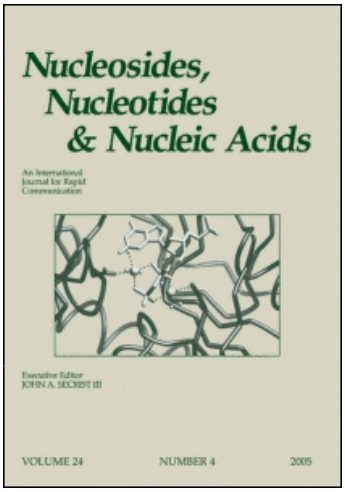

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SYNTHESIS AND ANTIVIRAL ACTIVITIES OF ENANTIOMERIC 1-[2-(HYDROXYMETHYL) CYCLOPROPYL] METHYL NUCLEOSIDES

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Dedicated in the memory of Gertrude B. Elion

Abstract Cyclopropyl carbocyclic nucleosides have been synthesized from the key intermediate **2** which was converted to the mesylated cyclopropyl methyl alcohol **3**. Condensation of compound **3** with various purine and pyrimidine bases gave the desired nucleosides. All synthesized nucleosides were evaluated for antiviral activity and cellular toxicity. Among them adenine **22** and guanine **23** derivatives showed moderate antiviral activity against HIV-1 and HBV. None of the other compounds showed any significant antiviral activities against HIV-1, HBV, HSV-1 and HSV-2 *in vitro* up to 100 μM.

Currently, carbohydrate-modified nucleosides are a major class of compounds as antiviral agents. During the past decade, numerous carbohydrate-modified nucleosides have been synthesized. In order to obtain biological activity as well as molecules resisting biodegradation suitable modifications have to be made. Among the alterations of the sugar moiety have been frequently utilized, which include deoxygenation, elimination, chain extention at C5'-position. The heteroatom substitutions at 3'-position was modified with replacement of the ribose ring by a cyclopropane,[1-4] cyclopentane,[5] cyclopentene,[6] oxatene,[7] cyclobutane[8] or even by an acyclic chain.[9,10]

It has been reported that carbocyclic analogs of oxetanocin exhibit potent antiviral activities.[11] Furthermore, carbovir[12] and cyclobut-G[13,14] are particularly interesting since they exhibit potent anti-HIV activity. Additionally, nucleosides with olefinic and cyclopropyl alcohols were reported, among which, 9-[[(z)-2-(hydroxymethyl)cyclopropan-1-yl]methyl]guanine and 9-[(z)-4-hydroxy-2-buten-1-yl]guanine showed moderate antiviral activity against HSV type-1 and type-2.[15] These acyclic nucleosides are efficiently phosphorylated by viral TK. These results suggested that the hydroxyl group of these nucleosides is in the right orientation for certain initial kinases, therefore, is suitable for phosphorylation.[16]

Recently, we have synthesized several cyclopropyl carbocyclic L- and D-nucleosides.[4,17-19] However, none of the compounds showed any significant antiviral activities. The lack of activity of these compounds indicated that the distance between the 5'-OH moiety and the heterocyclic base of nucleosides plays an important role on biological activity. In order to be biologically active, nucleosides must be phosphorylated by endogenous nucleoside kinases in the host cells, requiring an optimal geometry between the kinase and the nucleoside. In view of the fact, we compared the geometry of the cyclopropyl nucleosides with that of the X-ray structures of active compounds, such as ddC,[20] specifically the distance between the 5'-OH and the heterocyclic base of nucleosides. By extending the distance between the cyclopropyl and the base by one carbon, we discovered that such compound would have a closer distance between the 5'-OH and the heterocyclic moiety, when comparing to the compounds with antiviral activity.[21] These studies prompted us to synthesize the titled compounds, which is the subject of this article. Previously, Ashton, *et al.* has already reported the racemic guanine derivative, which showed significant anti-herpes activity.[15] Therefore, our present study extends the synthesis of various nucleosides by a different route as well as to report the comprehensive structure-activity relationships as potential antiviral agents against human immunodeficiency virus type-1(HIV-1) and hepatitis B virus (HBV).

RESULTS AND DISCUSSION

Although several synthetic pathways of cyclopropyl carbocyclic nucleosides have been

reported by several laboratories, none of the previous syntheses involved chiral intermediates. As a consequence, those nucleosides were prepared as racemic mixtures. Recently, the asymmetric synthesis of optically pure (1'S, 2'R)-cyclopropyl carbocyclic nucleosides have been accomplished in our laboratory.[17,18] In the present study, our synthetic strategy utilized the known compound **1** from our previous studies, from which the titled nucleosides could be readily prepared. The alcohol **2** was prepared in five steps from the starting material **1**. The desired nucleosides were prepared using a direct condensation method from **3**. Mesylation of cyclopropyl methyl alcohol **2** with methanosulfonyl chloride in the presence of triethylamine afforded the O-mesyl derivative **3** which was not stable enough to be purified by silica gel column chromatography. The crude compound **3** was directly treated with a base in the presence of K_2CO_3 and 18-crown-6 in DMF at 110°C to give the desired nucleosides in good yields.[11] The cleavage of isopropylidene group with 80% AcOH gave the dihydroxyalkyl cyclopropylmethyl nucleosides.[19] The final desired compounds were prepared by the oxidation of dihydroxyalkyl group to hydroxyalkyl group in presence of $NaIO_4$/NaBH4.[17]

All of the synthesized nucleosides were evaluated for antiviral activity against HIV-1, HBV, herpes simplex virus type-1 and type-2 (HSV-1 and HSV-2) (Table I). The adenine **22** and guanine **23** derivatives showed moderate antiviral activities against HIV in PBM cells (5.0 μM and 15.2 μM, respectively). The guanine analog also showed moderate anti-HBV activity in 2.2.15 cells (EC50 20.0 μM). None of other compounds showed any significant antiviral activity or toxicity up to 100 μ.

