Asymmetric Synthesis of (1′S,2′R)-Cyclopropyl Carbocyclic Nucleosides

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Received January 19, 1995®

Enantiomeric synthesis of cyclopropyl carbocyclic nucleosides has been accomplished. The key intermediates **7** and **9** were synthesized from D-glyceraldehyde acetonide **1**, which was converted to the α,β-unsaturated ester **2** and then reduced to give allylic alcohol **3a**. Stereoselective construction of the cyclopropyl ring of **3a** and **3b** followed by oxidation gave acid **5**, which was treated under Curtius rearrangement conditions to obtain the urea intermediate **7**. The urea intermediate was utilized to prepare uracil **14**, thymine **15**, and cytosine **18** nucleosides. The purine derivatives were prepared from cyclopropylamine **9** by condensation with 4,6-dichloro-5-formamidopyrimidine or 4,6-dichloro-2-aminopyrimidine.

Introduction

HIV reverse transcriptase (RT) is one of the crucial targets in combatting the etiologic agent of AIDS. To date, only nucleoside inhibitors (AZT, ddC, ddA, and d4T) have been approved by the FDA for the treatment of HIV. Nevertheless the usefulness of these drugs is limited due to their toxicities and side effects, as well as the emergence of drug resistant viral strains.[1-3] Therefore, it is necessary to search for less toxic and more effective anti-HIV agents, which do not have a cross-resistance with existing drugs.

A number of natural as well as synthetic carbocyclic nucleosides have been reported.[4-6] Due to the structural characteristics, carbocyclic nucleosides possess an increased metabolic stability against nucleoside phosphorylases[7] and have shown interesting antiviral activities against herpes virus,[8] human cytomegalovirus,[9] hepatitis B virus,[10] and human immunodeficiency virus.[11,12] Among them, carbovir[11] and the 6-cyclopropyl aminopurine analogue[13] are particularly interesting, and the latter is currently being evaluated in HIV-infected patients. Recently, we have reported the synthesis of optically active cyclopropyl carbocyclic nucleosides as a communication.[14] As a part of our drug discovery program for antiviral agents, herein we wish to report full accounts of the synthesis of cyclopropyl carbocyclic nucleosides.

The synthesis of cyclopropyl carbocyclic nucleosides have been reported by several laboratories. Katagiri[15,16] *et al.* reported the synthesis of cyclopropyl adenine and thymine, using *trans*- or *cis*-4-dibenzoxy-2-butene as the precursor. In an attempt to improve the efficiency of the initial phosphorylation reaction, Izawa *et al.*[17] synthesized (±)-2,2-bis(hydroxymethyl)cyclopropyl uracil and adenine derivatives starting from 3-chloro-2-(chloromethyl)propene. Recently, the synthesis of [2,2-difluoro-3,3-bis(hydroxymethyl)cycloprop-1-yl]thymine and related compounds was also reported.[18] However, none of the previous syntheses of cyclopropyl carbocyclic nucleosides involved asymmetric intermediates. As a consequence, those nucleosides were prepared as racemic mixtures. Thus, it was of interest to develop a novel synthetic methodology for optically active carbocyclic nucleosides. Retrosynthetic analysis of cyclopropyl carbocyclic nucleosides **A** and **B** reveals that the Simmons–Smith reaction[19] can be applied to the preparation of the optically pure cyclopropyl methyl alcohol derivative **D**, to obtain cyclopropyl intermediate **C** (X = H or $CONH_2$), which is a common intermediate in the synthesis of purine and pyrimidine nucleosides (Figure 1).

Results and Discussion

Our initial attempts to directly convert α,β-unsaturated ester **2** to the cyclopropyl derivative, using di-

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® Abstract published in *Advance ACS Abstracts,* August 1, 1995.

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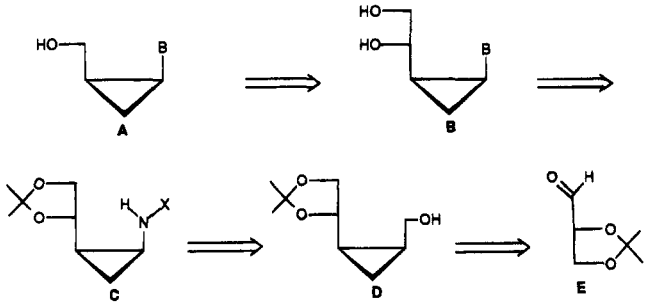

Figure 1. Retrosynthetic analysis of cyclopropyl carbocyclic nucleosides.

methyloxosulfonium methylide,[20] gave a low yield (*ca.* 10%) without stereoselectivity. Thus, the ester **2**,[21] which was prepared by the Wittig reaction of **1**, was reduced by DIBAL-H at −78 °C to **3a** in 84% yield (Scheme 1). Treatment of **3a** with Et_2Zn and chloroiodomethane at 0 °C gave optically pure cyclopropylmethyl alcohol **4a** as the major isomer.[14]

After the synthesis of the key intermediate **4a** had been accomplished in our laboratories, Morikawa *et al.*[22] reported the same intermediate **4a**. The reaction of **3a** with Et_2Zn/ICH_2Cl gave **4a** in a 70% yield with a 55% diastereomeric excess. However, the reported result of the reaction of **3a** with Et_2Zn/CH_2I_2 was 36% yield with 17% diastereomeric excess. When **3b** was used, a single diastereomer **4b** was obtained in 95% yield. This is in agreement with the reported result.[22] The cyclopropyl alcohol **4a**, prepared from either **3a** or **3b**, was oxidized with $NaIO_4$ in the presence of RuO_2 to obtain acid **5**, which was treated with triethylamine and chloroethyl formate followed by the treatment with sodium azide to give acyl azide **6**. The Curtius rearrangement of **6** was carried out in toluene at 100 °C to obtain isocyanate. Without isolation, anhydrous ammonia gas was introduced to obtain urea derivative **7** in 38% yield from **4a**. The urea derivative **7** was the key intermediate for the preparation of the pyrimidine nucleosides, the structure of which was confirmed by single crystal X-ray crystallography.[14] Treatment of **6** with benzyl alcohol and toluene gave benzyl carbamate **8** in 87% yield. Catalytic hydrogenolysis of **8** provided cyclopropylamine **9**, which was used as the key intermediate for the preparation of purine nucleosides.

The synthetic methodology initially developed by Shaw and Warrener[23] was applied for the preparation of uridine and thymidine analogues from **7** (Scheme 2). The reaction of **7** with β-methoxy-α-methacryloyl chloride and β-methoxy acryloyl chloride in pyridine gave intermediate **10** and **11**, respectively, which were treated with NH_4OH in hot ethanol to give thymine **12** and uracil **13** derivatives, respectively.

