An Efficient Synthesis of 4'-Vinylated Carbocyclic Nucleoside Analogues *via* Two Directional Ring-closing Metathesis

Hua Li and Joon Hee Hong*

*BK21-Project Team, College of Pharmacy, Chosun University, Gwangju 501-759, Korea. *E-mail: hongjh@chosun.ac.kr*

Received January 30, 2008

Two directional ring-closing metathesis (RCM) was applied successfully to the synthesis of 4'-vinylated carbocyclic nucleoside analogues from the trivinyl intermediate **12**, which was readily made using a sequential Claisen rearrangement and ring-closing metathesis (RCM) starting from Weinreb amide **5**. An antiviral evaluation of the synthesized compounds against various viruses such as HIV, HSV-1, HSV-2 and HCMV revealed that the guanine analogue **20** have moderate anti-HIV activity in the MT-4 cell line (EC_{50} = 10.2 μM).

Key Words : Vinylated carbocyclic nucleoside, Antiviral agents, Weinreb amide

Introduction

Recently, several branched nucleosides[1] have been synthesized and evaluated as potent antitumor or antiviral agents. Among them, 4'α-ethenyl and 4'α-ethynyl thymidine analogues **1**[2] and **2**[3] which have an additional double or triple bond at the 4'-position, were reported to have potent antiviral and antitumor activities (Figure 1). Carbocyclic nucleosides[4] are a group of compounds that are structurally similar to natural nucleosides, in which the furanose oxygen is replaced by a methylene group. Replacement of the furanose ring oxygen by carbon is of particular interest because the resulting carbocyclic nucleosides show greater metabolic stability to phosphorylase,[5] which cleaves the glycosidic bond of nucleosides. The recent discovery of carbovir **3**[6] and abacavir **4**[7] as anti-HIV agents has increased interest in the synthesis of novel nucleosides in this class of compounds.

Stimulated by these interesting molecular structures and their antiviral activity relationship, in this study a novel class of carbocyclic nucleosides containing 4'-electron-rich branch such as vinyl group was synthesized.

Weinreb amide **5**, which was the starting material, was readily synthesized from the commercially available ethyl glycolate.[8] Vinylation of amide **5** using vinylmagnesium bromide gave the alkyl vinyl ketone derivative **6**. Compound **6** was subjected to Horner-Wadsworth-Emmons (HWE) reaction conditions[9] to provide α,β-unsaturated ethyl ester **7** as an *E*/*Z* isomeric mixture. It was unnecessary to separate the isomers because they were merged into a single isomer in the subsequent reaction. Ester **7** was reduced to allylic alcohol **8** using diisobutylaluminum hydride, which underwent a [3,3]-sigmatropic rearrangement[10] using triethyl orthoacetate to give a γ,δ-unsaturated ester **9**. The direct conversion of ester **9** to aldehyde **10** was made possible by the slow addition of DIBALH to the reaction mixture in toluene solvent system at −78 °C. Aldehyde **10** was subjected to carbonyl addition by CH_2=CHMgBr to yield trivinyl derivative **11** (Scheme 1).

Two directional cyclization of trivinyl **11** was performed under standard ring-closing metathesis conditions[11] using a 2nd generation Grubbs catalyst[9] to provide cyclopentenols **12**α and **12**β, respectively. The relative stereochemical assignments were determined by proton NOE experiments. Upon irradiation of C_1-H, relatively strong NOE was observed at the methylene protons of the hydroxymethyl group **12**α but not at the methylene protons of **12**β (Figure

