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Synthesis and Antiviral Activity of Novel C-Methyl Branched Cyclopropyl Nucleosides

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A series of novel cyclopropyl nucleosides was synthesized using the highly stereoselective Simmons-Smith reaction starting from 1,2:5,6-di-O-isopropylidene-D-mannitol. The structural assignments of these nucleosides were determined by NMR studies and X-ray crystallography. All the synthesized nucleosides were assayed against several viruses.

Key words: Cyclopropyl nucleoside, Antiviral agent, Simmons-Smith cyclopropanation

INTRODUCTION

The discovery of novel nucleosides as antiviral and anticancer agents has been the goal of nucleoside chemists for decades. In particular, since the emergence of the HIV pandemic, an extensive effort has been concentrated on various modifications in the sugar moiety of nucleosides, resulting in FDA approved anti-HIV agents such as AZT (Furman *et al.*, 1986), ddC (Yarchoan *et al.*, 1988), ddI (Yarchoan *et al.*, 1989), d4T (Lin *et al.*, 1987), 3TC (Schinazi *et al.*, 1992), Abacavir (Daluge *et al.*, 1997) and bis (POC)PMPA (Arimilli *et al.*, 1997). In addition, several nucleosides have been synthesized as anti-HBV agents, including L-F-ddC (Lin *et al.*, 1994), and L-FMAU (Chu *et al.*, 1995), which are at various stages of development. Among these compounds, 3TC (lamivudine) is being clinically used as an anti-HIV agent and anti-HBV agent (Dienstag *et al.*, 1995).

Recently, a number of cyclopropyl nucleoside analogues (Qiu *et al.*, 1998; Iwayama *et al.*, 1998) were synthesized and showed significant antiviral activities. Among the compounds, trisubstituted cyclopropyl nucleosides with an additional hydroxymethyl group at 1'-position were prepared by Sekiyama *et al.* (1998), along with other congeners, which showed more potent antiviral activity against HSV-1 than acyclovir (ACV) and penciclovir, and comparable to VZV (Fig. 1).

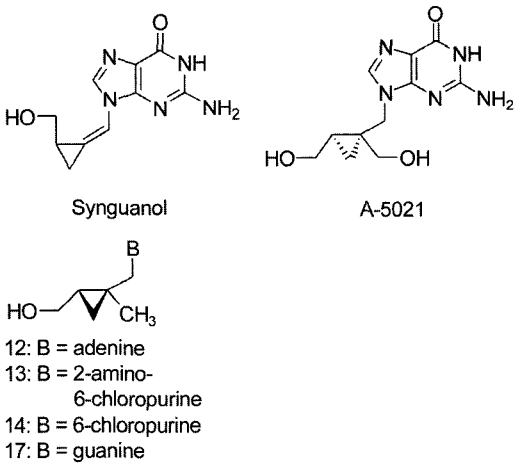

Fig. 1. Structares of cyclopropyl nucleosides

Encouraged by these interesting structures and antiviral activities, we decided to synthesize novel classes of nucleosides comprising trisubstituted cyclopropyl nucleosides with an additional methyl group at the 1'-position. Our efforts to synthesize novel nucleoside analogues and determine their antiviral activities are reported herein.

MATERIALS AND METHODS

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. Nuclear magnetic

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resonance (NMR) data for ^{1}H-NMR studies were taken on Bruker AC80 and Varian UNITY *plus* 300 spectrometers and are reported in δ (ppm) downfield from tetramethylsilane (TMS). The following abbreviation are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet. Thin layer chromatography (TLC) was carried out using precoated plates with silica gel 60F 254 purchased from Merck.

(*E*,4'*S*)-1-(*tert*-Butyldiphenylsilyloxy)-3-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-2-methylprop-2-ene (2)

To a solution of allylic alcohol **1** (0.2 g, 1.16 mmol) in CH_2Cl_2 (10 mL), imidazole (0.24 g, 3.35 mmol) and TBDPSCl (0.46 mL, 1.5 mmol) were added. The mixture was stirred at room temperature for 2 h. After removing the solvent, the residue was treated with water and extracted with EtOAc. The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was chromatographed on silica gel column eluting with *n*-hexane-EtOAc (20:1) to give **2** (0.46 g, 97 %) as a colorless oil: ^{1}H-NMR (80MHz, $CDCl_3$) δ 7.99-7.32 (10H, m, Ar), 5.57 (1H, dq, *J* = 1.41, 8.52 Hz, =C<u>H</u>), 4.83 (1H, m, C$^{4'}$-<u>H</u>), 4.24-3.98 (3H, m, C<u>H</u>$_2$OTBDPS, C$^{5'}$-<u>H</u>), 3.51 (1H, t, *J* = 7.89 Hz, C$^{5'}$-<u>H</u>), 1.67 (3H, d, *J* = 1.17 Hz, C$^{2'}$-C<u>H</u>$_3$), 1.41 (6H, s, C$^{2'}$-(C<u>H</u>$_3$)$_2$), 1.07 (9H, s, *tert*-butyl); IR (neat) cm^{-1}: 3064 (aromatic CH).