The isopropylidene group of **12** was removed by concd HCl in methanol at room temperature to give thymidine derivative **14** in 60% yield from **7**. Single crystal X-ray crystallographic data (Figure 2) of **14** indicated that the methyl group on C-5 of the pyrimidine ring was located away from the substituent on C-2′ of the cyclopropyl ring (*syn*-conformation).[24]

Oxidative cleavage of the vicinal diol in **14** by sodium periodate gave an aldehyde which, without isolation, was reduced to thymidine analogue **16** in 85% yield. A similar procedure was used for the preparation of the uridine derivative **17** from **15**. The synthesis of cytosine derivative **20** was accomplished by the reported method.[25] Protection of the primary hydroxyl group of **17** by acetyl group to **18** (99%) followed by the treatment of **18** with 1,2,4-triazole and chlorophenyl phosphorodichloridate in pyridine gave triazole derivative **19**. Subsequent hydrolysis of **19** with ammonium hydroxide afforded cytidine analogue **20** in 60% yield from **19**.

Nucleosides **29** and **30** were synthesized by the modified procedure reported by Harnden *et al.*[26] (Scheme 3). Coupling reaction of the key intermediate cyclopropylamine **9** with 4,6-dichloro-5-formamidopyrimidine in the presence of triethylamine provided **21** in 85% yield. Heating of **21** in diethoxymethyl acetate resulted in the formation of the imidazole ring to yield 6-chloropurine derivative **22** (91%). Treatment of **22** with ammonia in methanol at 90 °C gave adenine derivative **23** (98%). The isopropylidene group of **23** was removed by 80% acetic acid to give diol **25**, which was treated with sodium periodate followed by $NaBH_4$ reduction to provide the desired nucleoside **27** in good yield. Upon treatment with mercaptoethanol and sodium methoxide under reflux in methanol, the compound **22** was converted to hypoxanthine derivative **24** (76%). In a similar procedure described above, compound **24** was hydrolyzed with 80% acetic acid to yield diol nucleoside **26**, which was then treated with $NaIO_4$ followed by $NaBH_4$ reduction to afford the hypoxanthine nucleoside **28** in 95% yield.

The guanine derivative **32** was prepared by the procedure of Shealy *et al.*[27-29] The coupling reaction of cyclopropylamine **9** with 2-amino-4,6-dichloropyrimidine in the presence of triethylamine gave **29** in 70% yield. The protecting group in **29** was removed by concd HCl to obtain the diol, which was used for diazotization with (*p*-chlorophenyl)diazonium chloride. The diazo derivative was reacted with zinc dust to give 5-amino derivative **30**. Treatment of **30** with triethyl orthoformate in the presence of concd HCl yielded a 6-chloropurine nucleoside, which was hydrolyzed by 2 N HCl to provide guanine derivative **31**. Oxidation of the diol group of **31** with sodium periodate followed by *in situ* $NaBH_4$ reduction afforded the desired guanine derivative **32** (yield 10% from **29**).

Biological evaluations of the synthesized compounds are under investigation and will be reported elsewhere.

Experimental Section

2,3-*O*-Isopropylidene-D-glyceraldehyde (1).[30] To a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (30.0 g, 114.3 mmol) in ethyl acetate (500 mL) was added lead tetraacetate (95 g, 114.5 mmol) portionwise at 5−10 °C. The suspension was vigorously stirred for 3 h and filtered, and the filtrate was treated with sodium carbonate (6.0 g) for 30 min. The

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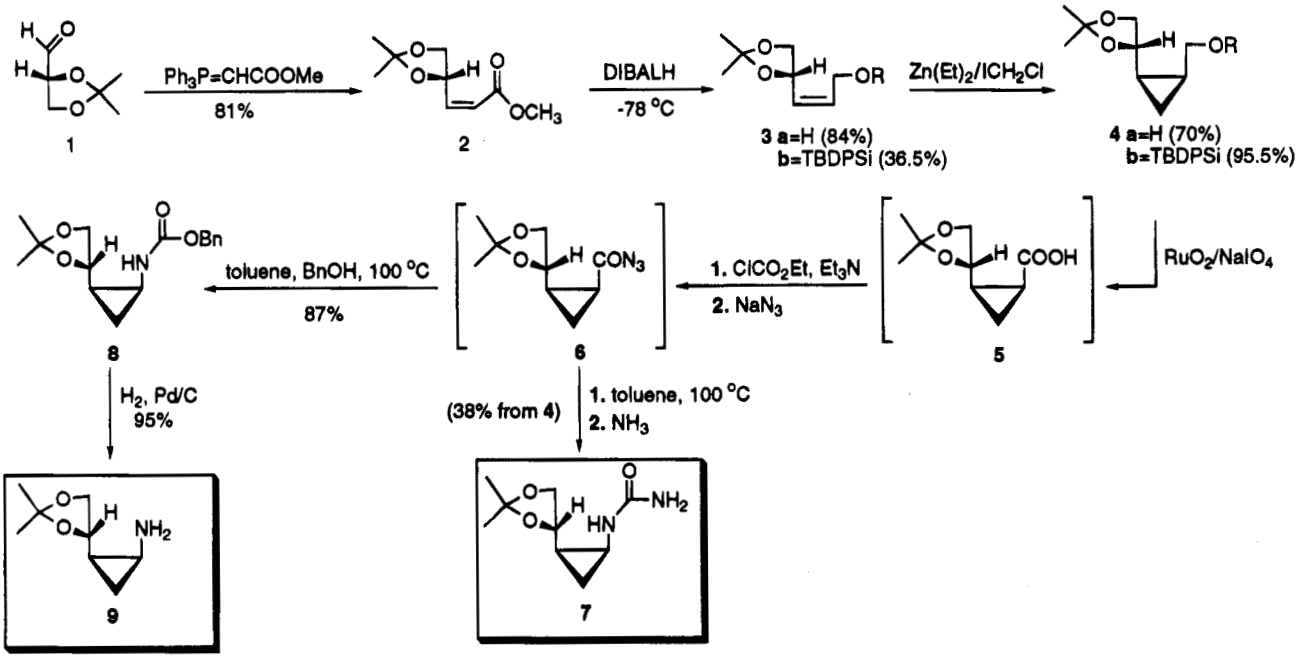
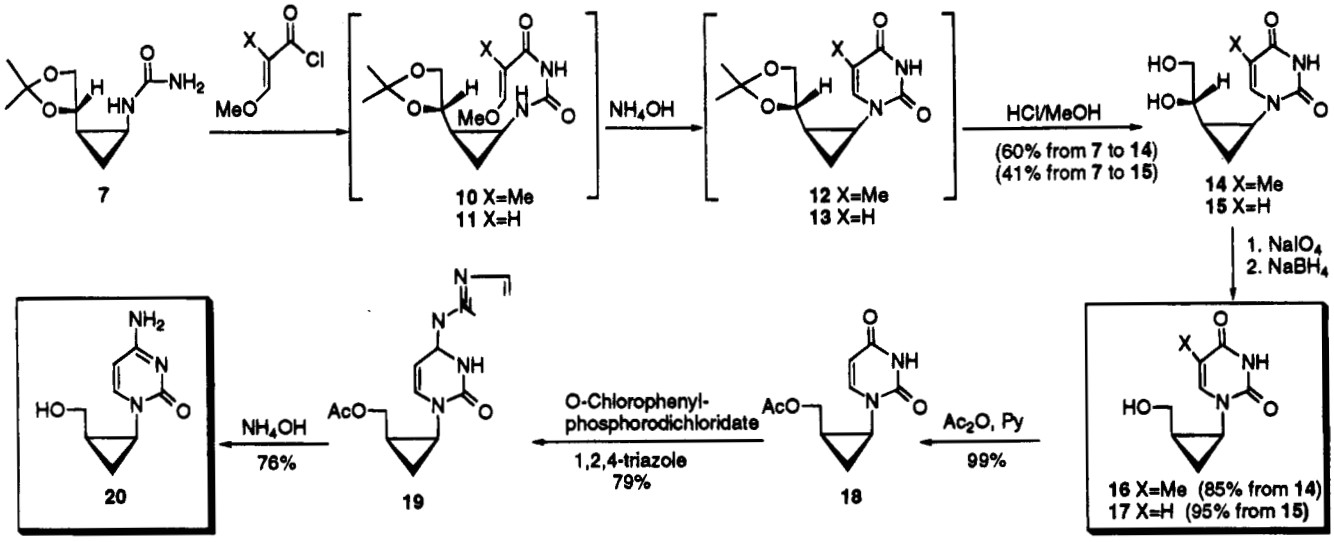
Scheme 1



