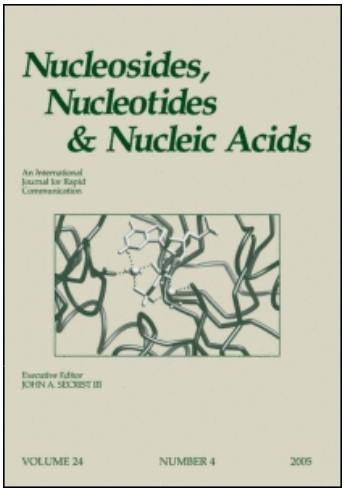

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Novel Synthesis and Anti-HIV Activity of 4'-Branched Exomethylene Carbocyclic Nucleosides Using a Ring-Closing Metathesis of Triene

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NOVEL SYNTHESIS AND ANTI-HIV ACTIVITY OF 4′-BRANCHED EXOMETHYLENE CARBOCYCLIC NUCLEOSIDES USING A RING-CLOSING METATHESIS OF TRIENE

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□ *The exomethylene of **6** was successfully constructed from the aldehyde **5** using Eschenmoser's reagents. A triene compound **7** was cyclized successfully using Grubbs' II catalyst to give an exomethylene carbocycle nucleus for the target compound. A Mitsunobu reaction was successfully used to condense the natural bases (adenine, thymine, uracil, and cytosine). The synthesized cytosine analogue **20** showed moderate anti-HIV activity ($EC_{50} = 10.67\ \mu M$).*

Keywords Quaternary carbon; triene; ring-closing metathesis; Mitsunobu reaction

INTRODUCTION

The carbocyclic nucleosides[1] can potently inhibit viral infection. Due to the absence of a true glycosidic bond, carbocyclic nucleoside analogues are chemically more stable and not subject to the enzymatic degradation that occurs in conventional nucleosides.[2] The recent discovery of olefinic carbocyclic nucleosides, such as carbovir **1**[3] and entecavir **2**,[4], as potential antiviral agents has attracted considerable attention in the search for novel nucleosides of this class. Recently, a number of 4′α-substituted nucleoside[5] analogues showed significant antitumor or antiviral activities. Among them, 4′-methyl-2′-deoxycytidine,[6] 4′-fluoromethyl-2′-deoxycytidine,[7] 4′-hydroxymethylthymidine,[8] and 4′-azidomethylthymidine[9] demonstrated very potent biological activities, but their high toxicity rendered them ineffectual as drugs.

Based on these results and as part of our drug discovery program, we have designed novel 4′-branched exomethylene carbocyclic nucleosides that

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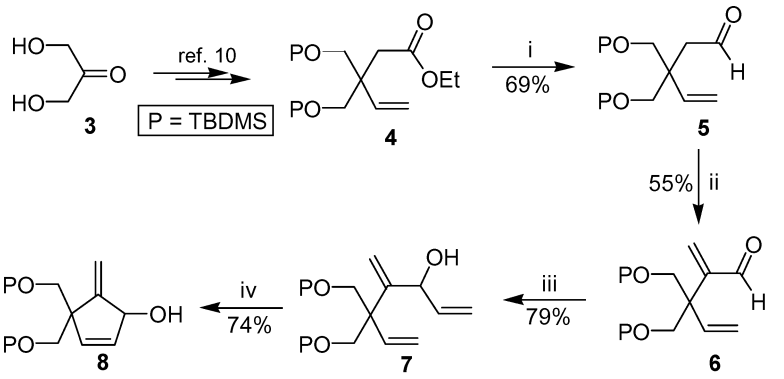


Reagents: i) DIBALH, toluene, -78 °C; ii) methylene-*N,N*-dimethylamineammonium iodide, Et_3N, CH_2Cl_2; iii) CH_2=CHMgBr, THF; (iv) Grubbs' catalyst II.

