Enantiomeric Synthesis of L-(or 1′*R*,2′*S*)-Carbocyclic Cyclopropyl Nucleosides

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The enantiomeric synthesis of carbocyclic cyclopropyl L-nucleosides has been accomplished from L-gulonic γ-lactone. The key intermediate **3** was stereoselectively synthesized by DIBAL-H reduction and silyl protection followed by cyclopropanation from ester **2**, which was in turn prepared from L-gulonic γ-lactone (**1**) in five steps. Desilylation of cyclopropyl intermediate **3** gave alcohol **4**, which was then converted to the urea derivative **5** and cyclopropylamine **7** by Curtius rearrangement of an acyl azide. The urea intermediate **5** was utilized to prepare thymine **10**, uracil **11**, and cytosine **14** derivatives. The hypoxanthine, adenine, and guanine nucleosides **21**, **22**, and **24** were synthesized from the amino intermediate **7**.

Introduction

A number of carbocyclic nucleosides have been reported as potential anti-HIV[1,2] and anti-HBV[3] agents. Among them, carbovir[1] and its 6-(cyclopropylamino)purine analogue[4] are the most interesting compounds, and the latter is currently undergoing clinical trials as anti-HIV agent. As a part of our ongoing drug discovery program, we have previously reported the asymmetric synthesis of optically pure carbocyclic cyclopropyl D-nucleosides as potential antiviral agents.[5] Recently, several L-nucleosides including (−)-(2′*R*,5′*S*)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine (3TC),[6−8] (−)-β-L-2′,3′-dideoxy-5-fluoro-3′-thiacytidine (FTC),[9] β-L-2′,3′-dideoxy-5-fluorocytidine (L-FddC),[10,11] and β-L-2′-fluoro-5-methyl-1-(arabinofuranosyl)uracil (L-FMAU)[12] have been reported as potent, promising anti-HIV and anti-HBV agents. These interesting L-nucleosides prompted us to synthesize the enantiomerically pure carbocyclic cyclopropyl L-nucleosides. A preliminary account of L-cyclopropyl nucleosides has recently been reported by us.[13] We now report herein a full account of the synthesis of these carbocyclic cyclopropyl L-nucleosides.

Results and Discussion

For the synthesis of the target L-isomers, we utilized the same general strategy that we developed for the synthesis of carbocyclic cyclopropyl D-nucleosides[5,13] (Scheme 1). Compound **2** was prepared from L-gulonic γ-lactone (**1**) in three steps[14] and converted to cyclopropane **3** with the desired chirality (1*R*,2*S*,4*R*) in three steps.[15] Key intermediates, the urea derivative **5** for the synthesis of pyrimidine nucleosides and the cyclopropylamine derivative **7** for purine nucleosides, were derived from the compound **3**.[5,13]

Pyrimidine nucleosides was synthesized by utilizing procedures known in the literature[5,16,17] (Scheme 2). Reaction of **5** with β-methoxy-α-methylacryloyl chloride or β-methoxyacryloyl chloride followed by cyclization and deprotection gave the diol **8** or **9**. Oxidative cleavage of the diols with $NaIO_4$ followed by *in situ* reduction of the resulting aldehyde with $NaBH_4$ gave thymine **10** and uracil **11** nucleosides in good yields. The protected uracil nucleoside was converted to the desired cytosine nucleoside **14** through the triazole intermediate **12**.[5,17]

Purine derivatives **21**, **22**, and **24** were prepared by the reported methods[5,18−22] (Scheme 3). The cyclopropylamine **7** was reacted with 4,6-dichloro-5-formamidopyrimidine followed by cyclization with diethoxymethyl acetate to give the 6-chloropurine **16**. The treatment of **16** with mercaptoethanol and sodium methoxide or

