mL) was refluxed for 5 h and neutralized with Amberite IR120 ion-exchange resin (H^+). After removal of the resin by filtration, the filtrate was evaporated to a residue, which was purified by silica gel column chromatography ($CHCl_3$:MeOH = 10:1) and crystallized from EtOAc−MeOH (4:1) to give compound **5a** (100 mg, 54%) as a white solid: mp 200−2 °C; [α]$^{25}_{D}$ +35.0° (*c* 0.25, H_2O); UV (H_2O) λ_{max} 248.5 nm (ϵ 13 860, pH 7), 253.0 nm (ϵ 11 930, pH 11), 248.5 nm (ϵ 10 670, pH 2); ^{1}H NMR (DMSO-d_6) δ 12.32 (s, 1H), 8.21 (s, 1H), 8.01 (s, 1H), 6.13 (d, 1H, *J* = 2.5 Hz), 4.77 (t, 1H, *J* = 5.6 Hz), 4.12 (m, 1H), 3.45 (m, 2H), 1.99 (m, 1H), 1.80 (m, 1H), 1.09 (m, 1H), 0.61 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 160.0, 151.6, 149.4, 141.1, 127.5, 87.0, 82.8, 64.9, 22.4, 22.2, 6.6; FABMS (*m*/*z*) 249 (M + 1)$^+$. Anal. Calcd for $C_{11}H_{12}N_4O_3$·0.2MeOH: C, 52.82; H, 5.07; N, 22.00. Found: C, 52.52; H, 4.84; N, 22.11.

9-(2,3-Dideoxy-2,3-*endo*-methylene-α-D-pentofuranosyl)-hypoxanthine (5b). Compound **5b** (30 mg, 52%) was prepared as a white solid from compound **27b (**58 mg, 0.22 mmol) using the same conditions as for compound **5a**: mp 194−5 °C; [α]$^{25}_{D}$ +14.6° (*c* 0.25, H_2O); UV (H_2O) λ_{max} 248.5 (ϵ 13 110, pH 7), 254.0 (ϵ 11 800, pH 11), 248.5 (ϵ 10 650, pH 2); ^{1}H NMR (DMSO-d_6) δ 12.11 (s, 1H), 8.28 (s, 1H), 8.07 (s, 1H), 6.07 (d, 1H, *J* = 1.68 Hz), 4.82 (s, 1H), 4.22 (m, 1H), 3.44 (m, 2H), 2.06 (m, 2H), 0.75 (m, 1H), 0.56 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 162.1, 152.3, 150.1, 141.2, 127.5, 87.3, 82.3, 64.4, 21.5, 22.5, 6.5; FABMS (*m*/*z*) 249 (M + 1)$^+$. Anal. Calcd for $C_{11}H_{12}N_4O_3$·0.25MeOH: C, 52.73; H, 5.11; N, 21.87. Found: C, 52.55; H, 4.76; N, 21.53.

9-(2,3-Dideoxy-2,3-*endo*-methylene-*β*-D-pentofuranosyl)-6-thiohypoxanthine (6a). Compound **27a** (150 mg, 0.56 mmol) was dissolved in anhydrous MeOH (10 mL). The solution was refluxed with bubbling of H_2S gas for 30 min. NaOMe (0.5 N) (2.0 mL) presaturated with H_2S gas was added slowly to the refluxing solution. The reaction mixture was refluxed with bubbling of H_2S gas for an additional 1 h, cooled to rt, and neutralized with 1 N HCl in MeOH. After removal of the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 5:1) and crystallized from MeOH to give compound **6a** (90 mg, 61%) as a white solid: mp 201−3 °C; [α]$^{25}_{D}$ +65.3° (*c* 0.21, DMSO); UV (H_2O) λ_{max} 320.0 nm (ϵ 24 420, pH 7), 311.0 nm (ϵ 22 960, pH 11), 325.0 nm (ϵ 11 400, pH 2); ^{1}H NMR (DMSO-d_6) δ 13.81 (s, 1H), 8.44 (s, 1H), 8.22 (s, 1H), 6.21 (d, 1H, *J* = 2.7 Hz), 4.83 (t, 1H, *J* = 5.6 Hz), 4.19 (m, 1H), 3.51 (m, 2H), 2.07 (m, 1H), 1.88 (m, 1H), 1.03 (m, 1H), 0.66 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 179.4, 148.8, 147.3, 143.8, 138.6, 87.3, 83.0, 65.0, 22.5, 22.4, 6.6; FABMS (*m*/*z*) 265 (M + 1)$^+$. Anal. Calcd for $C_{11}H_{12}N_4O_2S$·0.2H_2O: C, 49.32; H, 4.67; N, 20.91; S, 11.89. Found: C, 49.08; H, 4.49; N, 20.79; S, 11.86.

