Arch Pharm Res Vol 26, No 11, 887-891, 2003

Archives of Pharmacal Research
http://apr.psk.or.kr

Synthesis and Antiviral Activity of Novel *trans*-2,2-Dimethyl Cyclopropyl Nucleosides

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(Received September 4, 2003)

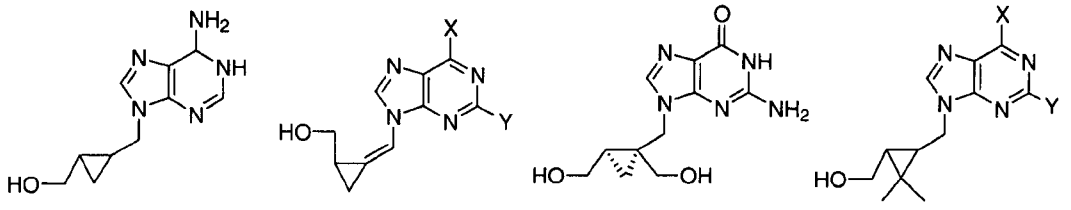
Novel *trans*-2,2-dimethylcyclopropyl nucleosides were synthesized as potential antiviral agents. The key intermediate, **3**, was synthesized *via* five steps from ethyl chrysanthemate and condensed with purine bases using the Mitsunobu reaction to give six cyclopropyl nucleosides. These synthesized nucleosides did not show any significant antiviral activity against HSV-1, HSV-2, EMCV, Cox B3, or VSV, at concentrations up to 100 μM.

Key words: 2,2-Dimethylcyclopropyl nucleoside, Antiviral agent, Ethyl chrysanthemate

INTRODUCTION

The discovery of novel nucleosides as antiviral and anticancer agents has been the research goal of nucleoside chemists for a few decades (Chu *et al.*, 1993). Acyclonucleosides can be considered as derivatives of classical nucleosides or carbo-nucleosides by omitting any bond from the pentose or cyclopentane rings (Agrofolio *et al.*, 1998). Because of their structural flexibility, many of them such as acyclovir (Elion *et al.*, 1977), ganciclovir (Martin *et al*, 1983), penciclovir (Earnshaw *et al.*, 1992) and famciclovir (Vere Hodge *et al.*, 1989) possess biological properties as antiviral agents despite their lack of chirality.

Recently, novel nucleosides containing a cyclopropane moiety were also synthesized as conformationally constrained analogues of acyclic nucleosides (Kwak *et al.*, 2000a and 2003b). Among them, the *E*-configuration of the adenine nucleoside (Fig. 1a) showed moderate antiviral activity (Ashton *et al.*, 1988). The purine derivatives such as synadenol (Qiu *et al.*, 1998a) and synguanol (Qiu *et al.*, 1998b) (Fig. 1b), of which the ribofuranoside moiety is replaced with a methylene cyclopropane ring, were



(Synadenol: X=NH_2, Y=H
Synguanol: X=OH, Y=NH_2

6 X=Cl, Y=H
7 X=Cl, Y=NH_2
8 X=NH_2, Y=H
9 X=OH, Y=H
10 X=NH_2, Y=NH_2
11 X=OH, Y=NH_2

Fig. 1. Novel cyclopropyl nucleosides

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found to have potent antiviral activity, particularly against human cytomegalovirus (HCMV). In addition, the guanine derivative (A-5021) (Fig. 1c), which was one of the trisubstituted cyclopropane nucleosides with an additional hydroxymethyl group at 1'-position, showed more potent antiviral activity against HSV-1 than acyclovir (Sekiyama *et al.*, 1998). Encouraged by these interesting structures and antiviral activities, we determined to synthesize a novel class of nucleosides (Fig. 1d) with the dimethyl group on the cyclopropyl ring.

MATERIALS AND METHODS

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. Nuclear magnetic resonance (NMR) data for ^{1}H-NMR were taken on Bruker AC80 and Varian UNITY *plus* 300 spectrometers and are reported in ppm downfield from tetramethylsilane (TMS). The following abbreviations 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.

