Chiral Synthesis of Carbocyclic Analogues of L-ribofuranosides

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Introduction

Natural products, D-(−)-aristeromycin and neplanocin A, are representatives of biologically interesting carbocyclic nucleosides. Natural as well as synthetic carbocyclic nucleosides[1,2] have shown interesting antitumor[3] and antiviral activities against cytomegalovirus,[4] herpes virus,[5] hepatitis B virus,[6] and human immunodeficiency virus (HIV).[7,8] Carbocyclic nucleosides possess an increased metabolic stability against nucleoside phosphorylases[9] because of the absence of a true glycosidic bond. Among them, carbovir[7] and 6-cyclopropylaminopurine analogue, 1592U89(Abacavir),[10] are the most interesting compounds due to their potent anti-HIV activities. 1592(Abacavir) has recently been approved by the FDA. Recently, a novel carbocyclic nucleoside, BMS-200475, has been reported to exhibit potent anti-HBV activity, and it is currently undergoing phase II clinical trials.[11]

In recent years, a number of L-nucleosides, including (−)-(2′*R*, 5′*S*)-1-(2-hydroxymethyloxathiolan-5-yl)cytosine (3TC),[12,13] (−)-β-L-2′,3′-dideoxy-5-fluoro-3′-thiacytidine (FTC),[14] β-L-2′,3′-dideoxy-5-fluorocytidine (L-FddC),[15,16] and β-L-2′-fluoro-5-methylarabinofuranosyl uracil (L-FMAU)[17] have shown promising antiviral activity. Both L-nucleosides, 3TC and FTC, exhibit more potent antiviral activity against HIV and hepatitis B virus (HBV) and decreased toxicity in comparison to their D-counterparts.[13,18] Therefore, it was of interest to synthesize the corresponding L-carbocyclic nucleosides in anticipation of interesting antiviral activity. We have previously reported a preliminary account of L-cyclopentyl carbocyclic nucleoside.[19] In this paper, we report the experimental details, X-ray structure, and confirmation of L-cyclopentyl carbocyclic ribonucleosides.

Results and Discussion

The total synthesis of racemic aristeromycin and its analogues has been described by Shealy et al.[20] The first enantiospecific synthesis of the natural D-(−)-aristeromycin was reported by Arita et al.[21] by a chemicoenzymatic approach. Several optically active L-carbocyclic nucleosides have been prepared by the resolution from racemic mixtures by enzymatic methods,[1,2,22] and no total synthetic methods had been reported until our paper appeared.[19] Therefore, it was of interest to develop procedures for asymmetric synthesis of optically active L-cyclopentyl carbocyclic nucleosides.

A retrosynthetic analysis indicates that L-cyclopentyl carbocyclic nucleosides can be prepared by direct coupling of a functionalized carbocyclic moiety with the corresponding heterocycles or construction of the desired heterocycles by linear approaches from cyclopentylamine. For the synthesis of L-cyclopentyl nucleosides, we selected the (+)-cyclopentanol **3** as a chiral intermediate, which was prepared from the chiral enone **1**.[23] The procedure for the synthesis of L-aristeromycin **13** is analogous to the synthetic methodology of D-aristeromycin previously reported by Borchardt and co-workers.[31] Treatment of **1**

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(30) X-ray data for compound **13**: crystal dimension, 0.40 × 0.20 × 0.20 mm; crystal color, habit: colorless, needle; empirical formula, $C_{11}H_{15}N_5O_3$; formula weight, 265.27; crystal system, orthorhombic; lattice parameters $a = 6.87(2)$ Å, $b = 12.25(1)$ Å, $c = 13.893(4)$ Å; space group, $P212121$(#19); $Z = 4$.

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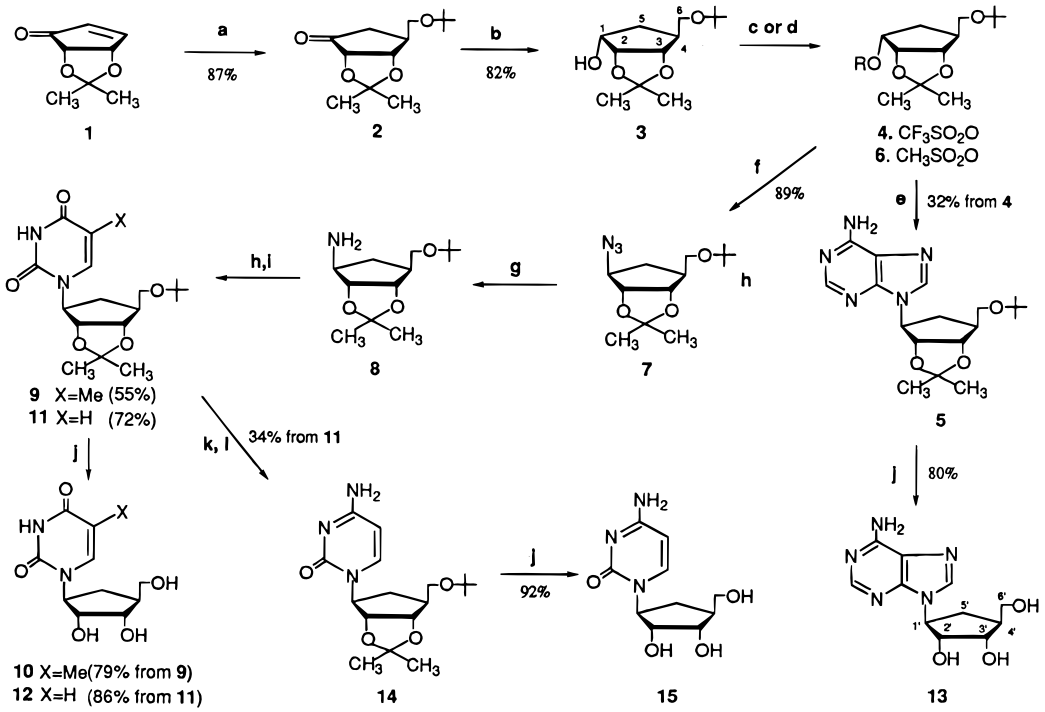
Scheme 1[a]



