New Neplanocin Analogues. 6. Synthesis and Potent Antiviral Activity of 6′-Homoneplanocin A[1]

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The design, synthesis, and antiviral activities of 6′-homoneplanocin A (HNPA, **3**) and its congeners having nucleobases other than adenine, such as 3-deazaadenine (**4**), guanine (**5**), thymine (**6**), and cytosine (**7**), were described. Starting from the known cyclopentenone derivative **8**, the optically active (mesyloxy)cyclopentene derivative **15** was prepared, which was condensed with nucleobases then deprotected to give target compounds **3**−**7**. Of these compounds, HNPA showed an antiviral activity spectrum that was comparable to, and an antiviral specificity that was higher than, that of neplanocin A. HNPA proved particularly active against human cytomegalovirus, vaccinia virus, parainfluenza virus, vesicular stomatitis virus, and arenaviruses, which is compatible with an antiviral action targeted at *S*-adenosylhomocysteine hydrolase. HNPA appears to be a promising candidate drug for the treatment of these viruses.

Introduction

S-Adenosylhomocysteine hydrolase (AdoHcy hydrolase), which is responsible for the hydrolysis of *S*-adenosyl-L-homocysteine to adenosine (Ado) and L-homocysteine (Hcy),[2,3] has been recognized as a good target for broad-spectrum antiviral agents.[2−4] AdoHcy hydrolase is a key enzyme in the transmethylation reaction using *S*-adenosyl-L-methionine (AdoMet) as the methyl donor. Such transmethylation reactions are involved in the maturation of viral mRNAs and are critical in the virus replicative cycle. Several Ado analogues are assumed to achieve their broad-spectrum antiviral activity through an inhibition of AdoHcy hydrolase. In fact, a close correlation has been found between the antiviral activity of a series of Ado analogues and their inhibitory effects on AdoHcy hydrolase.[5]

Neplanocin A (NPA, **1**, Chart 1),[6] one of the most potent AdoHcy hydrolase inhibitors, has broad-spectrum antiviral activity.[7] However, NPA itself is apparently cytotoxic to host cells.[8] It has been recognized that the detrimental toxicity of NPA could be derived, for the most part, from phosphorylation of the primary hydroxyl group at its 6′-position (the 6′-position of NPA corresponds to the 5′-position of Ado) by Ado kinase and subsequent metabolism by cellular enzymes.[8] NPA is also rapidly deaminated by Ado deaminase to a chemotherapeutically inactive inosine congener,[9a] which may account for the reduced therapeutic potency of NPA, especially *in vivo*. On the basis of these observations, chemical modifications of NPA have been extensively studied to develop efficient antiviral agents.[9,10]

Because the 5′-hydroxymethyl moiety of Ado has an essential role in recognition as a substrate by all of these enzymes that interact with NPA, we have modified the 6′-hydroxymethyl moiety of NPA to develop NPA derivatives that are neither phosphorylated by Ado kinase nor deaminated by Ado deaminase but inhibit AdoHcy hydrolase significantly.[9] Throughout the study we found that (6′*R*)-6′-*C*-methylneplanocin A (RMNPA, **2a**) has excellent antiviral activity against various DNA and RNA viruses, while its cytotoxicity was reduced significantly compared with that of NPA.[9a,c] In fact, RMNPA is assumed not to be phosphorylated by Ado kinase[11] and not to be deaminated by Ado deaminase, although it inhibits AdoHcy hydrolase significantly.[9a] Although RMNPA has a potent antiviral effect, the corresponding 6′-diastereomer **2b** (SMNPA) is almost completely biologically inactive.[9a,c] This suggests that the conformation as well as the bulkiness around the 6′-hydroxyl group of NPA would be important for being recognized as the substrate by these three enzymes. It may also be that the distance between the adenine base and the primary 5′-hydroxyl of Ado (the 6′-hydroxyl of NPA) is an essential factor for being recognized as the substrate by the three enzymes. Accordingly, other modifications of the 6′-position of NPA that change the three-dimensional location of the 6′-hydroxyl group may be of interest. Therefore, we planned to synthesize the 6′-homologue of NPA (HNPA, **3**), a regioisomer of RMNPA, as another type of 6′-modified NPA derivative. The location of the 6′-hydroxymethyl group of NPA in space would be restricted, compared with the corresponding 5′-hydroxymethyl group of Ado, because the 6′-hydroxymethyl group of NPA is attached to a conformationally rigid 4′-sp^2 carbon in the cyclopentene ring. The 6′-homologue of NPA would have increased conformational flexibility around the hydroxymethyl group, and the distance between the adenine and the primary hydroxyl in HNPA would be different from that in NPA.

NPA congeners having nucleobases other than adenine have been synthesized, and some of them have excellent biological effects.[10b,12] Especially, the cytosine and 3-deazaadenine congeners of NPA have been known to have significant antiviral[10b,12c] and antitumor ef-

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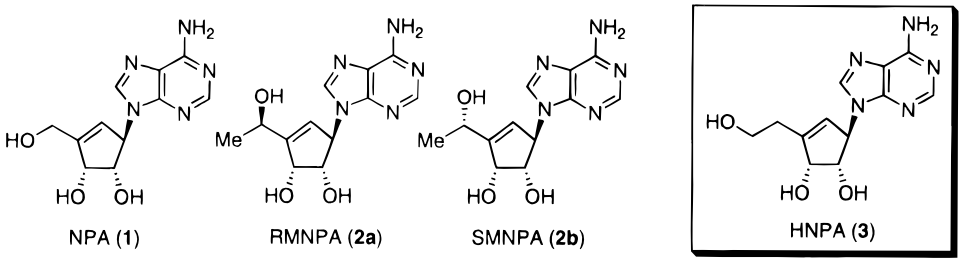
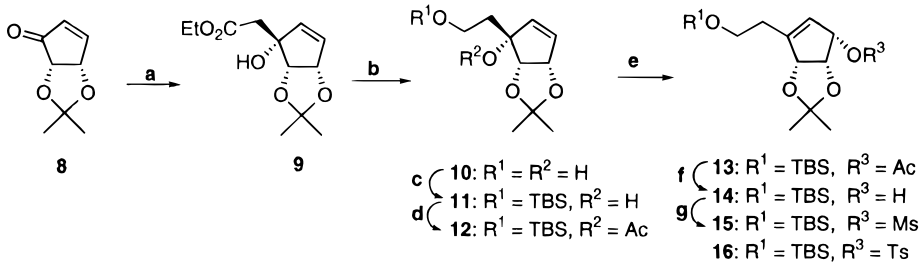
Chart 1



Scheme 1[a]



[a] Reagents: (a) $(TMS)_2NH$, BuLi, EtOAc, THF; (b) $LiBH_4$, THF; (c) TBSCl, imidazole, THF; (d) Ac_2O, DMAP, Et_3N, THF; (e) $PdCl_2(MeCN)_2$, *p*-benzoquinone, THF; (f) K_2CO_3, MeOH; (g) MsCl, DMAP, CH_2Cl_2.

fects.[12a,b] Consequently, the biological activity of analogues of HNPA having nucleobases other than adenine would also be interesting. In this paper, we describe the synthesis of HNPA (**3**) and its analogues, **4**−**7**, and the evaluation of their antiviral activity.