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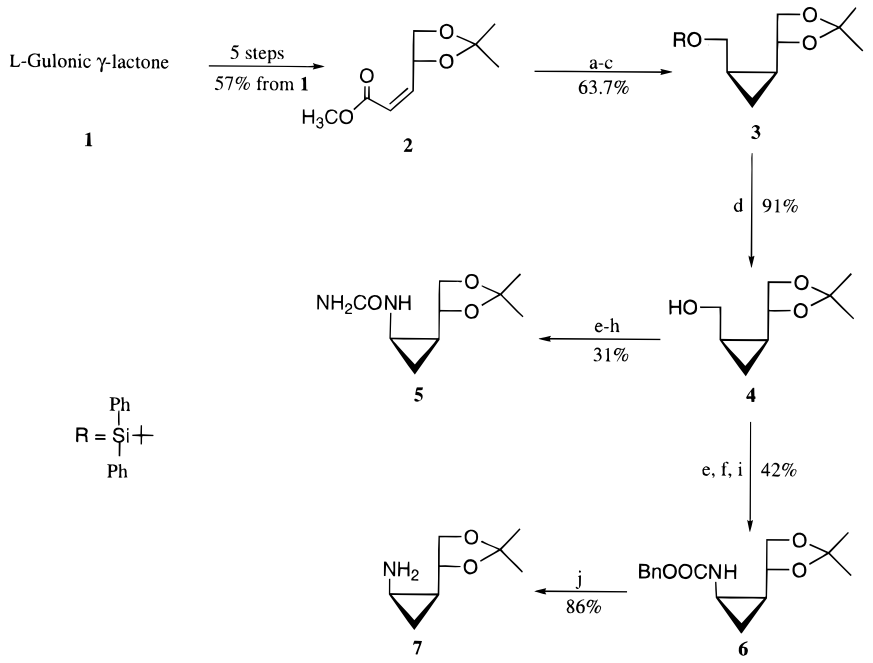
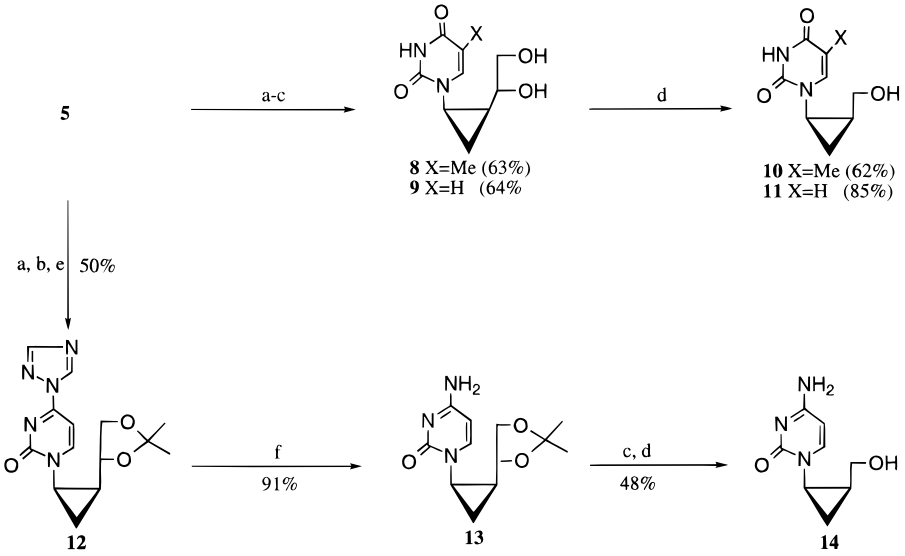
Scheme 1[a]



[a] Key: (a) DIBAL-H, CH_2Cl_2, −78 °C; (b) TBDPSiCl, imidazole, CH_2Cl_2, DMF; (c) $Zn(Et)_2$, CH_2I_2, CH_2Cl_2, 0 °C; (d) *n*-Bu_4NF, THF; (e) $NaIO_4$, RuO_2, K_2CO_3, $CH_3CN/CHCl_3/H_2O$; (f) (1) Et_3N, $ClCO_2Et$; (2) NaN_3, H_2O; (g) toluene, 100 °C; (h) NH_3, Et_2O; (i) BnOH, toluene, reflux; (j) H_2, 10% Pd/C.