[a] Reagents: (a) $(t\text{-BuOCH}_2)_2\text{CuLi}$, *t*-BuOMe/THF, −30 °C, 30 min; (b) DIBAL-H, CH_2Cl_2, −78 °C, 2 h; (c) $(CF_3SO_2)_2O$, py, 0 °C, 30 min (for **4**); (d) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 45 min (for **6**); (e) adenine/NaH, 18-crown-6, DMF, 0−20 °C, 30 h; (f) LiN_3, DMF, 140 °C, 4 h; (g) 5% Pd/C, EtOH, rt, 20 psi, 1.5 h; (h) *β*-methoxy-α-methacryloyl isocyanate, DMF, −20 to 20 °C, 10 h (for **9**) or *β*-methoxyacryloyl isocyanate, DMF, −20 to 20 °C, 10 h (for **11**); (i) 30% NH_4OH, EtOH/dioxane (1:1), 80−100 °C, 10 h; (j) CF_3CO_2H/H_2O (2:1), 50 °C, 3 h; (k) *p*-chlorophenylphosphorodichloridate, 1,2,4-triazole, rt, 2 d; (l) 30% NH_4OH, dioxane, rt, 16 h.

with lithium bis(*tert*-butoxymethyl)cuprate gave optically pure cyclopentanone **2** as a single isomer in 87% yield. Reduction of cyclopentanone **2** with diisobutylaluminum hydride gave α-alcohol **3** in 82% yield. The treatment of compound **3** with trifluoromethanesulfonic anhydride gave triflate **4**, which reacted with the sodium salt of adenine and 18-crown-6 in DMF to provide the protected nucleoside **5** in 32% yield. Due to the low yields of the coupling reactions of the triflate **4** with heterocyclic bases, a modified linear approach was applied. Reaction of **3** with methanesulfonyl chloride afforded the mesyl derivative **6** in quantitative yield. The treatment of **6** with lithium azide in hot DMF for 4 h gave the azide **7** in 89% yield. Hydrogenation of **7** in the presence of 5% Pd/C at 20 psi for 1.5 h afforded the amino derivative **8** (Scheme 1).

The synthetic methodology reported by Shealy et al.[24,25] was applied for the preparation of thymine and uracil analogues from **8**. Reaction of **8** with *β*-methoxy-α-methacryloyl isocyanate and *β*-methoxy acryloyl isocyanate followed by treatment with 30% NH_4OH at 80−100 °C gave the thymine **9** and uracil **11** derivatives, respectively. Removal of the protective groups of **9** and **11** with trifluoroacetic acid/H_2O (2:1) at 50−60 °C for 3 h afforded the thymine **10** and uracil **12** nucleosides, respectively. L-Aristeromycin **13** was obtained by the deprotection of **5** with trifluoroacetic acid/H_2O in 80% yield. Preparation of the cytosine derivative **15** was accomplished by the reported method.[26] Treatment of **11** with 4-chlorophenyl dichlorophosphate and 1,2,4-triazole followed by the hydrolysis with concd NH_4OH gave **14** (34%), which was deblocked with trifluoroacetic acid/H_2O to afford the final cytosine nucleoside **15** in 90% yield (Scheme 1).

The inosine derivative was synthesized by the modified procedure of Harnden et al (Scheme 2).[27] The cyclopentylamine **8** reacted with 4,6-dichloro-5-formamidopyrimidine in the presence of triethylamine to provide **16** in 80% yield. Cyclization of **16** with diethoxymethyl acetate gave the 6-chloropurine derivative **17** in 96% yield. The treatment of **17** with mercaptoethanol and sodium methoxide in refluxing methanol gave the hypoxanthine analogue **18** in 96% yield. Compound **18** was deblocked with trifluoroacetic acid/H_2O to afford the hypoxanthine nucleoside **19** in 91% yield. The 6-mercaptopurine analogue **20** was obtained by the treatment of **17** with thiourea in refluxing ethanol followed by the deblocking procedure described above. The guanine derivative **23** was prepared by the procedure described by Shealy et al.[28,29] The coupling reaction of cyclopentylamine **8** with 2-amino-4,6-dichloropyrimidine in the presence of triethylamine afforded compound **21**. The isopropylidene group of **21** was selectively removed by a mixture of concd HCl and MeOH (1:75, v/v) to obtain a diol. Diazotization of the obtained diol with (*p*-chlorophenyl)diazonium chloride followed by the reaction with zinc dust gave diamino derivative **22**. The treatment of **22** with triethyl orthoformate in the presence of concd HCl followed by the treatment with 2 N HCl afforded the desired guanine derivative **23**.

The nucleosides obtained were characterized by spectroscopic methods comparing to those of known D-isomers or racemic forms. Furthermore, the configuration of compound **13** has been unambiguously determined by

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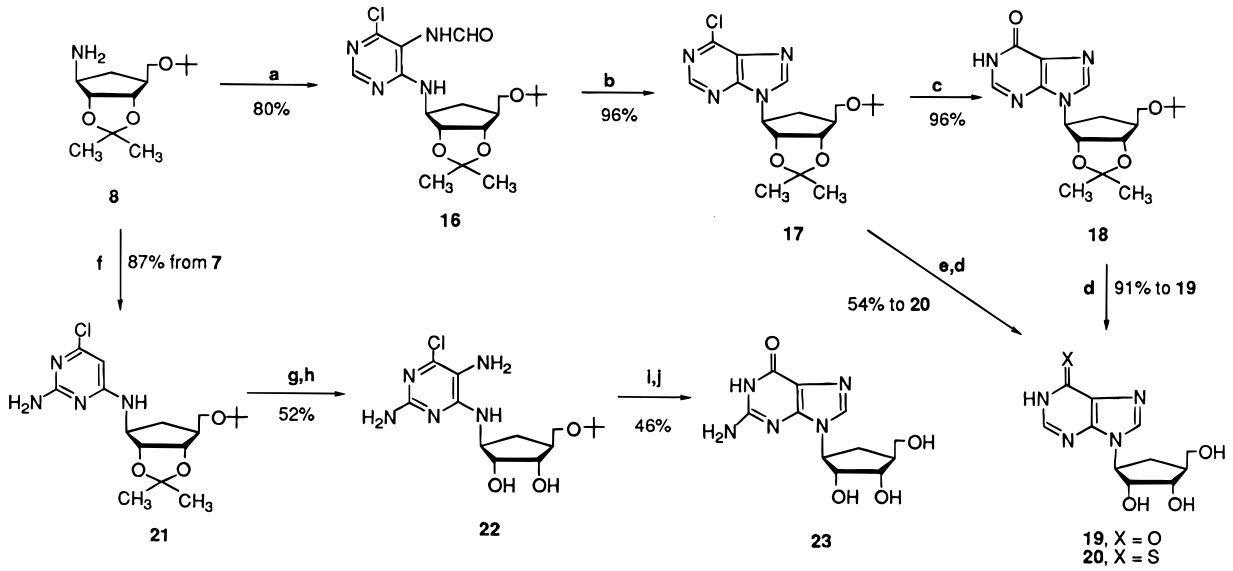
Scheme 2[a]



[a] Reagents: (a) 4,6-dichloro-5-formamidopyrimidine, Et_3N, dioxane, reflux, 1.5 h; (b) diethoxymethylacetate, 120−130 °C, 12 h; (c) $HSCH_2CH_2OH$, NaOMe, MeOH, reflux, 24 h; (d) CF_3CO_2H/H_2O (2:1), 50 °C, 3 h; (e) thiourea, EtOH, reflux, 1 h; (f) 2-amino-4,6-dichloropyrimidine, Et_3N, EtOH, reflux, 48 h; (g) (1) HCl/MeOH, rt, 2 h, (2) *p*-$ClC_6H_4N_2Cl$. rt, 18 h; (h) Zn/AcOH, H_2O/EtOH, 70 °C, 20 min; (i) $CH(OEt)_3$, HCl; (j) 2 N HCl, reflux, 5 h.