Scheme 2



resulting solid was removed by filtration and the filtrate was concentrated under reduced pressure to give **1** (29.6 g, 99%) as a colorless syrup, which was used for the next reaction without further purification.

(Z,4'S)-Methyl 3-(2,2-Dimethyl-1,3-dioxolan-4-yl)acrylate (2).[21] To a solution of **1** (29.2 g, 0.22 mol) in methanol (260 mL) was added carbomethoxymethylenetriphenylphosphorane (78.5 g, 0.22 mol) and stirred at room temperature overnight, and the solvent was evaporated under reduced pressure. The residue was treated with ice-cold ether and filtered. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel column using hexane–ethyl acetate (95:5) as the eluent to give **2** (33.9 g, 81%) as a colorless syrup: $[\alpha]^{25}_D$ 117.48 (c = 2.13, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.33 (dd, J = 11.0, 6.0 Hz, 1 H), 5.78 (dd, J = 11.0, 1.5 Hz, 1 H), 5.45 (ddd, J = 8.0, 8.0, 6.0 Hz, 1 H), 4.35 (dd, J = 15.0, 8.0 Hz, 1 H), 3.68 (s, 3 H), 3.50 (dd, J = 15.0, 8.0 Hz, 1 H), 1.43 (s, 3 H), 1.37 (s, 3 H).

(Z,4S)-4,5-(Isopropylidenedioxy)pent-2-en-1-ol (3a). To a solution of compound **2** (12.6 g, 67.8 mmol) in dichloromethane (300 mL) was added DIBAL-H (1.0 M in hexanes, 170 mL, 170 mmol) dropwise at −78 °C under argon. After stirring the mixture for 30 min under the same conditions, the reaction was quenched by the addition of methanol (30 mL) and filtered, and the resulting solid was washed with ethyl acetate. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (hexane:ethyl acetate, 3:1) to obtain **3a** (9.0 g, 84%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 5.40–6.0 (m, 2 H), 4.86 (m, 1 H), 4.15–4.40 (m, 2 H), 4.09 (dd, J = 7.2, 5.4 Hz, 1 H), 3.56 (t, J = 7.2 Hz, 1 H), 2.75 (br s, 1 H), 1.42 (s, 3 H), 1.39 (s, 3 H).

(1S,2R,4'S)-1-(Hydroxymethyl)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropane (4a).[22] **Method A.** A solution of compound **3a** (7.9 g, 50 mmol) in dichloroethane (60 mL) was added to a mixture of diethylzinc (1 M in hexanes, 110 mL, 110 mmol) and chloroiodomethane (16.0 mL, 200 mmol) at 0 °C under nitrogen. The mixture was stirred for 30 min and quenched with a saturated ammonium chloride solution (100 mL), which was extracted with ether (400 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was chromatographed on a silica gel column (hexane–ethyl acetate, 3:1) to give the major compound **4a** (6.04 g, 70%) as a colorless syrup: $[\alpha]^{24}_D = -17.2°$ (c = 0.75, $CHCl_3$); (lit.[22] $[\alpha]^{28}_D = -19.8°$ (c = 0.72, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.16 (dd, J = 7.9, 5.7 Hz, 1H), 3.84 (m, 2H), 3.72 (t, J = 7.9 Hz, 1H), 3.46 (dd, J = 11.1, 8.8 Hz, 1H), 1.91 (br s, 1H), 1.45 (s, 3H), 1.36 (s, 3H),

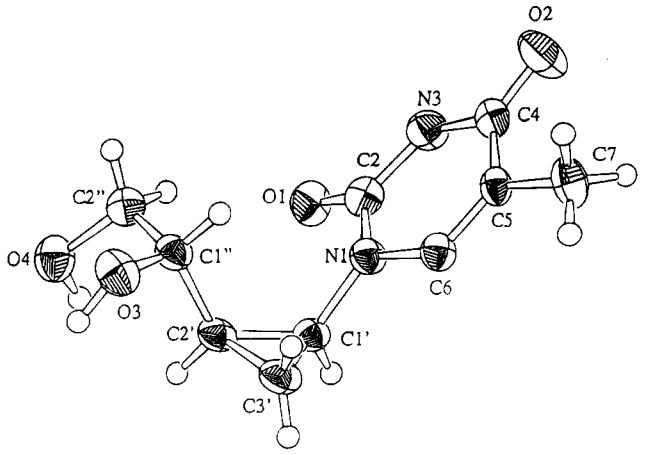


Figure 2. ORTEP drawing of compound 14.

1.25 (m, 1H), 1.06 (m, 1H), 0.92 (m, 1H), 0.47 (m, 1H). Anal. Calcd for $C_9H_{19}O_3$: C, 62.76; H, 9.36. Found: C, 62.60; H, 9.48.

Method B via (1*S*,2*R*,4′*S*)-1-[(*tert*-Butyldiphenylsilyloxy)methyl]-2-(2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropane (4b). To a solution of allylic alcohol **3a** (26 g, 165 mmol) in DMF (500 mL) at 0 °C were added imidazole (24.5 g, 196 mmol) and *tert*-butyldiphenylsilyl chloride (45 mL, 257 mmol). The mixture was stirred at room temperature for 2 h. The DMF was removed under reduced pressure, and the residue was treated with water and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give an oil. The oil was purified by column chromatography with hexane:ethyl acetate (20:1) to give compound **3b** (62.85 g, 96.5%): ^{1}H NMR ($CDCl_3$) δ 7.3–7.7 (m, 10 H, 2 x Ph), 5.81 (dt, J = 11.2, 6.1 Hz, 1 H), 5.46 (dd, J = 11.1, 8.6 Hz, 1 H), 4.63 (m, 1 H), 4.29 (m, 2 H), 3.89 (dd, J = 8.1, 6.2 Hz, 1 H), 3.43 (dd, J = 8.0, 7.9 Hz, 1 H), 1.43 (s, 3 H, CH_3), 1.38 (s, 3 H), 1.04 (s, 9 H).