9-(2,3-Dideoxy-2,3-*endo*-methylene-α-D-pentofuranosyl)-6-thiohypoxanthine (6b). Compound **6b** (20 mg, 62%) was prepared as a white solid from compound **27b** (30 mg, 0.11 mmol) using the same conditions as for compound **6a**: mp 194−5 °C; [α]$^{25}_{D}$ −18.0° (*c* 0.21, DMSO); UV (H_2O) λ_{max} 320.0 nm (ϵ 29 590, pH 7), 311.0 nm (ϵ 24 650, pH 11), 325.0 nm (ϵ 25 910, pH 2); ^{1}H NMR (DMSO-d_6) δ 13.75 (s, 1H), 8.47 (s, 1H), 8.22 (s, 1H), 6.09 (s, 1H), 4.83 (t, 1H, *J* = 5.6 Hz), 4.23 (m, 1H), 3.41 (m, 2H), 2.09 (m, 2H), 0.76 (m, 1H), 0.56 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 180.1, 149.0, 147.1, 144.1, 138.2, 87.5, 82.9, 65.4, 22.2, 21.9, 6.1; FABMS (*m*/*z*) 265 (M + 1)$^+$. Anal. Calcd for $C_{11}H_{12}N_4O_2S$·0.2H_2O: C, 49.32; H, 4.67; N, 20.91; S, 11.89. Found: C, 49.41; H, 4.56; N, 20.69; S, 11.78.

2-Amino-9-(5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-2,3-*endo*-methylene-*β*/α-D-pentofuranosyl)-6-chloro-9*H*-purine (28). A mixture of 2-amino-6-chloropurine (1.4 g, 8.26 mmol) and 60% NaH (0.4 g, 9.93 mmol) in anhydrous DMF (40 mL) was stirred under a nitrogen atmosphere for 30 min at rt. The chloride **22** in anhydrous DMF (20 mL), prepared from the acetate **21** (1.7 g, 4.14 mmol), was added over 30 min at 0 °C, and the resulting mixture was stirred for 3 h at rt. After removal of the solvent under reduced pressure, the obtained residue was dissolved in CH_2Cl_2 (100 mL), washed with water (20 mL), and dried over $MgSO_4$. After removal of the drying agent by filtration, the filtrate was evaporated under reduced pressure to a residue, which was separated by silica gel column chromatography ($CHCl_3$:MeOH = 40:1 to 20:1) to give compound **28** (850 mg, 40%) as an anomeric mixture (*β*/α = 9/1, determined by NMR): UV (H_2O) λ_{max} 308.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.12 (s, 0.9H), 8.11 (s, 0.1H), 7.68 (m, 4H), 7.41 (m, 6H), 6.15 (d, 0.9H, *J* = 2.7 Hz), 6.05 (s, 0.1H), 5.25 (s, 2H), 4.40 (m, 1H), 3.87−3.60 (m, 2H), 2.06 (m, 1H), 1.96 (m, 1H), 0.95 (s, 9H), 0.88 (m, 1H), 0.70 (m, 1H); FABMS (*m*/*z*) 520 (M + 1)$^+$.

2-Amino-6-chloro-9-(2,3-dideoxy-2,3-*endo*-methylene-α/*β*-D-pentofuranosyl)-9*H*-purine (29). Compound **28** (600 mg, 1.15 mmol) was desilylated as described in the preparation of compounds **1a** and **1b**, and purified by silica gel column chromatography ($CHCl_3$:MeOH = 60:1) to give compound **29** (308 mg, 95%) as a white solid: mp 163−165 °C; UV (H_2O) λ_{max} 308.0 nm; ^{1}H NMR (CD_3OD) δ 8.23 (s, 0.9H), 8.22 (s, 0.1H), 6.15 (d, 0.9H, *J* = 2.8 Hz), 6.05 (s, 0.1H), 4.35−4.20 (m, 1H), 3.65−3.55 (m, 2H), 2.12 (m, 1H), 1.75 (m, 1H), 1.02−0.67 (m, 2H); FABMS (*m*/*z*) 282 (M + 1)$^+$.