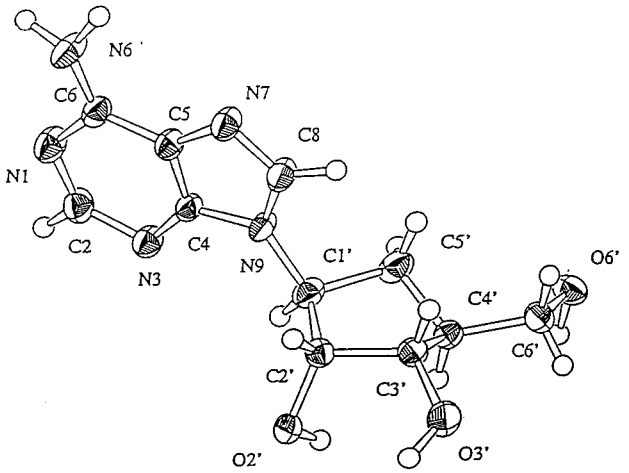


Figure 1. ORTEP drawing of compound **13**.

single-crystal X-ray crystallography [30] (Figure 1). The X-ray study indicated that L-aristeromycin **13** adopts a sugar puckering with the pseudorotation phase angle $P = 226.6°$ and $\nu_{max} = 46.16°$, the 5′-OH orientation $\gamma = -171.2°$ ($C_{3'}-C_{4'}-C_{6'}-O_{6'}$), and the base orientation $\chi = 124.5°$ ($C_{5'}-C_{1'}-N_9-C_4$).

Anti-HIV and anti-HBV activities of the synthesized compounds were evaluated in PBM and 2.2.15 cells, respectively. The cytosine **15** and 6-mercaptopurine **20** exhibit weak activity against HIV with EC_{50} values of 53 and 49.8 μM, respectively, while they do not show any significant anti-HBV activity up to10 μM. No significant activities of other synthesized nucleosides were observed against HBV and HIV. The toxicities of these nucleosides were also assessed, and these compounds did not exhibit any significant toxicities at concentration up to 100 μM in CEM, PBM, and Vero cells.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz with tetramethylsilane as the internal standard. Column chromatography was performed on silica gel G (TLC grade, >440 mesh).

(2*S*,3*S*,4*S*)-4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy)-1-cyclopentanone (2). Potassium *tert*-butoxide (16.43 g, 146.4 mmol) was suspended in anhydrous *tert*-butylmethyl ether (525 mL) under nitrogen. After being cooled to −78 °C, the well-stirred mixture was treated with *sec*-butyllithium (1.3 M in cyclohexane, 112.7 mL, 146.4 mmol) over 10 min. After the mixture was stirred for 2.5 h at −78 °C, a solution of LiBr (2 M, 145 mL) in THF was added dropwise over 10 min at −78 °C, and the resulting solution was stirred at −15 °C for 30 min. Upon recooling to −78 °C, a solution of $CuBr\cdot SMe_2$ (15.05 g, 71.75 mmol) in diisopropyl sulfide (75 mL) was added dropwise over 10 min. The resulting viscous dark solution was stirred for 1 h at −78 °C and treated with a solution of the enone **1** (7.4 g, 48 mmol) in THF (67 mL) over 5 min. The reaction mixture was allowed to warm to −30 °C over 15 min. After 30 min at −30 °C, 1:1 acetic acid−methanol (168 mL) was added and the mixture poured into 1680 mL of NH_4Cl/NH_4OH (pH = 9). After removal of the aqueous layer, the organic layer was washed with a 1:1 mixture of saturated NH_4Cl and 3% NH_4OH solutions (3 × 400 mL) and then brine (400 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated, and purified through flash silica gel column chromatography with 2−5% EtOAc in hexanes to give **2** (10.13 g, 87.1%) as a solid: mp 64−65 °C; $[\alpha]^{26}_D$ 185.36° (*c* 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.62 (d, J = 5.3 Hz, 1H), 4.23 (d, J = 5.3 Hz, 1H), 3.50 (dd, J = 2.3, 8.5 Hz, 1H), 3.35 (dd, J = 2.6, 8.5 Hz, 1H), 2.71 (dd, J = 8.9,17.9 Hz, 1H), 2.54 (d, J = 8.9 Hz, 1H), 2.05 (d, J = 17.9 Hz, 1H), 1.43 (s, 3H), 1.35 (s, 3H), 1.11 (s, 9H); HR-FAB MS obsd: *m*/*z* 243.1596, calcd for $C_{13}H_{23}O_4$ *m*/*z* 243.1596 $(M + H)^+$. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.18; H, 9.13.

(1*R*,2*R*,3*S*,4*S*)-4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy)cyclopentan-1-ol (3). Diisobutylaluminum hydride (DIBAL-H, 59.44 mL, 1 M in CH_2Cl_2) was added dropwise over 5 min to a solution of ketone **2** (9.6 g, 39.62 mmol) in anhydrous CH_2Cl_2 (480 mL) at 0−5 °C. The reaction mixture was stirred for 2.5 h at this temperature and then cautiously quenched with MeOH (480 mL). The colloidal suspension was concentrated, and the white solid was treated with ether (600 mL). The suspension was filtered, washing thoroughly with Et_2O (3 × 300 mL), and the filtrate was concentrated to give an oil that was purified by flash silica gel column chromatography eluted with 5−10% EtOAc in hexanes to give **3** (7.95 g, 82.1%) as a syrup: $[\alpha]^{25}_D$ 11.81° (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.45 (m, 2H), 4.24 (m, 1H), 3.32(dd, J = 4.4, 8.8 Hz, 1H), 3.21 (dd, J = 4.6, 8.8 Hz,

1H), 2.45 (d, J = 8.9 Hz, 1H, D_2O exchangeable), 2.22 (m, 1H), 1.84−1.88 (m, 2H), 1.36 (s, 3H), 1.49 (s, 3H), 1.14 (s, 9H); HR-FAB MS obsd; m/z 245.1728, calcd for $C_{13}H_{25}O_4$ m/z 245.1753 $(M + H)^+$. Anal. Calcd for $C_{13}H_{24}O_4 \cdot 0.25H_2O$: C, 62.74; H, 9.92. Found: C, 62.73; H, 9.80.