To a solution of **3b** (20.3 g, 51.26 mmol) in 1,2-dichloroethane (200 mL) at −30 °C under an argon atmosphere was added diethylzinc solution (1 M in hexanes, 105 mL, 105 mmol) followed by addition of chloroiodomethane (15.3 mL, 210 mmol) and stirred for 20 min at 0 °C. The reaction was quenched by the addition of saturated ammonium chloride solution. The reaction mixture was extracted with chloroform, dried, and evaporated to dryness to give exclusively **4b**. To a solution of **4b** in THF (100 mL) was added n-Bu_4NF solution (1 M in THF, 60 mL, 60 mmol), and the reaction mixture was stirred at room temperature overnight. The solvent was removed, and the residue was purified by silica gel chromatography (hexane–ethyl acetate, 3:2) to give alcohol **4a** (8.42 g, 95.5%).

(1*S*,2*R*,4′*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropylurea (7). To a solution of compound **4a** (5.60 g, 32.6 mmol) in $CH_3CN/CHCl_3/H_2O$ (35 mL, 2:2:3) were added sodium periodate (26.1 g, 122 mmol), ruthenium dioxide (10 mg), and potassium carbonate (1.35 g, 9.8 mmol), and the mixture was stirred for 16 h and filtered through a Celite pad. The Celite pad was washed with ethyl acetate, and the combined organic layer was dried (Na_2SO_4) and concentrated to give acid **5** (4.0 g). Without further purification, a mixture of the acid **5** (4.0 g, 21.5 mmol), triethylamine (3.88 mL, 28.0 mmol), and ethyl chloroformate (3.0 mL, 31.4 mmol) in acetone (130 mL) was stirred at 0 °C for 1 h. To this solution, a solution of sodium azide (2.36 g, 35.9 mmol) in water (40 mL) was added and stirred for 1 h at room temperature. The mixture was diluted with water and extracted with ether, and the organic layer was dried ($MgSO_4$) and then concentrated to dryness. The resulting residue was purified by silica gel column chromatography (hexane–ethyl acetate, 3:1) to obtain azide **6** (4.0 g) as a colorless syrup. This was dissolved in anhydrous toluene (40 mL), heated at 90–100 °C for 1.5 h, and then evaporated to dryness to give isocyanate. Without purification the isocyanate was immediately dissolved in anhydrous ether (60 mL), and ammonia gas was introduced for 30 min to obtain a white precipitate, which was collected by filtration and washed with cold ether to give compound **7** (2.6 g, 38% yield from **4a**) as white crystals: mp 189–190 °C; $[\alpha]^{24}_D$ = −117.1° (c = 0.52, MeOH); ^{1}H NMR ($CDCl_3$) δ 4.86 (br s, NH, 1H), 4.66 (br s, NH_2, 2H), 4.15 (dd, J = 8.1, 5.9 Hz, 1H), 3.88 (m, 1H), 3.77 (dd, J = 8.1, 7.3 Hz, 1H), 2.73 (m, 1H), 1.45 (s, 3H), 1.35 (s, 3H), 1.13 (m, 2H), 0.75 (m, 1H). Anal. Calcd for $C_9H_{16}O_3N_2$: C, 53.98; H, 8.05; N, 13.99. Found: C, 53.94; H, 8.08; N, 13.94.

(1*S*,2*R*,4′*S*)-*N*-(Benzyloxycarbonyl)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropylamine (8). Method A. A solution of azide **6** (384 mg, 1.71 mmol) in toluene (10 mL) was heated at 90 °C for 1.5 h. After it cooled to room temperature, a heterogeneous mixture of benzyl alcohol (247 mg, 2.05 mmol), CuCl (183 mg, 1.71 mmol), and DMF (8 mL) was added to the above solution. The reaction mixture was stirred for 20 min, diluted with ether (30 mL), washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed on a silica gel column (hexane–ethyl acetate, 3:1) to give **8** (249 mg, 47%) as a white solid: mp 68–69 °C; $[\alpha]^{25}_D$ = −89.12° (c = 1.28, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 5H), 5.10 (s, 2H), 4.02 (m, 1H), 3.78 (m, 2H), 2.84 (m, 1H), 1.87 (s, D_2O exchangeable,1H), 1.43 (s, 3H), 1.33 (s, 3H), 1.06 (m, 2H), 0.66 (m, 1H). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.99; H, 7.36; N, 4.89.