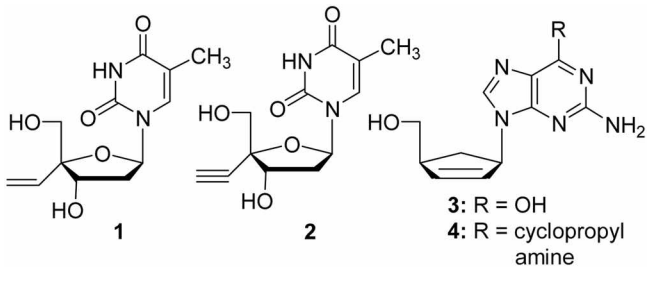
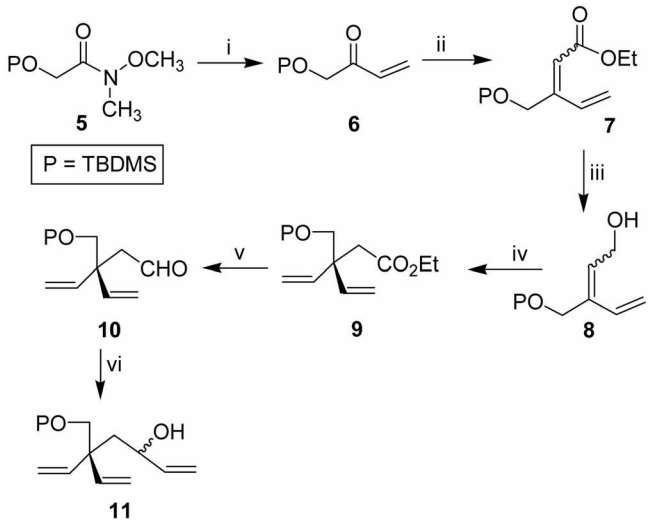


Figure 1. Structures of potent nucleosides as antiviral agents.



Scheme 1. Synthesis route of trivinyl intermediate **11**. Reagents: i) vinylmagnesium bromide, THF, 0 °C; ii) triethylphosphonoacetate, NaH, THF; iii) DIBALH, CH_2Cl_2; iv) triethylorthoacetate, propionic acid, overnight, 135-140 °C; v) DIBALH, toluene, −78 °C; vi) vinylmagnesium bromide, THF, −78 °C.

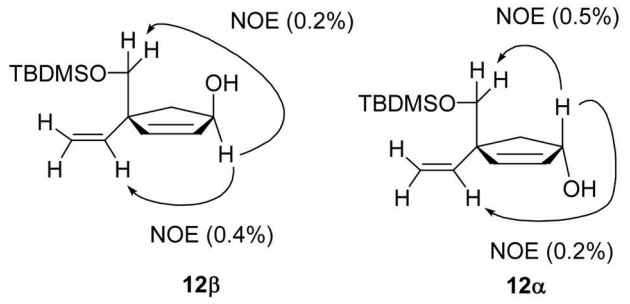
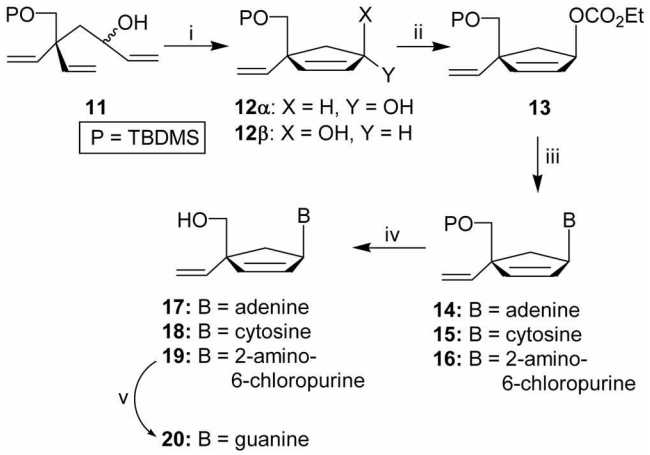


Figure 2. NOE comparisons of compounds **12**α and **12**β.

2).

Initially, an attempt was made to synthesize the target compounds *via* mesylation and nucleophilic substitution from **12**α. However, the reaction produced a very low yield and was not reproducible. In order to couple the nucleosidic bases (adenine, cytosine, 2-amino-6-chloropurine) to allylic derivative **12**β using well known palladium(0)-catalysis,[12] cyclopentenol **12**β was transformed to the allylic formate analogue **13** using ethyl chloroformate. Compound **13** was coupled with the nucleosidic base anions generated by NaH/DMSO using a catalyst [tris(dibenzylidene-acetone)-dipalladium(0)-chloroform] adduct to provide the carbocyclic nucleoside analogues **14-16**. Removal of the silyl protecting group from them was preformed by treating the compounds with tetrabutylammonium fluoride (TBAF) to give nucleosides **17-19**. Treatment of compound **19** with 2-mercaptoethanol and sodium methoxide in methanol, followed by neutralization with acetic acid gave the desired guanine carbocyclic nucleoside analogue **20** (Scheme 2).