Ethyl *trans*-2,2-dimethyl-3-hydroxymethylcyclopropanecarboxylate (1)

To an ethanolic solution of ethyl *trans*-2,2-dimethyl-3-formylcyclopropanecarboxylate from ethyl chrysanthemate (de Montellano *et al.*, 1978), $NaBH_4$ (1.02 g, 26.4 mmol) was added and the mixture was stirred for 1 h at 0°C. After quenching with saturated NH_4Cl solution, the mixture was extracted with ether. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography on a silica column (hexane/EtOAc, 2.5/1) to afford **1** (2.5g, 82.2%) as a colorless oil: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.13 (2H, dq, *J* = 1.5, 5.4 Hz, OCH_2CH_3), 3.74 (1H, dd, *J* = 6.9, 11.4 Hz, CH_2OH), 3.61 (1H, dd, *J* = 8.3, 11.4 Hz, CH_2OH), 1.76-1.66 (1H, ddd, *J* = 8.0, 6.8, 5.5 Hz, ring proton), 1.40 (1H, d, *J* = 5.5 Hz, ring proton), 1.26 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.25 and 1.23 (6H, 2s, ring CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.17, 61.85, 60.39, 34.42, 31.50, 27.08, 21.08, 20.72, 14.31; IR (neat) cm^{-1} : 3433 (OH), 1724 (ester C=O).

Ethyl *trans*-3-(*tert*-butyldiphenylsilanyloxymethyl)-2,2-dimethylcyclopropanecarboxylate (2)

To a solution of **1** (4.2 g, 24.67 mmol) and imidazole (3.36 g, 49.34 mol) in DMF (100 mol), *tert*-butyldiphenylsilyl chloride (11 mL, 41.94 mmol) was added dropwise at 0°C and the mixture was stirred at the same temperature for 2 h. After removing the solvent, water was added to the residue, which was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to a yellow syrup under reduced pressure, which was chromatographed on a silica gel column (hexane/EtOAc, 20/1) to afford **2** (8.43 g, 84.2%) of product as a colorless oil.: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70-7.30 (10H, m, aromatic), 4.10 (2H,dq, *J* = 4.8, 7.2Hz, OCH_2CH_3), 3.79 (1H, dd, *J* = 6.3, 11.1 Hz, $CH_2OTBDPS$), 3.59 (1H, d, *J* = 8.4, 11.1 Hz, $CH_2OTBDPS$), 1.71 (1H, dt, *J* = 9.0, 6.0Hz, ring proton) 1.27 (1H, d, *J* = 5.4 Hz, ring proton), 1.24 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.23 and 1.13 (6H, 2s, ring CH_3), 1.04 (9H, s, *tert*-butyl); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.32, 135.58, 133.74, 133.71, 129.61, 127.63, 62.91, 60.15, 34.50, 31.28, 27.19, 26.77, 21.23, 20.73, 19.16, 14.36; IR (neat) cm^{-1} : 1724 (ester C=O).

trans-[3-(*tert*-Butyldiphenylsilanyloxymethyl)-2,2-dimethylcyclopropyl]methanol (3)

To a solution of compound **2** (4.22 g, 10.28 mmol) in dry CH_2Cl_2 (120 mL), DIBAL-H (1.0 M in toluene, 41.1 mL, 41.12 mmol) was added dropwise at -78°C under argon. After stirring the mixture for 1 h under the same conditions, the resulting solution was stirred at room temperature, quenched by the addition of methanol and filtered, concentrated under reduced pressure, and the residue was chromatographed on a silica gel column (hexane/EtOAc, 3/1) to give **3** (3.25 g, 85.9% yield) as a colorless oil.: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.7-7.3 (10H, m, aromatic), 3.67 (2H, d, *J* = 7.0 Hz, CH_2OH), 3.60 (1H, dd, *J* = 11.4, 7.1Hz, $CH_2OTBDPS$), 3.54 (1H, dd, *J* = 11.4, 7.8 Hz, $CH_2OTBDPS$), 1.11 and 1.04 (6H, 2s, ring CH_3), 1.05 (9H, s, *tert*-butyl), 0.80-0.65 (2H, m, ring protons); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 135.60, 135.58, 133.97, 133.74, 129.58, 127.61, 64.06, 63.31, 31.69, 31.48, 26.84, 21.77, 21.63, 20.60, 19.16; IR (neat) cm^{-1} : 3352 (OH).