(1*S*,2*S*,4'*S*)-1-[(*tert*-Butyldiphenylsilyloxy)methyl]-2-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-1-(methyl)cyclopropane (3)

To a solution of **2** (2.84 g, 6.92 mmol) in CH_2Cl_2 (50 mL) at -30°C under argon, diethylzinc solution (1 M in hexanes, 24.67 mL, 24.67 mmol) and diiodomethane (4.46 mL, 55.33 mmol) were added and the mixture was stirred for 1 h at 0°C. The reaction was quenched by the addition of saturated NH_4Cl solution. The reaction mixture was extracted with chloroform, and the combined extracts were washed with saturated NaCl solution, dried ($NaSO_4$), filtered, and evaporated under reduced pressure. The residue was chromatographed on silica gel column eluting with *n*-hexane-EtOAc (20:1) to give **3** (2.73 g, 92.5%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.65-7.62 (10H, m, Ar), 4.07 (1H, dd, *J* = 5.7, 7.8 Hz, C$^{5'}$-<u>H</u>), 3.71(1H, m, C$^{4'}$-<u>H</u>), 3.64 (1H, t, *J* = 7.5 Hz, C$^{5'}$-<u>H</u>), 3.52 (1H, d, *J* = 9.9 Hz, C<u>H</u>$_2$OTBDPS), 3.24 (1H, d, *J* = 10.2 Hz, C<u>H</u>$_2$OTBDPS), 1.44, 1.36 (each 3H, s, C$^{2'}$-(C<u>H</u>$_3$)$_2$), 1.14 (3H, s, C^1-C<u>H</u>$_3$), 1.01 (9H, s, *tert*-butyl), 0.81-0.71 (2H, m, cyPr CH), 0.42 (1H, t, *J* = 4.8 Hz, cyPr CH); IR (neat) cm^{-1}: 3070 (aromatic CH).

(1*S*,2*S*,4'*S*)-[2-(2',2'-Dimethyl-1',3'-dioxolan-4'-yl)-1-hydroxymethyl-1-methyl] cyclopropane (4)

To a solution of **3** (2.25 g, 5.27 mmol) in THF (20 mL) *n*-Bu_4NF solution (1 M in THF, 10.55 mL, 10.55 mmol) was added, and the reaction mixture was stirred overnight at room temperature. The solvent was removed, and the residue was chromatographed on silica gel column eluting with *n*-hexane-EtOAc (1:1) to give **4** (1.01 g, 95%) as a colorless oil. ^{1}H-NMR (80 MHz, $CDCl_3$) δ 4.09 (1H, m, C$^{5'}$-<u>H</u>), 3.77-3.62 (2H, m, C$^{4'}$-<u>H</u>, C$^{5'}$-<u>H</u>), 3.32 (2H, d, *J* = 1.02 Hz, C<u>H</u>$_2$OH), 2.44 (1H, br s, O<u>H</u>), 1.43, 1.35 (each 3H, s, C$^{2'}$-(C<u>H</u>$_3$)$_2$), 1.14 (3H, s, C^1-C<u>H</u>$_3$), 0.84-0.78 (2H, m, cyPr CH), 0.47 (1H, m, cyPr CH); IR (neat) cm^{-1} : 3421(OH).

(1'*S*,2'*S*,4"*S*)-9-[[2'-(2,2-Dimethyl-1,3-dioxolan-4-yl)-1'-methyl]cycloprop-1'-yl]adenine (6)

