Stereoselective Synthesis and Antiviral Activity of Novel 4′(α)-Hydroxymethyl and 6′(α)-Methyl Dually Branched Carbocyclic Nucleosides

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The stereoselective synthesis 4′,6′-dually branched carbocyclic nucleosides was accomplished in this study. The introduction of a methyl group in the 6′(α)-position was accomplished by Felkin-Anh controlled alkylation. The construction of the required 4′(α)-quaternary carbon was carried out using a [3,3]-sigmatropic rearrangement. Bis-vinyl **6** was successfully cyclized using a Grubbs' catalyst II. The natural bases (adenine, cytosine) were efficiently coupled using a Pd(0) catalyst. When the synthesized compounds were examined for their activity against several viruses such as the HIV-1, HSV-1, HSV-2 and HCMV, the cytosine analogue **13** exhibited good antiviral activity against the HCMV.

Key Words : Antiviral agent, Branched carbocyclic nucleoside, Felkin-Anh model, [3,3]-Sigmatropic rearrangement

Introduction

Emerging drug-resistant virus strains in addition to the toxicity of various drugs are major problem in antiviral chemotherapy. Therefore, there has been a great deal of research into the synthesis of a number of structurally modified nucleosides. Recently, several branched-nucleosides were synthesized and evaluated as potent antitumor or antiviral agents. Among them, 4′(α)-*C*-hydroxymethylthymidine **1**[1], which has an additional branch at the 4′-position, was reported to exhibit potent antiviral activity (Figure 1).

Furthermore, more fundamental modifications of the pentofuranose moiety, such as carbocyclic nucleosides, have been reported to correlate with their antiviral activities. Carbocyclic nucleoside[2] is a group of compounds that are structurally similar to natural nucleosides where the furanose oxygen is replaced by a methylene group. The replacement of the furanose ring oxygen by carbon is of particular interest because the resulting carbocyclic nucleosides have a greater metabolic stability to phosphorylase,[3] which cleaves the glycosidic bond of nucleosides. Because the cyclopentane ring of carbocyclic nucleosides can emulate the furanose moiety, a number of these compounds have interesting biological activities, particularly in the areas of antiviral and anticancer chemotherapy. The recent discovery of branched carbocyclic nucleosides such as 6′(α)-hydroxymethyl carbovir **2**[4] and 6′(α)-methyl-carbathymidine **3**[5] as potential antiviral and antitumor agents has encouraged the search of novel nucleosides in this class of compounds (Figure 1).

Carbocyclic nucleosides are also believed to be potent inhibitors of the cellular enzyme, *S*-adenosyl-*L*-homocysteine (AdoHcy) hydrolase, which is very important in regulating the *S*-adenosylmethionine (SAM) dependent methylation reactions, and has emerged as a specific target for the reversible hydrolysis of the AdoHcy linkage to adenosine and homocysteine.[6] Inhibition of the enzyme on intact cellular systems results in AdoHcy accumulation. A higher AdoHcy concentration suppresses the enzyme activity by acting as a product inhibitor of the AdoMet-dependent methylation reaction.[7] Methyltransferases are essential for the maturation of mRNA. Therefore, inhibiting the methyl transferases by blocking the AdoHcy metabolism can disrupt the viral mRNA maturation. AdoHcy inhibitors usually display a broad-spectrum of antiviral activities. Moreover, this mechanism might be used in a combination therapy in association with the nucleosides with a different mechanism of action.

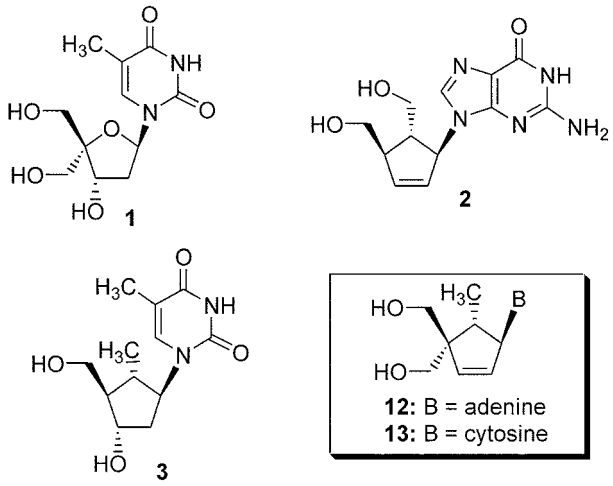

Figure 1. Structures of branched furanose nucleoside, carbocyclic nucleosides and target nucleosides.