In view of the results of antiviral activity shown in Table I, the chain extended cyclopropyl carbocyclic nucleosides, particulary the adenine and guanine derivatives, may be phosphorylated by kinases although the phosphorylation rate may not be as fast as clinically useful compounds. The triphosphate analogs must also be able to inhibit the viral polymerase and act as a DNA chain terminator. Explanation for the lack of activity at the molecular level would be the difference in conformation between the synthesized compounds and active compounds such as ddA (Figure I) which are related to the phoshorylation rate and viral polymerase inhibition. However, we could not confirm the earlier findings in which the guanine derivative showed moderate antiviral activity against herpes virus.[15]

Table I. Anti-HIV, anti-HBV and HSV activities of cyclopropyl carbocyclic nucleosides.

Compounds	HIV-1 (PBM cells)	HBV (2.2.15 cells)	HSV (I or II)	Toxicity		
	EC_{50} (μM)	EC_{50} (μM)	EC_{50} (μM)	PBM IC_{50} (μM)	CEM IC_{50} (μM)	Vero IC_{50} (μM)
dihydroxyuracil **(6)**	> 100	> 10	> 50	-	> 100	> 100
dihydroxythymine **(7)**	56.1	> 10	> 50	> 100	> 100	> 100
uracil **(8)**	> 100	> 10	> 50	-	> 100	> 100
thymine **(9)**	> 100	> 10	> 50	> 100	> 100	> 100
cytosine **(12)**	> 100	> 10	> 50	> 100	> 100	> 100
dihydroxyhypoxanthine **(18)**	> 100	> 10	> 50		> 100	> 100
dihydroxyadenine **(19)**	> 100	> 10	> 50		> 100	> 100
dihydroxyguanine **(20)**	> 100	> 10	> 50	> 100	> 100	> 100
hypoxanthine **(21)**	> 100	> 10	> 50	-	> 100	> 100
adenine **(22)**	5.0[15]	> 20	> 50 (5)[15]	-	> 100	> 100
guanine **(23)**	15.2 [15]	20.0	>25 (3)[15]	-	> 100	> 100

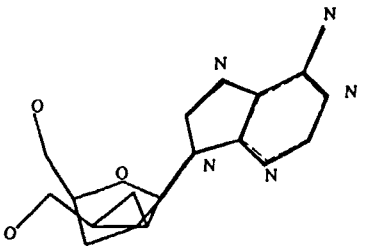


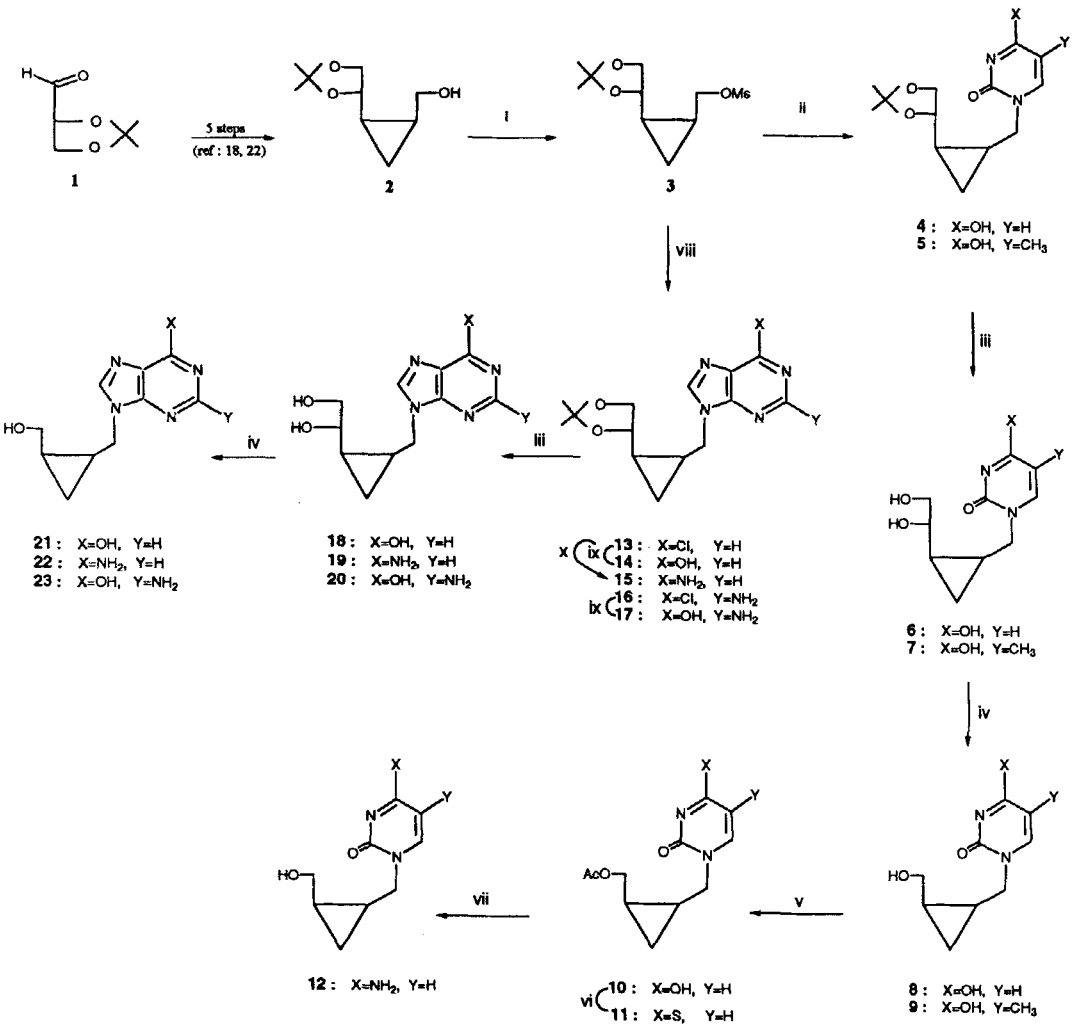
Figure I. Overlap of compound **22** and ddA.