p-TsCl (706 mg, 3.71 mmol) was added to a solution of **4** (230 mg, 1.24 mmol) and DMAP (905 mg, 7.41 mmol) in CH_2Cl_2 (6 mL) at 0°C, and the mixture was stirred at 0°C for 1 h. The solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered, and evaporated (76% crude yield). The residue (crude **5**) was used for the next reaction without further purification. A solution of **5** in DMF (16 mL) was added to a mixture of adenine (200 mg, 1.48 mmol), K_2CO_3 (205 mg, 1.48 mmol), and 18-crown-6 (392 mg, 1.48 mmol) in DMF (8.5 mL), and the resulting mixture was stirred at 60°C for 2 h. After concentration in reduced pressure, the residue was chromatographed on silica gel column eluting with $CHCl_3$-MeOH (20:1) to give **6** (160 mg, 42.7%) as a white solid: mp 206-207°C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 8.36, 7.82 (each 1H, s, C^2-<u>H</u>, C^8-<u>H</u>), 6.02 (2H, bs, N<u>H</u>$_2$), 4.03-3.50 (5H, m, C$^{4'}$-<u>H</u>, C$^{5'}$-<u>H</u>$_2$, C<u>H</u>$_2$N), 1.44, 1.34 (each 3H, s, C$^{2'}$-(C<u>H</u>$_3$)$_2$), 1.24-1.10 (2H, m, cyPr CH), 1.05 (3H, s, C^1-C<u>H</u>$_3$), 0.66 (1H, t, *J* = 4.6 Hz, cyPr CH); IR (KBr) cm^{-1}: 3289, 3110 (NH_2) UV (MeOH) λ_{max} 262 nm (ε 15704).

(1'*S*,2'*S*,4"*S*)-2-Amino-9-[[2'-(2,2-dimethyl-1,3-dioxolan-4-yl)-1'-methyl]cycloprop-1'-yl]-6-chloropurine (7a) and its 7-isomer (7b)

A solution of crude **5** in DMF (62 mL) was added to a mixture of 2-amino-6-chloropurine (973 mg, 5.74 mmol), K_2CO_3 (793 mg, 5.73 mmol), and 18-crown-6 (1.52 g, 5.73 mmol) in DMF (33 mL), and the resulting mixture was stirred at 60°C for 2 h. After concentration *in vacuo*, the residue was chromatographed on silica gel column eluting with $CHCl_3$-MeOH (20:1) to give **7a** (860 mg, 53.3 %) as a white solid. The 7-isomer **7b** was eluted afterward (550 mg, 34.1%): **7a**: mp 174-175°C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.77 (1H, s, C^8-<u>H</u>), 5.09 (2H, br s, N<u>H</u>$_2$), 3.98-3.83 (3H, m, C$^{5'}$-<u>H</u>, C<u>H</u>$_2$N), 3.70 (1H, m, C$^{4'}$-<u>H</u>), 3.55 (1H, t, *J* = 7.65 Hz, C$^{5'}$-<u>H</u>), 1.46, 1.34 (each 3H, s, C$^{2'}$-(C<u>H</u>$_3$)$_2$), 1.27, 1.08 (each 1H, m, cyPr CH), 1.04 (3H, s, C^1-C<u>H</u>$_3$), 0.67 (1H, t, *J* = 5.4 Hz, cyPr CH); IR (KBr) cm^{-1}: 3487, 3296 (NH_2); UV (MeOH) λ_{max} 310 nm (ε 6684); **7b**: mp

decomposed from 156°C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.04 (1H, s, C^8-H), 5.08 (2H, br s, NH_2), 4.29 (1H, d, *J* = 14.7 Hz, CH_2N), 4.23 (1H, d, *J* = 14.7 Hz, CH_2N), 4.05 (1H, dd, *J* = 5.85, 7.95 Hz, $C^{5'}$-H), 3.78 (1H, m, $C^{4'}$-H), 3.59 (1H, t, *J* = 7.8 Hz, $C^{5'}$-H), 1.44, 1.35 (each 3H, s, $C^{2'}$-$(CH_3)_2$), 1.13 (3H, s, C^1-CH_3) 1.04 (2H, m, cyPr CH), 0.72 (1H, t, *J* = 4.5 Hz, cyPr CH); IR (KBr) cm^{-1}: 3400, 3311 (NH_2); UV (MeOH) λ_{max} 322 nm (ε 5433).

(1'*S*,2'*S*,4'*S*)-9-[[2'-(2,2-Dimethyl-1,3-dioxolan-4-yl)-1'-methyl]cycloprop-1'-yl]-6-chloropurine (8a) and its 7-isomer (8b)