Scheme 2[a]



[a] Key: (a) β-methoxy-α-methylacryloyl chloride (for **10**) or β-methoxyacryloyl chloride (for **11**, **12**), pyridine, CH_2Cl_2, 0 °C; (b) 30% NH_4OH, EtOH, 80−100 °C; (c) concd HCl, MeOH; (d) (1) $NaIO_4$, H_2O; (2) $NaBH_4$; (e) 1,2,4-triazole, 4-chlorophenyl dichlorophosphate, pyridine; (f) 30% NH_4OH.

ammonia in refluxing methanol gave the protected hypoxanthine **17** or adenine **18**, which was converted to the target compounds **21** or **22** by hydrolysis and the oxidation−reduction reactions used above.

The synthesis of guanine derivative **24** was accomplished by using procedures described by Shealy *et al.*[5,19−21] and Rosenguist *et al.*[22] The precursor **23** was obtained in 61% yield by treating 2-amino-4,6-dichloropyrimidine with the amine **7** in the presence of Et_3N. The target compound **24** was then synthesized from **23** in four steps according to the reported procedures.[5,19−22]

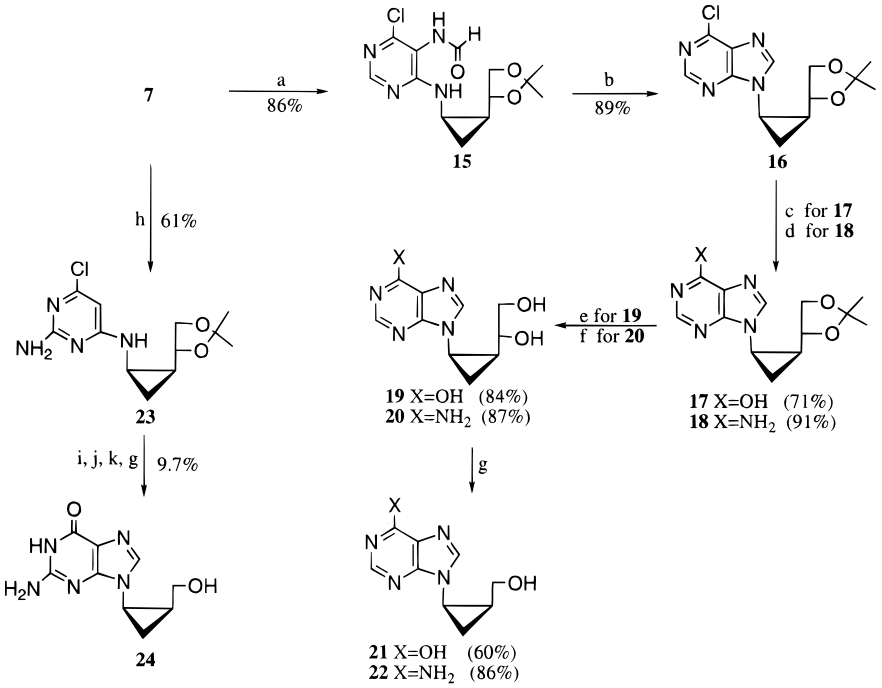
The antiviral evaluation of the synthesized L-carbocyclic cyclopropyl nucleosides are in progress and will be reported elsewhere.

Experimental Section

Melting points (mp) were uncorrected. ^{1}H-NMR spectra were recorded in the indicated solvents. All reactions were monitored by thin-layer chromatography carried out on silica gel glass plates (0.25 mm). Silica gel chromatography was performed on silica gel 60 (230−400 mesh) using the indicated solvents.

(1*R*,2*S*,4*R*)-1-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-(2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropane (3). The cyclopropane **3** was prepared from **2** according to procedures for its D-isomer[5] in 64% overall yield as a colorless syrup: $[\alpha]^{25}_D$ +14.07° (*c* 0.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.20−7.30 (m, 10H), 4.21 (m, 1H), 3.90−3.70 (m, 2H), 3.50−3.30 (m, 2H), 1.47 (s, 3H), 1.38 (s, 3H), 1.25 (m, 1H), 1.03 (s, 9H), 0.90−0.70 (m,

Scheme 3[a]



[a] Key: (a) 4,6-dichloro-5-formamidopyrimidine, Et_3N, dioxane; (b) (1) diethoxymethyl acetate, 120 °C; (2) 30% NH_4OH; (c) $HSCH_2CH_2OH$, $NaOCH_3$, MeOH, reflux; (d) NH_3, MeOH, 90 °C; (e) concd HCl, MeOH, rt; (f) 80% AcOH, rt; (g) (1) $NaIO_4$, H_2O; (2) $NaBH_4$; (h) 2-amino-4,6-dichloropyrimidine, Et_3N, EtOH, reflux; (i) 4-$ClC_6H_4N_2^+Cl^-$; (j) Zn dust, AcOH, EtOH, H_2O; (k) concd HCl, triethyl orthoformate, DMF.