EXPERIMENTAL SECTION

Melting points were determined on a Mel-temp II apparatus and are uncorrected. NMR spectra were recorded on a Bruker 400 AMX spectrometer at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR with Me_4Si as internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or bs (broad singlet). Mass spectra were recorded on a Micromass Autospec high-resolution mass spectrometer. TLC were performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either silica gel-60 (220-440 mesh) for flash chromatography or silica gel G (TLC grade, > 440 mesh) for vacuum flash column chromatography. UV spectra were obtained on a Beckman DU 650 spectrophotometer. Elemental analysis were performed by Atlantic Microbial lab, Inc., Norcross, GA, or Galbraith Laboratories, Inc., Knoxville, TN.

(1*S*,2*R*,4'*S*)-1-(Hydroxymethyl)-2-(2,2-dimethyl-1,3-dioxoloan-4-yl)cyclopropane (2). Compound **2** was prepared in 5 steps starting from 1,2:5,6-di-*O*-isopropylidene-D-mannitol (in 35 % overall yield) according to our previously published procedure.[18]

(1'*S*,2'*R*,4"*S*)-1-[[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]methyl]uracil (4). To a solution of **2** (500 mg, 2.9 mmol) and Et_3N (2.5 mL, 17.4 mmol) in dry CH_2Cl_2 (30 mL) was added methanesulfonyl chloride (MsCl) (0.3 mL, 3.77 mmol) dropwise at 0°C. The reaction mixture was stirred for 1 h and the solvent was removed under reduced pressure to give the mesylated sugar **3**. A suspension of uracil (976 mg, 8.7 mmol), K_2CO_3



Reagents: (i) MsCl, Et_3N, CH_2Cl_2; (ii) pyrimidine bases, 18-crown-6, K_2CO_3, DMF; (iii) AcOH 80%; (iv) $NaIO_4$, $NaBH_4$, MeOH; (v) Ac_2O, pyridine; (vi) Lawesson's reagent, CH_2Cl_2; (vii) MeOH/NH_3, 100°C: (viii) purine bases, 18-crown-6, K_2CO_3, DMF; (ix) $HS(CH_2)_2OH$, MeONa, MeOH; (x) MeOH/NH_3, 90°C

Scheme I Synthesis of (1'*S*,2'*R*)-1[[(1,*S*)-1,2-hydroxyethyl]cyclopropyl]methyl]pyrimidines and purines

(1200 mg, 8.7 mmol), and 18-crown-6 (1500 mg, 5.8 mmol) in dry DMF (30 mL) was stirred at 100-150°C for 4 h. The crude sugar **3** was dissolved in dry DMF (60 mL) and added under argon to the base suspension. The reaction mixture was warmed to the 80-90°C and stirred overnight. The DMF was removed under reduced pressure and the residue was diluted with CH_2Cl_2, washed with water, dried over sodium sulfate and concentrated to dryness. The residue was purified by silica gel column chromatography (30-70% EtOAc in hexanes) to give **4** (362 mg, 46.9%): $[\alpha]^{25}_D$ = -54.34° (c = 0.41, CH_2Cl_2); UV (MeOH) λ_{max} 266.0 nm; ^{1}H NMR ($CDCl_3$) δ 0.60, 0.83 (2m, 2H, cyPrCH$_2$), 1.03, 1.19 (2m, 2H, 2 cyPrCH), 1.36 (d, 6H, J = 28.0 Hz, 2CH$_3$), 3.45 (m, 1H, CHO), 3.45-3.88 (m, 2H, CH$_2$O), 4.06 (m, 2H, CH$_2$N), 5.62 (d, 1H, J = 7.7 Hz, 6-H), 7.23 (d, 1H, J = 7.7 Hz, 5-H), 8.36 (s, 1H, NH, D_2O exchangeable); HRMS calcd for $C_{13}H_{19}N_2O_4$ 267.1345, found 267.1327; Anal. Calcd for $C_{13}H_{18}N_2O_4 \cdot 0.5MeOH$: C, 57.43; H, 7.14; N, 9.92. Found: C, 57.82; H, 7.04; N, 9.54.

(1'*S*,2'*R*,4"*S*)-1-[[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]-methyl]thymine (5). The mesylated sugar **3** was prepared from compound **2** (500 mg, 2.9 mmol) as described for compound **4**. A suspension of thymine (1097 mg, 8.7 mmol), K_2CO_3 (1200 mg, 8.7 mmol), and 18-crown-6 (1500 mg, 5.8 mmol) in dry DMF (30 mL) was stirred at 100-120°C for 4h. The crude sugar **3**, was dissolved in DMF (30 mL) and added under argon to the base suspension. The reaction mixture was warmed to 80-90°C and stirred overnight. The DMF was removed under reduced pressure and the residue was diluted with CH_2Cl_2, washed with water, dried over sodium sulfate and concentrated to dryness. The residue was purified by silica gel column chromatography (30-70% EtOAc in hexanes) to give **5** (378 mg, 46.5%): $[\alpha]^{25}_D$ = -4.91° (c = 1.00, MeOH); UV (MeOH) λ_{max} 270.0 nm; ^{1}H NMR ($CDCl_3$) δ 0.58, 0.82 (2m, 2H, cyPrCH$_2$), 1.01, 1.27 (2m, 2H, 2 cyPrCH), 1.32 (d, 6H, J = 24.0 Hz, 2CH$_3$), 1.70 (s, 3H, CH$_3$), 3.61 (t, 1H, J = 8.0 Hz, CHO), 3.70-3.81 (2m, 2H, CH$_2$O), 4.03 (m, 2H, CH$_2$N), 7.06 (s, 1H, 6-H), 8.62 (s, 1H, NH, D_2O exchangeable); HRMS calcd for $C_{14}H_{21}N_2O_4$ 281.1501, found 281.1522; Anal. Calcd for $C_{14}H_{20}N_2O_4 \cdot 0.8H_2O$: C, 57.05; H, 7.39; N, 9.50. Found: C, 57.35; H, 7.27; N, 9.12.