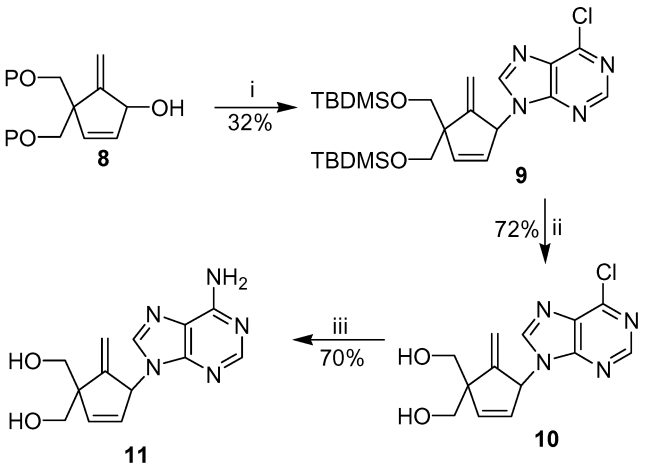
SCHEME 1 Synthesis of exomethylene cyclopentene intermediate **8**

mimic the properties of potent olefinic carbocyclic nucleosides, as well as biologically active 4′-branched furanose nucleosides. Herein, we disclose their de novo synthetic routes that employed a versatile three-step sequence ([3,3]-sigmatropic rearrangement, Eschenmoser's methylenation, Grubbs ring closing metathesis) from a simple acyclic precursor, 1,3-dihydroxyl acetone.

RESULTS AND DISCUSSION

The synthetic route for the key intermediate **8** in the synthesis of the target nucleosides is illustrated in Scheme 1. The quaternary carbon of γ,δ-unsaturated ester **4** was constructed successfully from the 1,3-dihydroxyacetone using a previously reported procedure.[10] The addition of one equivalent of DIBALH to a solution of the ester **4** in anhydrous toluene at –78°C produced the aldehyde **5**. The treatment of carbonyl **5** with Eschenmoser's salt (methylene-*N,N*-dimethylammonium iodide)[11] gave exomethylene acyclic divinyl derivative **6**. We next turned our attention to the construction of a triene system for the metathesis cyclization reaction. Thus, the addition of vinylmagnesium bromide to the divinyl aldehyde **6** furnished the desired acyclic triene **7**, which was subjected to standard ring-closing metathesis conditions using a second-generation Grubbs' catalyst [(Im)Cl_2PCy_3RuCHPh][12] to provide the required exomethylene cyclopentenol **8** (Scheme 1).

We initially hypothesized that palladium(0)-catalyzed reactions[13] could introduce functional groups into allylic positions of synthetic organic compounds, including the exomethylene cyclopentene derivative **8**, through an ethyl formate analogue. To our surprise, we could not find any nucleoside analogues and therefore needed an alternative coupling method. The



Reagents: i) 6-chloropurin, DIAD, PPh_3, dioxane/DMF; ii) TBAF, THF/CH_3CN; iii) NH_3/MeOH, steel bomb.

SCHEME 2 Synthesis of adenine nucleoside analogue **11**

Mitsunobu reactions can couple a cyclopentenol or cyclopentanol with nucleosidic bases, allowing us to synthesize our target nucleosides with the desired regio- and stereochemistry.[14] The success of a Mitsunobu reaction in the synthesis of nucleoside analogues depends on the reaction conditions, such as the solvent system, temperature, and addition procedure, to control the regiochemistry of the desired nucleosides. Instead of THF only, a 2:1 cosolvent mixture of dioxane/DMF was used for the coupling of the cyclopentenol **8** with the nucleobases; the heterocyclic bases had better solubility in the dioxane-DMF mixture, resulting in better yields.[15] The slow addition of diisopropylazodicarboxylate (DIAD) to a mixture of cyclopentenol **8**, triphenylphosphine, and the corresponding purine base in an anhydrous solvent produced a yellow solution, which was then stirred for 2 hours at –20°C to yield the 6-chloropurine analogue **9** without the formation of *N*-7 isomers. The *N*-9 isomer of the coupling was confirmed by UV spectra data [λ_{max} (MeOH) 264 nm].[16] The desilylated nucleoside **10** was obtained from the corresponding nucleoside **9** by treatment with tetrabutylammonium fluoride (TBAF) in a THF/CH_3CN (1/1) co-solvent system. The target adenosine analogue **11** was synthesized from the corresponding nucleoside analogue **10** by treatment with a saturated solution of methanolic ammonia in a steel bomb at 90–95°C overnight (Scheme 2).