All the synthesized compounds **17~20** were tested against several viruses such as HIV-1 (MT-4 cells), HSV-1 and HSV-2 (CCL 18 cells), and HCMV (AD-169).[13] As shown in Table 1, some of the compounds showed antiviral activity. In particular, the guanine nucleoside analogue **20**, exhibited moderate anti-HIV activity in MT-4 cells (EC_{50} = 10.2 μM). It is believed that the arrangement in the carbocyclic guanine



Scheme 2. Synthesis route of taregt nucleosides. Reagents: i) Grubbs catalyst (II), CH_2Cl_2; ii) $ClCO_2Et$, pyridine, DMAP; iii) nucleosidic bases, $Pd_2(dba)_3$-$CHCl_3$, P(O-*i*-Pr)$_3$, NaH, THF/DMSO; iv) TBAF, THF; v) (a) 2-mercaptoethanol, NaOMe, MeOH, (b) CH_3COOH.

Table 1. The antiviral activity of the synthesized compounds

	HIV-1 EC_{50}(μM)	HSV-1 EC_{50}(μM)	HSV-2 EC_{50}(μM)	HCMV EC_{50}(μM)	cytotoxicity CC_{50}(μM)
17	95	>100	>100	>100	95
18	77.9	>100	90.5	23.7	>100
19	>100	>100	>100	61.2	>100
20	**10.2**	65.8	>100	41.5	99
AZT	0.01	ND	ND	ND	1.15
GCV	ND	ND	ND	0.8	>10
ACV	ND	0.2	ND	ND	>100

AZT: Azidothymidine; GCV: Ganciclovir; ACV: Acyclovir. ND: Not Determined. EC_{50} (μM): Concentration required to inhibit 50% of the virus induced cytopathicity. CC_{50} (μM): Concentration required to reduce the cell viability by 50%

nucleoside analogue **20** may be conformationally similar to that in natural nucleosides containing ribose. Hence, this arrangement will enhance the level of phosphorylation by kinase to produce the active monophosphate form. This suggests that this class of 4'-vinylated carbocyclic *N*-nucleoside, which has no hydroxy group in the 3'-position, can be a novel structural template for the development of new antiviral agents.

In summary, a convenient method for synthesizing 4'-vinylated carbocyclic nucleoside analogues *via* two directional RCM from the Weinreb amide was developed. Based on this strategy, the syntheses of other nucleosides such as acetylated carbocyclic nucleosides with different nucleobases are currently underway.

Experimental Section

The melting points were determined on a Mel-temp II laboratory device and are 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 on a Beckman DU-7 spectrophotometer. The elemental analyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Unless specified otherwise, all reactions were carried out in a N_2 atmosphere. Dry dichloromethane, benzene and pyridine were obtained by distillation from CaH_2. Dry THF was obtained by distillation from Na and benzophenone immediately before use.

2-(*tert*-Butyldimethylsilyloxy)-1-vinyl-ethanone (6). Vinylmagnesium bromide (18.0 mL, 1.0 M solution in THF) was added slowly to a solution of Weinreb amide **5** (3.5 g, 14.99 mmol) in dry THF (70 mL) at 0 °C. After 5 h, a saturated NH_4Cl solution (18 mL) was added, and the reaction mixture was warmed slowly to rt. The mixture was extracted with EtOAc (2 × 100 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give compound **6** (2.07 g, 69%) as

a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.53 (dd, J = 17.7, 10.8 Hz, 1H), 6.27 (d, J = 17.4 Hz, 1H), 5.67 (d, J = 10.5 Hz, 1H), 4.27 (s, 2H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 198.78, 131.67, 128.87, 68.56, 25.76, 18.34, −5.47.

(*E*) and (*Z*)-4-(*tert*-Butyldimethylsilyloxy)-3-vinyl-but-2-enoic acid ethyl ester (7). Triethyl phosphonoacetate (3.73 g, 16.64 mmol) was added dropwise to a suspension of sodium hydride (0.4 g, 16.64 mmol) in distilled THF (80 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. The ketone **6** (3.33 g, 16.64 mmol) was then added to this mixture and the mixture was stirred for 2 h. The solution was neutralized with AcOH (3.5 mL), poured into H_2O (120 mL) and extracted with EtOAc (120 mL × 2). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give compound **7** (3.28 g, 73%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.78 (dd, J = 17.1, 10.5 Hz, 1H), 5.30 (dd, J = 16.2, 0.9 Hz, 1H), 5.26 (d, J = 16.0 Hz, 1H), 5.20 (s, 1H), 4.22 (t, J = 7.0 Hz, 2H), 4.12 (s, 2H), 4.05 (q, J = 6.9 Hz, 2H), 1.19 (t, J = 6.8 Hz, 3H), 0.84 (s, 9H), 0.02 (m, 6H).