(1'*S*,2'*R*)-1-[[2-[(1*S*)-1,2-Dihydroxyethyl]cyclopropyl]methyl]uracil (6). A solution of compound **4** (330 mg, 1.24 mmol) in 80% AcOH (31 mL) was strirred at room

temperature for 28 h. The solvent was removed to the dryness and coevaporated with toluene. The crude mixture which was purified by silica gel column chromatography (10% MeOH in CH_2Cl_2) to give **6** (108 mg, 74.1%): $[\alpha]^{25}_D$ = +31.44° (c = 0.46, MeOH); UV (MeOH) λ_{max} 266.0 nm; ^{1}H NMR (MeOH) δ 0.57, 0.83 (2m, 2H, cyPrCH$_2$), 1.04, 1.34 (2m, 2H, 2 cyPrCH), 3.30 (m, 1H, CHO), 3.30-3.43 (m, 2H, CH_2O), 3.59, 4.06 (2m, 2H, CH_2N), 5.66 (d, 1H, J = 7.7 Hz, 6-H), 7.66 (d, 1H, J = 7.7 Hz, 5-H); HRMS calcd for $C_{10}H_{15}N_2O_4$ 227.1032, found 227.1040; Anal. Calcd for $C_{10}H_{14}N_2O_4 \cdot 0.7H_2O$: C, 50.29; H, 6.50; N, 11.73. Found: C, 50.26; H, 6.43; N, 11.61.

(1'*S*,2'*R*)-1-[[2-[(1*S*)-1,2-Dihydroxyethyl]cyclopropyl]methyl] thymine (7). The compound was prepared by starting from compound **5** (311mg, 1.11 mmol) as described for compound **6** and purified by silica gel column chromatography (10% MeOH in CH_2Cl_2) to give (205 mg, 76.9%) pure compound: $[\alpha]^{25}_D$ = +27.28° (c = 0.83, MeOH); UV (MeOH) λ_{max} 270.0 nm; ^{1}H NMR (MeOH) δ 0.57, 0.79 (2m, 2H, cyPrCH$_2$), 1.03, 1.33 (2m, 2H, 2 cyPrCH), 1.92 (d, 3H, CH_3), 3.52 (m, 1H, CHO), 3.52 (m, 2H, CH_2O), 3.52, 4.02 (2m, 2H, CH_2N), 7.50 (s, 1H, 6-H); HRMS calcd for $C_{11}H_{17}N_2O_4$ 241.1188, found 241.1200; Anal. Calcd for $C_{11}H_{16}N_2O_4 \cdot 0.7H_2O$: C, 52.25; H, 6.94; N, 11.08. Found: C, 52.38; H, 6.86; N, 10.92.

(1'*S*,2'*R*)-1-[[2-(Hydroxymethyl)cyclopropyl]methyl]uracil (8). To a solution of **6** (106 mg, 0.6 mmol) in MeOH (78 mL) was added a solution of sodium periodate (300 mg, 1.35 mmol) in H_2O (8 mL) dropwise. After the mixture was stirred for 5 min, sodium borohydride (98 mg, 2.55 mmol) was added to the reaction mixture and stirred for another 5 min, the solution was filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (5% MeOH in $CHCl_3$) to give **8** (102 mg, 86.6%): $[\alpha]^{25}_D$ = +31.95° (c = 0.42, MeOH); UV (MeOH) λ_{max} 266.5 nm (ε 9000) (pH 2), λ_{max} 266.5 nm (ε 9900) (pH 7), λ_{max} 264.5 nm (ε 8300) (pH 11), ^{1}H NMR (DMSO-d_6) δ 0.26, 0.65 (2m, 2H, cyPrCH$_2$), 1.16, 1.25 (2m, 2H, 2 cyPrCH), 3.05 (m, 1H, CHO), 3.05-3.59 (2m, 2H, CH_2O), 3.59, 4.37 (2m, 2H, CH_2N), 5.56 (d, 1H, J = 7.7 Hz, 6-H), 7.51 (d, 1H, J = 7.7 Hz, 5-H), 11.00 (s, 1H, NH, D_2O exchangeable); HRMS calcd for $C_9H_{13}N_2O_3$ 197.0926, found 197.0918; Anal. Calcd for $C_9H_{12}N_2O_3 \cdot 0.2CH_2Cl_2$: C, 52.44; H, 5.92; N, 13.35. Found: C, 52.71; H, 6.34; N, 12.95.