Results and Discussion

Chemistry. The target compounds **3**−**7** were synthesized from optically active cyclopentene derivative **15** and nucleobases. We selected a cyclopentenone derivative **8**, which was readily prepared from D-ribose,[13] as a synthon to prepare **15**. Johnson and coworkers showed that cyclopentenone **8** was an efficient synthon for constructing the backbone structure of NPA.[14] Recently, we also synthesized 6′-modified NPA derivatives starting from **8**.[9c]

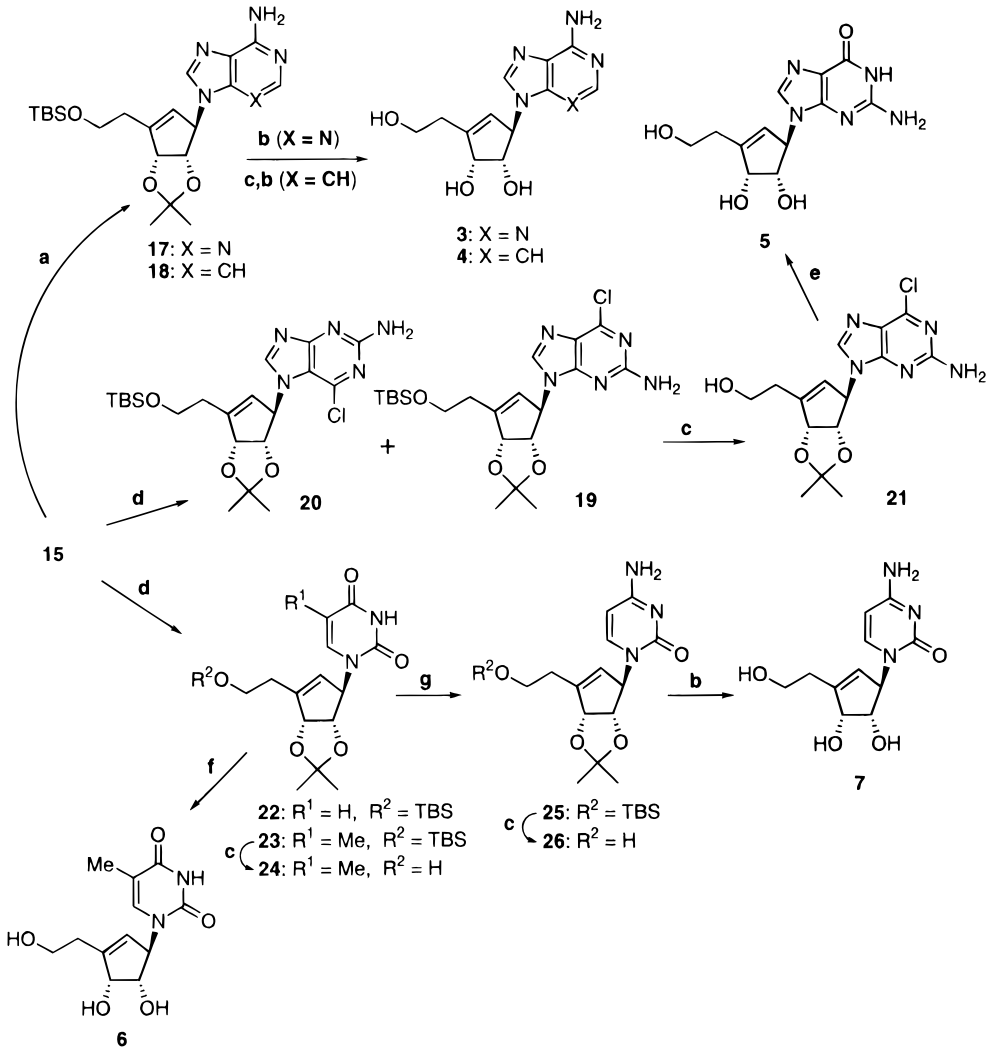
An addition reaction of a carbanion of EtOAc, which was prepared by treating EtOAc with $LiN(TMS)_2$,[15] to **8** in THF at −82 °C proceeded from the least hindered β-face highly stereoselectively to give **9** in 86% yield (Scheme 1). Reduction of the ester group of **9** with $LiBH_4$ in THF afforded diol **10** in 74% yield, which was then treated with TBSCl/imidazole in THF to give **11**. The tertiary hydroxyl of **11** was acetylated by treating it with a large excess of Ac_2O and Et_3N in the presence of DMAP to give acetate **12** in high yield. Allylic rearrangement of the acetoxy group of **12** with Pd^{2+} catalyst[16] was next investigated. When **12** was heated with $PdCl_2(MeCN)_2$ and benzoquinone in THF,[14] the desired rearrangement proceeded effectively to give **13** in 88% yield. The acetyl group of **13** was removed by treating it with K_2CO_3/MeOH to give **14**, which was then converted to the corresponding mesylate **15** by the usual method. The mesylate **15** was used immediately for the next reaction because of its instability. Although, using TsCl instead of MsCl, formation of the corresponding tosylate **16** from **14** was also detected on TLC, it was too unstable to be isolated.

An S_N2 substitution reaction of **15** at the allylic position was done with a sodium salt of adenine as a nucleophile by heating it at 80 °C in DMF in the presence of 15-crown-5 to give the corresponding carbocyclic nucleoside derivative **17** in 30% yield (Scheme 2). Similarly, the 3-deazaadenine derivative **18** was prepared. The guanine derivative **5** was synthesized *via* the 2-amino-6-chloropurine derivative **19**. Reaction of **15** and 2-amino-6-chloropurine in DMF in the presence of K_2CO_3 and 18-crown-6 gave the desired 9-substituted derivative **19** and the corresponding 7-substituted derivative **20** in 54% and 12% yield, respectively. The pyrimidine analogues, **6** and **7**, were also synthesized from **15**. Reactions of **15** and thymine or uracil were done under similar conditions for preparing 2-amino-6-chloropurine derivative **19** as described above to give **22** and **23**, respectively. The uracil derivative **22** was converted to the corresponding cytosine derivative **25** by the usual procedure.

The protecting groups of **17** were removed simultaneously by treating with HCl in aqueous MeOH to give HNPA (**3**) in high yield. On the other hand, treatment of **18**, **19**, **23**, and **25** with TBAF in THF, followed by acidic hydrolysis of the isopropylidene group, gave the desired carbocyclic nucleosides **4**−**7**, respectively.