(*E*) and (*Z*)-4-(*tert*-Butyldimethylsilyloxy)-3-vinyl-but-2-en-1-ol (8). DIBALH (31.08 mL, 1.0 M solution in hexane) was added slowly to a solution of compound **7** (4.0 g, 14.8 mmol) in CH_2Cl_2 (120 mL) at −20 °C, and stirred for 2 h at the same temperature. Methanol (30 mL) was then added to this mixture. The mixture was stirred at room temperature for 2 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give alcohol **8** (2.97 g, 88%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.78 (s, 1H), 5.59 (dd, J = 16.2, 10.2 Hz, 1H), 5.41 (d, J = 16.2 Hz, 1H), 5.19 (d, J = 10.2 Hz, 1H), 4.22 (t, J = 6.8 Hz, 2H), 4.18 (s, 2H), 0.83 (m, 9H), 0.02 (m, 6H).

(±)-3-(*t*-Butyldimethylsilyloxymethyl)-3-vinyl-pent-4-enoic acid ethyl ester (9). A solution of allylic alcohol **8** (5.2 g, 22.76 mmol) in triethyl orthoacetate (90 mL) and 0.2 mL of propionic acid was heated overnight at 135-140 °C with constant stirring under the conditions for the distillative removal of ethanol. The excess triethyl orthoacetate was distilled off and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **9** (5.36 g, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92-5.87 (m, 2H), 5.79 (m, 2H), 5.10-5.04 (m, 2H), 4.05-3.95 (m, 4H), 2.83 (d, J = 4.2 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.71, 147.61, 142.98, 116.54, 111.49, 68.98, 60.38, 48.21, 39.56, 25.77, 18.49, 14.21, −5.56.

(±)-3-(*t*-Butyldimethylsilyloxymethyl)-3-vinyl-pent-4-enal (10). DIBALH (6.1 mL, 1.5 M solution in toluene) was added slowly to a solution of compound **9** (2.5 g, 8.37 mmol) in toluene (40 mL) at −78 °C, and stirred for 10 minutes at the same temperature. Methanol (7 mL) was then added to this mixture. The resulting mixture was stirred at room temperature for 1 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **10** (1.45 g, 68%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.69 (s, 1H), 5.90-5.82 (m, 2H), 5.75-5.67 (m, 2H), 5.11-5.04 (m, 2H), 3.99 (dd, J = 12.8, 8.8 Hz, 2H), 2.90 (dd, J = 10.8, 4.2 Hz, 2H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 202.87, 147.54, 143.04, 117.19, 112.65, 69.25, 48.87, 39.56, 25.59, 18.74, −5.61.

(±)-5-(*t*-Butyldimethylsilyloxymethyl)-5-vinyl-hepta-1,6-dien-3-ol (11): Vinylmagnesium bromide (18.86 mL, 1.0 M solution in THF) was added slowly to a solution of compound **10** (4.0 g, 15.72 mmol) in dry THF (60 mL) at −78 °C. After 5 h, a saturated NH_4Cl solution (20 mL) and water (100 mL) was then added, and the reaction mixture was slowly warmed to rt. The mixture was extracted with EtOAc (2 × 120 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **11** (3.37 g, 76%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.04-5.72 (m, 3H), 5.26-4.95 (m, 3H), 5.12-5.05 (m, 3H), 3.65 (m, 3H), 1.67-1.54 (m, 2H), 0.83 (m, 9H), 0.02 (m, 6H).

