Synthesis and Antiviral Activity of Novel Anomeric Branched Carbocyclic Nucleosides

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Novel anomeric branched carbocyclic nucleosides were synthesized from 1,3-dihydroxy acetone. 4'-Hydroxymethyl was installed by [3,3]-sigmatropic rearrangement reaction and 1'-methyl group was introduced by carbonyl addition of methylmagnesium bromide. The coupling of nucleosidic bases and desilylation afforded a series of novel nucleosides. The synthesized compounds 16~19 were evaluated for their antiviral activity against HIV-1, HSV-1, HSV-2, and EMCV. Compounds 16 and 19 exhibit toxicity non-related to any anti-HIV-1 activity.

Key words: Antiviral agents, Anomeric branched carbocyclic nucleoside, [3,3]-Sigmatropic rearrangement

INTRODUCTION

Nucleoside analogues have been the cornerstone of antiviral chemotherapy over the past decades. Although structure-activity relationship studies have not led to a pharmacophore model for the antiviral activities of nucleosides, some structural features have been particularly successful. Since the discovery of 3'-azido-3'-deoxy-thymidine (AZT) as an antiviral agent for the treatment of acquired immunodeficiency syndrome (AIDS), much attention has been focused on nucleosides as reverse transcriptase inhibitors in the search more active and less toxic compounds. However, side effects (Parker et al., 1994) and the emergence of drug-resistant mutants continue to be a problem with these antiviral agents (Chatis et al., 1992). It is now clear that judicious combination chemotherapy is the optimum way to improve the quality of life and survival of patients infected with HIV-1.

Recently, several branched nucleosides were synthesized and evaluated as potent antitumor or antiviral agents. Among them, 4'(α)-C-hydroxymethyl thymidine (1) (Youssefyeh et al., 1979), and 4'(α)-C-fluoromethyl-2'-deoxycytidine (2) (Kitano et al., 1997), which have additional branch at the 4α-position, were reported to exhibit potent antiviral activity (Fig. 1).

The replacement of the oxygen on the furanose ring by carbon is of particular interest because the resulting carbocyclic nucleosides (Agrofoglio et al., 1994; Borthwick et al., 1992) possess a greater metabolic stability to phosphorylase (Herdewijn et al., 1985), which cleaves the glycosidic bond of nucleosides. Since the cyclopentane ring of the carbocyclic nucleosides can emulate the furanose moiety, a number of these compounds exhibit interesting biological activities, particularly in the areas of antiviral and anticancer chemotherapy. The discovery of olefinic carbocyclic nucleosides, such as abacavir (3)
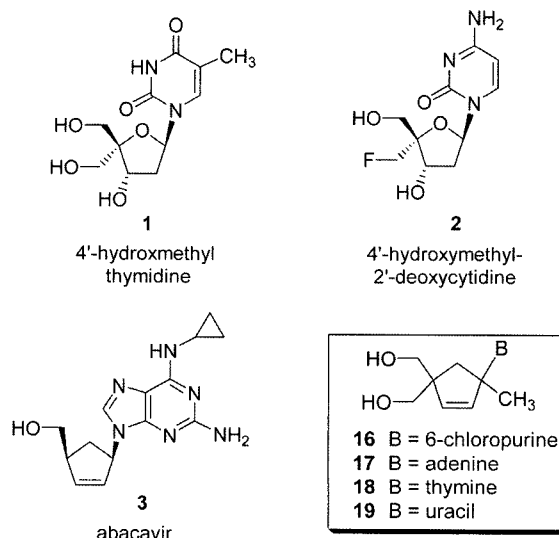

Fig. 1. Chemical Structures of the target nucleosides

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(Daluge *et al.*, 1997) being potential antiviral agents has given a strong impetus to the search for novel nucleosides in this class of compounds. In view of the stimulating results of 4'-branched nucleosides and as part of our ongoing drug discovery efforts to search for less toxic and more effective antiviral agents, this study aimed to synthesize anomeric branched carbocyclic nucleosides.