(1'*S*,2'*R*)-1-[[2-(Hydroxymethyl)cyclopropyl]methyl]thymine (9). The compound was prepared by starting from compound **7** (140 mg, 0.6 mmol) as described for

compound **8** and purified by silica gel column chromatography (5% MeOH in $CHCl_3$) to give (106 mg, 83.5%) pure compound: $[\alpha]^{25}_D$ = +39.00° (c = 0.61, MeOH); UV (MeOH) λ_{max} 271.5 nm (ε 10500) (pH 2), λ_{max} 272.5 nm (ε 10000) (pH 7), λ_{max} 267.5 nm (ε 8500) (pH 11); ^{1}H NMR (DMSO-d_6) δ 0.25, 0.64 (2m, 2H, cyPrCH$_2$), 1.15 (m, 2H, 2 cyPrCH), 1.79 (s, 3H, CH_3), 3.30-3.67 (2m, 2H, CH_2O), 3.57, 3.80 (2m, 2H, CH_2N), 4.62 (t, 1H, J = 5.0 Hz, OH, D_2O exchangeable), 7.65 (s, 1H, 6-H), 11.23 (s, 1H, NH, D_2O exchangeable); HRMS calcd for $C_{10}H_{15}N_2O_3$ 211.1083, found 211.1095; Anal. Calcd for $C_{10}H_{14}N_2O_3 \cdot 0.2H_2O$: C, 56.17; H, 6.79; N, 13.10. Found: C, 56.19; H, 6.65; N, 12.79.

(1'*S*,2'*R*)-1-[[2-(Acetoxymethyl)cyclopropyl]methyl]uracil (10). A solution of compound **8** (96 mg, 0.46 mmol) and acetic anhydride (1.9 mL, 20.6 mmol) in pyridine (2.7 mL) was stirred at room temperature for 4 h. The solvent was evaporated to dryness and the crude mixture was purified by silica gel column chromatography (5% MeOH in $CHCl_3$) to give **10** (108 mg, 98.7%): $[\alpha]^{25}_D$ = +26.28° (c = 0.16, MeOH); UV (MeOH) λ_{max} 265.5 nm; ^{1}H NMR (DMSO-d_6) δ 0.42, 0.76 (2m, 2H, cyPrCH$_2$), 1.23, 1.33 (2m, 2H, 2 cyPrCH), 2.08 (d, 3H, J = 2.4 Hz, CH_3), 3.57-3.82 (2m, 2H, CH_2O), 3.82, 4.29 (2m, 2H, CH_2N), 5.73 (d, 1H, J = 8.0 Hz, 6-H), 7.69 (d, 1H, J = 8.0 Hz, 5-H), 11.25 (s, 1H, NH, D_2O exchangeable); HRMS calcd for $C_{11}H_{15}N_2O_4$ 239.1032, found 239.1027; Anal. Calcd for $C_{11}H_{14}N_2O_4 \cdot 0.5H_2O$: C, 53.44; H, 6.11; N, 11.33. Found: C, 53.81; H, 6.04; N, 11.31.

(1'*S*,2'*R*)-1-[[2-(Acetoxymethyl)cyclopropyl]methyl]-4-thio-pyrimidine-2(1*H*)-one (11). To a solution of compound **10** (98 mg, 0.41 mmol) in CH_2Cl_2 was added Lawesson's reagent (116 mg, 0.29 mmol). The reaction mixture was refluxed for 20 h and the solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (1% MeOH in CH_2Cl_2) to give **11** (88 mg, 84.2%): $[\alpha]^{25}_D$ = +31.36° (c = 0.28. MeOH); UV (MeOH) λ_{max} 338.0 nm, 248.0 nm; ^{1}H NMR (DMSO-d_6) δ 0.52. 0.86 (2m, 2H, cyPrCH$_2$), 1.32, 1.45 (2m, 2H, 2 cyPrCH), 2.10 (s, 3H, CH_3), 3.70, 3.90 (2m, 2H, CH_2O), 3.90, 4.39 (2m, 2H, CH_2N), 6.36 (dd, 1H, J = 7.2 and 1.5 Hz, 6-H), 7.72 (dd, 1H, J = 7.2 and 1.4 Hz, 5-H), 8.38 (s, 1H, N-H, D_2O exchangeable); HRMS calcd for $C_{11}H_{15}N_2O_3S$ 255.0803, found 255.0798; Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.85; H, 5.55; N, 11.02. Found: C, 51.71; H, 5.56; N, 10.86.

(1'*S*,2'*R*)-1-[[2-(Hydroxymethyl)cyclopropyl]methyl]cytosine (12). A solution of compound **11** (27 mg, 0.106 mmol) in MeOH/NH_3 was heated at 100°C in a steel bomb for 4 h. The solvent was removed under reduced pressure and the crude mixture was purified

by silica gel column chromatography (15% MeOH in $CHCl_3$) to give **12** (18 mg, 87.0%) which was crystallized from isopropanol: mp 180°C ; $[\alpha]^{25}_D$ = +24.84° (c = 0.32, MeOH); UV (MeOH) λ_{max} 283.5 nm (ε 12700) (pH 2), λ_{max} 273.5 nm (ε 8600) (pH 7), λ_{max} 273.5 nm (ε 9300) (pH 11); ^{1}H NMR (DMSO-d_6) δ 0.18, 0.58 (2m, 2H, cyPrCH$_2$), 1.13 (2m, 2H, 2 cyPrCH), 3.28-3.63 (2m, 2H, CH_2O), 3.54, 3.78 (2m, 2H, CH_2N), 4.65 (t, 1H, J = 5.4 Hz, OH, D_2O exchangeable), 5.62 (d, 1H, J = 7.2 Hz, 6-H), 6.93, 7.00 (2bs, 2H, NH_2, D_2O exchangeable), 7.65 (d, 1H, J = 7.2 Hz, 5-H); HRMS calcd for $C_9H_{14}N_3O_2$ 196.1086, found 196.1080; Anal. Calcd for $C_9H_{13}N_3O_2 \cdot 0.4H_2O$: C, 53.40; H, 6.87; N, 20.76. Found: C, 53.64; H, 6.74; N, 20.36.