Encouraged by these interesting structures and the

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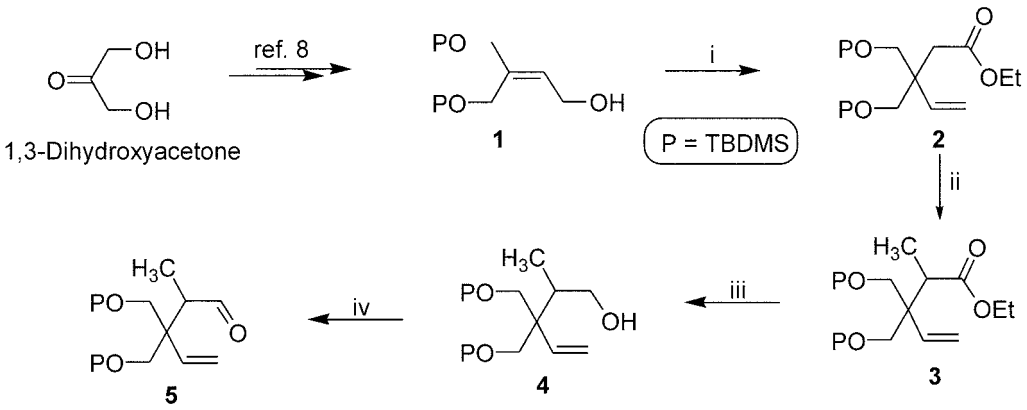


Scheme 1. reagents: i) Triethylorthoacetate, propionic acid, 140 °C; ii) LiHMDS, CH_3I, THF, −78 °C; iii) Dibal-H, CH_2Cl_2, 0 °C; iv) PCC, 4A MS, CH_2Cl_2, 4 h, rt.

biological activities of branched furanose and carbocyclic nucleosides, novel class of nucleosides comprising branched carbocyclic nucleosides with additional branches at 4′,6′-position were synthesized.

Results and Discussion

As shown in Scheme 1, the α,β-unsaturated ester **1**, which is readily accessible from 1,3-dihydroxy acetone using a previously reported method,[8] was converted to the γ,δ-unsaturated ester **2** by Claisen rearrangement.

First, an attempt was made to methylate the ester derivative **2** using a typical alkylation procedure (LiHMDS/CH_3I), which produced compound **3** in a high yield. The addition of DIBALH to a solution of the ester **3** in CH_2Cl_2 at 0 °C gave the alcohol derivative, **4**, which was subjected to oxidation conditions using PCC. The resulting aldehyde, **5** was subjected to Grignard reactions by vinyl magnesium bromide to yield a 10 : 1 mixture of bis-olefin **6**, as determined by ^{1}H NMR. The precise stereochemical assignment was performed in the subsequent reaction, because the mixture was difficult to separate at this stage.

Without separating compound **6**, the bis-olefin was subjected to standard ring-closing metathesis conditions[9] using a Grubbs' catalyst II [(Im)$Cl_2PCy_3RuCHPh$] to provide the required cyclopentenol **7** as a major isomer (72%) together with an unwanted and less polar compound **8** (7%). A systematic NOE study on the cyclized product (Figure 2), together with a mechanistic rational of the favored π-facial selection based on the Felkin-Anh rule depicted in Figure 3, strongly suggests that the stereochemical assignment of the

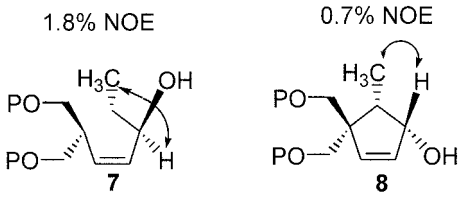


Figure 2. NOE observation of compound **7** and **8**.