MATERIALS AND METHODS

All the chemicals were of reagent grade and were used as purchased. All the moisture-sensitive reactions were performed in an inert atmosphere with either N_2 or Ar using distilled dry solvents. The melting points were determined using a Mel-temp II laboratory device and were uncorrected. The NMR spectra were recorded on a JEOL 300 Fourier transform spectrometer; the chemical shifts are reported in parts per million (δ) and the signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublets). The UV spectra were obtained using a Beckman DU-7 spectrophotometer. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

(±)-4,4-Bis-(*tert*-butyldimethylsilanyloxymethyl)-hex-5-en-2-ol (6)

To a solution of compound 5 (2.0 g, 5.3 mmol) in dry THF (100 mL), methyl magnesium bromide (6.44 mL, 1.0 M solution in THF) was added slowly at -78 °C. After 5 h, a saturated NH_4Cl solution (5 mL) was added, and the reaction mixture was warmed slowly to room temperature. The mixture was extracted with EtOAc (250 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give 6 (1.73 g, 84%) as a colorless oil; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 5.71 (dd, J = 18.0, 11.1 Hz, 1H), 5.07 (d, J = 11.4 Hz, 1H), 4.96 (d, J = 17.7 Hz, 1H), 3.90 (m, 1H), 3.60 (dd, J = 12.6, 9.9 Hz, 2H), 3.40 (s, 2H), 1.56-1.45 (m, 2H), 1.10 (d, J = 6.3 Hz, 3H), 0.82 (s, 18H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 141.62, 114.44, 66.98, 65.51, 63.59, 64.07, 43.72, 25.85, 24.46, 18.25, -5.58.

4,4-Bis-(*tert*-butyldimethylsilanyloxymethyl)-hex-5-en-2-one (7)

To a solution of compound 6 (2.48 g, 6.4 mmol) in CH_2Cl_2 (100 mL), 4 Å molecular sieves (3.75 g) and PCC (3.45 g, 16.05 mmol) were added slowly at 0°C, and stirred at room temperature for 5 h. To the mixture, excess diethyl ether (400 mL) was then added. The mixture was stirred vigorously at the same temperature for 5 h, and the

resulting solid was filtered through a short silica gel column. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:40) to give compound 7 (1.98 g, 80%) as a colorless oil; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 5.82 (dd, J = 18.0, 11.4 Hz, 1H), 5.09 (d, J = 8.7 Hz, 1H), 5.01 (d, J = 18.0 Hz, 1H), 3.56 (dd, J = 12.4, 9.6 Hz, 4H), 2.52 (s, 2H), 2.09 (s, 3H), 0.84 (s, 18H), 0.03 (s, 12H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 207.97, 140.38, 114.17, 64.79, 45.15, 32.02, 25.64, 18.22, -5.65.

(±)-5,5-Bis-(*tert*-butyldimethylsilanyloxymethyl)-3-methyl-hepta-1,6-dien-3-ol (8)

To a solution of compound 7 (4.5 g, 11.63 mmol) in dry THF (200 mL), vinyl magnesium bromide (13.96 mL, 1.0 M solution in THF) was added slowly at -78°C. After 4 h, a saturated NH_4Cl solution (10 mL) was added, and the reaction mixture was warmed slowly to room temperature. The mixture was extracted with EtOAc (350 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:35) to give 8 (3.76 g, 78%) as a colorless oil; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 5.95 (dd, J = 17.4, 10.8 Hz, 1H), 5.72 (dd, J = 18.0, 10.5 Hz, 1H), 5.25 (d, J = 17.1 Hz, 1H), 5.04 (d, J = 11.4 Hz, 1H), 4.89 (t, J = 9.6 Hz, 2H), 3.50-3.40 (m, 4H), 1.78 (d, J = 14.7 Hz, 1H), 1.69 (d, J = 14.7 Hz, 1H), 1.18 (s, 3H), 0.84 (s, 18H), 0.04 (s, 12H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 146.82, 142.69, 113.91, 110.16, 74.79, 66.36, 65.99, 65.74, 46.58, 45.89, 31.35, 25.72, 21.96, 20.71, 18.35, -5.50.