To synthesize the pyrimidine nucleoside analogues, that is, the N^3 or N^4-benzoyl bases, we used a similar Mitsunobu procedure on the thymine, uracil and cytosine bases to give the protected nucleoside analogues **12**, **13**, and **18**. The regioisomers were easily confirmed by comparison of the UV literature data.[16] The desilylations of the nucleoside intermediates

TABLE 1 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)
11	55.5	70.4	99	99	99
16	66	99	99	95	99
17	58	84	49	99	99
20	**10.67**	50.5	95	41.5	95
AZT	0.009	ND	ND	ND	1.17
GCV	ND	ND	ND	0.6	>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 virus-induced cytopathicity.
CC_{50} (μM): Concentration required to reduce cell viability by 50%.</tfn1>

were performed similarly to that for adenine nucleoside **10** to produce pyrimidine the nucleosides **14**, **15**, and **19**, which were debenzoylated by treatment with sodium methoxide in methanol to produce nucleosides **16**, **17,** and **20**.

The antiviral activity against HIV-1, HSV-1, HSV-2, and HCMV was measured. The synthesized cytosine analogue **20** showed moderate anti-HIV activity ($EC_{50} = 10.67\ \mu$M, MT-4 cell lines) without any cytotoxicity up to 100 μM (Table 1).

The rigid arrangement in the exomethylene carbocyclic cytosine nucleoside analogue **20** may be conformationally similar to carbovir and entecavir. Hence, this arrangement will enhance the level of phosphorylation by kinase to produce the active monophosphate form.[17]

In summary, we developed a convenient method for synthesizing exomethylene carbocyclic nucleoside analogues via the triene intermediate **7**. Based on this strategy, the syntheses of other nucleosides such as branched carbocyclic nucleosides with different nucleobases are currently underway.

EXPERIMENTAL SECTION

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a JEOL 300 Fourier transform spectrometer (JEOL, Tokyo, Japan); chemical shifts are reported in parts per million (δ) and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublets). UV spectra were obtained on a Beckman DU-7 spectrophotometer (Beckman, South Pasadena, CA, USA). The elemental analyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA). Mass spectra were measured with FAB-MS modified Finninggan MAT 312 spectrometer (Arcade, NY 14009, USA). All reactions were carried out under an atmosphere of nitrogen unless specified. Dry dichloromethane, benzene, and

pyridine were obtained by distillation from CaH_2. Dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

(±)-3,3-Bis-(tert-butyldimethylsilanyloxymethyl)-pent-4-enal (5): To a solution of **4** (3.5 g, 8.39 mmol) in toluene (100 mL), DIBALH (6.16 mL, 1.5 M solution in toluene) was added slowly at −78°C, and stirred for 10 minutes at the same temperature. Methanol (10 mL) was then added to the mixture. The mixture was stirred at room temperature for 2 hours, 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 **5** (4.4 g, 69%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 5.67 (dd, J = 17.7, 11.1 Hz, 1H), 5.21 (d, J = 11.1 Hz, 1H), 5.14 (d, J = 17.7 Hz, 1H), 3.58 (dd, J = 17.7, 10.2 Hz, 2H), 2.45 (s, 1H), 0.87 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 202.68, 139.65, 115.45, 65.74, 46.79, 46.61, 25.81, 18.22, -5.62; MS (FAB+) m/z 273 $(M+H)^+$.

(±)-3,3-Bis-(tert-butyldimethylsilanyloxymethyl)-2-methylene-pent-4-enal (6): Eschenmoser's salt, methylene-*N*,*N*-dimethylammonium iodide, (2.18 g, 11.82 mmol) was added to a solution of aldehyde **5** (2.2 g, 5.91 mmol) and triethylamine (2.46 mL, 17.73 mmol) in CH_2Cl_2 at room temperature. The mixture was stirred overnight at room temperature. After adding saturated aq. $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/n-hexane, 1:30) to give compound **6** (1.25 g, 55%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.12 (s, 1H), 6.09 (d, J = 0.6 Hz, 1H), 5.80 (d, J = 0.8 Hz, 1H), 5.60–5.52 (m, 1H), 5.06–4.98 (m, 2H), 3.61 (d, J = 10.8 Hz, 1H), 3.52 (d, J = 10.8 Hz, 1H), 0.89 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 202.86, 154.42, 136.78, 133.72, 109.71, 66.32, 52.43, 25.43, 18.39, −5.54; MS (FAB+) m/z 385 $(M+H)^+$; Anal. calcd. for $C_{20}H_{40}O_3Si_2$: C, 62.44; H, 10.48. Found: C, 62.58; H, 10.39.