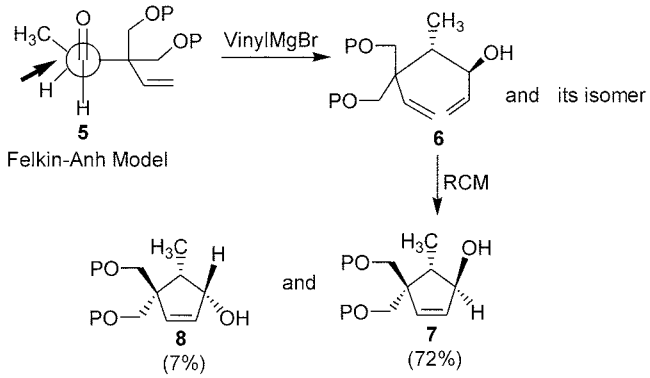
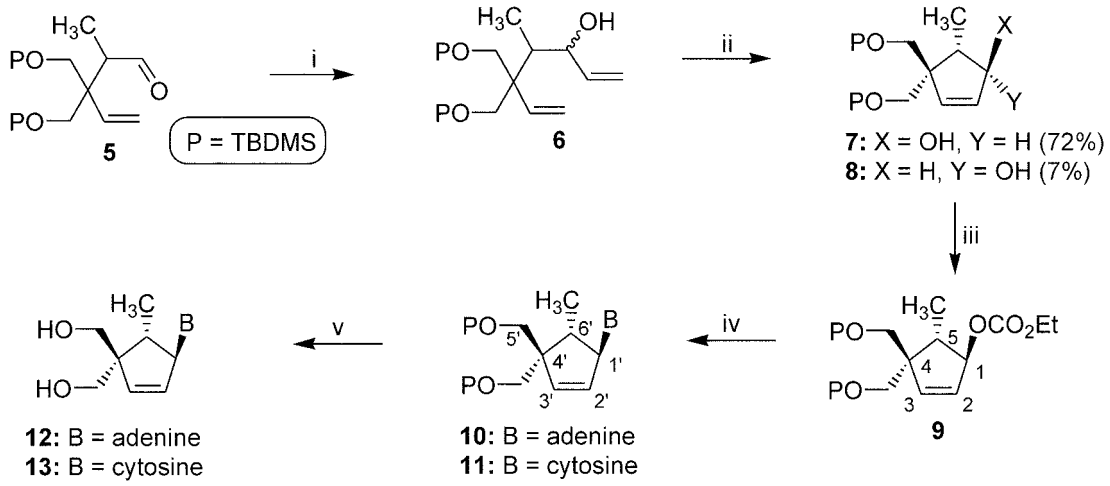


Figure 3. Addition of nucleophile to aldehyde **5** using Felkin-Anh rule.

cyclopentenols **7** and **8** was correct. On irradiation of C_1-H, relatively strong NOE was observed at the methyl protons of **7** (1.8% NOE), but not at the methyl protons those of **8** (0.7% NOE). Indeed, according to the ^{1}H NMR data, the integral was almost identical to the ratio of the separated **7** and **8** isomers (10/1).

In order to couple the cyclopentenol **7** with the bases (A = adenine, C = cytosine), the cyclopentenol **7** was transformed to the ethoxycarbonyl derivative **9** using ethyl chloroformate. Compound **9** was coupled with adenine and cytosine anions generated by NaH/DMSO using the [tris(dibenzylideneacetone)-dipalladium(0)-chloroform] adduct to give the compounds **10** and **11** (Scheme 2). The required β-stereochemistry of the nucleosides **10** and **11** was successfully controlled from the β-configuration of compounds **7** *via* a Pd(0) catalyzed π-allyl complex mechanism. Compounds **10** and **11** were desilylated by treating them with tetrabutylammonium fluoride (TBAF) to give the final nucleosides **12** and **13** in high yields.