(±)-4,4-Bis-(*tert*-butyldimethylsilanyloxymethyl)-1-methyl-cyclopent-2-enol (9)

To a solution of compound 8 (2.05 g, 4.94 mmol) in dry CH_2Cl_2 (30 mL), second generation Grubbs' catalyst (25 mg, 0.03 mmol) was added. The reaction mixture was refluxed overnight, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give the cyclopentenol 9 (1.72 g, 90%); ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 5.73 (d, J = 5.7 Hz, 1H), 5.49 (d, J = 5.4 Hz, 1H), 3.60 (d, J = 9.3 Hz, 1H), 3.51 (d, J = 9.3 Hz, 1H), 3.39 (d, J = 9.3 Hz, 1H), 3.34 (d, J = 9.3 Hz, 1H), 1.75 (d, J = 13.8 Hz, 1H), 1.61 (d, J = 14.1 Hz, 1H), 0.86 (s, 18H), 0.03 (s, 12H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 139.82, 134.37, 80.97, 68.17, 67.11, 56.93, 46.77, 25.77, 18.57, 18.14, -5.57.

(±)-9-[4,4-Bis-(*tert*-butyldimethylsilanyloxymethyl)-1-methylcyclopent-2-enyl]-6-chloropurine (10)

To a solution of compound 9 (696 mg, 1.8 mmol), triphenylphosphine (1.41 g, 5.4 mmol) and 6-chloropurine (694 g, 4.48 mmol) in anhydrous dioxane (10 mL) and DMF (5 mL) was added diisopropyl azodicarboxylate

(0.97 mL) dropwise at -20°C for 30 min under nitrogen. The reaction mixture was stirred at -20°C for 1 h under nitrogen. The solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:4) to give the compound 10 (254 mg, 27%) as a yellow oil; UV (MeOH) λ_{max} 266.0 nm; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 8.86 (s, 1H), 8.22 (s, 1H), 5.83 (s, 1H), 5.45 (s, 1H), 3.85 (d, J = 11.4 Hz, 1H), 3.69 (d, J = 11.2 Hz, 1H), 3.43 (d, J = 9.3 Hz, 1H), 3.18 (d, J = 9.4 Hz, 1H), 2.44 (d, J = 18.0 Hz, 1H), 2.23 (d, J = 18.0 Hz, 1H), 1.92 (s, 3H), 0.87 (s, 18H), 0.04 (s, 12H); ^{13}C-NMR (CDCl$_3$ 75 MHz) δ 152.23, 151.72, 150.93, 144.21, 141.48, 133.35, 72.15, 65.93, 65.70, 58.90, 45.07, 27.62, 25.65, 18.57, -5.61.

(±)-9-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-1-methylcyclopent-2-enyl]-adenine (11)

Compound 10 (68 mg, 0.13 mmol) was dissolved in saturated methanolic ammonia (10 mL) and the resulting solution was stirred at 90°C for 15 h in a steel bomb. After removal of reaction solvent, the residue was purified by silica gel column chromatography (CH$_2$Cl$_2$/MeOH, 10:1) to give the compound 11 (51 mg, 78%) as a white solid; UV (MeOH) λ_{max} 267.0 nm; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 8.60 (s, 1H), 7.96 (s, 1H), 5.50 (s, 1H), 5.40 (s, 1H), 3.34 (d, J = 10.5 Hz, 1H), 3.19 (d, J = 10.2 Hz, 1H), 2.39 (d, J = 17.7 Hz, 1H), 2.23 (d, J = 17.7 Hz, 1H), 1.88 (s, 3H), 0.89 (s, 18H), 0.05 (s, 12H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 156.34, 152.41, 147.01, 145.05, 122.33, 66.93, 62.91, 53.74, 52.86, 41.87, 27.43, 25.42, 18.60, -5.51.