***β*-D-2′,3′-Dideoxy-2′,3′-*endo*-methyleneguanosine (7a).** A mixture of compound **29** (300 mg, 1.06 mmol), 2-mercaptoethanol (0.18 mL), and 0.5 N NaOMe (4.0 mL) in MeOH (80 mL) was refluxed for 17 h, neutralized with 0.1 N HCl, and concentrated to a residue, which was partially purified by silica gel column chromatography ($CHCl_3$:MeOH = 10:1 to 5:1), further purified by HPLC (5% CH_3CN in water, reversed-phase C-18 column), and recrystallized from water to give compound **7a** (80 mg, 29%) as a pure *β*-isomer: mp 208−210 °C; [α]$^{25}_{D}$ −61.9° (*c* 0.20, H_2O); UV (H_2O) λ_{max} 252.0 nm (ϵ 14 840, pH 7), 254.0 nm (ϵ 6860, pH 11), 254.0 nm (ϵ 10 020, pH 2); ^{1}H NMR (D_2O) δ 7.98 (s, 1H), 5.94 (d, 1H, *J* = 2.7 Hz), 4.25 (m, 1H), 3.57 (m, 2H), 2.00 (m, 1H), 1.82 (m, 1H), 0.85 (m, 1H), 0.76 (m, 1H); ^{13}C NMR (D_2O + DMSO-d_6) δ 159.2, 155.4, 152.9, 136.9, 117.6, 85.4, 80.8, 63.5, 20.2, 19.8, 3.7; FABMS (*m*/*z*) 264 (M + 1)$^+$. Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.98; N, 26.60. Found: C, 49.94; H, 5.05; N, 26.47.

α/*β*-5-*O*-*tert*-Butyldiphenylsilyl-L-2,3-dideoxy-2,3-*endo*-methylenepentofuranose (33). Compound **33** was obtained from compound **30**[33,34] using the same method used for compound **20**: ^{1}H NMR and FABMS were identical to those of the D-enantiomer **20**.

α/*β*-5-*O*-*tert*-Butyldiphenylsilyl-L-2,3-dideoxy-2,3-*endo*-methylene-pentofuranosyl acetate (34). Compound **34** was obtained from compound **33** using the same method used for compound **21**: ^{1}H NMR and FABMS were identical to those of the D-enantiomer **21**.

α-5-*O*-*tert*-Butyldiphenylsilyl-L-2,3-dideoxy-2,3-*endo*-methylenepentofuranosyl Chloride (35). Compound **35** was obtained from compound **34** using the same method used for compound **22**: ^{1}H NMR and FABMS were identical to those of the D-enantiomer **22**.

1-(2,3-Dideoxy-2,3-*endo*-methylene-*β*-L-pentofuranosyl)-cytosine (8a) and 1-(2,3-dideoxy-2,3-*endo*-methylene-α-L-pentofuranosyl)cytosine (8b). Compounds **8a** and **8b** were obtained from compound **35** using method 2 used for compounds **1a** and **1b**. Data for compound **8a**: mp 200−3 °C; [α]$^{25}_{D}$ −152.9° (*c* 0.5, MeOH); UV (H_2O) λ_{max} 271.0 nm (ϵ 8370, pH 7), 271.5 nm (ϵ 8710, pH 11), 277.5 nm (ϵ 11 310, pH 2). Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.86; N, 18.82. Found: C, 53.76; H, 5.80; N, 18.69. Other data were identical

to those of the D-counterpart **1a**. Data for compound **8b**: mp 199−200 °C; $[\alpha]^{25}_D$ −6.2° (*c* 0.5, MeOH); UV (H_2O) λ_{max} 271.0 nm (ϵ 8670, pH 7), 270.5 nm (ϵ 8100, pH 11), 276.5 nm (ϵ 13 310, pH 2). Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.86; N,18.82. Found: C, 53.81; H, 5.76; N, 18.87. Other data were identical to those of the D-counterpart **1b**.