2H), 0.38 (m, 1H). Anal. Calcd for $C_{25}H_{34}O_3Si\cdot 0.2H_2O$: C, 72.48; H, 8.37. Found: C, 72.32; H, 8.25.

(1*R*,2*S*,4*R*)-1-(Hydroxymethyl)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropane (4). To a solution of **3** (20 g, 48.7 mmol) in THF (100 mL) was added *n*-Bu_4NF (49 mL, 1 M in THF) and the mixture stirred at rt for 2 h. The solvent was removed under reduced pressure, and the syrupy residue was purified by silica gel column chromatography (hexanes−EtOAc, 1:1) to give **4** as a colorless oil (7.6 g, 91%): $[\alpha]^{25}_D$ +16.80° (*c* 0.19, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.15 (dd, J = 7.9, 6.1 Hz, 1H), 3.8−3.9 (m, 2H), 3.70 (t, J = 7.9 Hz, 1H), 3.47 (dd, J = 11.2, 8.3 Hz, 1H), 1.65 (br s, 1H), 1.47 (s, 3H), 1.36 (s, 3H), 1.26 (m, 1H), 1.07 (m, 1H), 0.92 (m, 1H), 0.48 (m, 1H). Anal. Calcd for $C_9H_{16}O_3\cdot 0.1H_2O$: C, 62.12; H, 9.38. Found: C, 61.81; H, 9.26.

(1*R*,2*S*,4*R*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropylurea (5) and (1*R*,2*S*,4*R*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropylamine (7). Compounds **5** and **7** were prepared from **4** by using similar procedures for their D-isomers[5] in 36% and 35% overall yields, respectively.

Compound **5**: crystals; mp 182−183 °C; $[\alpha]^{25}_D$ +116.70° (*c* 0.29, MeOH); ^1H NMR ($CDCl_3$) δ 4.87 (br s, 1H), 4.66 (br s, 1H), 4.16 (dd, J = 8.0, 6.0 Hz, 1H), 3.88 (m, 1H), 3.78 (dd, J = 8.3, 7.2 Hz, 1H), 2.75 (m, 1H), 1.43 (m, 3H), 1.36 (m, 3H), 1.12 (m, 2H), 0.76 (m, 1H). Anal. Calcd for $C_9H_{16}N_2O_3$: C, 53.99; H, 8.05; N, 13.99. Found: C, 54.10; H, 8.10; N, 14.01.

Compound **7**: syrup; $[\alpha]^{25}_D$ +4.37° (*c* 0.50, MeOH); ^1H NMR (DMSO-d_6) δ 4.10 (m, 2H), 3.66 (m, 1H), 2.47 (m, 1H), 1.50 (s, D_2O exchangeable, 2H), 1.48 (s, 3H), 1.35 (s, 3H), 0.89 (m, 1H), 0.69 (m, 1H), 0.31 (m, 1H). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 10.00; N, 8.97. Found: C, 60.95; H, 9.82; N, 8.69.