(±)-1-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-1-methylcyclopent-2-enyl]-N^3-benzoylthymine (12)

Compound 12 was synthesized from 9 and N^3-benzoyl thymine using the method described for compound 10 as a white solid: yield 31%; UV (MeOH) λ_{max} 254.5 nm; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 7.90-7.43 (m, 6H), 5.99 (d, J = 5.4 Hz, 1H), 5.84 (d, J = 5.4Hz, 1H), 3.55-3.36 (m, 4H), 2.21 (d, J = 17.2 Hz, 1H), 2.13 (d, J = 17.4 Hz, 1H), 1.92 (s, 3H), 1.27 (s, 3H), 0.87 (s, 18H), 0.06 (s, 12H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 169.51, 163.09, 150.73, 137.84, 134.74, 133.17, 130.33, 129.08, 108.76, 74.78, 62.43, 61.78, 57.86, 27.83, 25.84, 12.69, -5.54.

(±)-1-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-1-methylcyclopent-2-enyl]-N^3-benzoyluracil (13)

Compound 13 was synthesized from 9 and N^3-benzoyl uracil using the method described for compound 10: yield 21%; UV (MeOH) λ_{max} 253.0 nm; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 7.85-7.40 (m, 6H), 5.97 (d, J = 5.4 Hz, 1H), 5.82 (d, J = 5.4 Hz, 1H), 5.72 (d, J = 8.0 Hz, 2H), 3.62-3.41 (m, 4H), 2.22 (d, J = 17.6 Hz, 1H), 2.11 (d, J = 17.4 Hz, 1H), 1.90 (s, 3H), 0.86 (s, 18H), 0.04 (s, 12H); ^{13}C-NMR

(CDCl$_3$, 75 MHz) δ 168.17, 162.09, 150.12, 134.23, 133.17, 131.78, 128.61, 107.62, 74.78, 64.26, 62.91, 55.21, 26.99, 25.45, 18.72, -5.40.

(±)-1-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-1-methylcyclopent-2-enyl]-thymine (14)

To a stirred solution of compound 12 (240 mg, 0.4 mmol) in MeOH (5 mL) was added NaOMe (0.5 mL, 1 M solution in MeOH) at 0°C under nitrogen. The reaction mixture was neutralized with acetic acid and concentrated. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 3:1) to give the compound 14 (118 mg, 60%): UV (MeOH) λ_{max} 270.0 nm; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 8.14 (br s, 1H), 7.25 (s, 1H), 5.96 (d, J = 6.0 Hz, 1H), 5.78 (d, J = 6.0 Hz, 1H), 3.54 (d, J = 9.3 Hz, 1H), 3.45 (d, J = 10.5 Hz, 2H), 3.35 (d, J = 9.6 Hz, 1H), 2.28 (d, J = 14.4 Hz, 1H), 2.09 (d, J = 14.4 Hz, 1H), 1.90 (s, 3H), 1.55 (s, 3H), 0.91 (s, 18H), 0.03 (s, 12H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 166.87, 153.65, 140.54, 138.21, 133.48, 108.55, 74.06, 66.21, 65.93, 57.73, 27.22, 25.84, 18.28, 12.57, -5.60.