(1'*S*,2'*R*,4''*S*)-1-[[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]-methyl]-6-chloropurine (13). The mesylated sugar **3** was prepared from compound **2** (500 mg, 2.9 mmol) as described for compound **4**. A suspension of 6-chloropurine (1300 mg, 8.7 mmol), K_2CO_3 (1200 mg, 8.7 mmol), and 18-crown-6 (1500 mg, 5.8 mmol) in dry DMF (30 mL) was stirred at 100°C for 4 h. The crude sugar **3** was dissolved in DMF (30 mL) and added under argon to the base suspension. The reaction mixture was warmed to 80-90°C and stirred for 20 h. The DMF was removed under reduced pressure and the residue was diluted with CH_2Cl_2, washed with water, dried over sodium sulfate and concentrated to dryness. The residue was purified by silica gel column chromatography (1% MeOH in CH_2Cl_2) to give **13** (318 mg, 35.5%): $[\alpha]^{25}_D$ = -23.38° (c = 0.60, MeOH); UV (MeOH) λ_{max} 264.0 nm; ^{1}H NMR ($CDCl_3$) δ 0.73, 0.86 (2m, 2H, cyPrCH$_2$), 1.06, 1.53 (2m, 2H, 2 cyPrCH), 1.35 (d, 6H, J = 24.0 Hz, 2CH_3), 3.60 (t, 1H, J = 7.7 Hz, CHO), 4.01-4.13 (2m, 2H, CH_2O), 4.38 (t, 2H, J = 3.4, CH_2N), 8.15, 8.69 (2s, 2H, 2-H, 8-H); HRMS calcd for $C_{14}H_{18}N_4O_2Cl$ 309.1118, found 309.1112; Anal. Calcd for $C_{14}H_{17}N_4O_2Cl$: C, 54.45; H, 5.55; N, 18.15. Found: C, 54.21; H, 5.72; N, 17.95.

(1'*S*,2'*R*,4''*S*)-1-[[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]-methyl]hypoxanthine (14). A solution of compound **13** (75 mg, 0.24 mmol), 2-mercaptoethanol (0.07 mL, 0.97 mmol), sodium methoxide (53 mg, 0.97 mmol) in MeOH (12 mL) was refluxed overnight under argon atmosphere. The reaction mixture was neutralized with DOWEX H^+ resin, filtered and the filtrate was concentrated to dryness. The residue was purified by silica gel column chromatography (0-4% MeOH in CH_2Cl_2) followed by PTLC (2% MeOH in CH_2Cl_2 developed 4 times) to give **14** (57 mg, 80.8%):

$[\alpha]^{25}_D$ = -18.20° (c = 0.41, MeOH); UV (MeOH) λ_{max} 249.0 nm; ^{1}H NMR (MeOH) δ 0.73, 0.91 (2m, 2H, cyPrCH$_2$), 1.15 (t, 1H, J = 7.1 Hz, cyPrCH), 1.37 (d, 6H, J = 26.8 Hz, 2CH$_3$), 1.60 (m, 1H, cyPrCH), 3.58 (t, 1H, J = 7.7 Hz, CHO), 3.93, 4.08 (2m, 2H, CH$_2$O), 4.29, 4.35 (2m, 2H, CH$_2$N), 8.05, 8.15 (2s, 2H, 2-H, 8-H); HRMS calcd for $C_{14}H_{19}N_4O_3$ 291.1457, found 291.1432; Anal. Calcd for $C_{14}H_{18}N_4O_3 \cdot 0.4H_2O$: C, 57.06; H, 6.52; N, 18.48. Found: C, 56.93; H, 6.19; N, 18.79.

(1'*S*,2'*R*,4"*S*)-1-[[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]-methyl]-6-adenine (15). A mixture of compound **13** (75 mg, 0.24 mmol) and MeOH/NH$_3$ (17 mL) was heated at 90°C in a steel bomb for 24 h. The solvent was removed under reduced pressure and the reaction mixture was purified by silica gel column chromatography (0-4% MeOH in CH_2Cl_2) to give **15** (56 mg, 79.6%): $[\alpha]^{25}_D$ = -23.57° (c = 0.53, MeOH); UV (MeOH) λ_{max} 260.5 nm; ^{1}H NMR (MeOH) δ 0.73, 0.93 (2m, 2H, cyPrCH$_2$), 1.14, 1.61 (2m, 2H, 2 cyPrCH), 1.36 (d, 6H, J = 27.9 Hz, 2CH$_3$), 3.56 (t, 1H, J = 7.6 Hz, CHO), 3.90, 4.07 (2m, 2H, CH$_2$O), 4.24, 4.39 (2m, 2H, CH$_2$N), 8.19, 8.21 (2s, 2H, 2-H, 8-H); HRMS calcd for $C_{14}H_{20}N_5O_2$ 290.1617, found 290.1609; Anal. Calcd for $C_{14}H_{19}N_5O_2 \cdot 0.75H_2O$: C, 55.52; H, 6.82; N, 23.12. Found: C, 55.79; H, 6.57; N, 22.78.