A solution of crude **5** in DMF (44 mL) was added to a mixture of 6-chloropurine (637 mg, 4.12 mmol), K_2CO_3 (570 mg, 4.12 mmol), and 18-crown-6 (1.09 g, 4.12 mmol) in DMF (24 mL), and the resulting mixture was stirred at 60°C for 2 h. After concentration *in vacuo*, the residue was chromatographed on silica gel column eluting with $CHCl_3$-MeOH (20:1) to give **8a** (240 mg, 21.6%). The 7-isomer **8b** was eluted afterward (50 mg, 4.5%): **8a**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.76, 8.15 (each 1H, s, C^8-H, C^2-H), 4.13 (2H, s, CH_2N), 3.96 (1H, dd, *J* = 6.0, 7.8 Hz, $C^{5'}$-H), 3.73 (1H, m, $C^{4'}$-H), 3.50 (1H, t, *J* = 7.8 Hz, $C^{5'}$-H), 1.45, 1.34 (each 3H, s, $C^{2'}$-$(CH_3)_2$), 1.30, 1.11(each 1H, m, cyPr CH), 1.06 (3H, s, C^1-CH_3), 0.72 (1H, t, *J* = 5.4 Hz, cyPr CH); UV (MeOH) λ_{max} 268 nm (ε 33081); **8b**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.90, 8.34 (each 1H, s, C^8-H, C^2-H), 4.48 (1H, d, *J* = 14.7 Hz, CH_2N), 4.38 (1H, d, *J* = 14.7 Hz CH_2N), 4.06 (1H, dd, *J* = 5.7, 7.8 Hz, $C^{5'}$-H), 3.81 (1H, m, $C^{4'}$-H), 3.60 (1H, t, *J* = 7.8 Hz, $C^{5'}$-H), 1.44, 1.35 (each 3H, s, $C^{2'}$-$(CH_3)_2$), 1.14 (3H, s, C^1-CH_3), 1.08, 0.88 (each 1H, m, cyPr CH), 0.78 (1H, t, *J* = 4.5Hz, cyPr CH); UV (MeOH) λ_{max} 266 nm (ε 18249).

(1'*S*,2'*S*)-9-[[2'-[(1S)-1,2-Dihydroxyethyl]-1'-methyl]cycloprop-1'-yl]methyl]adenine (9)

A solution of **6** (210 mg, 0.69 mmol) in 80 % AcOH (23 mL) was stirred at room temperature for 22 h. After the solvent was removed under reduced pressure, the residue was coevaporated with toluene to give **9** as a white solid. Recrystallization from MeOH gave white crystals (160 mg, 87.8%): mp 215-216°C; ^{1}H-NMR (80 MHz, DMSO-d_6) δ 8.17, 8.15 (each 1H, s, C^2-H, C^8-H), 7.11 (2H, br s, D_2O exchangeable NH_2), 4.40, 4.36 (each 1H, br s, OH, D_2O exchangeable), 3.95 (2H, m, CH_2N) 3.20 - 3.05 (3H, m, CH_2OH, CHOH), 1.10 (1H, m, cyPr CH), 0.93 (3H, s, C^1-CH_3), 0.80 (1H, m, cyPr CH), 0.37 (1H, t, *J* = 4.14 Hz, cyPr CH); IR (KBr) cm^{-1} : 3544 - 3211 (OH, NH_2); UV (MeOH) λ_{max} 262 nm (ε 13487).

(1'*S*,2'*S*)-2-Amino-9-[[2'-[(1S)-1,2-dihydroxyethyl]-1'-methyl]cycloprop-1'-yl]methyl]-6 chloropurine (10)

Treatment of 350 mg of **7a** (1.04 mmol) as described in the preparation of **9** gave **10** (280 mg, 90.8%) as a white solid: mp 94-95°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.16 (1H, s, C^8-H), 6.85 (2H, br s, NH_2), 4.44 (2H, br s, 2×OH), 3.91 (1H, d, *J* = 14.1 Hz, CH_2N), 3.79 (1H, d, *J* = 14.1 Hz, CH_2N), 3.17-3.06 (3H, m, CH_2OH, CHOH), 1.04 (1H, m, cyPr CH), 0.93 (3H, s, C^1-CH_3), 0.87 (1H, dd, *J* = 4.5, 9.0 Hz, cyPr CH), 0.37 (1H, t, *J* = 5.2 Hz, cyPr CH); IR (KBr) cm^{-1}: 3336-3214 (OH, NH_2); UV (MeOH) λ_{max} 294 nm (ε 12114).

(1'*S*,2'*S*)-9-[[2'-[(1S)-1,2-Dihydroxyethyl]-1'-methyl]cycloprop-1'-yl]methyl]-6-chloropurine (11)

Treatment of 200 mg of **8a** (0.62 mmol) as described in the preparation of **9** gave **11** (150 mg, 85.6%): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.75, 8.31 (each 1H, s, C^2-H, C^8-H), 4.34 (1H, d, *J* = 14.4 Hz, CH_2N), 3.94 (1H, d, *J* = 14.4 Hz, CH_2N), 3.57, 3.47, 3.35 (each 1H, m, CH_2OH, CHOH), 2.95 (2H, bs, 2×OH), 1.35 (1H, m, cyPr CH), 1.07 (1H, m, cyPr CH), 1.05 (3H, s, C^1-CH_3), 0.66 (1H, t, *J* = 5.4 Hz, cyPr CH); IR (KBr) cm^{-1}: 3394 (OH); UV (MeOH) λ_{max} 266 nm (ε 20917).