(1*R*,2*S*,4*R*)-[2-(Hydroxymethyl)cyclopropyl]thymine (10). To a solution of urea **5** (700 mg, 3.50 mmol) in CH_2Cl_2 (10 mL) and pyridine (5 mL) was added β-methoxy-α-methylacryloyl chloride (940 mg, 7.0 mmol) at 0 °C, and the mixture was stirred at rt for 3 h and poured into ice−water. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$−MeOH, 20:1) and redissolved in EtOH (25 mL) and NH_4OH (30%, 6 mL). The resulting solution was heated at 80−100 °C in a sealed bomb for 12 h. The solvent was evaporated to dryness under reduced pressure to give the protected thymine nucleoside, which was redissolved in MeOH (60 mL), concd HCl (1 mL) was added, and the mixture was stirred for 4 h at rt and then neutralized with Et_3N. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$−MeOH, 10:1) to give **8** as a white solid (570 mg, 63%). To a solution of **8** (160 mg, 0.70 mmol) in MeOH (15 mL) was added a solution of $NaIO_4$ (367 mg, 1.72 mmol) in water (15 mL) dropwise, the mixture was stirred at rt for 15 min, and $NaBH_4$ (100 mg, 2.64 mmol) was added. The mixture was stirred for an additional 15 min and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$−MeOH, 10:1) and recrystallized from EtOAc to give **10** (86 mg, 62%; overall yield from **5**, 39%): mp 180−181 °C; $[\alpha]^{25}_D$ +99.99° (*c* 0.33, MeOH); UV (H_2O) λ_{max} 270.5 (ϵ 10 367, pH 7), 270.5 (ϵ 10 929, pH 2), 269.5 nm (ϵ 10 681, pH 11); ^1H NMR (DMSO-d_6) δ 11.19 (s, 1H), 7.46 (s, 1H), 4.30 (t, J = 4.0 Hz, 1H), 3.22 (m, 2H), 3.05 (dd, J = 8.0, 4.0 Hz, 1H), 1.74 (s, 3H), 1.37 (m, 1H), 1.05 (ddd, J = 8.0, 8.0, 4.0 Hz, 1H), 0.84 (ddd, J = 8.0, 8.0, 4.0 Hz, 1H). Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.10; H, 6.16; N, 14.28. Found: C, 55.17; H, 6.21; N, 14.24.

(1*R*,2*S*)-1-[2-(Hydroxymethyl)cyclopropyl]uracil (11). Using the above procedures, reaction of **5** with β-methoxyacryloyl chloride followed by cyclization, deprotection, and oxidation−reduction reactions gave the uracil nucleoside **11** in 60% overall yield as white crystals: mp 146−148 °C; $[\alpha]^{25}_D$ +119.89° (*c* 0.45, MeOH); UV (H_2O) λ_{max} 265.5 (ϵ 10 646, pH 7), 266.5 (ϵ 6245, pH 2), 264.0 nm (ϵ 7475, pH 11); ^1H NMR (DMSO-d_6) δ 11.18 (br s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 5.48 (d, J = 8.0 Hz, 1H), 4.38 (m, 1H), 3.34 (m, 2H), 3.09 (m, 1H), 1.38 (dd, J = 16.0, 8.0 Hz, 1H), 1.07 (dd, J = 16.0, 8.0 Hz, 1H), 0.84 (dd, J = 12.0, 6.0 Hz, 1H). Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.48; H, 5.56; N, 15.20.

(1*R*,2*S*,4*R*)-1-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]-4-1,2,4-triazol-1-yl-1*H*-pyrimidin-2-one (12). To a solution of the protected uridine analogue (410 mg, 1.63

mmol) prepared above in pyridine (35 mL) were added 1,2,4-triazole (337 mg, 4.88 mmol) and 4-chlorophenyl phosphorodichloridate (1.2 g, 4.89 mmol), the mixture was stirred at rt for 3 days, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$−MeOH, 5:1) to give **12** as a white solid (268 mg, 54%; overall yield from **5**, 50%): mp 164−166 °C; $[\alpha]^{25}_D$ +431.98° (*c* 0.25, MeOH); UV (MeOH) λ_{max} 316.5, 250.5, 223.5 nm; ^{1}H NMR ($CDCl_3$) δ 9.27 (s, 1H), 8.12 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 4.10 (d, J = 8.0 Hz, 1H), 3.86 (dd, J = 8.0, 4.0 Hz, 1H), 3.72 (m, 1H), 1.65 (m, 2H), 1.35 (s, 3H), 1.28 (m, 1H), 1.19 (s, 3H). Anal. Calcd for $C_{14}H_{17}N_5O_3$.0.2 H_2O: C, 54.79; H, 5.71 N, 22.81. Found: C, 54.76; H, 5.70; N, 22.57.