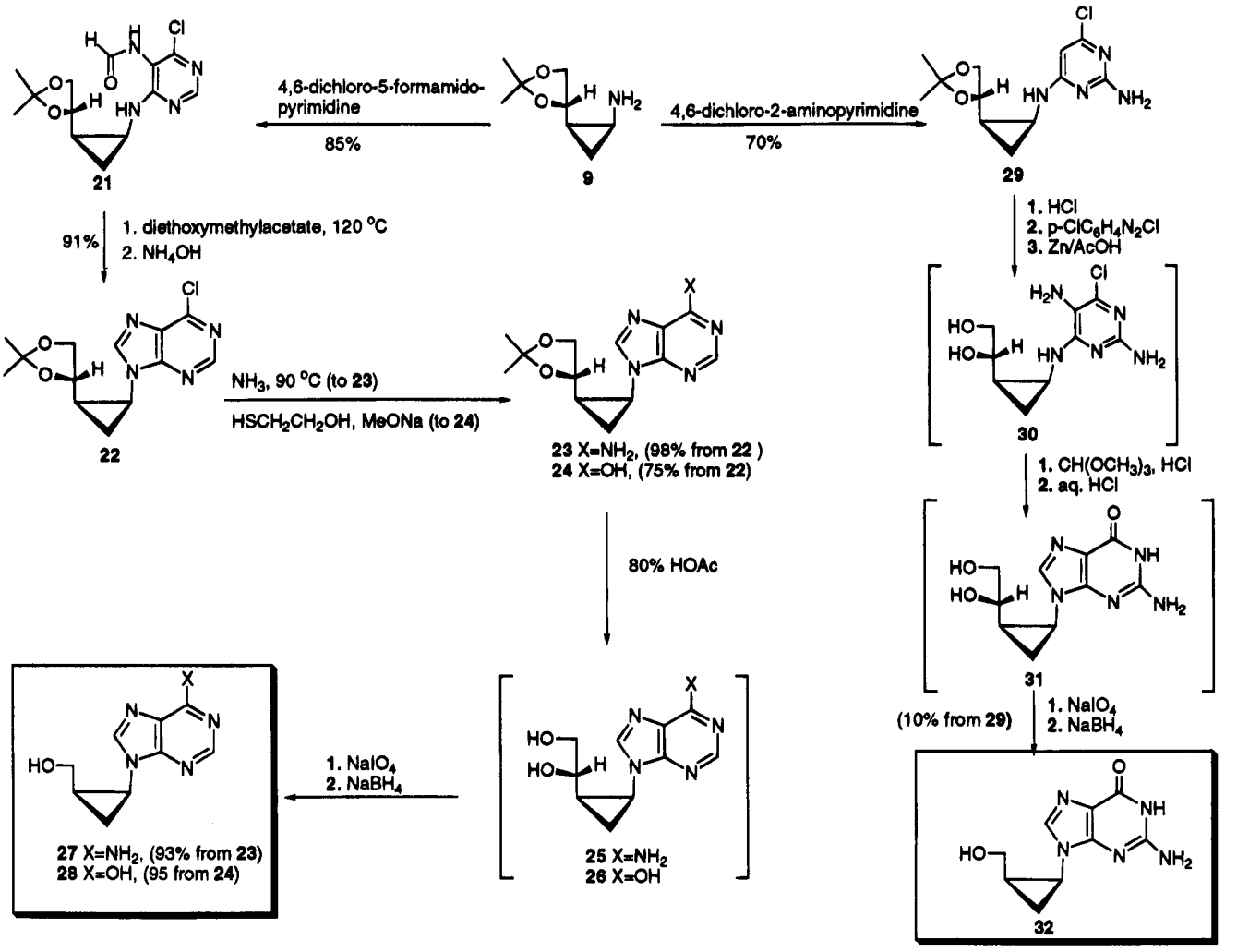
Method B. A mixture of azide **6** (2.45 g, 10.9 mmol), benzyl alcohol (2.5 mL, 24 mmol), and toluene (20 mL) was refluxed for 3 h. The solvent was removed under reduced pressure and the residue chromatographed on a silica gel column (hexanes–ethyl acetate, 3:1) to give **8** (2.94 g, 87%).

(1*S*,2*R*,4′*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropylamine (9). A mixture of carbamate **8** (635 mg, 2.18 mmol), 3% Pd/C (20 mg), and methanol (30 mL) was hydrogenated (30 psi) overnight. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 20:1) to give **9** (325 mg, 95%) as a colorless syrup: $[\alpha]^{25}_D$ = −4.72° (c = 1.35, MeOH); IR (film) 3376, 2872, 1372, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.12 (m, 2H), 3.66 (m, 1H), 2.47 (ddd, J = 7.4, 7.4, 4.3 Hz, 1H, NCH), 1.51 (s, D_2O exchangeable, 2H, NH_2), 1.45 (s, 3 H, CH_3), 1.37 (s, 3 H), 0.83 (m, 2H), 0.53 (m, 1H). Anal. Calcd for $C_8H_{15}NO_2.0.03CHCl_3$: C, 60.07; H, 9.39; N, 8.54. Found: C, 60.04; H, 9.36; N, 8.54.

(1′*S*,2′*R*)-1-[2-[(1*S*)-1,2-Dihydroxyethyl]cyclopropyl]-thymine (14). To a solution of the urea **7** (1.0 g, 5 mmol) in dichloromethane (24 mL) and pyridine (12 mL) was added β-methoxy-α-methacryloyl chloride (1.35 g, 10 mmol) stirred at room temperature for 24 h, poured into ice–water (40 mL), and extracted with chloroform (3 × 40 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (toluene–ethanol, 10:1) to give **10** (2.02 g), which was used for the next reaction without further purification. A mixture of **10** (2.02 g), 30% aqueous ammonia (5 mL), and ethanol (50 mL) was heated at 85–90 °C for 5 h. After the solvents were removed, the residue (crude **12**) was dissolved in methanol (30 mL) and concd HCl (0.5 mL) was added. The reaction mixture was stirred at room temperature overnight, neutralized with triethylamine, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column ($CHCl_3$–MeOH, 100:8) to give **14** as a white solid (0.68 g, 60%): mp 161–162.5 °C; $[\alpha]^{24}_D$ −106.43° (c = 0.43, MeOH); UV (H_2O) λ_{max} 272.0 nm (ϵ 8261) (pH 7), 272.0 (ϵ 10 607) (pH 2), 270.5 (ϵ 11 426) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.18 (s, 1H, NH), 7.43 (s, 1H), 4.48 (t, J = 5.7 Hz, 1H, OH), 4.43 (d, J = 5.2 Hz, 1H, OH), 3.36 (ddd, J = 11.4, 5.7, 4.8 Hz, 1H), 3.27 (ddd, J = 11.4, 6.4, 5.7 Hz, 1H), 3.08 (m, 2H), 1.73 (s, 3H), 1.19 (m, 2H), 0.95 (ddd, J = 8.4, 8.4, 5.4 Hz, 1H). Anal. Calcd for $C_{10}H_{14}O_4N_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.10; H, 6.23; N, 12.37.

(1′*S*,2′*R*)-1-[2-(Hydroxymethyl)cyclopropyl]thymine (16). To a solution of **14** (45 mg, 0.20 mmol) in methanol (2 mL) was added a solution of sodium periodate (50 mg, 0.23 mmol) in H_2O (5 mL) dropwise. After the mixture was stirred for 5 min, sodium borohydride (12 mg, 0.31 mmol) was added and the reaction mixture was stirred for another 5 min, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by preparative TLC ($CHCl_3$–

Scheme 3



MeOH, 10:1) to give **16** as white crystals (33 mg, 85%): mp 181–182 °C; $[\alpha]^{24}_D = -100.9°$ (c = 0.50, MeOH); UV (H_2O) λ_{max} 270.5 nm (ϵ 6485) (pH 7), 270.5 (ϵ 9314) (pH 2), 268.5 (ϵ 6456) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.24 (s, 1H, NH); 7.46 (s, 1H), 4.34 (t, J = 5.4 Hz, 1H, OH), 3.25 (m, 2H), 3.04 (ddd, J = 7.5, 7.5, 4.5 Hz, 1H), 1.73 (s, 3H), 1.35 (m, 1H), 1.05 (ddd, J = 9.0, 7.5, 6.4 Hz, 1H), 0.83 (ddd, J = 6.4, 6.4, 4.6 Hz, 1H). Anal. Calcd for $C_9H_{12}O_3N_2$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.19; H, 6.15; N, 14.22.