trans-9-[3-(*tert*-Butyldiphenylsilanyloxymethyl)-2,2-dimethylcyclopropylmethyl]-6-chloropurine (4)

To a stirred mixture of a 6-chloropurine (1.68 g, 10.85 mmol) and triphenylphosphine (2.85 g, 10.85 mmol) in dry THF (100 mL) under argon, diethyl azodicarboxylate (DEAD, 1.7 mL, 10.85 mmol) was added. The resulting mixture was stirred at room temperature for 10 min, and a solution of **3** (2 g, 5.43 mmol) in dry THF (20 mL) was added. The resulting mixture was stirred at room temperature until **3** was consumed (about 3-24 h). After removal of the solvent *in vacuo*, the residue was dissolved in ethyl acetate (250 mL), washed with water, dried ($MgSO_4$), and concentrated. Chromatography on a silica gel column (hexane/EtOAc, 1/1) gave TBDPS protected nucleoside **4** (1.5 g, 54.7% yield) as a white solid: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.73 (1H, s, C2-H), 8.19 (1H, s, C8-H), 7.63-7.35 (10H, m, aromatic), 4.30 (1H, dd, *J* = 7.2, 14.6 Hz, CH_2N), 4.27 (1H, dd, *J* = 7.3, 14.5 Hz, CH_2N), 3.68 (1H, dd, *J* = 6.8, 11.1 Hz, CH_2O), 3.62 (1H, dd, *J* = 6.5, 11.1 Hz,

CH_2O), 1.19 and 1.06 (6H, 2s, ring CH_3), 1.00 (9H, s, *tert*-butyl), 1.01-0.92 (2H, m, ring protons); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 151.78, 150.90, 144.74, 135.52, 133.61, 133.51, 131.61, 129.70, 127.67, 63.42, 44.78, 32.23, 27.79, 26.73, 21.83, 21.22, 20.95, 19.04

trans-9-[3-(*tert*-Butyldiphenylsilanyloxymethyl)-2,2-dimethylcyclopropylmethyl]-2-amino-6-chloropurine (5)

To a stirred mixture of a 2-amino-6-chloropurine (0.92 g, 5.43 mmol) and triphenylphosphine (1.43 g, 5.43 mmol) in dry THF (50 mL) under argon, diethyl azodicarboxylate (DEAD, 0.85 mL, 5.43 mmol) was added. The resulting mixture was stirred at room temperature for 10 min, and a solution of **3** (1.0 g, 2.71 mmol) in dry THF (10 mL) was added. The resulting mixture was stirred at room temperature until **3** was consumed (about 24 h). After removal of the solvent *in vacuo*, the residue was dissolved in ethyl acetate (120 mL), washed with water, dried ($MgSO_4$), and concentrated. Chromatography on a silica gel column (hexane/EtOAc, 1/1) gave TBDPS protected nucleoside **5** (0.6 g, 42.9%) as a white solid: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80 (1H, s, C8-H), 7.65-7.36 (10H, m, aromatic), 5.08 (2H, bs, NH_2), 4.02 (2H, d, J = 7.3 Hz, CH_2N), 3.68 (1H, dd, J = 6.6, 10.8Hz, CH_2O), 3.63 (1H, dd, J = 7.1, 11.7 Hz, CH_2O), 1.17 and 1.05 (6H, 2s, ring CH_3), 1.02(10H, s, *tert*-butyl), 0.96-0.87 (2H, m, ring protons)

trans-9-(2,2-Dimethyl-3-hydroxymethylcyclopropylmethyl)-6-chloropurine (6)