(1*R*,2*S*,4*R*)-4-Amino-1-[2-(2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl]-1*H*-pyrimidin-2-one (13). Compound **12** (220 mg, 0.73 mmol) was dissolved in NH_4OH (30%, 10 mL) and the mixture stirred at rt for 12 h. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$−MeOH, 12:1) to give **13** as a white solid (170 mg, 91%): mp 256−258 °C; $[\alpha]^{25}_D$ +359.75° (*c* 0.30, MeOH); UV (MeOH) λ_{max} 275 nm; ^{1}H NMR ($CDCl_3$) δ 7.34 (dd, J = 8.0, 4.0 Hz, 1H), 7.26 (d, J = 4.0 Hz, 1H), 5.64 (dd, J = 8.0, 4.0 Hz, 1H), 4.10 (m, 1H), 3.91 (m, 1H), 3.50−3.40 (m, 2H), 3.31 (m, 1H), 1.50 (m, 1H), 1.40 (s, 3H), 1.26 (s, 3H), 1.05 (s, 3H). Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.27; H, 6.81; N, 16.69.

(1*R*,2*S*)-1-[2-(Hydroxymethyl)cyclopropyl]cytosine (14). Deprotection of **13** followed by the oxidation−reduction as described for **10** and **11** gave a crude product, which was purified by silica gel chromatography ($CHCl_3$−MeOH, 10:1) to obtain the cytosine derivative **14** in 48% overall yield as white crystals: mp 271−273 °C; $[\alpha]^{25}_D$ +133.50° (*c* 0.10, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.55 (d, J = 8.0 Hz, 1H), 7.21 (br s, D_2O exchangeable, 1H), 7.11 (br s, 1H), 4.33 (m, 1H), 4.14 (m, 1H), 3.07 (m, 1H), 2.88 (m, 1H), 1.39 (m, 1H), 1.07 (m, 1H), 0.70 (m, 1H). Anal. Calcd for $C_8H_{11}N_3O_2$.0.1 H_2O: C, 52.51; H, 6.17; N, 22.96. Found: C, 52.43; H, 6.17; N, 22.92.

(1*R*,2*S*,4*R*)-6-[[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]amino]-4-chloro-5-formamidopyrimidine (15). A mixture of cyclopropylamine **7** (400 mg, 2.54 mmol), 4,6-dichloro-5-formamidopyrimidine (537 mg, 2.80 mmol), and Et_3N (6 mL, 0.04 mmol) in dioxane (25 mL) was refluxed for 3 h. After being cooled to rt, the suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$−MeOH, 20:1) to give **15** as a colorless syrup (680 mg, 86%): $[\alpha]^{25}_D$ +134.55° (*c* 0.48, MeOH); UV (MeOH) λ_{max} 276.5 (sh), 260.0, 219.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.31 (s, 2H), 8.07 (br s, D_2O exchangeable, 1H), 4.14 (m, 1H), 3.85 (m, 2H), 3.22 (m, 1H), 2.04 (br s, D_2O exchangeable, 1H), 1.58 (s, 3H), 1.34 (s, 3H), 1.21 (m, 2H), 0.80 (m, 1H). Anal. Calcd for $C_{13}H_{17}N_4ClO_3$: C, 50.39; H, 5.85; N, 16.10; Cl, 10.18. Found: C, 50.43; H, 6.07; N, 15.82; Cl, 10.27.

(1*R*,2*S*,4*R*)-9-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]-6-chloropurine (16). A mixture of compound **15** (1.20 g, 3.84 mmol) and diethoxymethyl acetate (20 mL) was heated at 120 °C for 4 h. After the solvent was removed under reduced pressure, the residue was redissolved in MeOH (30 mL) and concd NH_4OH (3 mL) and stirred at rt for 1 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$−MeOH, 30:1) to yield **16** as a colorless syrup (1.01 g, 89%): $[\alpha]^{25}_D$ +140.71° (*c* 0.48, MeOH); UV (MeOH) λ_{max} 265.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.77 (s, 1H), 8.08 (s, 1H), 3.89 (m, 2H), 3.65 (m, 1H), 3.52 (m, 1H), 1.67−1.60 (m, 2H), 1.52 (m, 1H), 1.34 (s, 3H), 1.05 (m, 3H). Anal. Calcd for $C_{13}H_{15}N_4O_2Cl$: C, 52.98; H, 5.13; N, 19.01, Cl, 12.03. Found: C, 52.74; H, 5.27; N, 18.77; Cl, 11.76.