Biological Activity. First, the compounds newly synthesized were preliminary evaluated for antiviral activity against vesicular stomatitis virus (VSV) and parainfluenza virus (PV-3), together with NPA as a positive control. The results are summarized in Table 1. It was noteworthy that HNPA (**3**) had significant antiviral effects with IC_{50} values of 1.0 μg/mL (VSV) and 0.35 μg/mL (PV-3), respectively, which are comparable to those of NPA [IC_{50} = 1.0 μg/mL (VSV); IC_{50} = 0.74 μg/mL (PV-3)]. Yet, NPA was rather cytotoxic (CC_{50} = 152 μg/mL, Vero cells); HNPA did not show any cytotoxic effect on host cells at concentrations up to 500 μg/mL. The 3-deazaadenine derivative **4** also showed antiviral activity against VSV (IC_{50} = 3.9 μg/mL); however, it was inactive against PV-3. Although significant antiviral activity of a cytosine congener of NPA, **27** (Chart 2), has been known,[12b] its 6′-homologue **7** was

Scheme 2[a]



[a] Reagents: (a) adenine or 3-deazaadenine, NaH, 15-crown-5, DMF; (b) HCl, aqueous MeOH; (c) TBAF, THF; (d) 2-NH_2-6-Cl-purine, thymine, or uracil, K_2CO_3, 18-crown-6, DMF; (e) 2 N HCl; (f) 70% HCOOH; (g) 2,4,6-triisopropylbenzenesulfonyl chloride, DMAP, MeCN, then 28% NH_4OH.

Table 1. Antiviral Activity against VSV and PV-3 and Cytotoxicity of Compounds **3**−**7** and NPA in Vero Cells

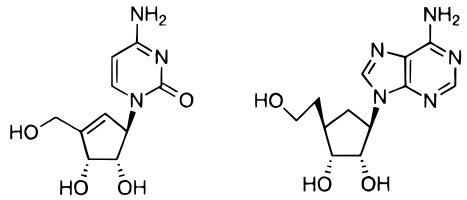
	antiviral activity (IC_{50}, μg/mL)[a]		cytotoxicity (CC_{50}, μg/mL)[b]
compd	VSV	PV-3	Vero cells
3	1.0	0.35	>500
4	3.9	>25	>500
5	>500	>25	>500
6	>500	>25	>500
7	>500	>25	>500
NPA	1.0	0.74	152

[a] 50% inhibitory concentration required to reduce virus-induced cytopathogenicity (VSV) or virus plaque formation (PV-3). [b] 50% cytotoxic concentration required to reduce the number of viable cells by 50%.

inactive. The derivatives having other nucleobases such as guanine analogue **5** and thymine analogue **6** were also inactive in this preliminary evaluation system. Therefore, we decided to investigate in more detail the biological activity of HNPA (**3**).

Because a close correlation between inhibitory effects of adenosine analogues on AdoHcy hydrolase and their antiviral potency has been demonstrated,[5] the inhibitory effect of HNPA on AdoHcy hydrolase was evaluated in a cell-free system with the enzyme from rabbit erythrocytes. HNPA apparently inhibited the enzyme (IC_{50} = 0.87 μg/mL), while NPA did so at an IC_{50} of 0.004 μg/mL.

Chart 2



The susceptibility of HNPA to Ado deaminase from calf intestine was also investigated (Figure 1). HNPA was completely resistant to the deamination by the enzyme in spite of having a primary hydroxyl, which is an essential functional group for Ado to be recognized as a substrate by Ado deaminase.[17] In contrast, NPA was rapidly deaminated to the inactive inosine congener under the same reaction conditions.

Next, the antiviral activity of HNPA (**3**), in direct comparison with NPA, was examined in detail in human embryonic skin muscle (E_6SM) fibroblasts, human

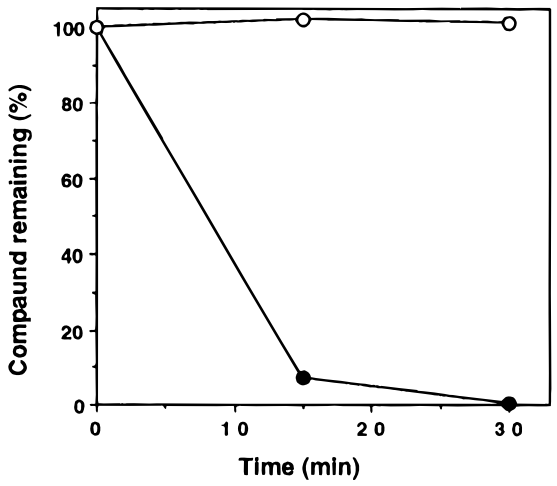


Figure 1. Effects of calf intestinal Ado deaminase on NPA (●) and HNPA (○).

Table 2. Antiviral Activity of HNPA (**3**) and NPA in Different Assay Systems

		IC_{50} or CC_{50} (μg/mL)[a]	
virus	cell	compd **3** (HNPA)	NPA
HSV-1 (KOS)	E_6SM	>400	≥70
HSV-2 (G)	E_6SM	>400	≥70
TK⁻ HSV-1 (B2006)	E_6SM	>400	40
vaccinia virus	E_6SM	0.1	0.7
VSV	E_6SM	1	7
cell morphology	E_6SM	>400	70
VZV (OKA)	HEL	>50	15
VZV (YS)	HEL	>50	9
TK⁻ VZV (07/1)	HEL	>50	10
TK⁻ VZV (YS/R)	HEL	>50	7
HCMV (AD-169)	HEL	0.15	0.3
HCMV (Davis)	HEL	0.5	0.4
cell growth	HEL	>50	≥20
VSV	HeLa	0.7	2
Coxsackie B4 virus	HeLa	>200	≥40
Polio-1 virus	HeLa	>200	≥40
cell morphology	HeLa	>400	≥40
PV-3	Vero	2	2
Reo-1 virus	Vero	70	4
Sindbis virus	Vero	>400	>10
Semliki forest virus	Vero	>400	>10
Junin virus	Vero	5	0.5
Tacaribe virus	Vero	20	2
cell morphology	Vero	>400	≥10

[a] 50% inhibitory concentration, required to reduce virus-induced cytopathogenicity by 50%, or 50% cytotoxic concentration, required to reduce cell growth by 50% or to cause microscopic alteration of normal cell morphology by approximately 50%.

embryonic lung (HEL) fibroblasts, as well as HeLa and Vero cell cultures (Table 2). HNPA was found active against vaccinia virus, vesicular stomatitis virus (VSV), human cytomegalovirus (HCMV), parainfluenza virus, and arenaviruses (Junin, Tacaribe) at concentrations that were lower than (VSV, vaccinia virus), comparable to (HCMV, PV-3), or higher than (reo- and arenaviruses) the concentrations at which NPA inhibited these viruses. HNPA did not show activity against herpes simplex virus (HSV), varicella-zoster virus (VZV) [including TK⁻ (thymidine kinase deficient) strains of HSV and VZV], picornaviruses (Coxsackie, polio), and togaviruses (Sindbis, Semliki forest virus). Under the conditions used for the antiviral activity assays, HNPA did not prove toxic to the host cells at concentrations up to 400 μg/mL. This contrasts with the behavior of NPA, which did show toxicity to the host cells at concentrations of 10 μg/mL and higher (Table 2).