(*rel*)-(1*R*,4*S*)-4-(*t*-Butyldimethylsilyloxymethyl)-4-vinyl-cyclopent-2-enol (12β); and (*rel*)-(1*S*,4*S*)-4-(*t*-Butyldimethylsilyloxymethyl)-4-vinyl-cyclopent-2-enol (12α). 2nd generation Grubbs catalyst (152 mg, 0.18 mmol) was added to a solution of compound **11** (1.56 g, 5.54 mmol) in dry CH_2Cl_2 (15 mL). The reaction mixture was refluxed overnight, and cooled to room temperature. The mixture was concentrated under vacuum, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give cyclopentenol **12β** (549 mg, 39%) and **12α** (535 mg, 38%) as colorless oils, respectively. Cyclopentenol **12β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.11-6.03 (m, 3H), 5.90-5.81 (m, 3H), 4.87 (dd, J = 7.4, 1.2 Hz, 1H), 3.54 (s, 2H), 2.65 (dd, J = 13.4, 7.0 Hz, 1H), 1.85 (dd, J = 13.4, 2.8 Hz, 1H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.29, 143.59, 140.49, 133.98, 75.34, 69.78, 57.82, 46.78, 25.45, 18.67, −5.50.

Cyclopentenol **12α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.13-6.06 (m, 3H), 5.92-5.84 (m, 3H), 4.85 (dd, J = 5.6, 1.4 Hz, 1H), 3.56 (s, 2H), 2.61 (dd, J = 13.2, 7.2 Hz, 1H), 1.86 (dd, J = 13.2, 3.3 Hz, 1H), 0.83 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.72, 142.51, 141.79, 132.29, 74.29, 68.49, 58.39, 44.28, 25.71, 18.59, −5.57.

(*rel*)-(1*R*,4*S*)-1-Ethoxy carbonyloxy-4-(*t*-butyldimethylsilyloxymethyl)-4-vinyl-cyclopent-2-ene (13): Ethyl chloroformate (1.87 mL, 17.3 mmol) and DMAP (85 mg, 0.7 mmol) were added to a solution of **12β** (2.2 g, 8.65 mmol) in anhydrous pyridine (15 mL). The reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with a saturated $NaHCO_3$ solution (2.0 mL) and concentrated under vacuum. The residue was extracted with EtOAc/H_2O, and the organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/

hexane, 1:10) to give compound **13** (1.97 g, 70%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.46 (d, J = 5.6 Hz, 1H), 6.37-6.29 (m, 2H), 6.09-5.94 (m, 2H), 5.75 (d, J = 4.6 Hz, 1H), 4.38 (q, J = 7.4 Hz, 2H), 3.89 (d, J = 9.2 Hz, 1H), 3.81 (d, J = 9.0 Hz, 1H), 2.61 (dd, J = 13.6, 6.8 Hz, 1H), 2.33 (dd, J = 13.6, 3.6 Hz, 1H), 1.42 (t, J = 7.4 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 6H): ^{13}C NMR ($CDCl_3$) δ 155.21, 145.65, 142.42, 140.54, 124.67, 82.54, 71.49, 63.88, 57.32, 40.96, 25.61, 18.70, 14.51, −5.60.

(*rel*)-(1'*R*,4'*S*)-9-[4-(*t*-Butyldimethylsilyloxymethyl)-4-vinyl-cyclopent-2-en-1-yl] adenine (14). Adenine (79.45 mg, 0.588 mmol) was added to a pure NaH (14.4 mg, 0.588 mmol) in anhydrous DMSO (3.6 mL). The reaction mixture was stirred for 30 min at 50-55 °C and cooled to room temperature. At the same time, P(O-*i*-Pr)$_3$ (0.0576 mL, 0.132 mmol) was added to a solution of $Pd_2(dba)_3$·$CHCl_3$ (2.76 mg, 1.5 mmol) in anhydrous THF (3.0 mL), and stirred for 30 min. The catalyst solution in THF and compound **13** (172.4 mg, 0.528 mmol) dissolved in anhydrous THF (3.0 mL) were added sequentially to the nucleosidic base solution of DMSO. The reaction mixture was heated and stirred overnight under reflux, and quenched with water (1.2 mL). The reaction solvent was removed under vacuum. The residue was purified by silica gel column chromatography (MeOH/EtOAc/Hexane, 0.1:1:2) to give compound **14** (76.5 mg, 39%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.33 (s, 1H), 8.01 (s, 1H), 6.42 (d, J = 5.4 Hz, 1H), 6.30-6.22 (m, 2H), 6.07-5.95 (m, 2H), 5.77 (dd, J = 6.6, 1.2 Hz, 1H), 3.87 (d, J = 9.2 Hz, 1H), 3.80 (d, J = 9.2 Hz, 1H), 2.90 (dd, J = 13.4, 8.4 Hz, 1H), 2.42 (dd, J = 13.4, 6.4 Hz, 1H), 0.82 (s, 9H), 0.01 (s, 6H): ^{13}C NMR ($CDCl_3$) δ 155.90, 152.40, 150.21, 145.71, 142.77, 141.70, 140.11, 125.65, 118.67, 70.34, 60.01, 46.32, 42.61, 25.67, 18.71, −5.69; Anal. Calcd. for $C_{19}H_{29}N_5OSi$: C, 61.42; H, 7.87; N, 18.85. Found: C, 61.50; H, 7.69; N, 18.91.

