Synthesis of Novel 4'α-Phenyl and 5'α-Methyl Branched Carbocyclic Nucleosides

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This paper describes the racemic and stereoselective synthetic route for a novel 4'α-phenyl and 6'α-methyl doubly branched carbocyclic nucleosides from an acyclic 2-hydroxy acetophenone. The installation of phenyl group at the 4'-position of carbocyclic nucleoside was successfully accomplished via a sequential [3,3]-sigmatropic rearrangement. The stereoselective introduction of a methyl group in the 6'α-position was accomplished by Felkin-Anh controlled alkylation. Bis-vinyl **11** compound was successfully cyclized using a Grubbs' catalyst II to desired carbocycles. The natural bases (adenine and cytosine) were efficiently coupled using a Pd(0) catalyst. Although all the synthesized compounds were examined for their activity against several viruses such as HIV-1, HSV-1, HSV-2 and HCMV, only cytosine analogues **17** exhibited weak antiviral activity against HCMV.

Key Words : Carbocyclic nucleoside, Antiviral agents, [3,3]-Sigmatropic rearrangement, Ring-closing metathesis

Introduction

Carbocyclic nucleosides[1] possess greater metabolic stability against nucleoside phosphorylase,[2] and show interesting antiviral activity against the human immunodeficiency virus, the hepatitis B virus owing to their structural characteristics. 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.[3] 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.[4] 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.

Recently, several branched nucleosides[5] have been synthesized and evaluated as potent antitumor or antiviral agents. Among them, 4'α-ethenyl compound **1**[6] and 4'α-ethynyl compound **2**[7] were reported to exhibit potent antiviral and antitumor activities. Furthermore, 6'α-hydroxymethyl carbovir **3**[8] and 6'α-methyl-carbothymidine **4**[9] also showed significant antiviral and antitumor activity (Figure 1). Based on these interesting findings of branched nucleosides, a novel class of nucleosides comprising 6'α-branched carbocyclic nucleosides with an additional phenyl group at 4'-position was synthesized.

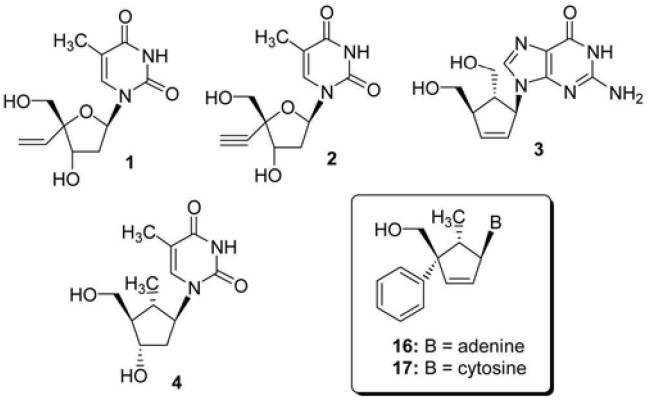
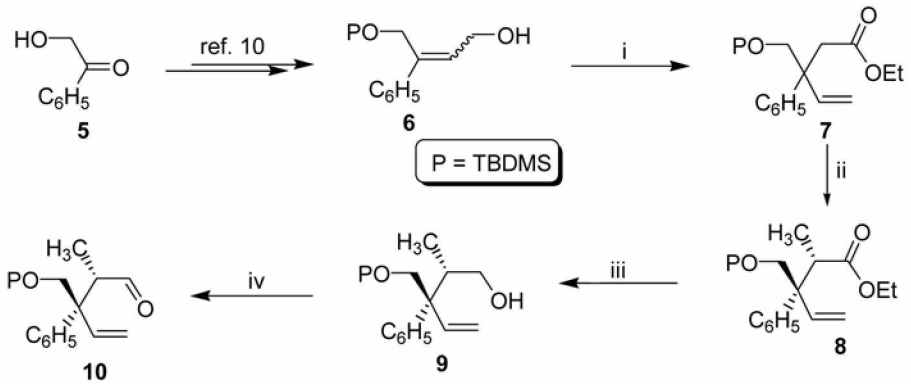


Figure 1. Rational design of target nucleosides.

It is well known that the [3,3]-sigmatropic rearrangement, RCM and Pd(0) catalyzed allylic alkylation have been employed widely in synthetic organic chemistry. A convenient and general synthetic procedure for branched nucleosides using these procedures is described in this paper.