Compounds **12** and **13** were tested against several viruses such as the HIV (MT-4 cells), HSV-1 (CCL81 cells), HSV-2 (CCL-81 cells), and HCMV (AD-169, Davis cells). It is interesting to note that the cytosine analogue **13** exhibited good antiviral activity against the HCMV (10.7 μg/mL), indicating that this virus might allow the sugar moiety can



Scheme 2. Reagents: i) CH_2-CHMgBr, THF, –78 °C; ii) Grubbs' catalyst II, benzene, reflux, overnight; iii) $ClCO_2Et$, DMAP pyridine, rt, overnight; iv) Bases (adenine, cytosine), $Pd_2(dba)_3$·$CHCl_3$, P(O-*i*-Pr)$_3$, NaH, THF/DMSO, reflux, overnight; v) TBAF, THF, rt.

serve as a template for phosphorylation as well as for DNA polymerase, which is unlike other viruses. However, the adenosine derivative **12** did not exhibit either antiviral activity or cytotoxicity when tested up to 100 μg/mL. For an evaluation of the anti-HCMV activity, HCMV strains AD-169 (ATTCC VR-583) and Davis (ATCC VR-807) were used and the standard CPE inhibition assay was used. The HEL 299 (human embryonic lung fibroblast) cells were used for the cytotoxicity assay.

In summary, this study developed a novel synthetic method for 4′(α),6′(α)-dually branched carbocyclic nucleosides from simple 1,3-dihyroxyacetone. When the synthesized compounds were tested against several viruses such as the HIV-1, HSV-1, HSV-2 and HCMV, the cytosine analogue **13** exhibit good antiviral activity against the HCMV. These results suggested that the 4′(α),6′(α)-dually branched sugar moiety can serve as a novel template for the development of new antiviral agents.

Experiments

All the chemicals were of reagent grade and were used as purchased. All the moisture-sensitive reactions were performed in an inert atmosphere of 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 JNM-LA 300 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. The elemental analyses were performed using an Elemental Analyzer System (Profile HV-3). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. The dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

3,3′-Bis-(*t*-butyldimethylsilyloxymethyl)-pent-4-enoic acid ethyl ester (2). A solution containing 15.0 g (43.3 mmol) of the allylic alcohol **1**, 250 mL of triethyl orthoacetate, and 1.0 mL of propionic acid was heated at 140 °C overnight with constant stirring under conditions for the removal of ethanol by distillation. The excess triethyl orthoacetate was distilled off and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 40) to give compound **2** (15.5 g, 86%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (dd, J = 18.0, 11.4 Hz, 1H), 5.09 (d, J = 11.1 Hz, 1H), 4.98 (d, J = 19.5 Hz, 1H), 4.05 (q, J = 7.5 Hz, 2H), 3.64 (dd, J = 15.6, 9.0 Hz), 2.40 (s, 2H), 1.22 (t, J = 7.5 Hz, 3H), 0.85 (s, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 171.92, 139.76, 114.48, 64.67, 59.88, 45.98, 36.84, 25.85, 18.25, 14.25, –5.56; Anal calc for $C_{21}H_{44}O_4Si_2$: C, 60.52; H, 10.64. Found: C, 60.39; H, 10.87.

(±)-3,3′-Bis-(*t*-butyldimethylsilyloxymethyl)-2-methyl-pent-4-enoic acid ethyl ester (3). To a stirred solution of LiHMDS (12.7 mL, 1.0 M solution in THF) in tetrahydrofuran (50 mL), compound **2** (2.6 g, 6.3 mmol) dissolved in tetrahydrofuran (10 mL) was added using a syringe at –78 °C. After stirring for 4 hr at the same temperature, the reaction mixture was warmed to –20 °C ~ –25 °C and stirred for an additional 2 hr at the same temperature. The reaction was quenched by the addition of a saturated ammonium chloride solution (10 mL). The resulting mixture was warmed to room temperature and partitioned between water (200 mL) and ethyl acetate (200 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (EtOAc/hexane, 1 : 50) to give compound **3** (2.2 g, 80%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.79 (dd, J = 11.7, 18.3 Hz, 1H), 5.12 (d, J = 11.4 Hz, 1H), 4.96 (d, J = 18.3 Hz, 1H), 4.06 (q, J = 6.9 Hz, 2H), 3.71 (d, J = 9.6, 1H), 3.65 (d, J = 9.6 Hz, 1H), 3.56 (d, J = 9.6 Hz, 1H), 3.49 (d, J = 9.6 Hz, 1H), 2.71 (q, J = 7.5 Hz, 1H), 1.05 (d, J = 7.5 Hz, 3H), 0.83 (s, 18H), 0.03 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.43, 142.54, 138.20, 115.43, 63.74, 61.71, 59.89, 47.94, 40.76, 25.82, 18.21, 14.27, 12.32, –5.63; Anal calc

for $C_{22}H_{46}O_4Si_2$: C, 61.34; H, 10.76. Found: C, 61.19; H, 9.67.