(±)-5,5-Bis-(tert-butyldimethylsilanyloxymethyl)-4-methylene-hepta-1,6-dien-3-ol (7): Vinyl magnesium bromide (7.8 mL, 1.0 M solution in THF) was added slowly to a solution of compound **6** (2.5 g, 6.5 mmol) in dry THF (100 mL) at −78°C. After 2 hours, saturated NH_4Cl solution (8 mL) was added, and the reaction mixture was warmed slowly to room temperature. The mixture was extracted with EtOAc (2 × 200 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give a triene **7** (2.12 g, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.85–5.37 (m, 3H), 5.37–5.30 (m, 2H), 5.14–4.93 (m, 3H), 4.65 (d, J = 2.4 Hz, 1H), 3.88 (d, J = 9.9 Hz, 1H), 3.75 (d, J = 9.9 Hz, 1H), 0.86 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 151.35, 140.35, 139.30, 116.56, 115.21, 113.93, 113.31, 70.98, 65.91, 64.18, 52.59, 25.88, 18.29, −5.43; Anal. calcd. for $C_{22}H_{44}O_3Si_2 \cdot 0.5$ EtOAc: C, 63.10; H, 10.59. Found: C, 63.19; H, 10.44.

(±)-4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-5-methylene-cyclopent-2-enol (8): A second generation Grubbs' catalyst (80 mg, 0.11 mmol) was added to a solution of compound **7** (3.92 g, 9.5 mmol) in dry CH_2Cl_2 (40 mL). The reaction mixture was refluxed overnight and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **8** (2.7 g, 74%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98 (dd, J = 6.0, 2.4 Hz, 1H), 5.68 (d, J = 6.0 Hz, 1H), 5.32 (s, 1H), 5.11 (s, 1H), 4.79 (dd, J = 10.8, 1.5 Hz, 1H), 3.74 (d, J = 9.3 Hz, 1H), 3.60 (d, J = 9.6 Hz, 1H), 3.50 (d, J = 9.3 Hz, 1H), 3.43 (d, J = 9.6 Hz, 1H), 0.87 (s, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 154.77, 137.14, 134.04, 110.04, 77.96, 67.01, 66.76, 57.72, 25.55, 18.39, −5.54; MS (FAB+) m/z 385 $(M+H)^+$, 407 $(M+Na)^+$; Anal. Calcd. for $C_{20}H_{40}O_3Si_2$: C, 62.44; H, 10.48. Found: C, 62.53; H, 10.54.

(±)-9-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-5-methylene-cyclopent-2-enyl]-6-chloropurine (9): To a solution containing compound **8** (173 mg, 0.45 mmol), triphenylphosphine (0.705 g, 1.35 mmol) and 6-chloropurine (173 mg, 1.12 mmol) in anhydrous 1,4-dioxane (4 mL) and DMF (2 mL), diisopropyl azodicarboxylate (0.25 mL) was added dropwise at –20°C for 30 minutes under nitrogen. The reaction mixture was stirred for 2 hours at –20°C under nitrogen. The solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give compound **9** (75 mg, 32%) as a white solid: m.p. 158–160°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.71 (s, 1H), 8.17 (s, 1H), 6.22 (m, 2H), 5.90 (dd, J = 5.7, 2.1 Hz, 1H), 5.26 (d, J = 2.4 Hz, 1H), 5.08 (d, J = 1.5 Hz, 1H), 3.85 (d, J = 9.3 Hz, 1H), 3.72 (d, J = 9.3 Hz, 1H), 3.60 (d, J = 9.6 Hz, 1H), 3.54 (d, J = 9.6 Hz, 1H), 0.84 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 155.34, 154.47, 152.45, 148.28, 147.20, 137.71, 134.51, 130.04, 111.77, 68.00, 63.35, 57.28, 25.51, 18.32, −5.60; MS (FAB+) m/z 521 $(M+H)^+$, 543 $(M+Na)^+$; Anal. Calcd. for $C_{25}H_{41}ClN_4O_2Si_2$: C, 57.61; H, 7.93; N, 10.75. Found: C, 57.67; H, 8.05; N, 10.82.