Results and Discussion

As shown in Scheme 1, the silyl protected γ,δ-unsaturated ester **7** was prepared from 2-hydroxyacetophenone using previously reported procedure.[10] First, an attempt was made to methylate the ester derivative **7** using a typical ester enolate alkylation procedure (LHMDS/CH_3I), which produced compound **8** in an only compound. The determination of relative stereochemisty was postponed to the latter stage. Also, the reasons of unexpected high stereochemical outcome of **8** are hard to say at this stage. The correct structure for this compound could readily be assigned through the NOE comparison between proximal protons in



Scheme 1. Synthesis of aldehyde intermediate **10**. 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.

the cyclopentenol structures (**12**α and **12**β). Addition of DIBALH to a solution of the ester **8** in CH_2Cl_2 at 0 °C gave the alcohol derivative, **9**, which was subjected to oxidation conditions using PCC to give aldehyde **10**.

The resulting carbonyl compound **10** was subjected to Grignard addition by vinylmagnesium bromide to yield a bis-olefin **11** as an inseparable mixture. Their accurate stereochemical assignments were also performed in the cyclopentenol structures, because the mixture was difficult to separate at this stage. Without separating diastereomers, the bis-olefin **11** was subjected to standard ring-closing metathesis conditions using a second-generation Grubbs' catalyst [(Im)$Cl_2PCy_3RuCHPh$][11] to predominantly provide the required cyclopentenol **12**β (81%) together with an undesired compound **12**α (5%). Now a systematic NOE study on the cyclized products (**12**α and **12**β), together with a mechanistic rational of the favored π-facial selection based on the Felkin-Anh rule[12] depicted in Figure 2, was pursued to strongly support that the stereochemical assignment of the cyclopentenols **12**α and **12**β was correct. This rule states that the bulkiest of the α ligand (L) is placed to perpendicular relationship to the plane of the carbonyl group anti to the incoming nucleophile, and the sterically next most demanding α substituent (M) is placed gauche to the carbonyl function. On irradiation of C_1-H, relatively strong

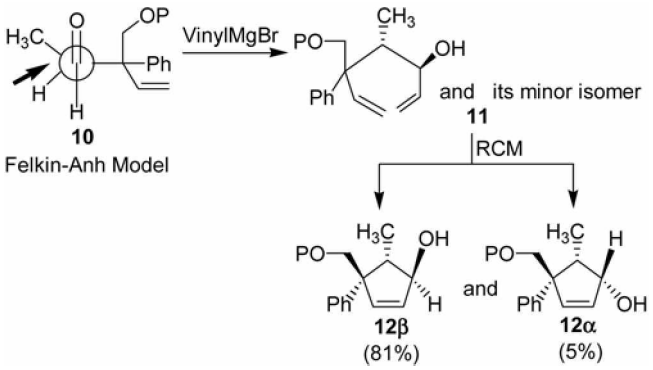


Figure 2. Addition of nucleophile to aldehyde **10** using Felkin-Anh rule.

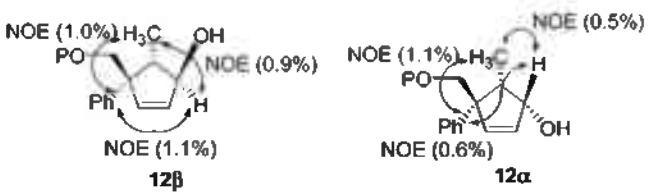


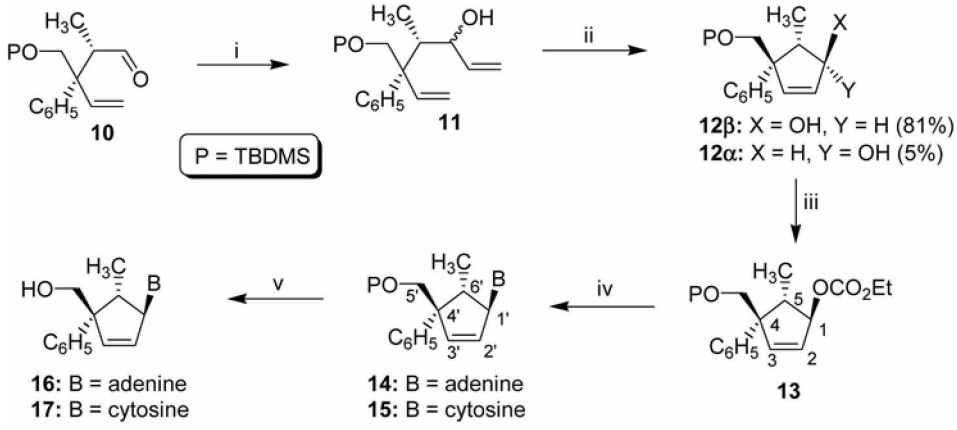
Figure 3. NOE results of compound **12**β and **12**α.