(1′*S*,2′*R*,3′*S*,4′*S*)-9-[4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy)cyclopentan-1-yl]adenine (5). Trifluoromethanesulfonic anhydride (1.1 g, 4.50 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of alcohol **3** (849 mg, 3.48 mmol) in CH_2Cl_2 (14 mL) and pyridine (84 mL) over 10 min at 0−5 °C. The reaction mixture was stirred at 0−5 °C for 30 min and then quenched with water (5 mL). The organic layer was separated, washed with water (2 × 30 mL), dried ($MgSO_4$), filtered, and concentrated to afford triflate **4** as an oil that was used for next step without further purification. The triflate **4** in dried DMF (4 mL) at 0 °C was added to an adenine suspension, which contained adenine (1.357 g, 10.04 mmol), sodium hydride (254 mg, 10.04 mmol), and 18-crown-6 (2.604 g, 10.04 mmol) in anhydrous DMF, heated to 70 °C under nitrogen for 4 h and then cooled to 0−5 °C. The reaction mixture was stirred at 0 °C for 9 h and then at room temperature for 24 h. The mixture was filtered and the filtrate washed with saturated KCl (2 × 150 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by preparative silica gel plates with 2% MeOH in $CHCl_3$ and triturated with 2-propanol and ether (1:2) to give **5** (400 mg, 32%): UV (MeOH) λ_{max} 261 nm; ^{1}H NMR ($CDCl_3$) δ 8.35 and 7.93 (two s, 2H), 5.65 (br s, 2H, exchangeable with D_2O), 5.00 (t, J = 6.3 Hz, 1H), 4.82 (m, 1H), 4.62 (dd, J = 4.5, 6.9 Hz, 1H), 3.56 (dd, J = 4.3, 8.8 Hz, 1H), 3.47 (dd, J = 5.8, 8.9 Hz, 1H), 2.54 (m, 1H), 2.43 (m, 1H), 2.36 (m, 1H), 1.58 (s, 3H), 1.32 (s, 3H), 1.23 (s, 9H); HR-FAB MS obsd; m/z 362.2190, calcd for $C_{18}H_{28}N_5O_3$ m/z 362.2192 $(M + H)^+$.

(1*R*,2*R*,3*S*,4*S*)-4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy)-1-[(methylsulfonyl)oxy]cyclopentane (6). Methanesulfonyl chloride (2.366 g, 20.66 mmol) was added dropwise to a solution of alcohol **3** (4.886 g, 20 mmol) and triethylamine (3.643 g, 36 mmol) in CH_2Cl_2 (130 mL) at 0 °C. After 45 min, the reaction mixture was quenched with cold water (200 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL), and the organic layers were combined, washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography with 10% EtOAc in hexanes to give **6** (quantitative yield) as a colorless oil: $[\alpha]^{25}_D$ 29.6° (c 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.10 (m, 1H), 4.60 (m, 1H), 4.39 (d, J = 4 Hz, 1H), 3.30 (dd, J = 4.0, 8.0 Hz, 1H), 3.19 (dd, J = 4.0, 8.0 Hz, 1H), 3.01 (s, 3H), 2.15 (m, 2H), 1.85 (m, 1H), 1.42 (s, 3 H), 1.26 (s, 3H), 1.10 (s, 9H). Anal. Calcd for $C_{14}H_{28}O_6S$: C, 52.15; H, 8.13; S, 9.94. Found: C, 52.27; H, 8.06; S, 9.83.

(1*S*,2*R*,3*S*,4*S*)-1-Azido-4-(*tert*-butoxymethyl)-2,3-(isopropylidenedioxy)cyclopentane (7). A solution of **6** (6.4 g, 20 mmol) in dry DMF (230 mL) in the presence of lithium azide (9.792 g, 200 mmol) was heated at 140 °C for 4 h with stirring. After the reaction was completed, the reaction mixture was concentrated to ca. 100 mL, diluted with ethyl acetate (1 L), and then washed with water (400 mL), saturated brine (400 mL), and water (400 mL) successively. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting yellow oil was purified by flash silica gel column chromatography with 1% EtOAc in hexanes to give **7** (4.776 g, 88.7%) as oil: $[\alpha]^{27}_D$ 48.92° (c 0.97, $CHCl_3$): IR^{neat} 2104 cm^{-1} (N_3); ^{1}H NMR ($CDCl_3$) δ 4.47 (dd, J = 2.0, 6.0 Hz, 1H), 4.39 (dd, J = 2.2, 6.0 Hz, 1H), 3.96 (m, 1H), 3.37 (dd, J = 6.8, 8.7 Hz, 1H), 3.28 (dd, J = 6.8, 8.7 Hz, 1H), 2.28 (m, 2H), 1.71 (m, 1H), 1.45 (s, 3H), 1.29 (s, 3H), 1.18 (s, 9H); HR-FAB MS obsd m/z 270.1818, calcd for $C_{13}H_{24}N_3O_3$ m/z 270.1818 $(M + H)^+$.

(1*S*,2*R*,3*S*,4*S*)-4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy)-1-cyclopentanamine (8). A suspension of compound **7** (890 mg, 3.3 mmol) and 5% Pd/C (240 mg) in absolute EtOH (70 mL) was shaken under 20 psi of H_2 for 1.5 h. The reaction mixture was filtered and the filtrate evaporated to give crude **8** (800 mg), which was used for the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 4.49 (dd, J = 2.6, 6.1 Hz, 1H), 4.23 (dd, J = 2.4, 6.0 Hz, 1H), 3,42 (m, 3H), 2.31 (m, 2H), 1.92 (br s, 2H, exchangeable with D_2O), 1.46 (s, 3H), 1.39 (m, 1H), 1.29 (s, 3H), 1.19 (s, 9H); HR-FAB MS obsd m/z 244.1911, calcd for $C_{13}H_{26}NO_3$ m/z 244.1923 $(M + H)^+$.