Based on the CC_{50}/IC_{50} ratios, HNPA may be considered to be more selective in its antiviral action than NPA; for example, for vaccinia virus, this ratio (selectivity index) could be estimated at >4000 for HNPA, as compared to 100 for NPA. The antiviral activity spectrum displayed by HNPA encompasses, in particular, human cytomegalovirus (HCMV), vaccinia virus, and (−)-RNA viruses [i.e. vesicular stomatitis virus, parainfluenza virus and arenaviruses (Junin, Tacaribe)]. This is compatible with an antiviral action targeted at AdoHcy hydrolase, as has been previously documented for neplanocin A itself[7] and several other carbocyclic adenosine analogues.[4a,9a] While the inhibitory effect of HNPA of rabbit erythrocyte AdoHcy hydrolase was weaker than that of NPA as described above, its antiviral activity was almost equal to that of NPA. Similarly, RMNPA and 2-fluoroneplanocin A also had equal or more significant antiviral potency compared with that of NPA, in spite of their rather weaker inhibitory effects on AdoHcy hydrolase than NPA. Since the three NPA derivatives are completely resistant to Ado deaminase, concentrations of these derivatives in vitro assay systems may be kept at relatively higher levels compared with that of NPA. Accordingly, these Ado deaminase resistant analogues of NPA would have an excellent antiviral activity.

The 6′-homologue of carbocyclic adenosine, **28**, which corresponds to the saturated analogue of HNPA, has been synthesized.[18] However, **28** has been known to be biologically inactive, in contrast to the potent antiviral effects of HNPA.[18b] This may suggest that the cyclopentenyl structure of NPA as well as its derivatives would be important for their biological activities.

The potency and selectivity of HNPA is such that it should be further pursued for its therapeutic potential as an antiviral drug.

Experimental Section

Melting points were determined on a Yanagimoto MP-3 micro-melting point apparatus and are uncorrected. The NMR spectra were recorded with a JEOL EX-270 or -400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts were reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by the addition of D_2O. Mass spectra were measured on a JEOL JMS-D300 spectrometer. Thin-layer chromatography was done on Merck coated plate $60F_{254}$. Silica gel chromatography and flash silica gel chromatography were done with Merck silica gel 5715 and 9385, respectively.

(1*R*,2*S*,3*S*)-1-[(Ethoxycarbonyl)methyl]-2,3-(isopropylidenedioxy)-4-cyclopenten-1-ol (9). To a solution of HN(TMS)$_2$ (3.42 mL, 16.2 mmol) in hexane (20 mL) was added dropwise a BuLi solution (1.62 M in hexane, 10 mL, 16.2 mmol) at −10 °C under an argon atmosphere. After 15 min, THF (100 mL) was added to the solution and the mixture was cooled to −82 °C. EtOAc (1.59 mL, 16.2 mmol) was added dropwise to the solution at −82 °C, and the solution was stirred for 25 min at the same temperature. A solution of (2*S*,3*S*)-2,3-(sopropylidenedioxy)-4-cyclopenten-1-one (**8**, 2.0 g, 13.0 mmol) in THF (20 mL) was added dropwise to the above solution, and the resulting solution was stirred at the same temperature for 1.5 h. The cooling bath was removed, and the reaction mixture was quenched by an addition of saturated NH_4Cl (10 mL). To the mixture were added $CHCl_3$ (400 mL) and water (100 mL), and the mixture was partitioned. The organic layer was dried over $MgSO_4$ and evaporated. The residue was

purified by flash chromatography (silica gel, hexane/EtOAc, 5:1) to give **9** as a syrup (2.7 g, 86%): ^{1}H NMR (270 MHz, $CDCl_3$) 5.86 (d, 1 H, H-4 or -5, J = 5.9 Hz), 5.83 (d, 1 H, H-4 or -5, J = 5.9 Hz), 5.11 (d, 1 H, H-3, J = 5.3 Hz), 4.72 (d, 1 H, H-2, J = 5.3 Hz), 4.13 (q, 2 H, CH_2, J = 6.9 Hz), 3.44 (s, 1 H, OH), 2.73 (d, 1 H, H-6$_a$, J = 14.9 Hz), 2.62 (d, 1 H, H-6$_b$, J = 14.9 Hz), 1.45 and 1.41 (each s, each 3 H, isopropyl-CH_3), 1.26 (t, 3 H, CH_3, J = 6.9 Hz); MS (FAB) m/z 243 (MH^+).

(1*R*,2*S*,3*S*)-1-(2-Hydroxyethyl)-2,3-(isopropylidenedioxy)-4-cyclopenten-1-ol (10). A solution of $LiBH_4$ (292 mg, 13.4 mmol) and **9** (2.7 g, 11.2 mmol) in THF (30 mL) was stirred for 2 days at room temperature and then heated under reflux overnight. The mixture was cooled to room temperature, EtOAc (150 mL) was added, and the resulting mixture was washed with brine (30 mL). The organic layer was filtered through Whatman 1PS filter paper, and the filtrate was evaporated. The residue was purified by flash chromatography (silica gel, hexane/acetone, 5:1) to give **10** as a syrup (1.66 g, 74%): ^{1}H NMR (270 MHz, $CDCl_3$) 5.85 (d, 1 H, H-4 or -5, J = 5.9 Hz), 5.82 (d, 1 H, H-4 or -5, J = 5.9 Hz), 5.05 (d, 1 H, H-3, J = 5.3 Hz), 4.46 (d, 1 H, H-2, J = 5.3 Hz), 3.85 (dd, 2 H, H-7, J = 5.6, 5.6 Hz), 3.40 (s, 1 H, 4-OH), 2.92 (br s, 1 H, 7-OH), 1.88 (dt, 1 H, H-6$_a$, J = 5.6, 14.5 Hz), 1.77 (dt, 1 H, H-6$_b$, J = 5.6, 14.5 Hz), 1.45 and 1.37 (each s, each 3 H, isopropyl-CH_3); MS (FAB) m/z 201 (MH^+).

(1*R*,2*S*,3*S*)-1-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2,3-(isopropylidenedioxy)-4-cyclopenten-1-ol (11). A mixture of **10** (1.48 g, 7.4 mmol), imidazole (1.26 g, 18.5 mmol), and TBSCl (2.23 g, 14.8 mmol) in THF (30 mL) was stirred at room temperature overnight. The solvent was evaporated, and the residue was partitioned between $CHCl_3$ (150 mL) and water (30 mL). The organic layer was filtered through Whatman 1PS filter paper, and the filtrate was evaporated. The residue was purified by flash chromatography (silica gel, hexane/acetone, 25:1) to give **11** as a syrup (2.35 g, 100%): ^{1}H NMR (270 MHz, $CDCl_3$) 5.81 (dd, 1 H, H-4, J = 1.7, 5.6 Hz), 5.76 (d, 1 H, H-5, J = 5.6 Hz), 5.04 (dd, 1 H, H-3, J = 1.7, 5.3 Hz), 4.60 (d, 1 H, H-2, J = 5.3 Hz), 3.83 (dt, 1 H, H-7$_a$, J = 10.6, 5.9 Hz), 3.71 (dt, 1 H, H-7$_b$, J = 10.6, 6.9 Hz), 3.34 (s, 1 H, OH), 1.83 (m, 2 H, H-6), 1.44 and 1.38 (each s, each 3 H, isopropyl-CH_3), 0.89 (s, 9 H, *t*-Bu), 0.06 and 0.05 (each s, each 3 H, $SiCH_3$); MS (FAB) m/z 315 (MH^+).