NOE was observed at the methyl protons of **12**β (0.9% NOE), but not at the methyl protons those of **12**α (0.5% NOE) (Figure 3). At last, the correct configuration of **8** could be assigned on the basis of spectroscopical comparisons observed in compounds **12**β and **12**α.

In order to couple the cyclopentenol **12**β with the bases (A = adenine, C = cytosine), the cyclopentenol **12**β was transformed to the ethoxycarbonyl derivative **13** using ethyl chloroformate. Compound **13** was coupled with adenine and cytosine anions generated by previously reported method to give the compounds **14** and **15** (Scheme 2). The required β-stereochemistry of the nucleosides **14** and **15** was successfully controlled from the β-configuration of compounds **12**β *via* a Pd(0) catalyzed π-allyl complex mechanism.[13] Compounds **14** and **15** were desilylated by treating them with tetrabutylammonium fluoride (TBAF) to give the final nucleosides **16** and **17**, respectively.

Based on extensive literature searching, compounds **16** and **17** appear to be novel nucleosides. Antiviral evaluations against various viruses such as HIV-1, HSV-1, HSV-2 and HCMV were performed. Cytosine analogue **17** showed weak anti-HCMV activity (EC_{50} = 47 μM) without any cytotoxicity up to 100 μM.

In summary, an efficient synthetic method for synthesizing 4'α-*C* phenyl branched carbocyclic nucleosides from a simple α-hydroxy ketone derivative was developed. Our procedure highlights the simplicity and efficiency in the installation of phenyl branch at cyclopentene ring systems. On the basis of this strategy, the enantiomeric syntheses of branched nucleosides with different nucleobases and substituents are in progress.



Scheme 2. Synthesis of target compounds. 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.

Experimental Section

All chemicals were reagent grade and were used as purchased. All moisture-sensitive reactions were performed in an inert atmosphere of either N_2 or Ar using distilled dry solvents. The elemental analysis was performed by Elemental Analyzer System (EA1112). NMR spectra were recorded on a JEOL JNM-LA 300 spectrometer.

(±)-3-(*t*-Butyldimethylsilyloxymethyl)-3-phenyl-pent-4-enoic acid ethyl ester (7): A solution of allylic alcohol **6** (19.3 g, 69.32 mmol) in triethyl orthoacetate (300 mL) and 0.9 mL of propionic acid was heated at 130-135 °C overnight with stirring to allow for the removal of ethanol. The excess of triethyl orthoacetate was removed by distillation and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 15) to give **7** (19.6 g, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.25 (m, 5H), 6.26 (dd, J = 18.0, 11.1 Hz, 1H), 5.31 (dd, J = 11.4, 1.2 Hz, 1H), 5.16 (dd, J = 17.7, 0.6 Hz, 1H), 4.10-3.99 (m, 4H), 3.00 (s, 2H), 1.18 (t, J = 6.9 Hz, 3H), 0.99 (s, 9H), 0.02 (two s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.51, 143.17, 142.33, 127.82, 127.34, 126.30, 114.34, 67.73, 59.94, 48.70, 39.74, 25.76, 18.19, 14.07, −5.71.

(*rel*)-(2*S*,3*S*)-3-(*t*-Butyldimethylsilyloxymethyl)-3-phenyl-2-methyl-pent-4-enoic acid ethyl ester (8): To a stirred solution of LiHMDS (17.2 mL, 1.0 M solution in THF) in tetrahydrofuran (50 mL), compound **2** (3.0 g, 8.6 mmol) dissolved in tetrahydrofuran (10 mL) was added using a syringe at −78 °C. After stirring for 2 hr at the same temperature, the reaction mixture was warmed to −20 °C ~ −25 °C and stirred for an additional 1 hr at the same temperature. To this mixture was added iodomethane (1.83 g, 12.9 mmol) at the −78 °C and stirred for 3 h. The mixture was warmed to −20 °C ~ −25 °C and stirred for an additional 2 h. The reaction was quenched by the addition of a saturated ammonium chloride solution (15 mL). The resulting mixture was warmed to room temperature and partitioned between water (250 mL) and ethyl acetate (250 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (EtOAc/hexane, 1 : 40) to give compound **8** (2.37 g, 76%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57-7.31 (m, 5H), 6.62 (dd, J = 18.3, 11.7 Hz, 1H), 5.57 (dd, J = 11.1, 0.9 Hz, 1H), 5.28 (d, J = 18.0 Hz, 1H), 4.17 (d, J = 9.3 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H), 3.86 (d, J = 9.6 Hz, 1H), 3.66 (q, J = 7.5 Hz, 1H), 1.37 (d, J = 7.2 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H), 0.99 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.41, 143.64, 140.04, 128.02, 127.36, 126.19, 115.36, 66.63, 59.81, 50.96, 42.28, 25.82, 18.18, 13.89, −5.89.