(1′*S*,2′*R*)-1-[2-[(1*S*)-1,2-Dihydroxyethyl)cyclopropyl]-uracil (15). To a solution of urea **7** (2.0 g, 10 mmol) in CH_2Cl_2 (60 mL) and pyridine (30 mL), β-methoxyacryloyl chloride (2.81 g, 23.3 mmol) was added at −30 °C. The reaction mixture was warmed up to room temperature, stirred for 10 h, poured into ice–water (60 mL), and extracted with chloroform (3 × 40 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 50:1) to afford **11** (2.66 g) as a yellowish oil. Without further purification, compound **11** was heated in a mixture of 30% aqueous ammonia (15 mL) and ethanol (50 mL) at 80–85 °C in a steel bomb for 16 h. The reaction mixture was then concentrated under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 50:1) to give crude product **13** (1.07 g). To the crude compound **13** in methanol (40 mL) was added concd HCl (0.5 mL), stirred at room temperature for 16 h, and then neutralized with triethylamine. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 100:12) to give **15** (0.88 g, 41% from **7**) as a white solid: mp 132.5–133.5 °C; $[\alpha]^{25}_D = -267.8°$ (c = 0.64, MeOH); UV (MeOH) λ_{max} 266.5 nm; ^{1}H NMR (DMSO-d_6) δ 11.19 (br s, D_2O exchangeable, 1H, NH), 7.53 (dd, J = 7.9, 2.2 Hz, 1H), 5.43 (d, J = 7.9 Hz, 1H), 4.52 (t, J = 5.4 Hz, D_2O exchangeable, 1H), 4.46 (d, J = 5.1 Hz, D_2O exchangeable, 1H), 3.28 (m, 2H), 3.10 (m, 2H), 0.80–1.26 (m, 3H) Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.74; H, 5.76; N, 13.25.

(1′*S*,2′*R*)-1-[2-(Hydroxymethyl)cyclopropyl]uracil (17). To a solution of nucleoside **15** (270 mg, 1.27 mmol) in MeOH (50 mL) was added $NaIO_4$ (280 mg, 1.31 mmol) in H_2O (5.0 mL) at 0 °C. After the mixture was stirred for 10 min, $NaBH_4$ (70 mg, 1.84 mmol) was added, and the mixture was stirred for another 10 min and filtered. The filtrate was concentrated and the residue was purified by silica gel chromatography ($CHCl_3$–MeOH, 10:1) to give **17** (221 mg, 95%) as a white solid: mp 154.5–155.5 °C; $[\alpha]^{25}_D = -117.9°$ (c 0.54, MeOH); UV (H_2O) λ_{max} 265.7 nm (ϵ 8895) (pH 7), 265.7 (ϵ 8579) (pH 2), 264.0 (ϵ 6696) (pH 11); ^{1}H-NMR (DMSO-d_6) δ 11.20 (br s, D_2O exchangeable, 1H, NH), 7.59 (d, J = 7.9 Hz, 1H), 5.49 (dd, J = 7.9, 2.2 Hz, 1H), 4.43 (t, J = 5.4 Hz, D_2O exchangeable, 1H), 3.29 (m, 2H), 3.08 (ddd, J = 7.3, 7.3, 4.5 Hz, 1H), 1.36 (m, 1H), 1.07 (m, 1H), 0.83 (m, 1H). Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.64; H, 5.56; N, 15.32.

(1′*S*,2′*R*)-1-[2-(Acetoxymethyl)cyclopropyl]uracil (18). A mixture of uracil derivative **17** (182 mg, 1 mmol), pyridine (5 mL), and acetic anhydride (5 mL) was stirred at room temperature for 2 h. After the reaction mixture was concentrated under reduced pressure, the residue was purified by silica gel chromatography ($CHCl_3$–MeOH, 10:1) to give product **18** (221 mg, 99%) as a white solid: mp 141.5–142.5 °C; $[\alpha]^{25}_D = -155.6°$ (c = 0.27, MeOH); UV (MeOH) λ_{max} 264.7 nm; ^{1}H NMR (DMSO-d_6) δ 11.24 (br s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 5.49 (dd, J = 7.9, 2.2 Hz, 1H), 3.96 (dd, J = 11.8, 7.3 Hz, 1H), 3.73 (dd, J = 11.8, 7.3 Hz, 1H), 3.17 (ddd, J = 7.3, 7.3, 4.8 Hz,

1H), 1.55 (ddd, J = 7.3, 7.3, 7.3 Hz, 1H), 1.00–1.20 (m, 2H). Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.44; H, 5.33; N, 12.45.

(1′*S*,2′*R*)-1-[2-(Acetoxymethyl)cyclopropyl]-4-(1,2,4-triazol-1-yl)pyrimidin-2(1*H*)-one (19). To a solution of **18** (55 mg, 0.25 mmol) in pyridine (5 mL), were added 1,2,4-triazole (115 mg, 1.66 mmol) and *o*-chlorophenyl phosphorodichloridate (0.13 mL, 0.81 mmol) and stirred at room temperature for 72 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 50:1) to give compound **19** (54 mg, 79%) as a yellowish solid: mp 128–129 °C; $[\alpha]^{25}_D = -251.1°$ (c = 0.12, MeOH); UV (MeOH) λ_{max} 264.7 nm; ^{1}H NMR (DMSO-d_6) δ 9.27 (s, 1H), 8.12 (s, 1H), 7.88 (d, J = 7.1 Hz, 1H), 7.03 (d, J = 7.1 Hz, 1H), 3.98 (d, J = 7.2 Hz, 2H), 3.58 (ddd, J = 7.5, 7.5, 4.9 Hz, 1H), 2.03 (s, 3H), 1.91 (m, 1H), 1.43 (m, 1H), 1.09 (m, 1H). Anal. Calcd for $C_{12}H_{13}N_5O_3$: C, 52.36; H, 4.76; N, 25.44. Found: C, 52.19; H, 4.73; N, 25.46.

(1′*S*,2′*R*)-1-[2-(Hydroxymethyl)cyclopropyl]cytosine (20). Triazole derivative **19** (48 mg, 0.17 mmol) was stirred in 30% aqueous ammonia (10 mL) at room temperature for 20 h, and the solvent was removed to dryness. The residue was purified by preparative TLC ($CHCl_3$–MeOH, 5:1) to give compound **20** (24 mg, 76%) as a white solid: mp 272–273 °C; $[\alpha]^{25}_D$ = −130.3° (c = 0.12, MeOH); UV (H_2O) λ_{max} 273.2 nm (ϵ 7311) (pH 7), 282.2 (ϵ 0451) (pH 2), 273.0 (ϵ 7260) (pH 11); ^{1}H NMR (DMSO-d_6) δ 7.53 (d, J = 7.3 Hz, 1H), 7.17 (br s, D_2O exchangeable, 1H), 7.11 (br s, D_2O exchangeable, 1H), 5.71 (d, J = 7.4 Hz, 1H), 4.29 (dd, J = 8.8, 2.6 Hz, D_2O exchangeable, 1H), 3.29 (ddd, J = 11.7, 8.8, 5.6 Hz, 1H), 3.04 (ddd, J = 7.3, 7.3, 4.6 Hz, 1H), 2.86 (ddd, J = 11.7, 8.6, 2.6 Hz, 1H), 1.38 (m, 1H), 1.04 (m, 1H), 0.70 (m, 1H). Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.19; H, 6.12; N, 23.29.