A mixture of **4** (150 mg, 0.30 mmol) and 1.0 M *n*-Bu_4NF (0.59 mL, 0.59 mmol) in dry THF (5 mL) was stirred at room temperature for 2 h. After the mixture was concentrated under reduced pressure, the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH, 5/1) to give **6** (76.2 mg, 96.2% yield) as a white solid: mp 81-83°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.76(1H, s, C2-H), 8.73 (1H, s, C8-H), 4.40 (1H, dd, J = 7.2, 14.4 Hz, CH_2N), 4.20 (1H, dd, J = 8.1, 14.4 Hz, CH_2N), 3.35-3.29 (2H, m, CH_2O), 1.11 and 1.03 (6H, 2s, ring CH_3), 1.08-0.87 (2H, m, ring protons); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 151.89, 151.40, 148.87, 147.13, 130.82, 60.41, 44.25, 31.87, 27.36, 21.61, 20.95, 20.39; IR (KBr) cm^{-1} : 3367 (OH); UV (MeOH) λ_{max} 263 nm (7840).

trans-9-(2,2-Dimethyl-3-hydroxymethylcyclopropylmethyl)-2-amino-6-chloropurine (7)

A mixture of **5** (1.2 g, 2.31 mmol) and 1.0 M *n*-Bu_4NF (4.6 mL, 4.614 mmol) in dry THF (50 mL) was stirred at room temperature for 2 h. After the mixture was concentrated under reduced pressure, the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH, 5/1) to give **7** (0.55 g, 84.6% yield) as a white solid: mp 175-177 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.15 (1H, s, C8-H), 6.92 (2H, bs, NH_2), 4.09 (1H, dd, J = 7.2, 14.3 Hz, CH_2N), 4.01 (1H, dd, J = 7.7, 14.3 Hz, CH_2N), 3.40-3.25 (2H, m, CH_2O), 1.12 and 1.02 (6H, 2s, ring CH_3), 0.97-0.77 (2H, m, ring protons); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 159.71, 154.01, 149.17, 142.75, 123.30, 60.45, 43.34, 31.69, 27.20, 20.96, 20.09; IR (KBr) cm^{-1} : 3386-3217 (OH, NH_2); UV (MeOH) λ_{max} 250 nm (13700).

trans-9-(2,2-Dimethyl-3-hydroxymethylcyclopropylmethyl)adenine (8)

A mixture of **6** (120 mg, 0.45 mmol) and NH_3/MeOH (40 mL) was heated at 90°C in a steel bomb for 24 h. After the solvent was removed under reduced pressure, the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH, 7/1) to give **8** (110 mg, 98.9% yield) as a white solid: mp 189-191°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.14 (1H, s, C2-H), 8.12 (1H, s, C8-H), 7.17 (2H, bs, NH_2), 4.18 (1H, dd, J = 7.4, 14.3 Hz, CH_2N), 4.07 (1H, dd, J = 7.5, 14.3 Hz, CH_2N), 3.39 (1H, dd, J = 5.6, 11.4 Hz, CH_2O), 3.30 (1H, dd, J = 9.0, 13.7Hz, CH_2O), 1.13 and 1.02 (6H, 2s, ring CH_3), 1.01-0.81 (2H, m, ring protons); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 156.22, 152.59, 140.66, 60.89, 43.51, 32.06, 27.93, 21.95, 21.32, 20.41; IR (KBr) cm^{-1} : 3275-3151 (OH, NH_2); UV (MeOH) λ_{max} 261 nm (14465).

trans-9-(2,2-Dimethyl-3-hydroxymethylcyclopropylmethyl)-hypoxanthine (9)

A mixture of **6** (100 mg, 0.37 mmol), 2-mercaptoethanol (0.1 mL, 1.50 mmol), and 1M $NaOCH_3$ in methanol (1.5 mL, 1.50 mmol) in methanol (20 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 a silica gel column ($CHCl_3$/MeOH, 6/1) to afford **9** (80 mg, 85.9%) as a white solid: mp 239-242°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.26(1H, bs, C6-OH), 8.09(1H, s, C2-H), 8.02 (1H, s, C8-H), 4.18 (1H, dd, J = 7.4, 14.3Hz, CH_2N), 4.06 (1H, dd, J = 7.6, 14.3 Hz, CH_2N), 3.40-3.24 (2H, m, CH_2O), 1.12 and 1.03 (6H, 2s, ring CH_3), 0.98-1.80 (2H, m, ring protons); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 156.68, 148.24, 145.29, 139.78, 123.84, 60.48, 43.61, 31.69, 27.62, 21.57, 20.94, 20.18; IR (KBr) cm^{-1} : 3425 (OH), 1712 (lactam C=O); UV (MeOH) λ_{max} 250 nm (12310).