(*rel*)-(1'*R*,4'*S*)-1-[4-(*t*-Butyldimethylsilyloxymethyl)-4-vinyl-cyclopent-2-en-1-yl] cytosine (15). Compound **15** was synthesized from compound **13** using a similar procedure to that described for compound **14**. yield 44%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, J = 7.0 Hz, 1H), 6.44 (dd, J = 5.4, 1.2 Hz, 1H), 6.29-6.20 (m, 2H), 6.08-5.96 (m, 2H), 5.76 (dd, J = 6.6, 1.4 Hz, 1H), 5.54 (d, J = 7.0 Hz, 1H), 3.85 (d, J = 9.4 Hz, 1H), 3.79 (d, J = 9.2 Hz, 1H), 2.91 (dd, J = 13.4, 8.2 Hz, 1H), 2.44 (dd, J = 13.4, 6.4 Hz, 1H), 0.81 (s, 9H), 0.02 (s, 6H): ^{13}C NMR ($CDCl_3$) δ 165.41, 156.78, 145.90, 145.31, 142.20, 140.72, 123.61, 92.32, 69.68, 61.41, 47.78, 43.67, 25.40, 18.43, −5.48; Anal. Calcd. for $C_{18}H_{29}N_3O_2Si$: C, 62.21; H, 8.41; N, 12.09. Found: C, 62.31; H, 8.55; N, 11.95.

(*rel*)-(1'*R*,4'*R*)-9-[4-(*t*-Butyldimethylsilyloxymethyl)-4-vinyl-cyclopent-2-en-1-yl]2-amino-6-chloropurine (16). Nucleoside analogue **16** was synthesized from compound **13** using a similar procedure to that described for compound **14**: yield 35%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ8.70 (s, 1H), 6.38 (d, J = 5.4 Hz, 1H), 6.25-6.18 (m, 2H), 6.02-5.95 (m, 2H), 5.71 (d, J = 6.6 Hz, 1H), 3.90 (d, J = 9.4 Hz, 1H), 3.78 (d, J = 9.4 Hz, 1H), 2.90 (dd, J = 13.6, 8.4 Hz, 1H), 2.44 (dd, J = 13.6, 6.6 Hz, 1H), 0.83 (s, 9H), 0.01 (s, 6H): ^{13}C NMR ($CDCl_3$) δ 159.56, 154.88, 152.51, 145.32, 143.71, 142.90, 141.43, 132.77, 125.43, 69.99, 60.31, 46.54, 42.60, 25.67, 18.79, −5.58; Anal. Calcd. for $C_{19}H_{28}ClN_5OSi$: C, 56.21; H, 6.95; N, 17.25. Found: C, 56.11; H, 7.08; N, 17.12.