(1′*S*,2′*R*,3′*S*,4′*S*)-1-[4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy) cyclopentan-1-yl]thymine (9). Dried silver cyanate (3.04 g) was added to a solution of β-methoxy-α-methacryloyl chloride (1.274 g, 9.46 mmol) in anhydrous benzene (13.2 mL). The resulting mixture was heated under reflux for 0.5 h and allowed to cool to room temperature. After the solid phase had settled, 6.33 mL of the supernatant solution that contained β-methoxy-α-methacryloyl isocyanate was added to a solution of amine **8** (crude 820 mg) in dried DMF (16 mL) at −15 to −20 °C during 15 min. The reaction mixture was stirred at −20 °C for 2 h and then at room temperature for 8 h under nitrogen. The mixture was evaporated under reduced pressure, and the residue was purified by flash silica gel column chromatography with 5% MeOH in $CHCl_3$ to give a solid. A 550 mg portion of this solid was dissolved in dioxane (4 mL), ethanol (4 mL), and aqueous ammonia (30%, 3 mL). The reaction mixture was heated at 80−100 °C in a sealed bomb for 10 h. The solution was evaporated to dryness. The residue was purified by flash silica gel column chromatography with 0.3% MeOH in $CHCl_3$ to give **9** (314 mg, 55%) as a solid: mp 154−156 °C; $[\alpha]^{25}_D$ 35.53° (c 0.53, $CHCl_3$); UV (MeOH) λ_{max} 272.5 nm; ^{1}H NMR ($CDCl_3$) δ 7.08 (s, 1H), 4.68 (m, 2H), 4.46 (m, J = 4.2, 6.0 Hz), 3.46 (m, 2H), 2.33 (m, 2H), 1.97 (m, 1H,), 1.93 (s, 3H), 1.54 (s, 3H), 1.30 (s, 3H), 1.20 (s, 9H). Anal. Calcd for $C_{18}H_{28}N_2O_5$: C, 61.34; H, 8.01; N, 7.95. Found: C, 61.25; H, 8.04; N, 7.89.

(1′*S*,2′*R*,3′*S*,4′*S*)-1-[-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentan-1-yl]thymine (10). Compound **9** (118 mg, 0.335 mmol) was dissolved in 15 mL of CF_3CO_2H/H_2O (2:1) and heated to 50−60 °C for 3 h. The solution was then concentrated, and the residue was purified by flash silica gel column chromatography with 8−9% MeOH in $CHCl_3$ to give **10** (68 mg, 79.3%) as a foam: mp 122−124 °C (hygroscopic); $[\alpha]^{24}_D$ 42.49° (c 0.41, MeOH); UV (H_2O) λ_{max} 273 nm (ϵ 9236, pH 2), 273 nm (ϵ 8686, pH 7), 272 nm (ϵ 7032, pH 11); ^{1}H NMR (DMSO-d_6) δ 11.19 (s, 1H, D_2O exchangeable), 7.54 (s, 1H, 6-H), 4.81 (d, J = 6.5 Hz, 1H, D_2O exchangeable), 4.66 (t, J = 5.2 Hz, 1H, D_2O exchangeable), 4.60 (m, 1H), 4.54 (d, J = 4.1 Hz, 1H, D_2O exchangeable), 3.96 (m, 1H), 3.69 (m, 1H), 3.39 (m, 2H), 1.88−1.96 (m, 2H), 1.76 (s, 3H), 1.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 164.16, 151.64, 138.52, 109.24, 73.38, 71.61, 63.17, 59.85, 44.98, 28.04, 12.39; FAB-MS m/e 257 $(M + H)^+$. Anal. Calcd for $C_{11}H_{16}N_2O_5 \cdot 0.75H_2O$: C, 48.96; H, 6.54; N, 10.38. Found: C, 48.87; H, 6.51; N, 10.20.

(1′*S*,2′*R*,3′*S*,4′*S*)-1-[4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy)cyclopentan-1-yl]uracil (11). Dried silver cyanate (4.50 g) was added to a solution of β-methoxy acryloyl chloride (1.68 g, 14 mmol) in anhydrous benzene (18.5 mL). The resulting mixture was heated under reflux for 0.5 h and allowed to cool to room temperature. After the solid phase had settled, 12 mL of the supernatant solution that contained β-methoxy-acryloyl isocyanate was added within 15 min to a solution of amine **8** (1.6 g, 6.6 mmol) in dried DMF (30 mL) at −15 to −20 °C under nitrogen. The following procedure is same as the conversion of **8** to **9** to give **11** in 74% yield as a syrup: $[\alpha]^{25}_D$ 43.16° (c 0.67, $CHCl_3$); UV (MeOH) λ_{max} 266.5 nm; ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J = 8.0 Hz, 1H), 5.73 (d, J = 8.0 Hz, 1H), 4.72 (m, 2H), 4.48 (m, 1H), 3.46 (m, 2H), 2.37 (m, 2H), 1.97 (m, 1H), 1.55 (s, 3H), 1.30 (s, 3H), 1.19 (s, 9H). Anal. Calcd for $C_{17}H_{26}N_2O_5 \cdot 0.5H_2O$: C, 58.77; H, 7.83; N, 8.06. Found: C, 58.77; H, 7.69; N, 7.82.

(1′*S*,2′*R*,3′*S*,4′*S*)-1-[-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentan-1-yl]uracil (12). Conversion of **11** to **12** was accomplished using a procedure similar to that described for **10**. The obtained residue was purified by flash silica gel column chromatography with 9% MeOH in $CHCl_3$ to give **12** (112 mg, 85.6%) as a foam (hygroscopic): $[\alpha]^{26}_D$ 56.59° (c 0.61, MeOH); UV (H_2O) λ_{max} 267.5 nm (ϵ 9915, pH 2), 267.5 nm (ϵ 9720, pH 7), 266.5 nm (ϵ 7227, pH 11); ^{1}H NMR (DMSO-d_6) δ 11.23 (s, 1H, D_2O exchangeable), 7.69 (d, J = 8.0 Hz, 1H), 5.60 (dd, J = 2.2, 7.92 Hz, 1H), 4.61−4.87 (m, 2H, D_2O exchangeable), 4.64 (dd, J = 9.8, 18.9 Hz, 1H), 3.98 (dd, J = 5.3, 9.3 Hz, 1H), 3.71 (dd, J = 2.1, 5.0 Hz, 1H), 3.43 (m, 2H), 2.01 (m, 1H), 1.93 (m, 1H), 1.25 (m, 1H); FAB−MS m/e 243 $(M + 1)^+$. Anal. Calcd for $C_{10}H_{14}N_2O_5 \cdot 0.2MeOH$: C, 49.27; H, 6.00; N, 11.26. Found: C, 48.99; H, 6.10; N,10.87.