(1'*S*,2'*R*,4"*S*)-1-[[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]-methyl]-2-amino-6-chloropurine (16). The mesylated sugar **3** was prepared from compound **2** (500 mg, 2.9 mmol) as describe for compound **4**. A suspension of 2-amino-6-chloropurine (1500 mg, 8.7 mmol), K_2CO_3 (1200 mg, 8.7 mmol), and 18-crown-6 (1500 mg, 5.8 mmol) in dry DMF (30 mL) was stirred at 100-120°C for 4 h. The crude sugar **3** was dissolved in DMF (30 mL) and added under argon to the base suspension. The reaction mixture was warmed to the 80-90°C and stirred for 20 h. The DMF was removed under reduced pressure and the residue was diluted with CH_2Cl_2, washed with water, dried over sodium sulfate and concentrated to dryness. The residue was purified by silica gel column chromatography (2% MeOH in CH_2Cl_2) to give **16** (385 mg, 41.0%): $[\alpha]^{25}_D$ = -10.80° (c = 0.59, MeOH); UV (MeOH) λ_{max} 309.5 nm; ^{1}H NMR (DMSO-*d*$_6$) δ 0.68, 0.89 (2m, 2H, cyPrCH$_2$), 1.10, 1.55 (2m, 2H, 2 cyPrCH), 1.39 (d, 6H, J = 26.4 Hz, 2CH$_3$), 3.50 (m, 1H, CHO), 3.93 (m, 2H, CH$_2$O), 4.07, 4.22 (2m, 2H, CH$_2$N), 7.00 (s, 2H, NH$_2$, D$_2$O exchangeable), 8.24 (s, 1H, 8-H); HRMS calcd for $C_{14}H_{19}N_5O_2Cl$ 324.1227, found 324.1209; Anal. Calcd for $C_{14}H_{18}N_5O_2Cl \cdot 0.5H_2O$: C, 50.37; H, 5.77; N, 20.98. Found: C, 50.69; H, 5.59; N, 20.58.

(1'*S*,2'*R*,4''*S*)-1-[[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]-methyl]guanine (17). The compound was prepared by starting from compound **16** (376 mg, 1.22 mmol), as described compound **14** and purified by silica gel column chromatography (6% MeOH in CH_2Cl_2) to give (360 mg, 96.6%) pure compound: $[\alpha]^{25}_D$ = -9.49° (c = 0.82, MeOH); UV (MeOH) λ_{max} 254.5 nm; ^{1}H NMR (DMSO-d_6) δ 0.58, 0.81 (2m, 2H, cyPrCH$_2$), 1.01, 1.46 (2m, 2H, 2 cyPrCH), 1.39 (d, 6H, J = 26.4 Hz, 2CH$_3$), 3.41 (m, 1H, CHO), 3.91 (m, 2H, CH$_2$O), 3.91 (m, 2H, CH$_2$N), 6.46 (s, 2H, NH$_2$, D$_2$O exchangeable), 7.74 (s, 1H, 8-H), 10.57 (s, 1H, NH, D$_2$O exchangeable); HRMS calcd for $C_{14}H_{20}N_5O_3$ 306.1566, found 306.1535; Anal. Calcd for $C_{14}H_{19}N_5O_3$·1EtOH: C, 54.08; H, 7.07; N, 19.93. Found: C, 54.28; H, 6.69; N, 19.94.

(1'*S*,2'*R*)-1-[[2-[(1*S*)-1,2-Dihydroxyethyl]cyclopropyl]methyl] hypoxanthine (18). A solution of compound **14** (71 mg, 0.24 mmol) in 80% AcOH (6 mL) was stirred at room temperature for 28 h. The solvent was removed under dryness and coevaporated with toluene. The crude mixture was purified by silica gel column chromatography (5-20% MeOH in CH_2Cl_2) to give **18** (46 mg, 75.0%): $[\alpha]^{25}_D$ = +1.18° (c = 0.38, MeOH); UV (MeOH) λ_{max} 249.5 nm; ^{1}H NMR (MeOH) δ 0.73, 0.93 (2m, 2H, cyPrCH$_2$), 1.14, 1.61 (2m, 2H, 2 cyPrCH), 3.56 (t, 1H, J = 7.6 Hz, CHO), 3.90, 4.07 (2m, 2H, CH$_2$O), 4.24, 4.39 (2m, 2H, CH$_2$N), 8.19, 8.21 (2s, 2H, 2-H, 8-H); HRMS calcd for $C_{11}H_{15}N_4O_3$ 251.1144, found 251.1157; Anal. Calcd for $C_{11}H_{14}N_4O_3$·0.2H$_2$O: C, 52.04; H, 5.72; N, 22.07. Found: C, 51.93; H, 5.77; N, 21.89.

(1'*S*,2'*R*)-1-[[2-[(1*S*)-1,2-Dihydroxyethyl]cyclopropyl]methyl] adenine (19). The compound was prepared by starting from compound **15** as described for compound **18** and purified by silica gel column chromatography (5-16% MeOH in CH_2Cl_2) to give (57 mg, 88.3%) pure compound: $[\alpha]^{25}_D$ = +3.40° (c = 0.48, MeOH); UV (MeOH) λ_{max} 260.5 nm; ^{1}H NMR (MeOH) δ 0.66, 0.84 (2m, 2H, cyPrCH$_2$), 1.10, 1.55 (2m, 2H, 2 cyPrCH), 3.31 (m, 1H, CHO), 3.53, (m, 2H, CH$_2$O), 4.14, 4.66 (2m, 2H, CH$_2$N), 8.20, 8.21 (2s, 2H, 2-H, 8-H); HRMS calcd for $C_{11}H_{16}N_5O_2$ 250.1304, found 250.1326; Anal. Calcd for $C_{11}H_{15}N_5O_2$·0.8MeOH: C, 51.56; H, 6.67; N, 25.48. Found: C, 51.17; H, 6.29; N, 25.13.