(*rel*)-(1'*R*,4'*R*)-9-[4-(Hydroxymethyl)-4-vinyl-cyclopent-2-en-1-yl] adenine (17). TBAF (0.54 mL, 1.0 M solution in THF) was added to a solution of compound **14** (126 mg, 0.362 mmol) in THF (5 mL) at 0 °C. The mixture was stirred overnight at room temperature, and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:5) to give compound **17** (61 mg, 73%) as a white solid: mp 180-183 °C; UV (H_2O) λ_{max} 262.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.37 (s, 1H), 8.05 (s, 1H), 6.45 (dd, J = 5.4, 1.2 Hz, 1H), 6.33-6.25 (m, 2H), 6.08-5.99 (m, 2H), 5.79 (d, J = 6.8 Hz, 1H), 4.99 (t, J = 5.4 Hz, 1H), 3.83 (d, J = 9.2 Hz, 1H), 3.72 (d, J = 9.0 Hz, 1H), 2.92 (dd, J = 13.2, 8.2 Hz, 1H), 2.48 (dd, J = 13.2, 6.2 Hz, 1H): ^{13}C NMR (DMSO-d_6) δ155.71, 152.59, 151.33, 145.30, 144.20, 141.70, 140.47, 125.65, 119.61, 69.48, 60.54, 46.43, 41.20; Anal. Calcd. for $C_{13}H_{15}N_5O$: C, 60.69; H, 5.88; N, 27.22. Found: C, 60.80; H, 5.81; N, 27.32.

(*rel*)-(1'*R*,4'*R*)-1-[4-(Hydroxymethyl)-4-vinyl-cyclopent-2-en-1-yl] cytosine (18). Compound **18** was obtained from compound **15** using a similar procedure to that described for compound **17**. yield 68%; mp 160-163 °C; UV (H_2O) λ_{max} 271.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ7.29 (d, J = 6.9 Hz, 1H), 6.38 (d, J = 5.4 Hz, 1H), 6.20-6.08 (m, 4H), 5.79 (d, J = 6.6 Hz, 1H), 5.56 (d, J = 7.0 Hz, 1H), 3.87 (d, J = 9.4 Hz, 1H), 3.78 (d, J = 9.4 Hz, 1H), 2.95 (dd, J = 13.4, 8.0 Hz, 1H), 2.49 (dd, J = 13.4, 6.6 Hz, 1H): ^{13}C NMR (DMSO-d_6) δ 165.81, 156.51, 145.68, 144.87, 142.60, 140.82, 124.42, 93.57, 69.51, 60.67, 48.90, 42.77; Anal. Calcd. for $C_{12}H_{15}N_3O_2$·0.5 MeOH: C, 60.22; H, 6.86; N, 16.82. Found: C, 60.33; H, 6.98; N, 16.90.

(*rel*)-(1'*R*,4'*R*)-9-[4-(Hydroxymethyl)-4-vinyl-cyclopent-2-en-1-yl] 2-amino-6-chloropurine (19): Purine nucleoside analogue **19** was prepared from compound **16** using a similar procedure to that described for compound **17**; yield 69%; mp 178-180 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.71 (br s, 1H), 7.87 (s, 1H), 6.51 (br s, 2H), 6.41 (dd, J = 5.4, 1.2 Hz, 1H), 6.22-6.10 (m, 4H), 5.78 (d, J = 6.4 Hz, 1H), 5.01 (t, J = 5.2 Hz, 1H), 3.89 (d, J = 9.6 Hz, 1H), 3.78 (d, J = 9.4 Hz, 1H), 2.88 (dd, J = 13.4, 8.2 Hz, 1H), 2.45 (dd, J = 13.4, 6.8 Hz, 1H); ^{13}C NMR (DMSO-d_3) δ 160.02, 155.21, 152.98, 146.21, 143.43, 141.98, 140.72, 133.21, 124.59, 70.55, 61.32, 47.65, 43.65; Anal. Calcd. for $C_{13}H_{14}ClN_5O$ · 1.0 H_2O: C, 50.40; H, 5.20; N, 22.61. Found: C, 50.50; H, 5.18; N, 22.53.

(*rel*)-(1'*R*,4'*R*)-9-[4-(Hydroxymethyl)-4-vinyl-cyclopent-2-en-1-yl] guanine (20). Mercaptoethanol (0.18 mL, 2.58 mmol) and NaOMe (2.0 mL, 2.0 mmol, 1.0 M solution in MeOH) was added to a solution of compound **19** (128 mg, 0.44 mmol) in MeOH (10 mL), and refluxed overnight. After cooling, the reaction mixture was neutralized with a few drops of glacial AcOH and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (MeOH/CH_2Cl_2, 1:5) to give the carbovir analogue **20** (72 mg, 60%) as a solid: mp 186-188 °C; UV (H_2O) λ_{max} 253.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.75 (br s, 1H), 7.98 (s, 1H), 6.50 (br s, 1H), 6.40 (d, J = 5.2 Hz, 1H), 6.13-6.01 (m, 4H), 5.72 (dd, J = 6.6, 1.4 Hz, 1H), 4.98 (t, J = 5.2 Hz, 1H), 3.88 (d, J = 9.2 Hz, 1H), 3.74 (d, J = 9.4 Hz, 1H), 2.89 (dd, J = 13.2, 8.4 Hz, 1H), 2.47 (dd, J = 13.4, 6.6 Hz, 1H); ^{13}C NMR (DMSO-d_3) δ 157.84, 154.70, 152.29, 145.67, 142.51, 140.98, 136.40, 132.28, 117.39, 70.67, 61.39, 48.11, 42.97; Anal. Calcd. for $C_{13}H_{15}N_5O_2 \cdot 1.0$ H_2O: C, 53.60; H, 5.88; N, 24.04. Found: C, 53.52; H, 5.79; N, 24.48.