(1′*S*,2′*R*,3′*S*,4′*S*)-9-[-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentan-1-yl]adenine (13). A mixture of compound **5** (350 mg, 0.97 mmol) and CF_3CO_2H/H_2O (2:1, 30 mL) was heated at

50 °C for 3 h. The reaction mixture was concentrated to dryness. The residue was dissolved in MeOH, and then Et_2O was added. The mixture was allowed to stand overnight, filtered, and washed with MeOH to give **13** (205 mg, 80%) as a white solid: mp 215−217 °C dec; $[\alpha]^{25}_D$ 55.45° (*c* 0.38, DMF) [lit.[22] mp 208−210 °C; $[\alpha]^{23}_D$ 51.1° (*c* 0.3, DMF); lit[31] for the (−)-enantiomer, mp 211−213 °C dec; $[\alpha]^{25}_D$ −56° (*c* 0.366, DMF)]; UV (H_2O) λ_{max} 259.5 nm (ϵ 171 69, pH 2), 261.0 nm (ϵ 17 639, pH 7), 261.5 nm (ϵ 17 120, pH 11); ^{1}H NMR (DMSO-d_6) δ 8.20 and 8.12 (two s, 2H), 7.19 (br s, 2H, D_2O exchangeable), 4.94 (d, J = 6.6 Hz, 1H, D_2O exchangeable), 4.73 (t, J = 5.3 Hz, 1H), 4.66−4.71 (m, 2H, D_2O exchangeable), 4.34 (dt, J = 6.2, 9.1 Hz, 1H), 3.84 (m, 1H), 3.48−3.54 (m, 2H), 2.23 (dt, J = 8.1, 8.8 Hz, 1H), 2.02−2.06 (m, 1H), 1.68−1.76 (m, 1H); FAB−MS *m/e* 266 $(M + H)^+$. Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 49.84; H, 5.67; N, 26.26.

(1′*S*,2′*R*,3′*S*,4′*S*)-1-[4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy)cyclopentan-1-yl]cytosine (14). 4-Chlorophenyl dichlorophosphate (705 mg, 2.87 mmol) and 1,2,4-triazole (407 mg, 5.89 mmol) were added to a solution of compound **11** (300 mg, 0.887 mmol) in dried pyridine (15 mL) at 0 °C. The mixture was stirred at room temperature for 2 days and then evaporated in vacuo to dryness under 40 °C. The residue was dissolved in CH_2Cl_2 (40 mL), and the solution was washed with H_2O (2 × 30 mL) and saturated $NaHCO_3$ (30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was stirred in a mixture of 30% aqueous ammonia (20 mL) and 1,4-dioxane (20 mL) at room temperature for 16 h, and the solvent was removed to dryness. The residue was purified by flash silica gel column chromatography with 5% MeOH in $CHCl_3$ to give **14** (102 mg, 34.1%) as a solid: mp 134−136 °C; $[\alpha]^{27}_D$ 14.81° (*c* 0.28, $CHCl_3$); UV (MeOH) λ_{max} 276 nm; ^{1}H NMR ($CDCl_3$) δ 7.36 (d, J = 7.2 Hz, 1H,), 5.64 (d, J = 7.3 Hz, 1H), 4.93 (dd, J = 4.7, 6.7 Hz, 1H), 4.52 (t, J = 5.7 Hz, 1H), 4.43 (m, 1H), 3.55 (dd, J = 4.2, 8.7 Hz, 1H), 3.39 (dd, J = 6.7, 8.6 Hz, 1H), 2.27−2.36 (m, 2H), 2.16 (m, 1H), 1.62 (br s, 2H), 1.52 (s, 3H), 1.29 (s, 3H,), 1.18 (s, 9H). Anal. Calcd for $C_{17}H_{27}N_3O_4 \cdot 0.1CHCl_3$: C, 58.79; H, 7.82; N, 12.03. Found: C, 58.59; H, 7.82; N, 11.93.

(1′*S*,2′*R*,3′*S*,4′*S*)-1-[-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentan-1-yl]cytosine (15). Conversion of **14** (156 mg, 0.46 mmol) to **15** was accomplished using a procedure similar to that described for **10**. The residue was separated by HPLC (1% of MeOH in H_2O) to give **15** (103 mg, 92%) as a solid: mp 164−166 °C; $[\alpha]^{29}_D$ 55.58° (*c* 0.97, MeOH); UV (H_2O) λ_{max} 284.5 nm (ϵ 8708, pH 2), 275 nm (ϵ 6424, pH 7), 275 nm (ϵ 6586, pH 11); ^{1}HNMR (DMSO-d_6) δ 8.50 (br s, 1H, D_2O exchangeable), 7.88 (d, J = 7.6 Hz, 1H), 7.83 (br s, 1H, D_2O exchangeable), 5.91 (d, J = 7.6 Hz, 1H), 4.87 (br s, 1H, D_2O exchangeable), 4.68 (br s, 2H, D_2O exchangeable), 4.62 (dd, J = 10.1, 19.3 Hz, 1H), 3.99 (m, 1H), 3.73 (m, 1H), 3.38 (m, 2H), 2.04 (dt, J = 8.7, 8.6, 12.7 Hz, 1H), 1.93 (m, 1H), 1.27 (m, 1H). FAB-MS *m/e* 242 $(M + H)^+$. Anal. Calcd for $C_{10}H_{15}N_3O_4 \cdot 0.5H_2O$: C, 47.99; H, 6.44; N, 16.79. Found: C, 47.92; H, 6.08; N, 16.63.

(1′*S*,2′*R*,3′*S*,4′*S*)-6-[[4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy) cyclopentan-1-yl]amino]-4-chloro-5-formamidopyrimidine (16). A solution of compound **8** (788 mg, 3.24 mmol), 4,6-dichloro-5-formamidopyrimidine (740 mg, 3.7 mmol), and triethylamine (8 mL) in 1,4-dioxane (33 mL) was stirred at reflux for 1.5 h. After cooling, the suspension was filtered and the solvent removed. The residue was purified by flash silica gel column chromatography with 20−40% EtOAc in hexanes to give **16** (1.04 g, 80.5%) as a white solid: mp 163−164 °C; $[\alpha]^{27}_D$ 94.24° (*c* 0.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 8.39 (s, 1H,), 7.00 (br s, 1H, D_2O exchangeable), 4.40−4.68 (m, 3H), 3.45 (m, 2H), 2.58 (m, 1H), 2.45 (m, 1H), 2.39 (m, 1H), 1.51 (s, 3H), 1.30 (s, 3H), 1.20 (s, 9H). Anal. Calcd for $C_{18}H_{27}ClN_4O_4$: C, 54.20; H, 6.82; Cl: 8.89; N, 14.06. Found: C, 54.29; H, 6.86; Cl: 8.85; N, 13.99.