(±)-9-[4,4-Bis-(hydroxymethyl)-5-methylene-cyclopent-2-enyl]-6-chloropurine (10): TBAF (0.76 mL, 1.0 M solution in THF) at 0°C was added to a solution of compound **9** (100 mg, 0.191 mmol) in THF/CH_3CN(2/2 mL). The mixture was stirred overnight at room temperature and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:8) to give compound **10** (79.25 mg, 72%) as a white solid: m.p. 163–165°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.78 (s, 1H), 8.22 (s, 1H), 6.18 (d, J = 5.9 Hz, 1H), 6.02 (s, 1H), 5.93 (d, J = 6.0 Hz, 1H), 5.27 (br s, 1H), 5.13 (s, 1H), 4.94 (t, J = 5.0 Hz, 1H), 4,77 (t, J = 5.2 Hz, 1H), 3.88 (d, J = 9.9 Hz, 1H), 3.74 (d, J = 9.9 Hz, 1H), 3.64 (d, J = 9.6 Hz, 1H), 3.58 (d, J = 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 155.88, 154.54, 151.57, 148.66, 146.37, 138.98, 133.99, 130.02, 111.21, 78.09, 66.49, 56.32; MS (FAB+) m/z 293 $(M+H)^+$, 315 $(M+Na)^+$; Anal.

Calcd. for $C_{13}H_{13}ClN_4O_2$: C, 53.34; H, 4.48; N, 19.14. Found: C, 53.28; H, 4.52; N, 19.06.

(±)-9-[4,4-Bis-(hydroxymethyl)-5-methylene-cyclopent-2-enyl] adenine (11): Compound **10** (79 mg, 0.27 mmol) was dissolved in saturated methanolic ammonia (5 mL) and the resulting solution was stirred overnight at 90–95°C in a steel bomb. After removing the reaction solvent, the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 4:1) to give compound **11** (72.8 mg, 70%) as a white solid: m.p. 177–179°C; UV (H_2O) λ_{max} 261.5.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.10 (s, 1H), 8.01 (s, 1H), 6.12 (dd, J = 6.0, 1.5 Hz, 1H), 6.00 (t, J = 2.4 Hz, 1H), 5.94 (dd, J = 6.0, 2.1 Hz, 1H), 5.19 (d, J = 2.4 Hz, 1H), 4.96 (br s, 1H), 4.93 (t, J = 5.2 Hz, 1H), 4,76 (t, J = 5.2 Hz, 1H), 3.75 (d, J = 9.8 Hz, 1H), 3.65 (d, J = 9.8 Hz, 1H), 3.60 (d, J = 9.6 Hz, 1H), 3.55 (d, J = 9.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 155, 69, 154.77, 152.76, 150.34, 141.72, 137.14, 134.04, 119.64, 110.24, 67.01, 66.44, 62.43, 58.72; MS (FAB+) m/z 274 $(M+H)^+$, 296 $(M+Na)^+$; Anal. Calcd. for $C_{13}H_{15}N_5O_2 \cdot 1.0\ H_2O$: C, 53.59; H, 5.88; N, 24.04. Found: C, 53.48; H, 5.80; N, 23.86.

(±)-1-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-5-methylene-cyclopent-2-enyl]-N^3-benzoylthymine (12): The benzoylthymine analogue was synthesized using a similar reaction procedure as that described for compound **9** as a white solid: m.p. 160–163°C; yield 43%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89–7.85 (m, 2H), 7.61–7.55 (m, 1H), 7.45–7.40 (m, 2H), 7.15 (s, 1H), 6.31 (dd, J = 5.4, 1.8 Hz, 1H), 6.24 (dd, J = 5.4, 1.5 Hz, 1H), 5.98 (t, J = 1.8 Hz, 1H), 4.70 (d, J = 2.0 Hz, 2H), 3.67–3.57 (m, 4H), 1.88 (s, 3H), 0.86 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 169.05, 163.30, 149.70, 142.05, 140.58, 134.56, 131,70, 130.39, 129.03, 123.35, 110.64, 66.02, 64.59, 57.51, 25.89, 18.28, 12.38, -5.45; MS (FAB+) m/z 619 $(M+Na)^+$; Anal. Calcd. for $C_{32}H_{48}N_2O_5Si_2$: C, 64.39; H, 8.11; N, 4.69. Found: C, 64.51; H, 7.98; N, 4.58.