(1'*S*,2'*S*)-9-[[2'-Hydroxymethyl-1'-(methyl)cycloprop-1'-yl]methyl]adenine (12)

To a solution of **9** (130 mg, 0.49 mmol) in methanol (70 mL) at 0°C, a solution of $NaIO_4$ (237 mg, 1.11 mmol) in water (6.2 mL) was added and stirred at room temperature for 15 min, after which $NaBH_4$ (79 mg, 2.1 mmol) was added. The mixture was stirred for 30 min, the solvent was removed, and the residue was chromatographed on silica gel column eluting with $CHCl_3$-MeOH (8:1) to give **12** (110 mg, 95.5 %) as a white solid: mp 211.5-212°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.22, 8.13 (each 1H, s, C^2-H, C^8-H), 7.15 (2H, br s, NH_2), 4.74 (1H, t, *J* = 5.1 Hz, OH), 4.02 (1H, d, *J* = 13.95 Hz, CH_2N), 3.97 (1H, d, *J* = 13.95 Hz, CH_2N) 3.57 (2H, m, CH_2O), 1.24 (1H, m, cyPr CH), 0.97 (3H, s, C^1-CH_3), 0.88 (1H, dd, *J* = 4.8, 9.3 Hz, cyPr CH), 0.20 (1H, t, *J* = 5.1 Hz, cyPr CH); IR (KBr) cm^{-1}: 3350-3100 (OH, NH_2); UV (MeOH) λ_{max} 262 nm (ε 12172).

(1'*S*,2'*S*)-2-Amino-9-[[2'-hydroxyethyl-1'-(methyl)cycloprop-1'-yl]methyl]-6-chloropurine (13)

Treatment of 220 mg of **10** (0.739 mmol) as described in the preparation for **12** gave **13** (140 mg, 70.8%) as a white solid: mp 80-83°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.16 (1H, s, C^8-H), 6.85 (2H, br s, NH_2), 4.44 (2H, br s, OH), 3.91 (1H, d, *J* = 14.1 Hz, CH_2N), 3.79 (1H, d, *J* = 14.1 Hz, CH_2N), 3.17-3.06 (3H, m, $C^{4'}$-H, $C^{5'}$-H_2), 1.04 (1H, m, cyPr CH), 0.93 (3H, s, C^1-CH_3), 0.87 (1H, dd, *J* = 4.5, 9 Hz, cyPr CH), 0.37 (1H, t, *J* = 5.25 Hz, cyPr CH): IR (KBr) cm^{-1}: 3337-3200 (OH, NH_2); UV (MeOH) λ_{max} 294 nm (ε 4113).

(1'*S*,2'*S*)-9-[[2'-Hydroxyethyl-1'-(methyl)cycloprop-1'-yl]methyl]-6-chloropurine (14)

Treatment of 120 mg of **11** (0.424 mmol) as described in the preparation of **12** gave **14** (60 mg, 56%): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.75, 8.44 (each 1H, s, C^2-H, C^8-H), 4.35 (1H, d, *J* = 14.1 Hz, CH_2N), 4.24 (1H, d, *J* = 14.1 Hz, CH_2N), 3.95 (1H, m, CH_2O), 3.54 (1H, br s, OH), 3.47 (1H, m, CH_2O), 1.48 (1H, m, cyPr CH), 1.12 (3H, s, C^1-CH_3), 0.99 (1H, dd, *J* = 5.4, 9.3 Hz, cyPr CH), 0.44 (1H, t, *J* = 5.7 Hz, cyPr CH); IR (KBr) cm^{-1}: 3393 (OH); UV (MeOH) λ_{max} 264 nm (ε 7785).