(*rel*)-(2*S*,3*S*)-3-(*t*-Butyldimethylsilyloxymethyl)-3-phenyl-2-methyl-pent-4-enol (9): To a solution of compound **8** (4.5 g, 12.41 mmol) in CH_2Cl_2 (150 mL), DIBALH (26.1 mL, 1.0 M solution in hexane) was added slowly at 0 °C, and stirred for 2 h at the same temperature. To the mixture, methanol (25 mL) was added. The mixture was stirred at room temperature for 3 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 : 20) to give compound **9** (3.74 g, 94%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49-7.27 (m, 5H), 6.02 (dd, J = 18.0, 11.4 Hz, 1H), 5.46 (d, J = 11.5 Hz, 1H), 5.22 (d, J = 18.0 Hz, 1H), 4.09 (d, J = 9.9 Hz, 1H), 3.89 (d, J = 9.9 Hz, 1H), 3.77 (dd, J = 10.5, 3.6 Hz, 1H), 3.49 (dd, J = 10.2, 2.1 Hz, 1H), 2.70 (q, J = 6.6 Hz, 1H), 1.10 (d, J = 6.6 Hz, 3H), 0.95 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.86, 140.38, 128.04, 127.79, 126.13, 115.72, 66.82, 65.21, 51.70, 38.84, 25.73, 18.12, 12.64, −5.96.

(*rel*)-(2*S*,3*S*)-3-(*t*-Butyldimethylsilyloxymethyl)-3-phenyl-2-methyl-pent-4-enal (10): To a solution of compound **9** (2.5 g, 7.79 mmol) in CH_2Cl_2 (50 mL), 4 Å molecular sieves (5.5 g) and PCC (4.5 g, 21 mmol) were added slowly at 0 °C, and stirred overnight at room temperature. To the mixture, excess diethyl ether (300 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 : 40) to give compound **10** (2.03 g, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.83 (s, 1H), 7.46-7.31 (m, 5H), 6.11 (dd, J = 18.0, 11.4 Hz, 1H), 5.47 (d, J = 11.4 Hz, 1H), 5.24 (d, J = 17.7 Hz, 1H), 4.14 (d, J = 9.9 Hz, 3.93 (d, J = 9.9 Hz, 1H), 3.31 (q, J = 6.8 Hz, 1H), 1.14 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.98, 142.46, 140.21, 128.38, 128.17, 127.83, 126.67, 116.23, 66.63, 51.65, 49.37, 25.77, 18.20, 18.20, 9.49, −5.88.

(*rel*)-(3*R*,4*S*,5*S*)-5-(*t*-Butyldimethylsilyloxymethyl)-5-phenyl-4-methyl-hepta-1,6-dien-3-ol (11): To a solution of compound **10** (3.0 g, 9.42 mmol) in dry THF (80 mL), vinyl magnesium bromide (11.3 mL, 1.0 M solution in THF) was added slowly at −78 °C. After 3 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 (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 : 20) to give divinyl **11** (2.6 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.22 (m, 5H), 6.29 (dd, J = 18.3, 11.1 Hz, 1H), 5.97-5.86 (m, 1H), 5.37 (d, J = 11.2 Hz, 1H), 5.21 (d, J = 18.2 Hz, 1H), 5.13-5.06 (m, 2H), 4.50 (s, 1H), 4.05 (d, J = 10.2 Hz, 1H), 3.95 (d, J = 10.2 Hz, 1H), 2.71 (d, J = 3.0 Hz, 1H), 2.49 (q, J = 6.9 Hz, 1H), 0.90 (s, 9H), 0.86 (d, J = 6.9 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.18, 141.71, 141.22, 127.99, 126.16, 115.03, 113.52, 71.24, 66.47, 52.59, 42.10, 25.80, 18.22, 7.64, −5.78.