(±)-1-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-5-methylene-cyclopent-2-enyl]-N^3-benzoyluracil (13): The benzoyluracil derivative was synthesized by a procedure similar to that used to prepare **9** as a white solid: m.p. 157–159°C; yield 39%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92–7.88 (m, 2H), 7.63–7.56 (m, 1H), 7.48–7.42 (m, 2H), 7.27 (d, J = 8.1 Hz, 1H), 6.32 (dd, J = 5.4, 1.8 Hz, 1H), 6.27 (dd, J = 5.1, 1.5 Hz, 1H), 6.03 (t, J = 1.8 Hz, 1H), 5.76 (d, J = 8.1 Hz, 1H), 4.64 (d, J = 1.5 Hz, 2H), 3.68 (d, J = 9.0 Hz, 2H), 3.60 (d, J = 9.0 Hz, 2H), 0.85 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 168.56, 162.57, 149.65, 147.46, 144.65, 140.76, 134.52, 132.65, 130.21, 129.14, 129.07, 128.54, 102.21, 70.08, 64.68, 62.43, 57.64, 25.76, 18.32, −5.49; MS (FAB+) m/z 583 $(M+H)^+$, 605 $(M+Na)^+$; Anal. Calcd. for $C_{31}H_{46}N_2O_5Si_2$: C, 63.88; H, 7.95; N, 4.81. Found: C, 63.95; H, 8.06; N, 4.75.

(±)-1-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-5-methylene-cyclopent-2-enyl]-N^4-benzoylcytosine (18): The benzoylcytosine derivative

was synthesized by a procedure similar to that used to prepare **9** as a white solid: m.p. 167–169°C; yield 38%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90–7.83 (m, 2H), 7.78–7.73 (m, 2H), 7.48–7.41 (m, 2H), 7.29(d,J = 7.8 Hz, 1H), 6.35 (dd, J = 5.4, 1.8 Hz, 1H), 6.28 (dd, J = 5.1, 1.6 Hz, 1H), 6.00 (d, J = 1.9 Hz, 1H), 5.54 (d, J = 7.8 Hz, 1H), 4.71 (d, J = 1.6 Hz, 2H), 3.67–59 (m, 4H), 0.87 (s, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 165.92, 165.88, 164.48, 160.66, 159.28, 154.75, 140.45, 139.28, 137.14, 132.88, 131,84, 129.02, 127.26, 110.23, 93.80, 67.02, 65.83, 64.87, 59.32, 25.90, 18.27, −5.59; MS (FAB+) m/z 583 $(M+H)^+$; Anal. Calcd. for $C_{31}H_{47}N_3O_4Si_2$: C, 63.99; H, 8.14; N, 7.22. Found: C, 64.16; H, 8.23; N, 7.32.

(±)-1-[4,4-Bis-(hydroxymethyl)-5-methylene-cyclopent-2-enyl]-N^3-benzoylthymine (14): For the desilylation of benzoylthymine analogue **12**, the reaction procedure was similar to that described for compound **10** as a white solid: m.p. 155–157°C; Yield 73%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.88–7.84 (m, 2H), 7.60 (m, 1H), 7.46–7.41 (m, 2H), 7.09 (s, 1H), 6.30–6.25 (m, 2H), 5.99 (m, 1H), 4.89 (t, J = 5.4 Hz, 1H), 4.80 (t, J = 5.4 Hz, 1H), 4.65 (d, J = 1.8 Hz, 2H), 3.69–3.60 (m, 4H), 1.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.78, 163.03, 149.43, 147.80, 142.2, 139.90, 134,54, 131.43, 130.40, 129.32, 128.32, 120.35, 109.64, 66.32, 64.43, 58.32,12.22; MS (FAB+) m/z 369 $(M+H)^+$, 391 $(M+Na)^+$; Anal. Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.35; H, 5.30; N, 7.53.

(±)-1-[4,4-Bis-(hydroxymethyl)-5-methylene-cyclopent-2-enyl]-N^3-benzoyluracil (15): For the desilylation of benzoyluracil derivative **13**, the reaction procedure was similar to that used in the preparation of **10** as a white solid: m.p. 169–171°C; yield 80%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.88 (m, 2H), 7.59 (d, J = 6.2 Hz, 1H), 7.48–7.42 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H), 6.33–6.28 (m, 2H), 6.04 (d, J = 1.9 Hz, 1H), 5.73 (d, J = 8.0 Hz, 1H), 4.90 (t, J = 5.4 Hz, 1H), 4.80 (t, J = 5.4 Hz, 1H), 4.67 (d, J = 1.6 Hz, 2H), 3.67 (d, J = 9.1 Hz, 2H), 3.58 (d, J = 9.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 168.20, 163.11, 148.32, 146.67, 143.71, 141.77, 137.30, 133.81, 131.99, 130.71, 129.54, 129.02, 127.34, 101.76, 68.65, 63.21, 63.03, 58.65; MS (FAB+) m/z 355 $(M+H)^+$, 377 $(M+Na)^+$; Anal. Calcd. for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.57; H, 5.05; N, 7.89.