References

1. (a) O-Yang, C.; Wu, H. Y.; Fraser-Smith, E. B.; Walker, K. A. M. *Tetrahedron Lett.* **1992**, *33*, 37. (b) Maag, H.; Nelson, J. T.; Rios-Steiner, J. L.; Prisbe, E. J. *J. Med. Chem.* **1994**, *37*, 431. (c) Haraguchi, K.; Takeda, S.; Tanaka, H.; Nitanda, T.; Baba, M.; Dutschman, G. E.; Cheng, Y.-C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3775. (d) Kumamoto, H.; Nakai, T.; Haraguchi, K.; Nakamura, K. T.; Tanaka, H.; Baba, M.; Cheng, Y.-C. *J. Med. Chem.* **2006**, *49*, 7861.
2. Sugimoto, I.; Shuto, S.; Mori, S.; Shigeta, S.; Matuda, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 385.
3. Nomura, M.; Shuto, S.; Tanaka, M.; Sasaki, T.; Mori, S.; Shigeta, S.; Matuda, A. *J. Med. Chem.* **1999**, *42*, 2901.
4. (a) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745. (b) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229. (c) Ariona, O.; Gómez, A. M.; López, J. C.; Plumet, J. *Chem. Rev.* **2007**, *107*, 1919.
5. Ueland, P. M. *Pharmacol. Rev.* **1982**, *34*, 223.
6. (a) Vince, R.; Hua, M.; Brownell, J.; Daluge, S.; Lee, F. C.; Shannon, W. M.; Lavelle, G. C.; Qualls, J.; Weisolw, O. S.; Kiser, R. *Biochem. Biophys. Res. Commun.* **1988**, *156*, 1046. (b) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17. (c) Vince, R. *Nucleic Acids Symp. Ser.* **1991**, *25*, 193.
7. Symonds, W.; Cutrell, A.; Edwards, M.; Steel, H.; Spreen, B.; Powell, G.; McGuirk, S.; Hetherington, S. *Clin. Ther.* **2002**, *24*, 565.
8. (a) Nugiel, D. A.; Jakobs, K.; Kaltenbach, R. F.; Worley, T.; Patel, M.; Meyer, D. T.; Jadhav, P. K.; De Lucca, G. V.; Smyser, T. E.; Klabe, R. M.; Bacheler, L. T.; Rayner, M. M.; Seitz, S. P. *J. Med. Chem.* **1996**, *39*, 2156. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
9. Hong, J. H.; Ko, O. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 1289.
10. (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (b) Hong, J. H.; Gao, M. Y.; Chu, C. K. *Tetrahedron Lett.* **1999**, *40*, 231. (c) Hong, J. H.; Lee, K.; Choi, Y.; Chu, C. K. *Tetrahedron Lett.* **1988**, *39*, 3443. (d) Oh, C. H.; Hong, J. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 1520.
11. (a) Grubbs, R. H.; Miller, S. J. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Grubbs, R. H.; Chang, S. B. *Tetrahedron* **1998**, *54*, 4413.
12. (a) Trost, B. M.; Kallander, L. S. *J. Org. Chem.* **1999**, *64*, 5427. (b) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1996**, *118*, 3037.
13. Jeong, L. S.; Kim, H. O.; Moon, H. R.; Hong, J. H.; Yoo, S. J.; Choi, W. J.; Chun, M. W.; Lee, C. K. *J. Med. Chem.* **2001**, *44*, 806.