(1*S*,2'*S*,4"*S*)-9-[[2'-(2,2-Dimethyl-1,3-dioxolan-4-yl)-1'-methyl]cycloprop-1'-yl] guanine (15)

A mixture of **7a** (300 mg, 0.89 mmol), 2-mercaptoethanol (0.25 mL, 3.55 mmol), and $NaOCH_3$ (192 mg, 3.55 mmol) in methanol (45 mL) was refluxed for 20 h. The mixture was then cooled, neutralized with glacial AcOH, and concentrated under reduced pressure. The residue was chromatographed on silica gel column eluting with $CHCl_3$-MeOH (10:1) to give **15** as a white solid (240 mg, 84.6%): mp 273-275°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.50 (1H, s, C^6-OH), 7.70 (1H, s, C^8-H), 6.36 (2H, bs, NH_2), 3.91-3.36 (5H, m, $C^{4'}$-H, $C^{5'}$-H_2, CH_2N), 1.33, 1.24 (each 3H, s, $C^{2'}$-$(CH_3)_2$), 1.16 (2H, m, 2×cyPr CH), 0.94 (3H, s, C^1-CH_3), 0.46 (1H, t, *J* = 5.1 Hz, cyPr CH); IR (KBr) cm^{-1}: 3395-3160 (OH, lactam NH, NH_2), 1689 (lactam C=O); UV (MeOH) λ_{max} 254 nm (ε 10280).

(1'*S*,2'*S*)-9-[[2'-[(1S)-1,2-Dihydroxyethyl]-1'-methyl]cycloprop-1'-yl]methyl]guanine (16)

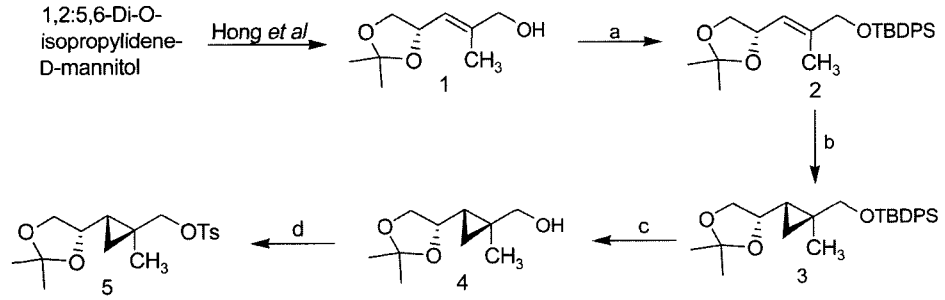
Treatment of 200 mg of **15** (0.626 mmol) as described in the preparation of **9** gave **16** (170 mg, 97.2%) as a white solid: mp 256-258°C decomposed: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.48 (1H, s, C^6-OH), 7.70 (1H, s, C^8-H), 6.36 (2H, br s, NH_2), 4.42 (2H, m, 2×OH), 3.78 (1H, d, *J* = 14.1 Hz, CH_2N), 3.69 (1H, d, *J* = 14.1 Hz, CH_2N), 3.19, 3.06 (3H, m, CH_2OH, CHOH), 0.97 (1H, m, cyPr CH), 0.93 (3H, s, C^1-CH_3), 0.86 (1H, m, cyPr CH), 0.34 (1H, t, *J* = 5.1 Hz, cyPr CH); IR (KBr) cm^{-1}: 3386 - 3145 (OH, lactam NH, NH_2), 1687 (lactam C=O); UV (MeOH) λ_{max} 254 nm (ε 11745).

(1'*S*,2'*S*)-9-[[2'-Hydroxymethyl-1'-(methyl)cycloprop-1'-yl]methyl]guanine (17)

Treatment of 140 mg of **16** (0.501 mmol) as described in the preparation of **12** gave **17** (120 mg, 96%) as a white solid: mp 252-254°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.49(1H, s, C^6-OH), 7.80 (1H, s, C^8-H), 6.36 (2H, br s, NH_2), 4.48 (1H, m, OH), 3.81 (1H, d, *J* = 13.8 Hz, CH_2N), 3.72 (1H, d, *J* = 13.8 Hz, CH_2N), 3.57, 3.20 (each 1H, m, CH_2OH), 1.71(1H, m, cyPr CH), 0.98 (3H, s, C^1-CH_3), 0.82 (1H, dd, *J* = 4.5, 9.0 Hz, cyPr CH), 0.18 (1H, t, *J* = 5.1 Hz, cyPr CH); IR (KBr) cm^{-1}: 3422-3172 (OH, lactam NH, NH_2), 1705 (lactam C=O); UV (MeOH) λ_{max} 256 nm (ε 13358).