(±)-1-[4,4-Bis-(hydroxymethyl)-5-methylene-cyclopent-2-enyl]-N^4-benzoylcytosine (19): For the desilylation of benzoylcytosine derivative **18,** the reaction procedure was similar to that used to prepare **10** as a white solid: m.p. 167–169°C; yield 71%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.89–7.84 (dd, J = 5.4, 1.8 Hz, 2H), 7.75–7.71 (m, 2H), 7.45 (m, 2H), 7.25 (d, J = 7.9 Hz, 1H), 6.32 (dd, J = 5.4, 1.9 Hz, 1H), 6.26 (dd, J = 5.2, 1.7 Hz, 1H), 6.01 (t, J = 2.0 Hz, 1H), 5.57 (d, J = 7.8 Hz, 1H), 4.86 (t, J = 5.3 Hz, 1H), 4.76 (br s, 1H), 4.68 (d, J = 1.7 Hz, 2H), 3.69 (d, J = 9.6 Hz, 2H), 3.56 (d, J = 9.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 166.43, 165.32, 163.67, 161.70, 158.21, 153.40, 142.21, 140.23, 136.90, 133.16, 131.22, 130.54, 128.52, 109.32, 94.01, 68.27, 64.67, 64.02, 57.30; MS (FAB+) m/z 254 $(M+H)^+$,

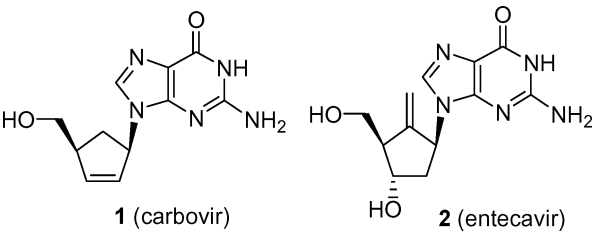
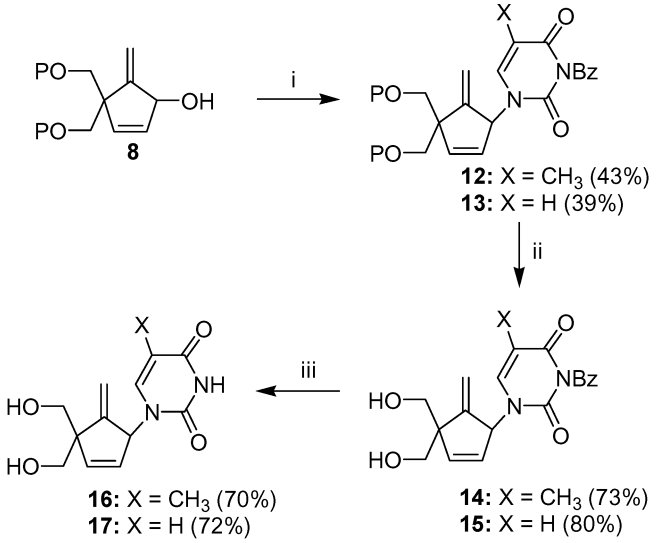


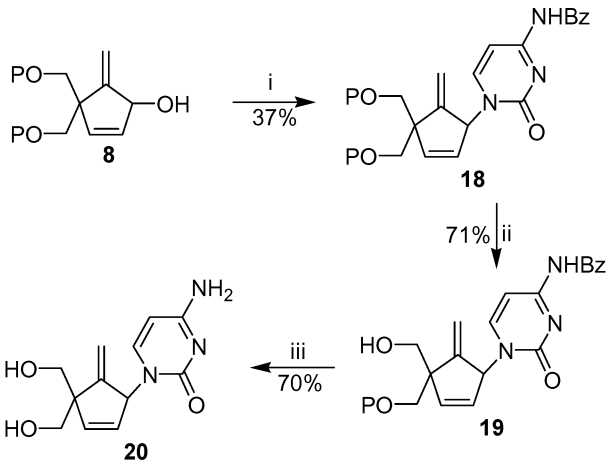
FIGURE 1 Examples of antiviral olefinic carbonucleosides.



SCHEME 3 Synthesis of thymine & uracil nucleoside analogues.