(1*R*,2*S*,3*S*)-1-Acetoxy-2,3-(isopropylidenedioxy)-1-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-cyclopentene (12). A mixture of **11** (2.35 g, 7.3 mmol), acetic anhydride (7.06 mL, 75 mmol), Et_3N (20.9 mL, 150 mmol), and DMAP (914 mg, 7.5 mmol) in THF (100 mL) was stirred at room temperature overnight. To the mixture were further added acetic anhydride (3.53 mL, 37.4 mmol), and Et_3N (10.4 mL, 75 mmol), and the resulting mixture was stirred at room temperature overnight. The solvent was evaporated, the residue was dissolved in $CHCl_3$ (150 mL), and the resulting solution was washed with water (30 mL). The organic layer was filtered through Whatman 1PS filter paper, and the filtrate was evaporated. The residue was purified by flash chromatography (silica gel, hexane/acetone, 20:1) to give **12** as a syrup (2.46 g, 92%): ^{1}H NMR (270 MHz, $CDCl_3$) 6.00 (d, 1 H, H-5, J = 5.9 Hz), 5.90 (dd, 1 H, H-4, J = 5.9, 1.7 Hz), 5.05 (dd, 1 H, H-3, J = 1.7, 5.3 Hz), 4.48 (d, 1 H, H-2, J = 5.3 Hz), 3.64 (m, 2 H, H-7), 2.35 (dt, 1 H, H-6$_a$, J = 5.3, 14.2 Hz), 2.06 (m, 4 H, H-6$_b$, Ac), 1.37 and 1.36 (each s, each 3 H, isopropyl-CH_3), 0.89 (s, 9 H, *t*-Bu), 0.04 (s, 6 H, $SiCH_3$); MS (FAB) m/z 357 (MH^+).

(1*S*,2*R*,3*R*)-1-Acetoxy-2,3-(isopropylidenedioxy)-4-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-cyclopentene (13). A mixture of **12** (1.0 g, 2.8 mmol), $PdCl_2(CH_3CN)_2$ (37 mg, 0.14 mmol), and *p*-benzoquinone (122 mg, 1.12 mmol) in THF (30 mL) was heated under reflux overnight. The mixture was cooled to room temperature and evaporated. The residue was purified by flash chromatography (silica gel, hexane/acetone, 15:1) to give **13** as a syrup (878 mg, 88%): ^{1}H NMR (270MHz, $CDCl_3$) 5.53 (br s, 1 H, H-5), 5.33 (m, 1 H, H-1), 4.87 (m, 2 H, H-2, -3), 3.80 (m, 2 H, H-7), 2.44 (m, 2 H, H-6), 2.11 (s, 3 H, Ac), 1.38 (s, 6 H, isopropyl-CH_3), 0.88 (s, 9 H, *t*-Bu), 0.05 (s, 6 H, $SiCH_3$); MS (FAB) m/z 357 (MH^+).

(1*S*,2*S*,3*R*)-2,3-(Isopropylidenedioxy)-4-[2-[(*tert*-butyldimethysilyl)oxy]ethyl]-4-cyclopenten-1-ol (14). A mixture of **13** (616 mg, 1.73 mmol) and K_2CO_3 (478 mg, 3.46 mmol) in MeOH (10 mL) was stirred at room temperature for 1.5 h. The solvent was removed, the residue was dissolved in $CHCl_3$ (50 mL), and the solution was washed with water (10 mL × 2). The organic layer was filtered through Whatman 1PS filter paper, and the filtrate was evaporated. The residue was purified by flash chromatography (silica gel, hexane/acetone, 15:1) to give **14** as a syrup (510 mg, 94%): ^{1}H NMR (270 MHz, $CDCl_3$) 5.54 (br s, 1 H, H-5), 4.86 (d, 1 H, H-3, J = 5.6 Hz), 4.67 (dd, 1 H, H-2, J = 5.6, 5.6 Hz), 4.48 (m, 1 H, H-1), 3.78 (m, 2 H, H-7), 2.67 (d, 1 H, OH, J = 9.9 Hz), 2.39 (m, 2 H, H-6), 1.41 and 1.40 (each s, each 3 H, isopropyl-CH_3), 0.88 (s, 9 H, *t*-Bu), 0.05 (s, 6 H, $SiCH_3$); MS (FAB) m/z 315 (MH^+).

(1*S*,2*R*,3*R*)-1-[(Methylsulfonyl)oxy]-2,3-(isopropylidenedioxy)-4-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-cyclopentene (15). A mixture of **14** (98 mg, 0.31 mmol), DMAP (114 mg, 0.94 mmol), and MsCl (48 μL, 0.62 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 3.5 h. Then $CHCl_3$ (30 mL) and water (6 mL) were added, and the resulting mixture was partitioned. The organic layer was washed with water (6 mL) and filtered through Whatman 1PS filter paper. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, hexane/acetone, 10:1) to give **15** (90 mg , 74%) as a syrup: ^{1}H NMR (270 MHz, $CDCl_3$) 5.58 (d, 1 H, H-5, J = 1.7 Hz), 5.39 (m, 1 H, H-1), 4.88 (m, 2 H, H-2 and 3), 3.76 (m, 2 H, H-7), 3.12 (s, 3 H, CH_3SO_2), 2.45 (m, 2 H, H-6), 1.40 (s, 6 H, isopropyl-CH_3), 0.88 (s, 9 H, *t*-Bu), 0.05 (s, 6 H, $SiCH_3$); MS (FAB) m/z 393 (MH^+).

9-[(1*R*,2*S*,3*R*)-2,3-(Isopropylidenedioxy)-4-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-cyclopenten-1-yl]adenine (17). A suspension of adenine (84 mg, 0.62 mmol) and NaH (50% in oil, 30 mg, 0.62 mmol) in DMF (1 mL) was stirred at room temperature for 1 h. To the resulting solution were added 15-crown-5 (62 μL, 0.31 mmol) and a solution of **15** (90 mg, 0.23 mmol) in DMF (1 mL), and the mixture was stirred at room temperature for 15 h, followed by heating at 80 °C for 2 h. The resulting mixture was cooled to room temperature and evaporated. EtOAc (50 mL) was added to the residue, and the resulting insoluble material was filtered off. The filtrate was washed with water (10 mL) and filtered through Whatman 1PS filter paper, and the filtrate was evaporated. The residue was purified by flash chromatography (silica gel, $CHCl_3$/CH_3OH, 15:1) to give **17** as a crystalline solid (30 mg, 30%): mp 133−134 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 8.41 and 7.63 (each s, each 1 H, H-8 and -2), 6.00 (br s, 2 H, NH_2), 5.65 (br s, 1 H, H-5′), 5.60 (br s, 1 H, H-1′), 5.28 (d, 1 H, H-3′, J = 5.6 Hz), 4.61 (d, 1 H, H-2′, J = 5.6 Hz), 3.90 (m, 2 H, H-7′), 2.46 (m, 2 H, H-6′), 1.47, 1.36 (each s, each 3 H, isopropyl-CH_3), 0.90 (s, 9 H, *t*-Bu), 0.09 (s, 6 H, $SiCH_3$); MS (FAB) m/z 432 (MH^+). Anal. ($C_{21}H_{33}N_5O_3Si$) C, H, N.