(1*R*,2*S*,4*R*)-9-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]hypoxanthine (17). To a solution of **16** (270 mg, 0.92 mmol) in MeOH (40 mL) were added $NaOCH_3$ (198 mg, 3.66 mmol) and 2-mercaptoethanol (0.26 mL, 3.66 mmol), the mixture was refluxed for 6 h, and the solvent was removed under reduced pressure. The syrupy residue was purified by silica gel column chromatography ($CHCl_3$−MeOH, 12:1) to give **17** as a white solid (180 mg, 71%): mp 228 °C dec; $[\alpha]^{25}_D$ +132.86° (*c* 0.11, MeOH); UV (MeOH) λ_{max} 250.5 nm; ^{1}H NMR ($CDCl_3$) δ 11.83 (br s, D_2O exchangeable, 1H), 8.06 (s, 1H), 7.78 (s, 1H), 3.87 (m, 2H), 3.57 (dd, J = 8.0, 4.0 Hz, 1H), 3.40 (m, 1H), 1.62 (m, 1H), 1.50−1.32 (m, 2H), 1.32 (s, 3H), 1.09 (m, 3H). Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.35; H, 5.82; N, 20.20.

(1*R*,2*S*)-9-[2-(Hydroxymethyl)cyclopropyl]hypoxanthine (21). Deprotection of compound **17** followed by oxidation−reduction reaction as described above gave a crude nucleoside, which was triturated with EtOH to obtain **21** in 50% overall yield as white crystals: mp 266−268 °C; $[\alpha]^{25}_D$ +39.21° (*c* 0.15, MeOH); UV (H_2O) λ_{max} 254.5 (ϵ 14 567, pH 7), 250.0 (ϵ 13 847, pH 2), 250.0 nm (ϵ 13 010, pH 11); ^{1}H NMR (DMSO-d_6) δ 12.30 (br s, D_2O exchangeable, 1H), 8.07 (s, 1H), 8.05 (s, 1H), 4.58 (t, J = 4.0 Hz, 1H), 3.54 (m, 1H), 3.16 (m, 2H), 3.10 (m, 1H), 1.50 (m, 1H), 1.31−1.19 (m, 2H). Anal. Calcd for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.37; H, 4.87; N, 27.07.

(1*R*,2*S*,4*R*)-9-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]adenine (18). A solution of **16** (220 mg, 0.75 mmol) in methanolic ammonia (60 mL) was heated at 90 °C for 20 h in a steel bomb. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$−MeOH, 20:1) to yield **18** as a white solid (187 mg, 91%): mp 165−167 °C; $[\alpha]^{25}_D$ +137.31° (*c* 0.60, MeOH); UV ($CHCl_3$) λ_{max} 260.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1H), 7.76 (s, 1H), 5.56 (br s, 2H), 3.92 (m, 2H), 3.58 (m, 1H), 3.30 (m, 1H), 1.61−1.50 (m, 3H), 1.29 (s, 3H), 1.14 (m, 3H). Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 56.72; H, 6.22; N, 25.44. Found: C, 56.59; H, 6.34; N, 25.19.

(1*R*,2*S*)-9-[2-(Hydroxymethyl)cyclopropyl]adenine (22). Using the above procedures, compound **18** was converted to adenine nucleoside **22** in 75% overall yield as white crystals: mp 125−126 °C; $[\alpha]^{25}_D$ +48.69° (*c* 0.41, MeOH); UV (H_2O) λ_{max} 260.5 (ϵ 11 032) (pH 7), 259.0 (ϵ 13 057, pH 2), 260.5 nm (ϵ 10 907, pH 11); ^{1}H NMR (DMSO-d_6) δ 8.14 (s, 1H), 8.11 (s, 1H), 7.31 (br s, 2H), 4.70 (s, 1H), 3.48 (m, 1H), 3.27 (m, 1H), 3.01 (m, 1H), 1.57 (m, 1H), 1.32 (m, 1H), 1.14 (m, 1H); HRMS calcd for ($C_9H_{11}N_5O$ + H) 206.1042, found (FAB) 206.1046. Anal. Calcd for $C_9H_{11}N_5O$·0.6MeOH: C, 51.37; H, 6.01; N, 31.20. Found: C, 51.57; H, 5.63; N, 30.91.