(1'*S*,2'*R*)-1-[[2-[(1*S*)-1,2-Dihydroxyethyl]cyclopropyl]methyl]guanine (20). The compound was prepared by starting from compound **17** as described for compound **18** and purified by silica gel column chromatography. Crystallization from MeOH to give (50 mg,

16% crystals) pure compound: mp 200°C; $[\alpha]^{25}_D$ = +12.25° (c = 0.32, MeOH); UV (MeOH) λ_{max} 253.5 nm, λ_s 271.5 nm; ^{1}H NMR (DMSO-d_6) δ 0.28, 0.66 (2m, 2H, cyPrCH$_2$), 1.13, 1.27 (2m, 2H, 2 cyPrCH), 3.39 (m, 1H, CHO), 3.87 (m, 2H, CH$_2$O), 4.25 (m, 2H, CH$_2$N), 4.63 (s, 2H, OH, D$_2$O exchangeable), 6.56 (s, 2H, NH$_2$, D$_2$O exchangeable), 7.82 (s, 1H, 8-H), 10.67 (s, 1H, NH, D$_2$O exchangeable); HRMS calcd for $C_{11}H_{16}N_5O_3$ 266.1253, found 266.1258; Anal. Calcd for $C_{11}H_{15}N_5O_3 \cdot 1.3H_2O$: C, 45.77; H, 6.14; N, 24.26. Found: C, 45.64; H, 5.95; N, 24.26.

(1'*S*,2'*R*)-1-[[2-(Hydroxymethyl)cyclopropyl]methyl]hypoxanthine (21). To a solution of **18** (30 mg, 0.1 mmol) in MeOH (13 mL) was added a solution of sodium periodate (50 mg, 0.22 mmol) in H$_2$O (1.3 mL) dropwise. After the mixture was stirred for 5 min, sodium borohydride (17 mg, 0.42 mmol) was added to the reaction mixture and stirred for another 5 min, the solution was filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (5-10% MeOH in CHCl$_3$) to give **21** (20 mg, 96.0%) which was crystallized from isopropanol: mp 210°C; $[\alpha]^{25}_D$ = +2.37° (c = 0.41, MeOH); UV (MeOH) λ_{max} 250.0 nm (ε 12400) (pH 2), λ_{max} 249.5 nm (ε 12500) (pH 7), λ_{max} 254.5 nm (ε 13200) (pH 11); ^{1}H NMR (DMSO-d_6) δ 0.36, 0.69 (2m, 2H, cyPrCH$_2$), 1.18, 1.36 (m, 2H, 2 cyPrCH), 3.27-3.73 (2m, 2H, CH$_2$O), 4.10, 4.27 (2m, 2H, CH$_2$N), 4.70 (s, 1H, OH, D$_2$O exchangeable), 8.05, 8.19 (2s, 2H, 2-H, 8-H), 10.41 (s, 1H, NH, D$_2$O exchangeable),; HRMS calcd for $C_{10}H_{13}N_4O_2$ 221.1038, found 221.1045; Anal. Calcd for $C_{10}H_{12}N_4O_2 \cdot 0.2H_2O$: C, 53.66; H, 5.58; N, 25.03. Found: C, 53.92; H, 5.58; N, 24.95.

(1'*S*,2'*R*)-1-[[2-(Hydroxymethyl)cyclopropyl]methyl]adenine (22). The compound was prepared by starting from compound **19** as described for compound **21** and purified by silica gel column chromatography (0-7% MeOH in CHCl$_3$) to give **22** (31 mg, 97.5%) which was crystallized from isopropanol: mp 285-290°C; $[\alpha]^{25}_D$ = +7.67° (c = 0.82, MeOH); UV (MeOH) λ_{max} 259.0 nm (ε 15200) (pH 2); λ_{max} 260.5 nm (ε 15900) (pH 7); λ_{max} 261.5 nm (ε 17400) (pH 11); ^{1}H NMR (DMSO-d_6) δ 0.31, 0.67 (2m, 2H, cyPrCH$_2$), 1.16 (m, 1H, cyPrCH), 1.34 (q, 1H, J = 7.8 and 13.5 Hz, cyPrCH), 3.37, 3.73 (2m, 2H, CH$_2$O), 4.11, 4.22 (2m, 2H, CH$_2$N), 4.78 (t, 1H, J = 5.1 Hz, OH, D$_2$O exchangeable), 7.19 (s, 2H, NH$_2$, D$_2$O exchangeable), 8.12, 8.22 (2s, 2H, 2-H, 8-H); HRMS calcd for $C_{10}H_{14}N_5O$ 220.1198, found 220.1190; Anal. Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94. Found: C, 54.61; H, 6.03; N, 31.81.

(1'*S*,2'*R*)-1-[[2-(Hydroxymethyl)cyclopropyl]methyl]guanine (23). The compound was prepared by starting from compound **20** as described for compound **21** and purified by silica gel column chromatography (10-15% MeOH in CH_2Cl_2) to give **23** (210 mg, 90.2%) which was crystallized from water: mp 310°C; $[\alpha]^{25}_D$ = +26.37° (c = 0.26, MeOH); UV (MeOH) λ_{max} 252.5 nm (ε 13900) λ_s 276.5 nm (pH 2), λ_{max} 251.5 nm (ε 14500) λ_s 266.0 nm (pH 7), λ_{max} 269.0 nm (ε 11900) λ_s 254.0 (pH 11); ^{1}H NMR (DMSO-d_6) δ 0.19, 0.58 (2m, 2H, cyPrCH$_2$), 1.04, 1.18 (2m, 2H, 2 cyPrCH), 3.72 (m, 2H, CH_2O), 3.97 (m, 2H, CH_2N), 4.56 (s, 1H, OH, D_2O exchangeable), 6.33 (s, 2H, NH_2, D_2O exchangeable), 7.67 (s, 1H, 2-H), 10.44 (s, 1H, NH, D_2O exchangeable); HRMS calcd for $C_{10}H_{14}N_5O_2$ 236.1147, found 236.1136; Anal. Calcd for $C_{10}H_{13}N_5O_2 \cdot 0.3H_2O$: C, 49.91; H, 5.70; N, 29.10. Found: C, 49.87; H, 5.56; N, 28.88.

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