trans-9-(2,2-Dimethyl-3-hydroxymethylcyclopropylmethyl)-2,6-diaminopurine (10)

A mixture of **7** (60 mg, 0.21 mmol) and NH_3/MeOH (40 mL) was heated at 90°C in a steel bomb for 24 h. After the solvent was removed under reduced pressure, the residue chromatographed on a silica gel column ($CHCl_3$/MeOH, 7/1) to give **10** (38 mg, 68% yield) as a white

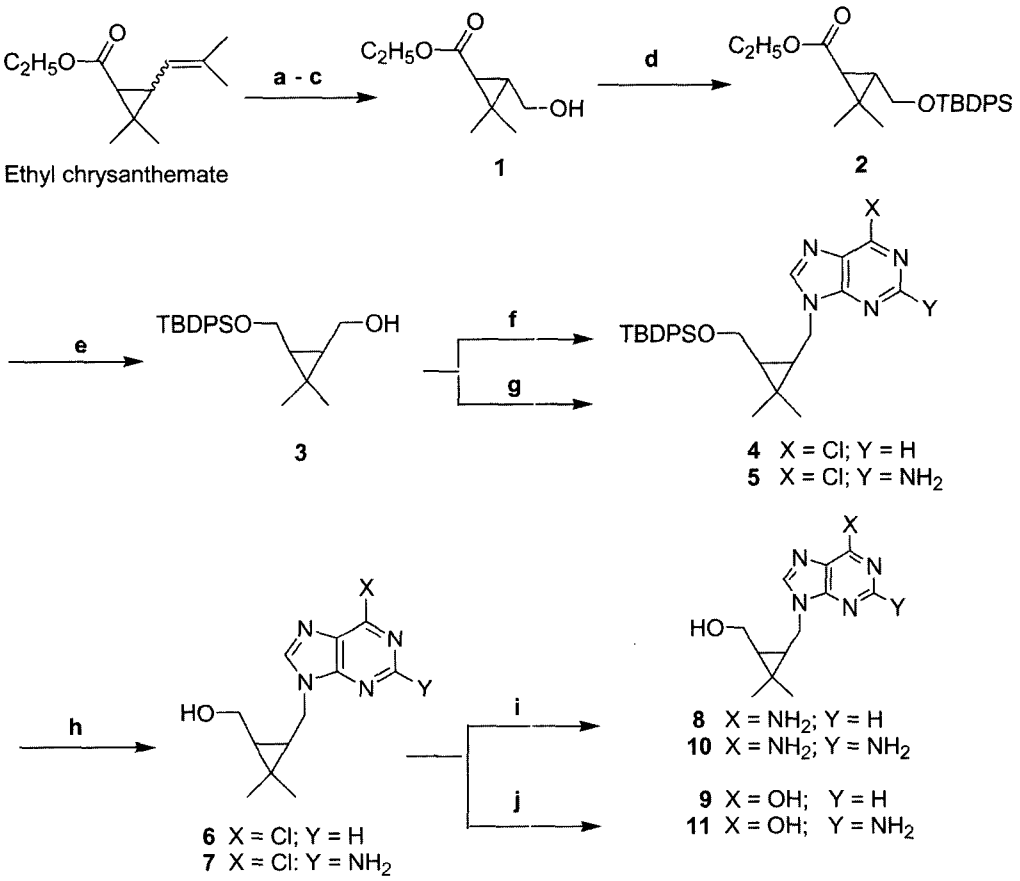
solid: decomp. 120°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.70 (1H, s, C8-H), 6.61 and 5.74 (4H, 2bs, 2 x NH_2), 3.98-3.61 (2H, m, CH_2N), 3.48-2.23 (2H, m, CH_2O), 1.12 and 1.03 (6H, 2s, ring CH_3), 0.96-0.75 (2H, m, ring protons); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 160.54, 156.37, 60.96, 42.97, 31.93, 27.88, 21.95, 21.38, 20.21; IR (KBr) cm^{-1} : 3479-3190 (OH, NH_2); UV (MeOH) λ_{max} 256 nm (10110), 282 nm (12630).