RESULTS AND DISCUSSION

Scheme 1 shows the synthesis of the cyclopropyl compound **5**, which is the key intermediate for the preparation of trisubstituted cyclopropyl nucleosides. The alcohol derivative **1** was prepared with use of the well-known procedure from commercially available 1,2:5,6-di-O-isopropylidne-D-mannitol (Hong *et al.*, 2000). In order to improve the diastereoselectivity and yield of the Simmons-Smith Reaction for cyclopropanation (Morikawa *et al.*, 1992) the hydroxyl group of **1** was protected by treatment with *tert*-butyldiphenylsilyl chloride (TBDPSCl). The treatment of **2** with Et_2Zn/CH_2I_2 produced **3** at 92.5% yield with high diastereoselectivity. The stereochemical assignment of **3** was made by comparing the natural compound reported result (Hukuyama *et al.*, 1992) in which (+)-bicyclohumulenone, a natural compound, was synthesized using stereoselective Simmons-Smith cyclopropanation and further stereochemical confirmation was established from the X-ray crystallography of final compound **12** (Fig. 2). The compound **3** was deprotected by *n*-Bu_4NF in THF to give



Regents: a) TBDPSCl, imidazole, CH_2Cl_2, rt, 97%;b) Et_2Zn/CH_2I_2 , CH_2Cl_2 , THF, -40°C-0°C, 92.5%; c) *n*-Bu_4NF, THF, rt, 95%; d) *p*-TsCl, DMAP, CH_2Cl_2 , 0°C, 76%.

Schime 1. Synthetic scheme for the cyclopropyl moiety

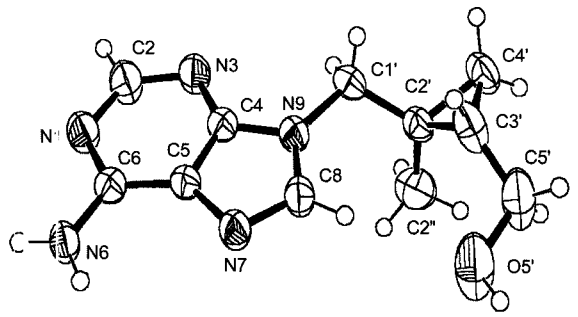
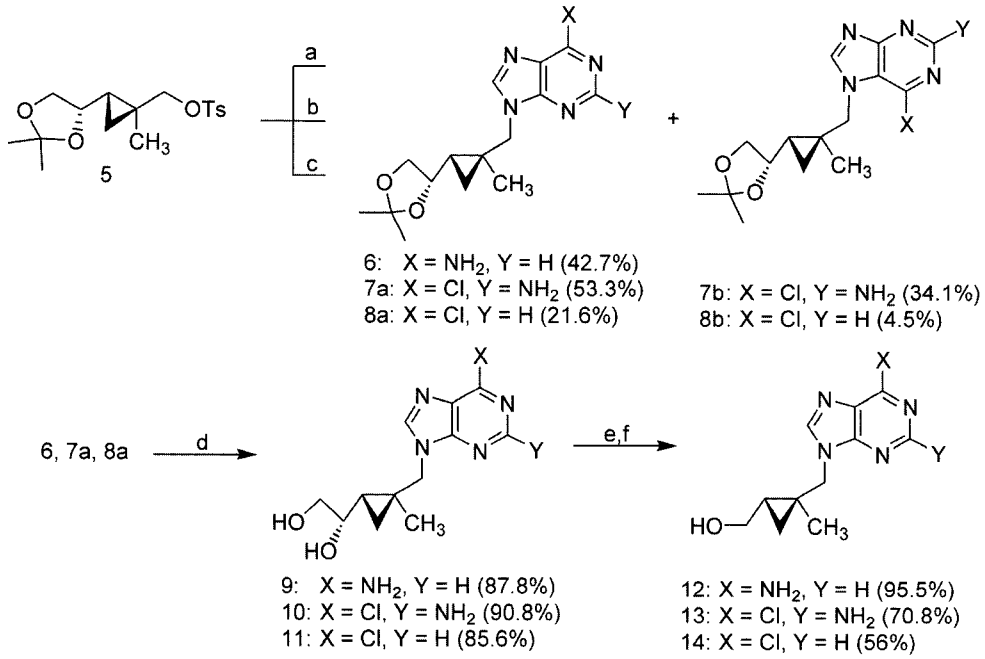


Fig. 2. Ortep drawing of compound **12**

the intermediate **4**.