9-[(1*R*,2*S*,3*R*)-2,3-Dihydroxy-4-(2-hydroxyethyl)-4-cyclopenten-1-yl]adenine (3, HNPA). A solution of **17** (920 mg, 2.13 mmol) in a mixture of MeOH (20 mL) and 2 N HCl (20 mL) was stirred at room temperature for 2 h. The solvent was evaporated, the residue was dissolved in MeOH (5 mL) and Et_3N (3 mL), and then the solvent was evaporated. To the residue was added $CHCl_3$, and the resulting insoluble solid was collected by filtration to give **3** as a crystalline solid (530 mg, 90%). An analytical sample was obtained by recrystallization from MeOH: mp 202−203 °C; $[\alpha]^{25}_D$ −144.1 (c = 0.10, MeOH); ^{1}H NMR (270 MHz, CD_3OD) 8.19 and 8.11 (each s, each 1 H, H-8 and -2), 5.81 (d, 1 H, H-5′, J = 1.7 Hz), 5.50 (m, 1 H, H-1′), 4.61 (d, 1 H, H-3′, J = 5.3 Hz), 4.34 (dd, 1 H, H-2′, J = 5.3, 5.3 Hz), 3.82 (m, 2 H, H-7′), 2.54 (br t, 2 H, H-6′, J = 6.3 Hz); MS (FAB) m/z 277 (MH^+); UV λ_{max} 260 (H_2O), 258 (0.1 N HCl), 262 nm (0.1 N NaOH). Anal. ($C_{12}H_{15}N_5O_3 \cdot {}^1/_2H_2O$) C, H, N.

9-[(1*R*,2*S*,3*R*)-2,3-(Isopropylidenedioxy)-4-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-cyclopenten-1-yl]-3-deazaadenine (18). A suspension of 3-deazaadenine (214 mg, 1.59 mmol) and NaH (50% in oil, 77 mg, 0.62 mmol) in DMF (5 mL) was stirred at room temperature for 2 h. A solution of **15** (285 mg, 0.73 mmol) in DMF (3 mL) and 15-crown-5 (158 μL, 0.80 mmol) was added, and the resulting mixture was stirred at room temperature overnight, followed by heating at 55 °C for 2.5 h. After cooling to room temperature, the

mixture was evaporated. To the residue was added EtOAc (50 mL), and the resulting insoluble material was filtered off. The filtrate was washed with water (10 mL) and filtered through Whatman 1PS filter paper, and the filtrate was evaporated. The residue was purified by flash chromatography (silica gel, $CHCl_3/CH_3OH$, 20:1) to give **18** as a crystalline solid (85 mg, 25%). An analytical sample was obtained by recrystallization from hexane: mp 148−149 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 7.85 (d, 1 H, H-2, J = 5.9 Hz), 7.68 (s, 1 H, H-8), 6.82 (d, 1 H, H-3, J = 5.9 Hz), 5.71 (br s, 1 H, H-5′), 5.31 (br s, 1 H, H-1′), 5.28 (br s, 2 H, NH_2), 5.23 (d, 1 H, H-3, J = 5.9 Hz), 4.50 (d, 1 H, H-2′, J = 5.9 Hz), 3.91 (m, 2 H, H-7′), 2.54 (m, 2 H, H-6′), 1.47, 1.35 (each s, each 3 H, isopropyl-CH_3), 0.90 (s, 9 H, *t*-Bu), 0.09 (s, 6 H, $SiCH_3$); MS (FAB) m/z 431 (MH^+). Anal. ($C_{22}H_{34}N_4O_3Si$) C, H, N.

9-[(1*R*,2*S*,3*R*)-2,3-Dihydroxy-4-(2-hydroxyethyl)-4-cyclopenten-1-yl]-3-deazaadenine (4). A solution of **18** (50 mg, 0.12 mmol) and TBAF (1 M in THF, 140 μL, 0.14 mmol) in THF (2 mL) was stirred at room temperature for 1 h. The resulting mixture was evaporated, and the residue was partitioned between $CHCl_3$ (100 mL) and water (10 mL). The organic layer was washed with saturated $NaHCO_3$ (20 mL) and water (20 mL) and filtered through Whatman 1PS filter paper, and the filtrate was evaporated. The residue was purified by flash chromatography (silica gel, $CHCl_3$/MeOH, 15:1) to give a crystalline solid which was dissolved in HCl/CH_3-OH (8.9 M, 2 mL), and the mixture was stirred at room temperature for 1 h. The solvent was evaporated, the residue was dissolved in water (2 mL), and the solution was purified by Dowex-1 column (OH^-, 1 × 1 cm, eluted with 20% MeOH) to give **4** as a crystalline solid (21 mg, 66%): mp 214−216 °C; $[\alpha]^{28}_D$ −123.5 (c = 0.10, H_2O); ^{1}H NMR (270 MHz, CD_3OD) 8.07 (s, 1 H, H-8), 7.67 (d, 1 H, H-2, J = 5.9 Hz), 6.93 (d, 1 H, H-3, J = 5.9 Hz), 5.84 (br s, 1 H, H-5′), 5.34 (m, 1 H, H-1′), 4.54 (br d, 1 H, H-3′, J = 5.6 Hz), 4.19 (dd, 1 H, H-2′, J = 5.6, 5.6 Hz), 3.84 (br t, 2 H, H-7′, J = 6.3 Hz), 2.54 (br t, 2 H, H-6′, J = 6.3 Hz); MS (FAB) m/z 277 (MH^+); HR-MS (FAB) calcd for $C_{13}H_{17}N_4O_3$ 277.130, found 277.128. UV λ_{max} 262 (H_2O), 262 (0.1 N HCl), 267 nm (0.1 N NaOH). Anal. ($C_{13}H_{16}N_4O_3 \cdot {}^1/_4H_2O$) C, H, N.

2-Amino-6-chloro-9-[(1*R*,2*S*,3*R*)-2,3-(isopropylidenedioxy)-4-[2-[(*tert*-butyl-dimethylsilyl)oxy]ethyl]-4-cyclopenten-1-yl]purine (19) and 2-Amino-6-chloro-7-[(1*R*,2*S*,-3*R*)-2,3-(isopropylidenedioxy)-4-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-cyclopenten-1-yl]purine (20). A mixture of **15** (874 mg, 2.23 mmol), 2-amino-6-chloropurine (1.54 g, 9.09 mmol), K_2CO_3 (1.26 g, 9.12 mmol), and 18-crown-6 (600 mg, 2.23 mmol) in DMF (35 mL) was stirred at room temperature for 9 days. The solvent was evaporated, EtOAc (100 mL) was added to the residue, and the resulting insoluble material was filtered off. The filtrate was washed with water (20 mL) and filtered through Whatman 1PS filter paper, and the filtrate was evaporated. The residue was purified by flash chromatography (silica gel, $CHCl_3$/acetone, 10:1) to give **19** (crystalline solid, 567 mg, 55%) and **20** (crystalline solid, 122 mg, 12%), respectively. **19**: mp 228−229 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 7.63 (s, 1 H, H-8), 5.60 (br s, 1 H, H-5′), 5.44 (br s, 1 H, H-1′), 5.26 (m, 3 H, H-3′ and NH_2), 4.56 (d, 1 H, H-2′, J = 5.3 Hz), 3.89 (m, 2 H, H-7′), 2.53 (m, 2 H, H-6′), 1.46, 1.37 (each s, each 3 H, isopropyl-CH_3), 0.89 (s, 9 H, *t*-Bu), 0.08 (s, 6 H, $SiCH_3$); MS (FAB) m/z 466 (MH^+); UV λ_{max} 310, 248, 223 nm (MeOH). Anal. ($C_{21}H_{32}ClN_5O_3Si$) C, H, N. **20**: mp 145−146 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 7.86 (s, 1 H, H-8), 5.76 (br s, 1 H, H-5′), 5.63 (br s, 1 H, H-1′), 5.09 (d, 1 H, H-3′, J = 5.3 Hz), 5.03 (br s, 2 H and NH_2), 4.45 (d, 1 H, H-2′, J = 5.3 Hz), 3.84 (m, 2 H, H-7′), 2.48 (m, 2 H, H-6′), 1.37, 1.28 (each s, each 3 H, isopropyl-CH_3), 0.84 (s, 9 H, *t*-Bu), 0.03 (s, 6 H, $SiCH_3$); MS (FAB) m/z 466 (MH^+); UV λ_{max} 325, 225 nm (MeOH). Anal. ($C_{21}H_{32}ClN_5O_3Si \cdot H_2O$) C, H, N.