1-(2,3-Dideoxy-2,3-*endo*-methylene-*β*-L-pentofuranosyl)-thymine (9a) and 1-(2,3-Dideoxy-2,3-*endo*-methylene-α-L-pentofuranosyl)thymine (9b). Compounds **9a** and **9b** were obtained from compound **35** using method 2 as used for compounds **1a** and **1b**. Data for compound **9a**: mp 159−160 °C; $[\alpha]^{25}_D$ −100.3° (*c* 0.6, MeOH); UV (H_2O) λ_{max} 266.5 nm (ϵ 11 570, pH 7), 263.5 nm (ϵ 11 690, pH 11), 267.0 nm (ϵ 11 820, pH 2). Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.75. Found: C, 55.41; H, 5.90; N, 11.62. Other data were identical to those of the D-counterpart **2a**. Data for compound **9b**: mp 150−152 °C; $[\alpha]^{25}_D$ −33.1° (*c* 0.5, MeOH); UV (H_2O) λ_{max} 266.5 nm (ϵ 11 340, pH 7), 264.0 nm (ϵ 11 710, pH 11), 266.5 nm (ϵ 11 220, pH 2). Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.75. Found: C, 55.33; H, 6.11; N, 11.63. Other data were identical to those of the D-counterpart **2b**.

9-(2,3-Dideoxy-2,3-*endo*-methylene-*β*-L-pentofuranosyl)adenine (10a). Compound **10a** was obtained from compound **35** using method 1 used for compound **4a**: mp 192−4 °C; $[\alpha]^{25}_D$ −29.7° (*c* 0.27, MeOH); UV (H_2O) λ_{max} 259.5 nm (ϵ 17 445, pH 7), 259.5 nm (ϵ 18 160, pH 11), 257.5 nm (ϵ 17 086, pH 2). Anal. Calcd for $C_{11}H_{13}N_5O_2 \cdot 0.5\ H_2O$: C, 51.56; H, 5.51; N, 27.33. Found: C, 51.82; H, 5.35; N, 27.34. Other data were identical to those of the d-counterpart **4a**.

9-(2,3-Dideoxy-2,3-*endo*-methylene-*β*-L-pentofuranosyl)-hypoxanthine (11a). Compound **11a** was obtained from compound **35** using the same method used for compound **5a**: mp 200−3 °C; $[\alpha]^{25}_D$ −34.9° (*c* 0.13, H_2O); UV (H_2O) λ_{max} 248.0 nm (ϵ 13 830, pH 7), 253.0 nm (ϵ 11 910, pH 11), 248.0 nm (ϵ 10 750, pH 2). Anal. Calcd for $C_{11}H_{12}N_4O_3 \cdot 0.2H_2O$: C, 52.57; H, 5.00; N, 22.05. Found: C, 52.46; H, 4.76; N, 22.25. Other data were identical to those of the d-counterpart **5a**.

***β*-L-2′,3′-Dideoxy-2′,3′-*endo*-methyleneguanosine (12a).** Compound **12a** was obtained from compound **35** using the same method used for compound **7a**: mp 208−210 °C; $[\alpha]^{25}_D$ +60.6° (*c* 0.15, H_2O); UV (H_2O) λ_{max} 252.0 nm (ϵ 14 942, pH 7), 254.0 nm (ϵ 10 410, pH 11), 254.0 nm (ϵ 14 936, pH 2). Anal. Calcd for $C_{11}H_{13}N_5O_3 \cdot 0.5H_2O$: C, 48.53; H, 5.18; N, 25.72. Found: C, 48.49; H, 4.90; N, 25.54. Other data were identical to those of the D-counterpart **7a**.

Adenosine Deaminase Assay.[40] The deamination assays were performed at 37 °C in PBS buffer (pH 7.4) with the adenosine derivatives **4a** and **10a** (24−400 μM) and adenosine deaminase (EC 3.5.4.4, Sigma) (0.15 unit). The kinetic parameters K_m and V_{max} were measured according to the Lineweaver−Burk equation. The half-life ($t_{1/2}$) of **4a** was measured at 100 μM with 0.15 unit of the adenosine deaminase by monitoring with UV spectroscopy, while that of **10a** was measured at 1 mM with 1.5 units of the enzyme by monitoring with TLC. The qualitative inhibition assays were performed with **4a** and **10a** (10−100 μM), adenosine (20 μM) as the substrate, and the adenosine deaminase (0.15 unit). The assays were monitored with UV spectroscopy at 265 nm. The result of this experiment is listed in Table 4.

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