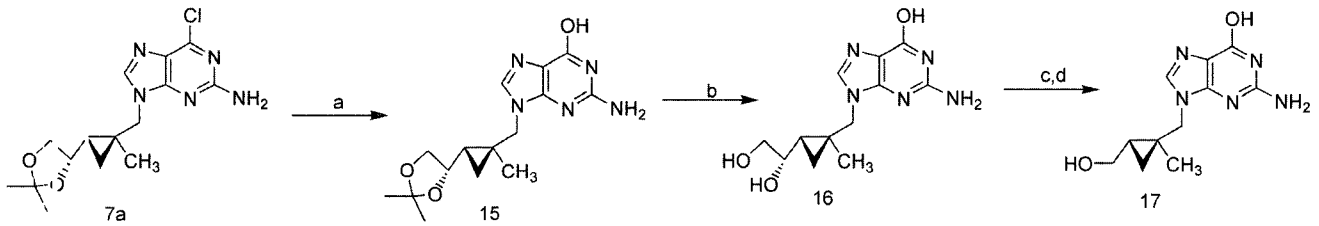
The synthesis of trisubstituted cyclopropyl nucleosides is shown in Scheme 2. In order to couple the sugar moiety by standard nucleophilic substitution reaction, compound **4** was converted to tosylate **5** at 76% yield by treatment of *p*-toluenesulfonyl chloride (*p*-TsCl) in CH_2Cl_2 in the presence of DMAP at 0°C in the 76% yield Tosylate **5** was coupled with adenine, 2-amino-6-chloropurine, and 6-chloro purine in the presence of potassium carbonate and 18-crown-6 in DMF at 60°C to give **6**, **7a** and **8a**, respectively (Jeon *et al.*, 1996; Hossain *et al.*, 1996). In the condensation reaction of 2-amino-6-chloropurine and 6-chloropurine, the 7-isomers, **7b** and **8b**, were also obtained. The UV spectra of compounds **7a** and **8a** showed absorption maxima at 264 and 310 nm, respectively. ^{1}H-NMR studies were also used for correct assignments (Kjellberg *et al.*, 1986). The isopropylidene groups of **6**, **7a** and **8a** were removed by treatment with 80% acetic acid to give diol nucleosides **9**, **10** and **11**, which were treated with sodium periodate followed by $NaBH_4$ to provide the final nucleosides **12**, **13** and **14**, respectively.

The synthetic route of guanine derivative **17** is depicted



Reagents: a) adenine, K_2CO_3, 18-crown-6, 60 °C; b) 2-amino-6-chloropurine, K_2CO_3, DMF, 60 °C; c) 6-chloropurine, K_2CO_3, DMF, 60 °C; d) 80% AcOH; e) $NaIO_4$; f) $NaBH_4$.

Scheme 2. Synthesis of compound **12**, **13**, and **14**



Reagents: a) $NaOCH_3$, 2-mercaptoethanol, MeOH, reflux, 84.6%; b) 80% AcOH, 97.2%; c) $NaIO_4$, d) $NaBH_4$, 96% for the two steps.

Scheme 3. Synthesis of compound **17**

Table I. Antiviral activities of the synthesized compounds

	HIV-1 EC_{50} (μg/mL)	HSV-1 EC_{50} (μg/mL)	HCMV EC_{50}(μg/mL)	CoxB3 EC_{50}(mg/mL)	cytotoxicity IC_{50}(μg/mL)
12	42.80	>100	72.06	>100	>100
13	>100	>100	>100	43.49	>100
14	>100	>100	>100	>100	>100
17	>100	>100	>100	>100	>100
AZT	0.0005	ND	ND	ND	0.5
Ganciclovir	ND	1.21	ND	ND	>10
Ribavirin	ND	ND	ND	30.96	>300

ND: Not Determined.

in Scheme 3. Upon treatment with mercaptoethanol and sodium methoxide at reflux in methanol, the compound **7a** was converted to **15** at 84.6% yield. In a similar procedure described for **12-14**, compound **15** was hydrolyzed with 80% acetic acid to give diol nucleoside **16**, which was then treated with sodium periodate followed by $NaBH_4$ to provide the guanine derivative **17**. The structures of the synthesized nucleosides were determined by ^{1}H-NMR spectroscopy along with single X-ray crystallography of **12** (Fig. 2).

The antiviral assays against HIV-1, HSV-1, HCMV and CoxB3 were performed and from the results shown in Table I, adenine **12** and 2-amino-6-chloropurine analogue **13** showed moderate activity against anti-HIV-1 and CoxB3, respectively, without showing significant toxicity to the host cell.

In conclusion, we successfully synthesized novel cyclopropyl nucleosides **12**, **13**, **14** and **17** starting from 1,2:5,6-di-*O*-isopropylidene-D-mannitol by employing the highly stereoselective Simmons-Smith reaction as the key step. The adenine derivative **12** exhibited moderate anti-HIV activity and the 2-amino-6-chloropurine derivative **13** also exhibited moderate anti-CoxB3 activity.

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