376 $(M+Na)^+$; Anal. Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.65; H, 5.38; N, 11.82. Figure 1, Scheme 3, Scheme 4

(±)-1-[4,4-Bis-(hydroxymethyl)-5-methylene-cyclopent-2-enyl]thymine (16): To the solution of benzoylthymine derivative **14** (79 mg, 0.214 mmol) in MeOH (5 mL), NaOMe (0.5 mL, 1.0 M solution in MeOH) was added and the mixture was stirred overnight at room temperature. Glacial acetic acid (0.1 mL) was added to the mixture for neutralization. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 4:1) to give compound **16** (39 mg, 70%) as a white solid: yield 79%; m.p. 169–171°C; UV (H_2O) λ_{max} 268.5.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.21 (br s, 1H), 7.11 (s, 1H), 6.29–6.24 (m, 2H), 6.01 (t, J = 1.9 Hz, 1H), 4.87 (t, J = 5.3 Hz, 1H), 4.79 (t, J = 5.4 Hz, 1H), 4.68 (s, 2H), 3.66 (d, J = 10.0 Hz, 2H), 3.53 (d, J =



Reagents: i) N^4-benzoylcytosine, DIAD, PPh_3, dioxane/DMF; ii) TBAF, THF/CH_3CN; iii) NaOMe, MeOH.

SCHEME 4 Synthesis of cytosine nucleoside analogue.

9.9 Hz, 2H), 1.89 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 164.58, 154.43, 151.39, 142.50, 137.29, 133.98, 109.28, 110.79, 66.99, 66.32, 61.47, 59.32, 12.43; MS (FAB+) m/z 265 $(M+H)^+$, 287 $(M+Na)^+$; Anal. Calcd. for $C_{13}H_{16}N_2O_4 \cdot 0.5$ MeOH: C, 57.84; H, 6.47; N, 9.99. Found: C, 57.74; H, 6.56; N, 10.09.

(±)-1-[4,4-Bis-(hydroxymethyl)-5-methylene-cyclopent-2-enyl]uracil (17): The uracil derivative was synthesized from **15** using a procedure similar to that described for the preparation of **16**: yield 72%; m.p. 163–165°C; UV (H_2O) λ_{max} 262.5.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.23 (br s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 6.02 (m, 2H), 6.01 (s, 1H), 5.69 (d, J = 8.0 Hz, 1H), 4.91 (t, J = 5.2 Hz, 1H), 4.82 (t, J = 5.3 Hz, 1H), 4.69 (s, 2H), 3.68 (d, J = 10.1 Hz, 2H), 3.55 (d, J = 10.0 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 163, 87, 154.21, 151.98, 145.87, 136.93, 134.21, 101.22, 111.01, 67.31, 66.94, 62.44, 58.99; MS (FAB+) m/z 251 $(M+H)^+$, 273 $(M+Na)^+$; Anal. Calcd. for $C_{12}H_{14}N_2O_4 \cdot 1.0\ H_2O$: C, 53.66; H, 6.01; N, 10.44. Found: C, 53.70; H, 5.94; N, 10.34.

(±)-1-[4,4-Bis-(hydroxymethyl)-5-methylene-cyclopent-2-enyl]cytosine (20): The cytosine derivative **20** was synthesized from **19** by a procedure similar to that used in the preparation of **16**: yield 70%; m.p. 166–168°C; UV (H_2O) λ_{max} 272.5.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.30 (d, J = 7.8 Hz, 1H), 7.07 (br d, 2H), 6.36 (dd, J = 5.4, 1.8 Hz, 1H), 6.27 (dd, J = 5.3, 1.6 Hz, 1H), 6.02 (br s, 1H), 5.56 (d, J = 7.8 Hz, 1H), 4.89 (t, J = 5.2 Hz, 1H), 4.79 (t, J = 5.3 Hz, 1H), 4.65 (d, J = 1.9 Hz, 2H), 3.65 (d, J = 9.9 Hz, 2H), 3.54 (d, J = 9.8 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 165, 21, 156.44, 153.97, 145.36, 134.51, 133.86, 93.58, 110.75, 67.76, 66.54, 63.02, 58.31; MS (FAB+) m/z 250 $(M+H)^+$, 272 $(M+Na)^+$; Anal. Calcd.

for $C_{12}H_{15}N_3O_3 \cdot 1.0\ H_2O$: C, 53.92; H, 6.41; N, 15.72. Found: C, 54.12; H, 6.29; N, 15.70

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