(±)-3,3′-Bis-(*t*-butyldimethylsilyloxymethyl)-2-methyl-pent-4-enol (4). To a solution of compound **3** (5.2 g, 12.1 mmol) in CH_2Cl_2 (150 mL), DIBALH (26.55 mL, 1.0 M solution in hexane) was added slowly at 0 °C, and stirred for 1 h at the same temperature. To the mixture, methanol (20 mL) was added. 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 : 30) to give compound **4** (4.3 g, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.67 (dd, J = 18.3, 11.4 Hz, 1H), 5.06 (d, J = 11.4 Hz, 1H), 4.86 (d, J = 18.3 Hz, 1H), 3.61-3.48 (m, 6H), 1.80 (m, 1H), 0.90 (d, J = 7.2 Hz, 3H), 0.82 (s, 18H), 0.04 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.67, 114.32, 64.44, 64.17, 63.90, 48.14, 38.68, 25.84, 18.23, 12.38, –5.62; Anal calc for $C_{20}H_{44}O_3Si_2$: C, 61.79; H, 11.41. Found: C, 61.87; H, 11.50.

(±)-3,3′-Bis-(*t*-butyldimethylsilyloxymethyl)-2-methyl-pent-4-enal (5). To a solution of compound **4** (5.0 g, 12.8 mmol) in CH_2Cl_2 (100 mL), 4 Å molecular sieves (7.5 g) and PCC (6.9 g, 32.1 mmol) were added slowly at 0 °C, and stirred for 4 h at room temperature. To the mixture, excess diethyl ether (500 mL) was then added. The mixture was stirred vigorously for 2 h at the same temperature, 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 : 50) to give compound **5** (4.3 g, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.74 (s, 1H), 5.82 (dd, J = 17.7, 11.1 Hz, 1H), 5.14 (d, J = 11.1 Hz, 1H), 5.00 (d, J = 17.7 Hz, 1H), 3.65 (d, J = 9.9 Hz, 2H), 3.59 (d, J = 9.9 Hz, 2H), 2.48 (q, J = 6.9 Hz, 1H), 1.02 (d, J = 6.9 Hz, 3H), 0.84 (s, 18H), 0.02 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.77, 139.27, 115.47, 63.88, 49.54, 47.98, 25.81, 18.23, 17.74, 8.71, –5.69; Anal calc for $C_{20}H_{42}O_3Si_2$: C, 62.12; H, 10.95. Found: C, 61.90; H, 10.86.

(*rel*)-(3*R* and 3*S*,4*S*)-5,5′-Bis-(*t*-butyldimethylsilyloxymethyl)-4-methyl-hepta-1,6-dien-3-ol (6). To a solution of compound **5** (5.0 g, 12.9 mmol) in dry THF (150 mL), vinyl magnesium bromide (19.4 mL, 1.0 M solution in THF) was added slowly at –78 °C. After 2 h, a saturated NH_4Cl solution (20 mL) was added, and the reaction mixture was warmed slowly to room temperature. The mixture was extracted with EtOAc (2 × 250 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 : 30) to give a diastereomeric mixture of the **6** (4.6 g, 85%) as a colorless oil: as a diastereomeric mixture for ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.73-5.63 (m, 2H), 5.21-4.84 (m, 4H), 3.69-3.48 (m, 5H), 1.77 (m, 1H), 0.82-0.78 (m, 21H), 0.02 (s,s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.82, 140.96, 113.97, 113.68, 69.96, 64.51, 63.86, 48.67, 41.86, 25.85, 18.29, 6.94, –5.62; Anal calc for $C_{22}H_{46}O_3Si_2$: C, 63.71; H, 11.18. Found: C, 63.51; H, 10.97.