2-Amino-6-chloro-9-[(1*R*,2*S*,3*R*)-2,3-(isopropylidenedioxy)-4-(2-hydroxyethyl)-4-cyclopenten-1-yl]purine (21). A solution of **19** (300 mg, 0.65 mmol) and TBAF (1 M in THF, 780 μL, 0.78 mmol) in THF (15 mL) was stirred at room temperature for 2.5 h. The solvent was evaporated, and the residue was partitioned between $CHCl_3$ (50 mL) and water (10 mL × 3). The organic layer was filtered through Whatman 1PS filter paper, and the filtrate was concentrated to give **21** as a solid (145 mg, 64%): ^{1}H NMR (270 MHz, $CDCl_3$) 7.77 (s, 1 H, H-8), 5.71 (br s, 1 H, H-5′), 5.42 (br s, 2 H, NH_2), 5.36 (d, 1 H, H-3′, J = 5.6 Hz), 5.36 (s, 1 H, H-1′), 4.59 (d, 1 H, H-2′, J = 5.6 Hz), 3.91 (m, 2 H, H-7′), 3.58 (dd, 1 H, OH, J = 8.3, 3.3 Hz), 2.61 (m, 2 H, H-6′), 1.49, 1.37 (each s, each 3 H, isopropyl-CH_3); MS (FAB) m/z 352 (MH^+).

9-[(1*R*,2*S*,3*R*)-2,3-Dihydroxy-4-(2-hydroxyethyl)-4-cyclopenten-1-yl]guanine (5). A mixture of **21** (45 mg, 0.13 mmol) in 2 N HCl (6 mL) was stirred at room temperature for 2 h, and then the mixture was heated under reflux for 2 h. The solvent was evaporated, and a small amount of water was added to the residue, and the solvent was evaporated again. After addition of water (5 mL) to the residue, the mixture was neutralized with Et_3N and then evaporated. To the residue was added $CHCl_3$, and the resulting insoluble solid was collected by filtratation to give **5** (37 mg, 99%). An analytical sample was obtained by recrystallizing from water: mp 203−205 °C; $[\alpha]^{22}_D$ = +7.99 (c = 0.05, H_2O); ^{1}H NMR (270 MHz, CD_3OD) 8.93 (br s, 1 H, H-8), 5.77 (br s, 1 H, H-5′), 5.45 (m, 1 H, H-1′), 4.62 (d, 1 H, H-3′, J = 5.6 Hz), 4.34 (dd, 1 H, H-2′, J = 5.6, 4.6 Hz), 3.82 (t, 2 H, H-7′, J = 6.3 Hz), 2.54 (br t, 2 H, H-6′, J = 6.3 Hz); MS (FAB) m/z 294 (MH^+); UV λ_{max} 253 (H_2O), 256 (0.1 N HCl), 268, 256 nm (0.1 N NaOH). Anal. ($C_{12}H_{15}N_5O_4 \cdot H_2O$) C, H, N.

1-[(1*R*,2*S*,3*R*)-2,3-(Isopropylidenedioxy)-4-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-cyclopenten-1-yl]uracil (22). Compound **22** was prepared as described above for **19**, with uracil instead of 2-amino-6-chloropurine. After purification by flash chromatography (silica gel, hexane/acetone, 4:1), **22** was obtained as a crystalline solid (201 mg, 35%): mp 166−167 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 8.54 (br s, 1 H, NH), 7.08 (d, 1 H, H-6, J = 7.9 Hz), 5.63 (dd, 1 H, H-5, J = 2.3, 7.9 Hz), 5.45 (br s, 1 H, H-5′), 5.42 (br s, 1 H, H-1′), 5.14 (br d, 1 H, H-3′, J = 5.6 Hz), 4.47 (d, 1 H, H-2′, J = 5.6 Hz), 3.87 (m, 2 H, H-7′), 2.49 (m, 2 H, H-6′), 1.34, 1.35 (each s, each 3 H, isopropyl-CH_3), 0.89 (s, 9 H, *t*-Bu), 0.07 (s, 6 H, $SiCH_3$); MS (FAB) m/z 409 (MH^+). Anal. ($C_{20}H_{32}N_2O_5Si$) C, H, N.

1-[(1*R*,2*S*,3*R*)-2,3-(Isopropylidenedioxy)-4-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-cyclopenten-1-yl]thymine (23). Compound **23** was prepared as described above for **19**, with thymine instead of 2-amino-6-chloropurine. After purification by flash chromatography (silica gel, $CHCl_3$/acetone, 5:1), **23** was obtained as a crystalline solid (192 mg, 31%): mp 43−45 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 8.95 (br s, 1 H, NH), 6.82 (d, 1 H, H-6, J = 1.3 Hz), 5.44 (br s, 1 H, H-5′), 5.41 (br s, 1 H, H-1′), 5.17 (br d, 1 H, H-3′, J = 5.9 Hz), 4.49 (d, 1 H, H-2′, J = 5.9 Hz), 3.88 (m, 2 H, H-7′), 2.49 (m, 2 H, H-6′), 1.88 (d, 3 H, CH_3, J = 1.3 Hz), 1.43, 1.35 (each s, each 3 H, isopropyl-CH_3), 0.90 (s, 9 H, *t*-Bu), 0.08 (s, 6 H, $SiCH_3$); MS (FAB) m/z 423 (MH^+). Anal. ($C_{21}H_{34}N_2O_5Si \cdot {}^1/_2H_2O$) C, H, N.