(±)-1-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-1-methylcyclopent-2-enyl]-uracil (15)

Compound 15 was prepared from 13 by the method as described for 14: UV (MeOH) λ_{max} 267.0 nm; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 8.21 (br s, 1H), 7.49 (d, J = 6.6 Hz, 1H), 5.98 (d, J = 5.8 Hz, 1H), 5.86 (d, J = 6.6 Hz, 1H), 5.78 (d, J = 5.8 Hz, 1H), 3.57-3.36 (m, 4H), 2.27 (d, J = 15.4 Hz, 1H), 2.010 (d, J = 15.2 Hz, 1H), 1.94 (s, 3H), 0.88 (s, 18H), 0.04 (s, 12H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ 166.87, 157.29, 143.72, 137.22, 131.67, 108.89, 75.16, 65.78, 65.81, 57.23, 27.02, 25.45, 18.81, -5.63.

(±)-9-[4,4-Bis-(hydroxymethyl)-1-methylcyclopent-2-enyl]-6-chloropurine (16)

To a solution of compound 10 (105 mg, 0.2 mmol) in THF (5 mL), TBAF (0.5 mL, 1.0 M solution in THF) at 0°C was added. The mixture was stirred at room temperature for 5 h, and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH$_2$Cl$_2$, 1:5) to give compound 16 (36.3 mg, 66%) as a white solid: m.p. 170-172°C; UV (H$_2$O) λ_{max} 266.5 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.72 (s, 1H), 8.12 (s, 1H), 5.81 (d, J = 3.4 Hz, 1H), 5.42 (d, J = 3.4 Hz, 1H), 5.01-4.90 (br s, 2H), 3.55-3.28 (m, 4H), 2.47 (d, J = 16.5 Hz, 1H), 2.15 (d, J = 16.0 Hz, 1H), 1.90 (s, 3H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ 152.17, 151.68, 151.26, 144.30, 143.63, 140.98, 133.45, 73.25, 66.68, 64.31, 55.21, 46.37, 27.25.

(±)-9-[4,4-Bis-(hydroxymethyl)-1-methylcyclopent-2-enyl]-adenine (17)

Compound 17 was synthesized from 11 using the method described for compound 16: yield 78%; UV (H$_2$O)

λ_{max} 253.0 nm: m.p. 174-176°C; UV (H_2O) λ_{max} 262.5 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.47 (s, 1H), 8.19 (s, 1H), 5.52 (s, 1H), 5.42 (s, 1H), 4.80 (t, J = 5.1 Hz, 1H), 4.17 (t, J = 5.1 Hz, 1H), 3.50-3.29 (m, 4H), 2.34 (d, J = 17.1 Hz, 1H), 2.19 (d, J = 17.1 Hz, 1H), 1.66 (s, 3H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ 156.87, 150.84, 147.31, 146.01, 133.87, 121.54, 113.54, 66.74, 64.22, 55.21, 53.67, 41.37, 25.25.

(±)-1-[4,4-Bis-(hydroxymethyl)-1-methylcyclopent-2-enyl]-thymine (18)

Compound 18 was synthesized from 14 using the method described for compound 16: yield 60%; m.p. 164-166°C; UV (H_2O) λ_{max} 269.0 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 11.08 (br s, 1H), 7.42 (s, 1H), 6.02 (d, J = 5.6 Hz, 1H), 5.86 (d, J = 5.6 Hz, 1H), 4.68-4.50 (br s, 2H), 3.45-3.33 (m, 4H), 2.27 (d, J = 16.4 Hz, 1H), 1.98 (d, J = 16.4 Hz, 1H), 1.80 (s, 3H), 1.45 (s, 3H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ 164.87, 150.65, 139.38, 138.78, 133.84, 106.87, 73.14, 64.66, 57.50, 57.24, 26.94, 12.19.