(1′*S*,2′*R*,4″*S*)-6-[[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-cyclopropyl]amino]-4-chloro-5-formamidopyrimidine (21). A mixture of **9** (962 mg, 6 mmol), 4,6-dichloroformamidopyrimidine (1.28 g, 6.67 mmol), and triethylamine (14 mL, 100 mmol) in dioxane (60 mL) was refluxed for 1.5 h. After cooling to room temperature, the resulting suspension was filtered, and the filtrate was concentrated to dryness and purified by silica gel column chromatography ($CHCl_3$–MeOH, 50:1) to give **21** (1.63 g, 85%) as a colorless syrup: $[\alpha]^{25}_D = -129.26°$ (c = 1.12, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1 H), 8.37 (s, 1 H), 8.06 (br s, D_2O exchangeable, 1H), 4.03 (m, 1 H), 3.80 (m, 2 H), 3.19 (m, 1 H), 1.85 (br s, D_2O exchangeable, 1H), 1.43 (s, 3H), 1.32 (s, 3 H), 1.19 (m, 2 H), 0.82 (m, 1 H); IR (film) λ_{max} 3254, 2986, 1696, 1576, 1497 cm^{-1}. Anal. Calcd for $C_{13}H_{17}N_4O_3Cl{\cdot}0.3CHCl_3$: C, 45.83; H, 5.00; N, 16.07. Found: C, 45.95; H, 5.40; N, 16.00.

(1′*S*,2′*R*,4″*S*)-9-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]-6-chloropurine (22). A solution of **21** (1.12 g, 3.58 mmol) in diethoxymethyl acetate (20 mL) was heated at 120 °C for 3 h. After the solvent was removed under reduced pressure, the residue was dissolved in MeOH (30 mL) and concd ammonia hydroxide (2.5 mL) and stirred at room temperature for 40 min. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 50:1) to give **22** (0.96 g, 91%) as a colorless syrup: $[\alpha]^{25}_D = -140.6°$ (c = 0.78, MeOH); UV (MeOH) λ_{max} 265 nm; ^{1}H NMR(DMSO-d_6) δ 8.78 (s, 1H), 8.10 (s, 1H), 3.89 (m, 2H), 3.65 (m, 1H), 3.51 (m, 1H), 1.50–1.85 (m, 3H), 1.33 (s, 3H), 1.06 (s, 3H). Anal. Calcd for $C_{13}H_{15}N_4O_2{\cdot}0.05CHCl_3$: C, 52.12; H, 5.04; N, 18.63. Found: C, 52.04; H, 5.15; N, 18.65.

(1′S,2′R,4″S)-9-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]adenine (23). A mixture of **22** (210 mg, 0.71 mmol) and NH_3/MeOH (50 mL) was heated at 90 °C in a steel bomb for 24 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 20:1) to give **23** (190 mg, 98%) as a white solid: mp 181–182 °C; $[\alpha]^{25}_D = -134.7°$ (c = 0.65, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.14 (s, 1H), 8.11 (s, 1H), 7.23 (br s, D_2O exchangeable, 2H), 3.76 (dd, J = 8.4, 6.8 Hz, 1H), 3.61 (dd, J = 8.4, 6.1 Hz, 1H), 3.55 (ddd, J = 7.4, 7.4, 4.5 Hz, 1H), 3.04 (ddd, J = 8.1, 6.4, 6.4 Hz, 1H), 1.58 (ddd, J = 5.1, 5.1, 5.0 Hz, 1H), 1.40 (m, 2H), 1.29 (s, 3H), 1.06 (s, 3H); UV (MeOH) λ_{max} 259.7. Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 56.72; H, 6.22; N, 25.44. Found: C, 56.88; H, 6.26; N, 25.51.

(1′*S*,2′*R*)-9-[2-(Hydroxymethyl)cyclopropyl]adenine (27). A solution of **23** (110 mg, 0.4 mmol) in 80% HOAc (10 mL) was stirred at room temperature for 48 h. After the solvent was removed under reduced pressure, the residue was coevaporated with water to give **25** as a white solid (94 mg, 100%), which was used for the next reaction without further purification. To a solution of **25** in methanol (50 mL) at 0 °C was added a solution of $NaIO_4$ (192 mg, 0.9 mmol) in water (5 mL) and stirred at room temperature for 15 min, and then $NaBH_4$ (65 mg, 1.70 mmol) was added. The mixture was stirred for 30 min, the solvent was removed, and the residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 50:1) to give **27** (76 mg, 93%) as a white solid: mp 125–126 °C; $[\alpha]^{25}_D$ = -49.50° (c = 0.55, MeOH); UV (H_2O) λ_{max} 260.7 (ϵ 13 476) (pH 7), 259.5 (ϵ 14 940) (pH 2), 260.5 (ϵ 13 569) (pH 11); ^{1}H NMR (DMSO-d_6) δ 8.14 (s, 1H), 8.11 (s, 1H), 7.25 (br s, D_2O exchangeable, 2H, NH_2), 4.72 (dd, J = 6.5, 4.6 Hz, 1H), 3.46 (ddd, J = 7.2, 7.2, 4.3 Hz, 1H), 3.27 (ddd, J = 11.7, 6.5, 5.6 Hz, 1H), 2.99 (ddd, J = 11.7, 8.2, 4.6 Hz, 1H), 1.51 (m, 1H), 1.27 (m, 1H), 1.18 (m, 1H). Anal. Calcd for $C_9H_{11}N_5O{\cdot}0.75H_2O$: C, 49.42; H, 5.72; N, 32.02. Found: C, 49.56; H, 5.63; 32.00.

(1′*S*,2′*R*,4″*S*)-9-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl)]hypoxanthine (24). A mixture of chloropurine **22** (333 mg, 1.13 mmol), 2-mercaptoethanol (0.32 mL, 4.52 mmol), and NaOMe (224 mg, 4.52 mmol) in methanol (50 mL) was refluxed for 20 h under N_2. The mixture was then cooled, neutralized with glacial AcOH, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 20:1) to give product **24** (236 mg, 75.6%) as a white solid: mp 220 °C dec; $[\alpha]^{25}_D = -134.0°$ (c = 0.17, MeOH); UV (MeOH) λ_{max} 250.5; ^{1}H NMR (DMSO-d_6) δ: 11.86 (br s, D_2O exchangeable, 1H), 8.06 (s, 1H), 8.04 (s, 1H), 3.70 (m, 2H), 3.55 (ddd, J = 7.4, 7.4, 4.6 Hz, 1H), 3.11 (m, 1H), 1.56 (m, 1H), 1.33–1.50 (m, 2H), 1.28 (s, 3H), 1.07 (s, 3H). Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.32; H, 5.72; N, 20.36.