trans-9-(2,2-Dimethyl-3-hydroxymethylcyclopropyl-methyl)guanine (11)

A mixture of **7** (0.1 g, 0.39 mmol), 2-mercaptoethanol (0.11 mL, 1.56 mmol), and 1M $NaOCH_3$ in methanol (1.56 mL, 1.56 mmol) in methanol (20 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 a silica gel column ($CHCl_3$/MeOH, 6/1) to afford **11** (82 mg, 79.8% yield) as a white solid: mp 250°C (decomp.); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.65 (1H, bs, C6-OH), 7.67 (1H, s, C8-H), 6.47 (2H, bs, NH_2), 4.00-3.80 (2H, m, CH_2N), 3.45-3.25 (2H, m, CH_2O), 1.11 and 1.03 (6H, 2s, ring CH_3), 0.88-0.78 (2H, m, ring protons); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 156.84, 153.48, 151.05, 136.86, 116.45, 60.55, 42.95, 31.57, 27.51, 21.58, 21.00, 19.95; IR (KBr) cm^{-1}: 3429-3194 (OH, NH_2), 1689 (lactam C=O); UV (MeOH) λ_{max} 254 nm (11310).

RESULTS AND DISCUSSION

Scheme 1 shows the synthetic route of the 2,2-dimethyl-cyclopropyl nucleosides. The hydroxymethyl ethyl ester **1** was obtained by reduction of ethyl *trans*-2,2-dimethyl formylcyclopropropane-carboxylate, which was prepared in two steps from commercially available ethyl chrysanthemate (de Montellano *et al.*, 1978). As a protecting



a) Ozone, argon, DMS, EtOH, -78°C, 30% Acetic acid; b) Sodium ethoxide, EtOH 25°C; c)$NaBH_4$, EtOH,0°C; d) TBDPSCl, imidazole, dry CH_2Cl_2, 0°C; e) DIBAL, dry CH_2Cl_2, 0°C; f) 6-Chloropurine, Ph_3P, DEAD, THF, rt; g) 2-Amino-6-chloro-purine, Ph_3P, DEAD, THF, rt; h) *n*-Bu_4NF, THF, rt; i) NH_3/MeOH, 90°C; j) $NaOCH_3$, 2-mercaptoethanol, MeOH, reflux

Scheme 1. Synthesis of trans-2,2-dimethylcyclopropyl nucleosides

group for the alcohol group, TBDPS·Cl was used instead of benzyl bromide because the latter is difficult to remove at the final stage. The key intermediate, **3**, which was synthesized from compound **2,** was coupled with purine bases by Mitsunobu reactions to give the protected purine nucleosides, **4** and **5**. Condensations were performed in THF in the presence of triphenyl phosphine (TPP) and diethyl azodicarboxylate (DEAD) at room temperature. The protected nucleosides **4** and **5** were deprotected by *n*-Bu_4NF in THF to give the dimethylcyclopropyl nucleosides **6** and **7,** respectively, which were further treated with ammonia in methanol at 90°C to give 6-adenine nucleoside **8** and 2,6-diaminopurine nucleoside **10**, respectively. The nucleosides **6** and **7** were also hydrolyzed with mercaptoethanol and sodium methoxide under reflux in methanol to give hypoxanthine derivative **9** and guanine derivative **11,** respectively. For the synthesized purine nucleosides (**6**, **7**, **8**, **9**, **10** and **11**), antiviral evaluation against HSV-1, HSV-2, EMCV, Cox B3 and VSV was performed, but none of them showed any significant antiviral activity at concentrations up to 100 μM.

ACKNOWLEDGMENT

This study was funded by Chonnam National University in the Program, 2000. We also thank Dr. C.-K Lee (KRICT) for his antiviral evaluations.

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