(1′*S*,2′*R*,3′*S*,4′*S*)-9-[4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy) cyclopentan-1-yl]-6-chloropurine (17). A solution of compound **16** (1.67 g, 4.19 mmol) in diethoxymethyl acetate (30 mL) was heated at 120−130 °C for 12 h. After the solvent was removed under reduced pressure, the residue was dissolved in MeOH (12 mL) and concd ammonium hydroxide (3.7 mL). The reaction mixture was stirred at room temperature for 1 h. The solvent was removed and coevaporated with EtOH to dryness. The residue was purified by flash silica gel column chromatography with 20% EtOAc in hexanes to give **17** (1.53 g, 96%) as a syrup: $[\alpha]^{26}_D$ 38.36° (*c* 1.31, $CHCl_3$); UV (MeOH) λ_{max} 265 nm; ^{1}H NMR ($CDCl_3$) δ 8.75 and 8.27 (two s, 2H), 4.93 (m, 2H), 4.62 (dd, J = 4.2, 6.6 Hz, 1H), 3.54 (dd, J = 4.2, 8.9 Hz, 1H), 3.49 (dd, J = 5.5, 8.9 Hz, 1H), 2.59 (m, 1H), 2.47 (m, 1H), 2.39 (m, 1H), 1.58 (s, 3H), 1.32 (s, 3H), 1.20 (s, 9H). Anal. Calcd for $C_{18}H_{25}ClN_4O_3$: C, 56.76; H, 6.62; N,14.71. Found: C, 56.64; H, 6.64; N, 14.58.

(1′*S*,2′*R*,3′*S*,4′*S*)-9-[4-(*tert*-Butoxymethyl)-2,3-(isopropylidenedioxy)cyclopentan-1-yl]hypoxanthine (18). A mixture of chloropurine analogue **17** (190 mg, 0.5 mmol), 2-mercaptoethanol (0.14 mL, 1.99 mmol), and NaOMe (100 mg, 2 mmol) in methanol (25 mL) was refluxed for 24 h. The mixture was then cooled, neutralized with glacial acetic acid, and concentrated under reduced pressure. The resulting residue was purified by flash silica gel column chromatography with 3% MeOH in $CHCl_3$ to give **18** (174 mg, 96.2%) as a solid: mp 226−227 °C; $[\alpha]^{27}_D$ 37.31° (*c* 0.69, $CHCl_3$); UV (MeOH) λ_{max} 249.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.08 and 7.94 (two s, 2H), 4.91 (t, J = 6.2 Hz, 1H), 4.82 (m, 1H), 4.60 (dd, J = 4.5, 6.7 Hz, 1H), 3.53 (dd, J = 4.3, 8.8 Hz, 1H), 3.47 (dd, J = 5.8, 8.9 Hz, 1H), 2.55 (m, 1H), 2.44 (m, 1H), 2.31 (m, 1H), 1.58 (s, 3H), 1.33 (s, 3H), 1.20 (s, 9H). Anal. Calcd for $C_{18}H_{25}N_4O_6 \cdot 0.25H_2O$: C, 58.92; H, 7.30; N,15.27. Found: C, 58.71; H, 7.10; N, 15.06.

(1′*S*,2′*R*,3′*S*,4′*S*)-9-[-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentan-1-yl] hypoxanthine (19). A mixture of compound **18** (164 mg, 0.453 mmol), CF_3CO_2H (10 mL), and H_2O (5 mL) was stirred at 50−60 °C for 3 h. The solution was concentrated to dryness and the residue triturated with a mixture of MeOH (1 mL) and ether (4 mL) to give **19** (110 mg, 91.2%) as a white solid: mp 245−247 °C dec; $[\alpha]^{29}_D$ 48.73° (*c* 0.26, DMF) [lit.[22] for the (−)-enantiomer: mp 237 °C dec; $[\alpha]^{25}_D$ −48.9° (*c* 0.2, DMF)]; UV (D_2O) λ_{max} 250 nm (ϵ 11 297, pH 2), 250 nm (ϵ 11 790, pH 7), 254.5 nm (ϵ 12 476, pH 11); ^{1}H NMR (DMSO-d_6) δ 12.05 (br s, 1H, D_2O exchangeable), 8.16 and 8.01 (two s, 2H), 4.93 (br s, 1H, D_2O exchangeable), 4.64−4.71 (m, 3H), 4.26 (dd, J = 5.3, 9.2 Hz, 1H), 3.80 (m, 1H), 3.46 (m, 2H), 2.21 (dt, J = 8.6, 8.7, 13.0 Hz, 1H), 2.01 (m, 1H), 1.63 (m, 1H); FAB−MS *m/e* 267 $(M + H)^+$. Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.51; H, 5.26; N, 20.98.

(1′*S*,2′*R*,3′*S*,4′*S*)-9-[-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentan-1-yl]-6-merpaptopurine (20). A solution of compound **17** (274 mg, 0.72 mmol) and thiourea (140 mg, 1.84 mmol) in ethanol (15 mL) was refluxed for 1 h. Upon cooling, the reaction mixture was concentrated to dryness. The residue was purified by silica gel column chromatography with 2−3% MeOH in $CHCl_3$ to a solid (142 mg). A mixture of the obtained solid (115 mg), CF_3CO_2H (8 mL), and H_2O (4 mL) was stirred at 50−60 °C for 3 h. The solution was concentrated to dryness and the residue triturated with a mixture of MeOH (2 mL) to give **20** (89 mg, 54%) as a white solid: mp 260 °C dec; $[\alpha]^{27}_D$ 60.41° (*c* 0.50, DMF); UV (H_2O) λ_{max} 321.5 nm (ϵ 11 042, pH 2), 319 nm (ϵ 12 549, pH 7), 310.5 nm (ϵ 12 923, pH 11); ^{1}H NMR (DMSO-d_6 + D_2O) δ 8.37 and 8.17 (two s, 2H), 4.71 (dd, J = 9.5, 19.0 Hz, 1H), 4.25 (dd, J = 5.2, 9.2 Hz, 1H), 3.80 (dd, J = 2.4, 4.9 Hz, 1H), 3.40−3.49 (m, 2H), 2.24 (dt, J = 8.6, 8.7, 12.8 Hz, 1H), 2.03 (m, 1H), 1.65 (m, 1H); HR-FAB MS obsd *m/z* 283.0857, calcd for $C_{11}H_{15}N_4O_3S$ *m/z* 283.0865 $(M + H)^+$. Anal. Calcd for $C_{11}H_{14}N_4O_3S \cdot 0.75H_2O$: C, 44.66; H, 5.28; N, 18.94; S, 10.84. Found: C, 44.51; H, 4.95; N, 18.91; S, 10.64.