(*rel*)-(1*R*,4*S*,5*S*)-4-(*t*-Butyldimethylsilyloxymethyl)-4-phenyl-5-methyl-cyclopent-2-enol (12β) and (*rel*)-(1*S*,4*S*,5*S*)-4-(*t*-Butyldimethylsilyloxymethyl)-4-phenyl-5-methyl-cyclopent-2-enol (12α): To a solution of compound **11** (2.7 g, 7.79 mmol) in dry benzene (20 mL), Grubbs' catalyst II (52 mg, 0.07 mmol) was added. The reaction mixture was refluxed overnight, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 15) to give the compound **12β** (2.0 g, 81%) and less polar **12α** (124 mg, 5%) as colorless oil, respectively: compound **12β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.22 (m, 5H), 6.05 (dd, J = 6.0, 1.5 Hz, 1H), 5.97 (dd, J = 6.0, 1.5 Hz, 1H), 4.60 (t, J = 7.5 Hz, 1H), 4.02 (d, J = 9.9 Hz, 1H), 3.68 (d, J = 9.9 Hz, 1H), 1.99 (quint, J = 7.0 Hz, 1H), 1.34 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.49, 137.43, 135.52, 128.32, 126.30, 125.99, 84.21, 65.47, 59.07, 54.51, 25.77, 18.11, 11.57, −5.55. compound **12α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24-7.10 (m, 5H), 5.99 (dd, J = 5.7, 2.1 Hz, 1H), 5.80 (d, J = 5.4 Hz, 1H), 4.15 (d, J = 10.8 Hz, 1H), 3.92 (d, J = 9.9 Hz, 1H), 3.55 (d, J = 9.9 Hz, 1H), 3.13 (d, J = 10.8 Hz, 1H), 2.11 (dd, J = 7.8, 5.7 Hz, 1H), 0.79 (s, 9H), 0.49 (d, J = 7.2 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.43, 136.57, 134.50, 128.44, 128.06, 127.46, 126.61, 84.04, 69.12, 48.73, 25.97, 18.52, 17.49, −5.48.

(*rel*)-(1*R*,4*S*,5*S*)-1-Ethoxycarbonyloxy-4-(*t*-butyldimethylsilyloxymethyl)-4-phenyl-5-methyl-cyclopent-2-ene (13): To a solution of compound **12β** (2.48 g, 7.8 mmol) in anhydrous pyridine (20 mL) ethyl chloroformate (1.2 mL, 8.4 mmol) and DMAP (83 mg, 0.6 mmol) were added. The reaction mixture was stirred overnight at room temperature. The reaction mixture was then quenched using a saturated $NaHCO_3$ solution (2.0 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 : 20) to give compound **9** (2.43 g, 80%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.21 (m, 5H), 6.08 (dd, J = 6.0, 1.5 Hz, 1H), 5.99 (dd, J = 6.0, 1.2 Hz, 1H), 5.47 (dt, J = 7.5, 1.5 Hz, 1H), 4.20 (q, J = 7.0, 2H), 4.05 (d, J = 10.2 Hz, 1H), 3.66 (d, J = 9.9 Hz, 1H), 2.30 (quint, J = 7.2 Hz, 1H), 1.30 (t, J = 7.5 Hz, 3H), 1.26 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.19, 144.59, 139.53, 131.56, 128.36, 126.49, 125.99, 89.46, 64.99, 63.67, 58.83, 49.91, 25.76, 18.10, 14.24, 11.42, −5.57.

(*rel*)-(1'*R*,4'*S*,6'*S*)-9-[4-(*t*-Butyldimethylsilyloxymethyl)-4-phenyl-6-methyl-cyclopent-2-en-1-yl] adenine (14): To pure NaH (27.1 mg, 1.2 mmol) in anhydrous DMSO (4.0 mL), adenine (154 mg, 1.13 mmol) was added. The reaction mixture was stirred for 30 min at 55-60 °C and then cooled to room temperature. Simultaneously, P(O-*i*-Pr)$_3$ (0.54 mL, 1.23 mmol) was added to a solution of $Pd_2(dba)_3$·$CHCl_3$ (26.56 mg, 14.4 mmol) in anhydrous THF (9.0 mL), which was then stirred for 40 min. To the adenine solution in DMSO, a catalyst solution of THF and compound **13** (391 mg, 1.0 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 : 10) to give compound **14** (135 mg, 31%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (s, 1H), 7.77 (s, 1H), 7.32-7.22 (m, 5H), 6.24 (dd, J = 6.0, 2.4 Hz, 1H), 6.05 (dd, J = 5.7, 1.8 Hz, 1H), 5.86 (s, 2H), 5.53 (dt, J = 8.4, 1.8 Hz, 1H), 4.08 (d, J = 9.9 Hz, 1H), 3.79 (d, J = 9.9 Hz, 1H), 2.39 (quint, J = 6.9 Hz, 1H), 1.28 (d, J = 6.9 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.44, 152.974, 144.53, 140.78, 138.95, 130.83, 128.59, 126.74, 126.03, 66.70, 65.67, 59.35, 53.89, 25.92, 18.23, 11.86, −5.45.