(*rel*)-(1*R*,5*S*)-4,4′-Bis-(*t*-butyldimethylsilyloxymethyl)-5-methyl-cyclopent-2-enol (7) and (*rel*)-(1*S*,5*S*)-4,4′-bis-(*t*-Butyldimethylsilyloxymethyl)-5-methyl-cyclopent-2-enol (8). To a solution of compound **6** (3.2 g, 7.7 mmol) in dry benzene (20 mL), Grubbs' catalyst II (50 mg, 0.06 mmol) was added. The reaction mixture was refluxed overnight, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 20) to give the less polar cyclopentenol **7** (2.1 g, 72%) and less polar compound **8** (208.0 mg, 7%) as colorless oil; compound **7**; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.80 (dd, J = 5.4, 1.8 Hz, 1H), 5.58 (d, J = 6.0 Hz, 1H), 4.26 (m, 1H), 3.57-3.43 (m, 4H), 1.75 (m, 1H), 1.05 (d, J = 7.5 Hz, 3H), 0.84 (s, 9H), 0.82 (s, 9H), 0.03, (s, 6H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.19, 134.67, 84.37, 67.51, 63.78, 57.04, 47.95, 25.81, 18.41, 18.13, 13.16, –5.60; Anal calc for $C_{20}H_{42}O_3Si_2$: C, 62.12; H, 10.95. Found: C, 62.07; H, 10.81. Compound **8**; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.04 (dd, J = 5.4, 2.1 Hz, 1H), 5.73 (d, J = 6.0 Hz, 1H), 4.29-4.22 (m, 1H), 3.61 (d, J = 9.9 Hz, 1H), 3.50 (d, J = 10.2 Hz, 2H), 3.36 (d, J = 9.6 Hz, 1H), 1.80 (m, 1H), 1.01 (d, J = 7.5 Hz, 3H), 0.86 (s, 18H), 0.03 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.39, 135.32, 77.24, 67.94, 63.05, 57.14, 42.70, 25.95, 25.80, 18.51, 18.17, 9.40, -5.57; Anal calc for $C_{20}H_{42}O_3Si_2$: C, 62.12; H, 10.95. Found: C, 62.36; H, 11.09.

(*rel*)-(1*R*,5*S*)-1-Ethoxycarbonyloxy-4,4′-(*t*-butyldimethylsilyloxymethyl)-5-methyl-cyclopent-2-ene (9). To a solution of compound **7** (2.0 g, 5.2 mmol) in anhydrous pyridine (10 mL) ethyl chloroformate (0.8 mL, 5.6 mmol) and DMAP (55 mg, 0.4 mmol) were added. The reaction mixture was stirred overnight at room temperature. The reaction mixture was then quenched using a saturated $NaHCO_3$ solution (0.5 mL) and concentrated under vacuum. The residue was extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 25) to give compound **9** (2.1 g, 88%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (dd, J = 5.7, 1.5 Hz, 1H), 5.80 (dd, J = 6.0, 1.2 Hz, 1H), 5.31 (dt, J = 6.9, 1.5 Hz, 1H), 4.18 (q, J = 6.9 Hz, 2H), 3.62-3.43 (m, 4H), 2.04 (m, 1H), 1.30 (t, J = 6.9 Hz, 3H), 1.15 (d, J = 7.5 Hz, 3H), 0.88 (s, 18H), 0.02 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.26, 139.25, 130.55, 90.07, 67.07, 63.70, 63.30, 56.90, 44.48, 25.88, 25.83, 18.25, 18.16, 14.29, 12.42, –5.59; Anal calc for $C_{23}H_{46}O_5Si_2$: C, 60.21; H, 10.11. Found: C, 60.49; H, 10.05.

(*rel*)-(1′*R*,6′*S*)-9-[4,4′-Bis-(*t*-butyldimethylsilyloxymethyl)-6-methyl-cyclopent-2-en-1-yl] adenine (10). To pure NaH (35.1 mg, 1.5 mmol) in anhydrous DMSO (5.0 mL), adenine (201 mg, 1.47 mmol) was added. The reaction mixture was stirred for 30 min at 50-55 °C and then cooled to room temperature. Simultaneously, P(O-*i*-Pr)$_3$ (0.7 mL, 1.6 mmol) was added to a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (34.5 mg, 18.8 μmol) in anhydrous THF (10.0 mL), which was then stirred for 40 min. To the adenine solution in DMSO, a catalyst solution of THF and compound **9** (605 mg, 1.3 mmol) dissolved in anhydrous THF (6 mL) was added slowly. The reaction mixture was stirred overnight under reflux and then quenched with water (5 mL). The reaction solvent was