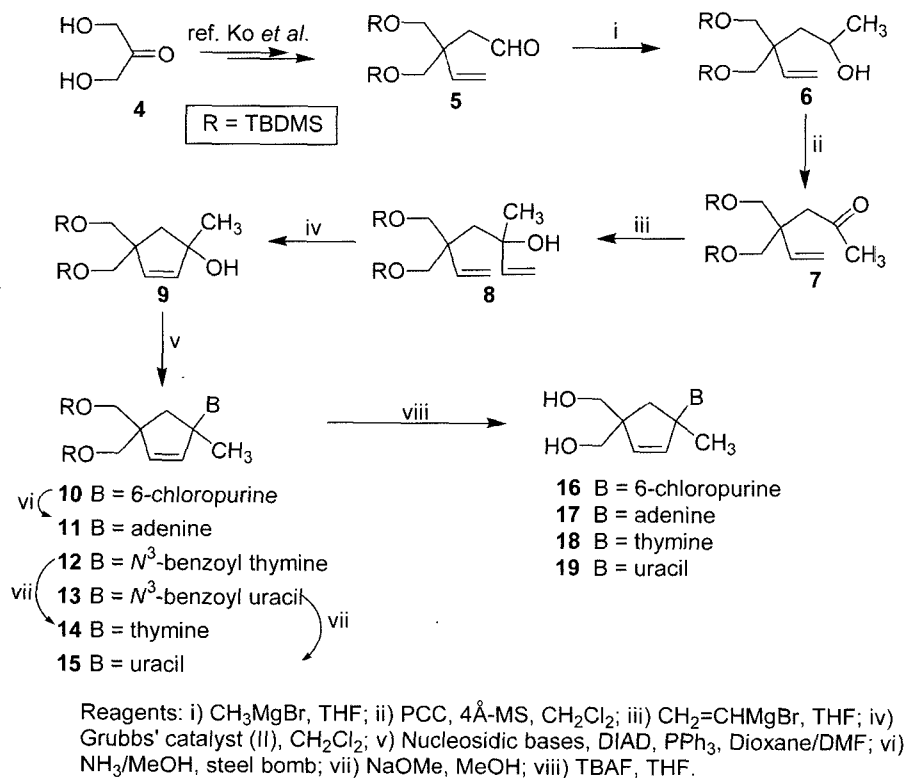### (±)-1-[4,4-Bis-(hydroxymethyl)-1-methylcyclopent-2-enyl]-uracil (19)

Compound 19 was synthesized from 15 using the method described for compound 16: yield 62%; m.p. 167-169°C; UV (H_2O) λ_{max} 267.0 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 11.12 (br s, 1H), 7.70 (d, J = 6.4 Hz, 1H), 6.01 (d,

J = 6.4 Hz, 1H), 5.91 (d, J = 5.0 Hz, 1H), 5.85 (d, J = 5.0 Hz, 1H), 4.60-4.43 (br d, 2H), 3.42-3.30 (m, 4H), 2.31 (d, J = 16.8 Hz, 1H), 2.07 (d, J = 16.8 Hz, 1H), 1.89 (s, 3H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ 165.99, 152.81, 144.45, 139.24, 134.12, 106.18, 72.23, 63.60, 58.77, 55.82, 27.02.

RESULTS AND DISCUSSION

As shown in Scheme 1, aldehyde 5, which is readily synthesized from 1,3-dihydroxy acetone using [3,3]-sigmatropic rearrangement as previously reported method, (Ko et al., 2002) was subjected to carbonyl addition of CH_3MgBr to give 6. Alcohol derivative 6 was oxidized using PCC to give ketone derivative 7, which again underwent Grignard addition by vinyl magnesium bromide to privide a divinyl 8. The bis-olefin 8 was cyclized by standard ring-closing metathesis conditions using a second-generation Grubbs' catalyst [(Im)Cl$_2$PCy$_3$RuCHPh] (Schwab et al., 1996; Dais et al., 1997) to provide the required cyclopentenol 9 (Scheme 1).