(*rel*)-(1'*R*,4'*S*,6'*S*)-1-[4-(*t*-Butyldimethylsilyloxymethyl)-4-phenyl-6-methyl-cyclopent-2-en-1-yl] cytosine (15): Compound **15** was synthesized from compound **13** using the method described for compound **14**: Yield 22%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (s, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.32-7.22 (m, 5H), 6.12 (dd, J = 6.0, 2.2 Hz, 1H), 6.00 (dd, J = 5.8, 2.0 Hz, 1H), 5.91 (d, J = 7.2 Hz, 1H), 5.53 (dt, J = 8.0, 1.8 Hz, 1H), 4.00 (d, J = 10.0 Hz, 1H), 3.76 (d, J = 10.0 Hz, 1H), 2.41 (dt, J = 7.0, 1.2 Hz, 1H), 1.22 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.13, 155.91, 143.23, 142.78, 140.78, 138.95, 130.83, 128.59, 126.88, 92.16, 67.12, 64.21, 58.87, 54.41, 25.86, 18.24, 11.72, −5.56.

(*rel*)-(1'*R*,4'*S*,6'*S*)-9-[4-(Hydroxymethyl)-4-phenyl-6-

methyl-cyclopent-2-en-1-yl] adenine (16): To a solution of compound **14** (200 mg, 0.46 mmol) in THF (8 mL), TBAF (0.69 mL, 1.0 M solution in THF) at 0 °C was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1 : 4) to give compound **16** (102 mg, 69%) as a white solid: mp 190-192 °C; UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.17 (s, 1H), 8.15 (s, 1H), 7.49-7.24 (m, 7H), 6.28 (dd, J = 5.4, 2.1 Hz, 1H), 6.16 (dd, J = 5.7, 1.8 Hz, 1H), 5.53 (dt, J = 8.7, 2.1 Hz, 1H), 4.89 (t, J = 4.8 Hz, 1H, D_2O exchangeable), 3.96 (dd, J = 10.8, 5.4 Hz, 1H), 3.80 (dd, J = 10.8, 4.5 Hz, 1H), 2.45 (quint, J = 6.9 Hz, 1H), 1.20 (d, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.99, 152.36, 149.74, 145.06, 139.94, 139.14, 131.25, 128.31, 126.32, 118.94, 65.91, 63.75, 58.76, 53.03, 11.24; Anal calc for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.45; H, 6.09; N, 21.66.

(*rel*)-(1'*R*,4'*S*,6'*S*)-1-[4-(Hydroxymethyl)-4-phenyl-6-methyl-cyclopent-2-en-1-yl] cytosine (17): Compound **15** was prepared from compound **11** using the method described for synthesizing compound **16**: yield 65%; mp 180-182 °C; UV (H_2O) λ_{max} 271.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.73 (d, J = 7.2 Hz, 1H), 7.50-7.10 (m, 7H), 6.17 (dd, J = 5.6, 2.1 Hz, 1H), 6.09 (dd, J = 5.8, 1.8 Hz, 1H), 5.87 (d, J = 7.2 Hz, 1H), 5.57 (dt, J = 8.4, 2.1 Hz, 1H), 5.01 (t, J = 5.0 Hz, 1H, D_2O exchangeable), 3.82 (dd, J = 10.8, 5.6 Hz, 1H), 3.71 (dd, J = 10.8, 4.2 Hz, 1H), 2.35 (quint, J = 7.0 Hz, 1H), 1.19 (d, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.61, 155.76, 142.31, 141.12, 138.44, 131.45, 128.50, 126.88, 126.23, 91.21, 67.42, 64.21, 58.56, 48.76, 12.87; Anal calc for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.89; H, 6.50; N, 14.04.

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