removed under reduced pressure. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1 : 15) to give compound **10** (242.0 mg, 33%) as a white solid: mp 172-175 °C; UV (MeOH) λ_{max} 261.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31 (s, 1H), 7.81 (s, 1H), 5.96 (d, J = 5.4 Hz, 1H), 5.82 (d, J = 5.4 Hz, 1H), 5.40 (d, J = 8.4 Hz, 1H), 3.63-3.54 (m, 4H), 2.25 (m, 1H), 1.11 (d, J = 6.9 Hz, 3H), 0.85 (s, 18H), 0.02 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.66, 152.87, 150.34, 140.43, 138.71, 130.08, 119.54, 66.48, 65.92, 63.72, 57.35, 47.77, 25.81, 18.20, 12.08, –5.58; Anal calc for $C_{25}H_{45}N_5O_2Si_2$: C, 59.60; H, 9.00; N, 13.90. Found: C, 59.50; H, 9.11; N, 14.04.

(*rel*)-(1′*R*,6′*S*)-1-[4,4′-Bis-(*t*-butyldimethylsilyloxymethyl)-6-methyl-cyclopent-2-en-1-yl] cytosine (11). Compound **11** was prepared from compound **9** using the method described for compound **10**: Yield 29%; mp 171-173 °C; UV (MeOH) λ_{max} 271.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (d, J = 7.2 Hz, 1H), 5.70 (d, J = 5.2 Hz, 1H), 5.61 (d, J = 7.2 Hz, 1H), 3.65-3.52 (m, 4H), 2.21 (m, 1H), 1.09 (d, J = 7.0 Hz, 3H), 0.84 (s, 18H), 0.03 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.40, 156.21, 145.34, 142.09, 137.81, 132.50, 84.12, 68.21, 64.55, 58.34, 48.78, 25.42, 18.12, 13.09, –5.51; Anal calc for $C_{24}H_{45}N_3O_3Si_2$: C, 60.08; H, 9.45; N, 8.76. Found: C, 59.88; H, 9.38; N, 8.80.

(*rel*)-(1′*R*,6′*S*)-9-Bis-[4,4′-(hydroxymethyl)-6-methyl-cyclopent-2-en-1-yl] adenine (12). To a solution of compound **10** (240 mg, 0.5 mmol) in THF (10 mL), TBAF (1.4 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 ($MeOH/CH_2Cl_2$, 1 : 4) to give compound **12** (97.0 mg, 74%) as a white solid: mp 180-182 °C; UV (H_2O) λ_{max} 262.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.10 (s, 1H), 8.01 (s, 1H), 7.17 (br s, 2H, D_2O exchangeable), 5.92 (dd, J = 5.4, 1.8 Hz, 1H), 5.83 (dd, J = 6.0, 1.5 Hz, 1H), 5.26 (dd, J = 8.4, 1.5 Hz, 1H), 4.61 (br s, 1H, D_2O exchangeable), 4.49 (br s, 1H, D_2O exchangeable), 3.46-3.34 (m, 4H), 2.25 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.97, 152.37, 149.76, 139.49, 138.77, 130.50, 118.81, 66.06, 64.62, 62.15, 57.14, 46.58, 11.95; Anal calc for $C_{13}H_{17}N_5O_2$: C, 56.71; H, 6.22; N, 25.44. Found: C, 56.89; H, 6.31; N, 25.51.

(*rel*)-(1′*R*,6′*S*)-1-Bis-[4,4′-(hydroxymethyl)-6-methyl-cyclopent-2-en-1-yl] cytosine (13). Compound **13** was prepared from compound **11** using the method described for synthesizing compound **12**: yield 79%; mp 174-176 °C; UV (H_2O) λ_{max} 272.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.74 (d, J = 7.2 Hz, 1H), 7.12 (br d, 2H, D_2O exchangeable), 5.71 (br s, 1H), 5.62 (d, J = 7.2 Hz, 1H), 4.80 (br s, 2H, D_2O exchangeable), 3.67-3.58 (m, 4H), 2.14 (m, 1H), 1.12 (d, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.65, 155.89, 145.22, 143.17, 138.82, 132.51, 85.12, 68.88, 63.81, 58.12, 48.69, 13.11; Anal calc for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.48; H, 6.90; N, 16.83.

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