First, attempt was made to couple the cyclopentenol 9 with the bases using convenient nucleophilic substitution type (S$_N$2) reaction. The allylic alcohol 9 was subjected to a mesylation condition (MsCl, TEA, CH_2Cl_2) (Jeon et al., 1996) Unexpectedly, the reaction was very complicated and was irreproducible. Therefore, our attention was turned to a Mitsunobu reaction to synthesize desired

Reagents: i) CH$_3$MgBr, THF; ii) PCC, 4Å-MS, CH$_2$Cl$_2$; iii) CH$_2$=CHMgBr, THF; iv) Grubbs' catalyst (II), CH$_2$Cl$_2$; v) Nucleosidic bases, DIAD, PPh$_3$, Dioxane/DMF; vi) NH$_3$/MeOH, steel bomb; vii) NaOMe, MeOH; viii) TBAF, THF.

Scheme 1. Synthesis of anomeric branched nucleosides

nucleosides. The success of Mitsunobu reactions in the synthesis of nucleoside analogues is known to depend on the condition employed (Wachmeister *et al.*, 1995; Jenny *et al.*, 1992; Roy *et al.*, 2003). Appropriate choice of solvent system, temperature and procedure are critical for the regioselectivity as well as the yield. In purine synthesis, a 2:1 mixture of dioxane and DMF was used as solvent instead of only THF solvent for the coupling of the cyclopentenol 9 with 6-chloropurine, because the use of a dioxane-DMF mixture allowed better solubility of the heterocyclic bases and better yields. Slow addition of diisopropylazodicarboxylate (DIAD) to a mixture of cyclopentenol 9, triphenylphosphine and the 6-chloropurine in anhydrous solvent gave a yellow solution which was stirred at -20°C for 1 h to give protected purine analogue 10. The 6-chloropurine derivative 10 was converted to a protected adenosine analogue 11 by treatment with a saturated solution of ammonia in methanol in a steel bomb at 90°C for 15 h. On the other hand, the synthesis of pyrimidine nucleosides was more complex than the purine case due to the formation of O^2-alkylated by-products. The formation of O^2-alkylated compounds was inevitable in the conditions tested, but the ratio of N^1- to O^2-alkylation improved by changing the solvent to 2:1 mixture of dioxane-DMF. The regioisomer of O^2-alkylated compounds was easily confirmed by the comparison of the UV literature data (Daiz *et al.*, 1999). Condensation of 9 with N^3-benzoyl thymine and uracil under the similar Mitsunobu conditions gave the protected nucleosides 12 and 13, which were debenzoylated with sodium methoxide to afford the corresponding nucleosides 14 and 15, respectively. The final nucleosides 16~19 was obtained from the corresponding protected nucleosides by the treatment of tetrabutylammonium fluoride (TBAF). Based on extensive literature searching, the compounds 16~19 appear to be novel nucleosides.

Antiviral activity assays were performed for all the final

nucleosides and their results are shown in Table I. Unfortunately, none of them showed any antiviral activity against HIV-1, HSV-1, HSV-2, and EMCV. Compounds 16 and 19 exhibited potent anti-HIV-1 activities, but these inhibitory effects were associated with the nonspecific cytotoxicity to MT-4 cells.

In conclusion, a simple synthetic method for synthesizing 1',4'-dually branched nucleosides from an α-hydroxy ketone derivative was developed. Compounds 16 and 19 exhibited toxicity non-related to any anti-HIV-1 activity.

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Table I. The antiviral activities of the synthesized compounds

	HIV-1 EC_{50} (μM)	HSV-1 EC_{50} (μM)	HSV-2 EC_{50} (μM)	EMCV EC_{50} (μM)	cytotoxicity CC_{50} (μM)
16	48.58	>100	>100	>100	48.58
17	>100	>100	>100	>100	>100
18	>100	>100	>100	>100	>100
19	23.21	>100	>100	>100	23.21
AZT	0.0005	ND	ND	ND	5.41
ACV	ND	1.81	1.81	ND	>10
Ribavirin	ND	ND	ND	20.12	300.00

ND: Not Determined

EC_{50} (μM): Concentration required to inhibit 50% of virus induced cytopathicity

CC_{50} (μM): Concentration required to reduce cell viability by 50%

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