1-[(1*R*,2*S*,3*R*)-2,3-(Isopropylidenedioxy)-4-(2-hydroxyethyl)-4-cyclopenten-1-yl]thymine (24). A mixture of **23** (50 mg, 0.12 mmol) and TBAF (1 M in THF, 142 μL, 0.14 mmol) in THF (2 mL) was stirred for 4 h and then evaporated. The residue was dissolved in water (30 mL) and washed with $CHCl_3$ (5 mL × 3). Activated charcoal (1 g) was added to the aqueous layer, and then the charcoal was packed in a column which was washed with water and eluted with 50% MeOH followed by MeOH. The fractions containing **24** were evaporated, a small amount of hot MeOH was added to the residue, and the resulting insoluble material was filtered off. The filtrate was evaporated, and the residue was purified by flash chromatography (silica gel, $CHCl_3$/MeOH, 10:1) to give **24** as a crystalline solid (29 mg, 79%): mp 62−63 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 9.47 (br s, 1 H, NH), 6.91 (d, 1 H, H-6, J = 1.3 Hz), 5.46 (br s, 1 H, H-5′), 5.25 (d, 1 H, H-3′, J = 5.6 Hz), 5.19 (br s, 1 H, H-1′), 4.64 (d, 1 H, H-2′, J = 5.6 Hz), 3.85 (br s, 2 H, H-7′), 2.74 (br s, 1 H, OH), 2.55 (m, 2 H, H-6′), 1.88 (s, 3 H, CH_3), 1.46, 1.34 (each s, each 3 H, isopropyl-CH_3); MS (FAB) m/z 309 (MH^+). Anal. ($C_{15}H_{20}N_2O_5 \cdot H_2O$) C, H, N.

1-[(1*R*,2*S*,3*R*)-2,3-Dihydroxy-4-(2-hydroxyethyl)-4-cyclopenten-1-yl]thymine (6). A solution of **24** (73 mg, 0.24 mmol) in 70% HCOOH (3 mL) was stirred at 70 °C for 40 h, and then the solvent was removed. To the residue was added

8% NH_4OH (3 mL), and the mixture was stirred for 1.5 h at room temperature. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, $CHCl_3/CH_3OH/H_2O$, 65:25:3) to give **6** as a crystalline solid (42 mg, 66%): mp 166−167 °C; $[\alpha]^{24}_D$ −82.12 (c = 0.21, H_2O); ^{1}H NMR (270 MHz, CD_3OD) 7.26 (s, 1 H, H-6), 5.54 (s, 1 H, H-5′), 5.45 (br s, 1 H, H-1′), 4.46 (br d, 1 H, H-3′, J = 5.6 Hz), 4.01 (m, 1 H, H-2′), 3.79 (br t, 2 H, H-7′, J = 6.3 Hz), 2.47 (br t, 2 H, H-6′, J = 6.3 Hz), 1.85 (s, 3 H, CH_3); MS (FAB) m/z 269 (MH^+); HR-MS (FAB) calcd for $C_{12}H_{17}N_2O_5$ 269.114; found 269.111; UV λ_{max} 274 (H_2O), 273 (0.1 N HCl), 271 nm (0.1 N NaOH). Anal. ($C_{12}H_{16}N_2O_5 \cdot {}^1/_5H_2O$) C, H, N.

1-[(1*R*,2*S*,3*R*)-2,3-(Isopropylidenedioxy)-4-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-cyclopenten-1-yl]cytosine (25). A mixture of **22** (155 mg, 0.78 mmol), DMAP (460 mg, 3.77 mmol), and 2,4,6-triisopropylbenzenesulfonyl chloride (460 mg, 1.52 mmol) in CH_3CN (5 mL) was stirred at room temperature overnight. After addition of 25% NH_4OH (5 mL), the mixture was further stirred for 5 h, $CHCl_3$ (50 mL) and water (10 mL) were added, and the resulting mixture was partitioned. The organic layer was washed with saturated NH_4Cl (10 mL) and filtered through Whatman 1PS filter paper, and the filtrate was evaporated. The residue was purified by flash chromatography (silica gel, $CHCl_3$/MeOH, 10:1) to give **25** as a crystalline solid (131 mg, 85%): mp 133−135 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 7.11 (d, 1 H, H-6, J = 7.3 Hz), 5.85 (d, 1 H, H-5, J = 7.3 Hz), 5.50 (br s, 1 H, H-5′), 5.40 (br s, 1 H, H-1′), 5.10 (br d, 1 H, H-3′, J = 5.6 Hz), 4.55 (d, 1 H, H-2′, J = 5.6 Hz), 3.85 (m, 2 H, H-7′), 2.47 (m, 2 H, H-6′), 1.41, 1.33 (each s, each 3 H, isopropyl-CH_3), 0.89 (s, 9 H, *t*-Bu), 0.07 (s, 6 H, $SiCH_3$); MS (FAB) m/z 408 (MH^+). Anal. ($C_{20}H_{33}N_3O_4Si$) C, H, N.

1-[(1*R*,2*S*,3*R*)-2,3-(Isopropylidenedioxy)-4-(2-hydroxyethyl)-4-cyclopenten-1-yl]cytosine (26). Compound **26** was prepared as described above for **24**. After purification by flash chromatography (silica gel, $CHCl_3/CH_3OH$, 5:1), **26** was obtained as a solid (37 mg, 86%): ^{1}H NMR (270 MHz, CD_3OD) 7.36 (d, 1 H, H-6, J = 7.6 Hz), 5.85 (d, 1 H, H-5, J = 7.6 Hz), 5.47 (br s, 1 H, H-5′), 5.40 (br s, 1 H, H-1′), 5.19 (br d, 1 H, H-3′, J = 5.9 Hz), 4.50 (d, 1 H, H-2′, J = 5.9 Hz), 3.81 (m, 2 H, H-7′), 2.50 (m, 2 H, H-6′), 1.40, 1.33 (each s, each 3 H, isopropyl-CH_3); MS (FAB) m/z 294 (MH^+).

1-[(1*R*,2*S*,3*R*)-2,3-Dihydroxy-4-(2-hydroxyethyl)-4-cyclopenten-1-yl]cytosine (7). A mixture of **26** (37 mg, 0.13 mmol) in HCl/MeOH (8.9 M, 3 mL) was stirred at room temperature for 1.5 h. The solvent was evaporated, the residue was dissolved in water (1 mL), and the solution was purified by a Dowex-1 column (OH^-, 1 × 2 cm, eluted with water) to give **7** as a crystalline solid (20 mg, 57%): mp >196 °C dec; $[\alpha]^{26}_D$ −35.13 (c = 0.074, MeOH); ^{1}H NMR (270 MHz, CD_3OD) 7.46 (d, 1 H, H-6, J = 7.3 Hz), 5.86 (d, 1 H, H-5, J = 7.3 Hz), 5.55 (d, 1 H, H-5′, J = 1.6 Hz), 5.45 (m, 1 H, H-1′), 4.48 (br d, 1 H, H-3′, J = 5.6 Hz), 3.99 (dd, 1 H, H-2′, J = 4.0, 5.6 Hz), 3.78 (br t, 2 H, H-7′, J = 6.6 Hz), 2.48 (br t, 2 H, H-6′, J = 6.6 Hz); MS (FAB) m/z 254 (MH^+); UV λ_{max} 273 (H_2O), 283 (0.1 N HCl), 273 nm (0.1 N NaOH). Anal. ($C_{11}H_{15}N_3O_4 \cdot {}^2/_5H_2O$) C, H, N.

Antiviral Assays. Antiviral assays were carried out according to previously reported methods.[7,9a,b,19]

Inhibitory Effect on Rabbit Erythrocyte AdoHcy Hydrolase and Effect of Adenosine Deaminase from Calf Intestine. Assays were carried out according to previously reported methods.[9a]

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