(1′*S*,2′*R*)-9-[2-(Hydroxymethyl)cyclopropyl]hypoxanthine (28). A solution of **24** (210 mg, 0.76 mmol) in 80% HOAc (30 mL) was stirred at room temperature overnight. After the solvent was removed under reduced pressure, the residue was coevaporated with water to give diol **26** as a white solid (178 mg, 100%), which was used in the next reaction without further purification. To a suspension of **26** in methanol (50 mL) was added $NaIO_4$ (244 mg, 1.14 mmol) in water (5 mL) at 0 °C and stirred at room temperature for 30 min, and then $NaBH_4$ (85 mg, 2.3 mmol) was added. The reaction mixture was stirred for 20 min and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$–MeOH, 10:1) to afford compound **28** (150 mg, 96%) as a white solid: mp 268–269 °C; $[\alpha]^{25}_D = -39.3°$ (c = 0.21, MeOH); UV (H_2O) λ_{max} 250.2 (ϵ 11 235) (pH 7), 250.0 (ϵ 10 880) (pH 2), 254.2 (ϵ 11 876) (pH 11); ^{1}H NMR (DMSO-d_6) δ 12.30 (br s, D_2O exchangeable, 1H), 8.06 (s, 1H), 8.04 (s, 1H), 4.58 (t, J = 5.2 Hz, D_2O exchangeable, 1H), 3.51 (m, 1H), 3.18 (ddd, J = 11.6, 6.2, 5.2 Hz, 1H), 3.10 (ddd, J = 11.6, 7.6, 5.2 Hz, 1H), 1.49 (m, 1H), 1.16–1.31 (m, 2H). Anal. Calcd for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.33; H, 4.96; N, 27.23.

(1′*S*,2′*R*,4″*S*)-1-[(2-Amino-4-chloro-6-pyrimidinyl)amino]-2-(2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropane (29).[31] To a solution of **9** (1.60 g, 10.19 mmol) in EtOH (180 mL) were added 2-amino-4,6-dichloropyrimidine (1.84 g, 11.21 mmol) and triethyl amine (1.03 g, 10.19 mmol), and the reaction mixture was refluxed for 50 h under argon. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 1:1) to obtain **29** (2.1 g, 70%) as a white solid: mp 69–70 °C; $[\alpha]^{24}_D$ = −120.5° (c = 0.3, $CHCl_3$); UV (MeOH) λ_{max} 286.0; ^{1}H-NMR ($CDCl_3$) δ 5.95 (s, 1H), 5.10 (br s, D_2O exchangeable, 1H), 4.91

(31) Rosenquist, A.; Kvarnstrom, I.; Svensson, S. C. T.; Classon, B; Samuelsson, B. *J. Org. Chem.* **1994**, *59*, 1779.

(br s, D_2O exchangeable, 2H), 3.97 (dd, J = 8.1, 4.5 Hz, 1H), 3.79 (m, 1H), 3.75 (dd, J = 8.1, 8.0 Hz, 1H), 2.76 (m, 1H), 1.44 (s, 3H), 1.32 (s, 3H), 1.19 (m, 2H), 0.78 (m, 1H). Anal. Calcd for $C_{12}H_{17}N_4O_2Cl \cdot 0.8EtOH + 0.05H_2O$: C, 50.65; H, 6.84; N, 17.37; Cl, 10.99. Found: C, 50.27; H, 6.38; N, 17.08; Cl, 10.68.

(1′*S*,2′*R*)-9-[2-(Hydroxymethyl)cyclopropyl]guanosine (32).[31] To a solution of **29** (1.30 g, 4.57 mmol) in MeOH (150 mL) was added concd HCl (2 mL) dropwise, stirred at room temperature for 2 h, and concentrated under reduced pressure. The resulting residue **33** was used in next reaction without further purification. To a cold (0 °C) solution of *p*-chlorobenzenediazonium chloride [prepared from *p*-chloroaniline (1.0 g, 7.85 mmol), concd HCl (2.0 g), water (10 mL), and sodium nitrite (0.6 g, 8.42 mmol) in water (10 mL)] was added a mixture of the diol compound, water (35 mL), acetic acid (35 mL), and sodium acetate trihydrate (14 g) at 0–5 °C, and the solution was allowed to warm to room temperature, stirred for 18 h, cooled in an ice bath, and then filtered. The resulting yellow precipitate, a 5-[(*p*-chlorophenyl)azo]pyrimidine derivative, was washed with cold water, dried *in vacuo* over phosphorus pentoxide, and dissolved in a mixture of ethanol (20 mL), water (25 mL), and acetic acid (2 mL). Zinc dust (1.5 g) was added to the above mixture portionwise during 5 min while heating at 70 °C, and the suspension was heated at 80 °C under argon for 3 h. The warm mixture was filtered and the filtrate cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform–methanol, 5:1) to give **30**. To a mixture of **30**, triethyl orthoformate (15 mL, 90 mmol), and DMF (10 mL) was added concd HCl (0.5 mL), stirred at 5 °C for 2 h, and then stirred at room temperature for 16 h. After the solvent was removed under reduced pressure, the residue was dissolved in 2 N HCl (50 mL), which was refluxed for 5 h and then cooled to room temperature. The pH was adjusted to 7 with 2 M sodium hydroxide. The mixture was concentrated, the residue was purified by a silica gel column (chloroform–methanol, 5:1) to obtain a crude compound **31**, which was dissolved in methanol (50 mL) at 0 °C, and sodium periodate (0.24 g, 1.13 mmol) in water (5 mL) was added. The reaction mixture was stirred at room temperature for 30 min, $NaBH_4$ (0.08 g, 2.2 mmol) was added, and the mixture was stirred for 30 min and filtered. The filtrate was concentrated to dryness, which was purified by a silica gel column ($CHCl_3$–MeOH, 10:1) to give **32** (0.1 g, 10% from **29**) as a white solid: mp 260–261 °C dec; $[\alpha]^{24}_D = -47.9°$ (c = 0.30, MeOH); UV (H_2O) λ_{max} 251.5 (ϵ 12 283) (pH 7), 256.0 (ϵ 11 118) (pH 2), 267.0 (ϵ 11 212) (pH 11); ^1H NMR (DMSO-d_6) δ 10.55 (br s, D_2O exchangeable, 1H, NH), 7.70 (s, 1H), 6.51 (br s, D_2O exchangeable, 2H, NH_2), 4.52 (dd, J = 6.5, 4.3 Hz, D_2O exchangeable, 1H), 3.20–3.30 (m, 2H), 3.06 (m, 1H), 1.44 (m, 1H), 1.21 (m, 1H), 1.08 (m, 1H). Anal. Calcd for $C_9H_{11}N_5O_2.0.5\ H_2O$: C, 46.96; H, 5.25; N, 30.40. Found: C, 46.95; H, 5.24; N, 30.33.

Acknowledgment. This research was supported by the U.S. Public Health Service Research Grants (AI 32351 and AI 33655) and the Research Center for New Drug Development, Seoul National University.

JO950115Z