(1*R*,2*S*,4*R*)-1-[(2-Amino-4-chloro-6-pyrimidinyl)amino]-2-(2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropane (23). To a solution of cyclopropylamine **7** (541 mg, 3.44 mmol) in EtOH (35 mL) were added 2-amino-4,6-dichloropyrimidine (620 mg, 3.78 mmol) and Et_3N (35 mL) at rt and the mixture refluxed for 40 h under N_2. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$−MeOH, 25:1) to give **23** as a white solid (600 mg, 61%): mp 118−120 °C; $[\alpha]^{25}_D$ +151.38° (*c* 0.35, MeOH); UV (MeOH) λ_{max} 286.0, 237.0, 222.0 nm; ^{1}H NMR ($CDCl_3$) δ 5.96 (s, 1H), 5.07 (br s, D_2O exchangeable, 1H), 4.85 (br s, D_2O exchangeable, 2H), 3.97 (dd, J = 8.0, 4.0 Hz, 1H), 3.79 (m, 2H), 2.76 (m, 1H), 1.44 (s, 3H), 1.32 (s, 3H), 1.20 (m, 2H), 0.77 (m, 1H). Anal. Calcd for $C_{12}H_{17}N_4O_2Cl$·0.2H_2O: C, 49.99; H, 6.08; N, 19.43. Found: C, 49.72; H, 6.11; N, 19.24.

(1′*R*,2′*S*)-9-[(2-Hydroxymethyl)cyclopropyl]guanine (24). To a solution of *p*-chloroaniline (485 mg, 3.8 mmol) in concd HCl (2.2 mL) and H_2O (6.4 mL) was added a solution of $NaNO_2$ (280 mg, 4.0 mmol) in H_2O (3 mL) dropwise at 0 °C. The resulting cold solution was added to a mixture of compound **23** (540 mg, 1.90 mmol), H_2O (17 mL), AcOH (7 mL), and sodium acetate trihydrate (7.2 g). The reaction mixture was stirred at rt for 18 h and cooled in an ice bath to obtain a yellow precipitate. The resulting solid was collected by filtration, washed with ice−water, and dried (P_2O_5) under vacuum to yield a diazo compound as a yellow solid (800 mg, 60%). To a mixture of the diazo compound (390 mg, 1.10 mmol), H_2O (27 mL), EtOH (27 mL), and AcOH (27 mL) was added Zn dust (1.05 g), and the mixture was refluxed for 4 h and filtered. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$−MeOH, 6:1) to give a diamino compound as a brown

solid (150 mg, 52%). To a stirred mixture of the diamino compound (46 mg, 0.18 mmol), triethyl orthoformate (0.3 mL, 0.18 mmol), and DMF (3 mL) was added concd HCl (0.05 mL) at 0 °C and the mixture stirred at rt for 16 h. The solvent was removed under reduced pressure, and the residue was redissolved in HCl (2 N, 4 mL). The mixture was refluxed for 3 h and neutralized with NaOH (2 N). The solvent was removed under reduced pressure to give a crude diol nucleoside (50 mg, 0.20 mmol), which was converted to the guanine derivative **24** as a white solid (12 mg, 31%; overall yield from **23**, 10%): mp 258−260 °C; $[\alpha]^{25}_{D}$ +50.8 (*c* 0.35, MeOH); UV (H_2O) λ_{max} 251.5 (ϵ 12 091, pH 7), 256.0 (ϵ 10 928, pH 2), 267.0 nm (ϵ 11 109, pH 11); ^{1}H NMR (DMSO-d_6) δ 10.60 (br s, D_2O exchangeable, 1H, NH), 7.66 (s, 1H), 6.61 (br s, D_2O exchangeable, 2H, NH_2), 4.57 (br s, D_2O exchangeable, 1H), 2.89 (m, 1H), 2.73 (m, 1H), 1.43 (m, 1H), 1.22 (m, 2H), 1.06 (m, 1H); HRMS calcd for ($C_9H_{11}N_5O_2$ + H) 222.0991. found (FAB) 222.0985.

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