(1′*S*,2′*R*,3′*S*,4′*S*)-2-Amino-4-[[4-(*tert*-butoxymethyl)-2,3-(isopropylidenedioxy)cyclopentan-1-yl]amino]-6-chloropyrimidine (21). A suspension of compound **7** (960 mg, 3.56 mmol) and 5% Pd/C (260 mg) in absolute EtOH (75 mL) was shaken under 20 psi of H_2 for 1.5 h. The reaction mixture was filtered and the filtrate evaporated to give crude **8** (820 mg), which was used for the next step without further purification. To a solution of cyclopentylamine **8** in EtOH (65 mL) were added 2-amino-4,6-dichloropyrimidine (890 mg, 5.43 mmol) and Et_3N (0.5 mL) at room temperature and the mixture refluxed for 48 h under nitrogen. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (0−0.2% MeOH in $CHCl_3$) to give **21** (1.145 g, 86.7%) as a solid: mp 74−76 °C; $[\alpha]^{26}_D$ −37.45° (*c* 0.62, $CHCl_3$); UV (MeOH) λ_{max} 286.0 nm, 237.5 nm, 213.5 nm; ^{1}H NMR ($CDCl_3$) δ 6.42 (d, 1H, D_2O exchangeable), 5.71(s, 1H), 4.31−4.53 (2 d, 2H), 3.39−3.59 (m, 3H), 2.64 (m, 1H), 2.39 (m, 1H),

1.48 (s, 3H), 1.45 (m, 1H), 1.29 (s, 3H), 1.27 (s, 9H); HR-FAB MS obsd *m/z* 371.1810, calcd for $C_{17}H_{28}ClN_4O_3$ *m/z* 371.1850 $(M + H)^+$. Anal. Calcd for $C_{17}H_{27}ClN_4O_3$: C, 55.05; H, 7.34; N, 15.11. Found: C, 55.16; H, 7.31; N, 15.07.

(1′*S*,2′*R*,3′*S*,4′*S*)-4-[[4-(*tert*-Butoxymethyl)-2,3-dihydroxycyclopentan-1-yl]amino]-6-chloro-2,5-diaminopyrimidine (22). A solution of compound **21** (1.86 g, 5.02 mmol) in MeOH (200 mL) containing concd HCl (2.67 mL) was stirred at room temperature for 2 h. The reaction mixture was neutralized with solid $NaHCO_3$ at 0 °C, and the mixture was concentrated to dryness. The residue was washed with MeOH and filtered. The filtrate was concentrated to dryness, and the residue was used in the next step without further purification. To a solution of *p*-chloroaniline (1.00 g, 7.84 mmol) in concd HCl (4.55 mL) and water (9.1 mL) was added a solution of $NaNO_2$ (593.5 mg, 8.60 mmol) in water (7.3 mL) dropwise at 0 °C. The resulting cold solution was added to the solution of the above residue in water (34 mL), AcOH (34 mL), and sodium acetate trihydrate (14.55 g) at 0−5 °C. The reaction mixture was stirred at room temperature for 18 h and the yellow solid precipitated. The solid was collected by filtration and purified by silica gel column chromatography with 1−5% MeOH in $CHCl_3$ to give a yellowish solid (1.89 g). Zinc dust (2.61 g, 350 mesh) was added to a mixture of the yellowish solid (1.88 g), THF (34 mL), ethanol (34 mL), water (30 mL), and acetic acid (3.02 mL) at 70 °C, and the mixture was stirred at this temperature for 20 min. The reaction mixture was filtered and the filtrate concentrated to dryness. The residue was purified by silica gel column chromatography with 1−3% MeOH in $CHCl_3$ to give **22** (890 mg, 52%) as a foam: $[\alpha]^{28}_D$ −4.05° (*c* 0.45, MeOH); UV λ_{max} 204, 304 nm (pH 7), λ_{max} 237.5, 298.5 nm (pH 1); ^{1}H NMR (DMSO-d_6 + D_2O) δ 4.16 (dd, J = 8.2, 16.0 Hz, 1H), 3.65 (m, 2H), 3.20−3.30 (m, 2H), 2.18 (m, 1H), 1.90 (m, 1H), 1.11 (s, 9H), 1.00 (m, 1H); HR-FAB MS obsd; *m/z* 346.1677, calcd for $C_{14}H_{25}ClN_5O_3$ *m/z* 346.1646 $(M + H)^+$. Anal. Calcd for $C_{17}H_{24}ClN_5O_3 \cdot 0.27H_2O$: C, 47.94; H, 7.03; N, 19.96. Found: C, 48.32; H, 6.63; N, 19.56.

(1′*S*,2′*R*,3′*S*,4′*S*)-9-[-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentan-1-yl]guanine (23). A mixture of **22** (130 mg, 0.36 mmol), triethyl orthoformate (3 mL), concd HCl (75 μL), and DMF (1.5 mL) was stirred at 0−5 °C for 8 h and then at room temperature for 8 h. After the solvent was removed under reduced pressure, the residue was stirred in 50% HOAc (4 mL) for 16 h at room temperature. The mixture was concentrated, and the residue was stirred in ammonia−methanol (10 mL) at room temperature for 4 h. The mixture was concentrated again to dryness. The residue was dissolved in 2 N HCl (10 mL), and the mixture was heated under reflux for 5 h. The mixture was then concentrated in vacue at 50 °C. Several portions of ethanol (3 × 5 mL) were added and evaporated in vacuo. The residue was triturated with a mixture of MeOH and ether, allowed to stand, and filtered to give **23** (46 mg, 46%) as a white solid: mp 250 °C dec; $[\alpha]^{27}_D$ 39.99° (*c* 0.21, DMF); UV (H_2O) λ_{max} 254.5 nm (ϵ 9300, pH 2), 252.5 nm (ϵ 10 976, pH 7), 268.0 nm (ϵ 8241, pH 11); ^{1}H NMR (DMSO-d_6 + D_2O) δ 8.64 (s, 1H), 4.61 (dd, J = 9.3, 8.4 Hz, 1H), 4.21 (dd, J = 5.2, 9.2 Hz, 1H), 3.80 (m, 1H), 3.42 (m, 2H), 2.22 (m, 1H), 2.00 (m, 1H), 1.55 (m, 1H); HR-FAB MS obsd *m/z* 282.1202, calcd for $C_{11}H_{16}N_5O_4$ *m/z* 282.1202 $(M + H)^+$. Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot H_2O$: C, 44.15; H, 5.73; N, 23.40. Found: C, 44.09; H, 5.64; N, 23.27.

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