Articles

Synthesis of Novel Carbovir Analogue

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The synthesis of 4'-phenyl and 1'-methyl doubly branched carbocyclic nucleoside was accomplished from 2-hydroxy acetophenone. The 4'-phenyl group was installed *via* a [3,3]-sigmatropic rearrangement reaction, and the carbonyl addition of methylmagnesium bromide was used to introduce the 1'-methyl group. Cyclization of divinyl **9** was performed using 2nd generation Grubbs catalyst. The coupling of cyclopentenol **12**α with 6-chloropurine by Mitsunobu reaction and desilylation was used to synthesize the target nucleoside **15**.

Key Words : Antiviral agents, Branched nucleoside, Mitsunobu reaction

Introduction

Nucleoside analogues have been the cornerstone of antiviral chemotherapy over the past decades. Although structure-activity relationship studies have not led to a pharmacophore model for the antiviral activities of nucleosides, some structural features have been particularly successful. Therefore, the development of structurally new nucleoside derivatives, which have potent antiviral activities and low toxicity, as well as novel resistance profile, are urgently needed to provide better choices for the combination chemotherapy. Recently, several branched nucleosides were synthesized and found to be potent antitumor or antiviral agents. Among them, 4'α-*C*-ethenylthymidine **1**,[1] 4'α-*C*-ethynylthymidine **2**[2] are of particular interest as they represent a new class of compounds and exhibit significant biological activity (Figure 1).

The replacement of the oxygen atom on the furanose ring by carbon is of particular interest because the resulting carbocyclic nucleosides[3] have a greater metabolic stability to phosphorylase,[4] which cleaves the glycosidic bond of nucleosides. Many carbocyclic nucleosides have interesting biological activities, particularly in the areas of antiviral and anticancer chemotherapy, because the cyclopentane ring of these compounds can imitate the furanose moiety. The recent discovery of olefinic carbocyclic nucleosides, such as carbovir (**3**)[5] and abacavir (**4**),[6] which are potential anti-HIV agents, have increased interests in the search for novel nucleosides in this class of compounds. Carbocyclic nucleosides are also believed to be potent inhibitors of the cellular enzyme, *S*-adenosyl-*L*-homocysteine (AdoHcy) hydrolase, which is very important for regulating the *S*-adenosyl-methionine (SAM) dependent methylation reactions, and has emerged as a specific target for the reversible hydrolysis of the AdoHcy linkage to adenosine and homocysteine. However, the side effects[7] with these antiviral agents as well as the emergence of drug-resistant mutants are a continuing problem.[8]

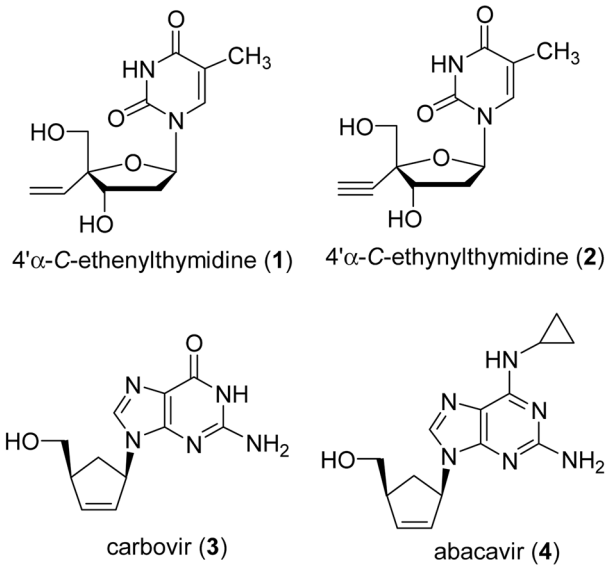
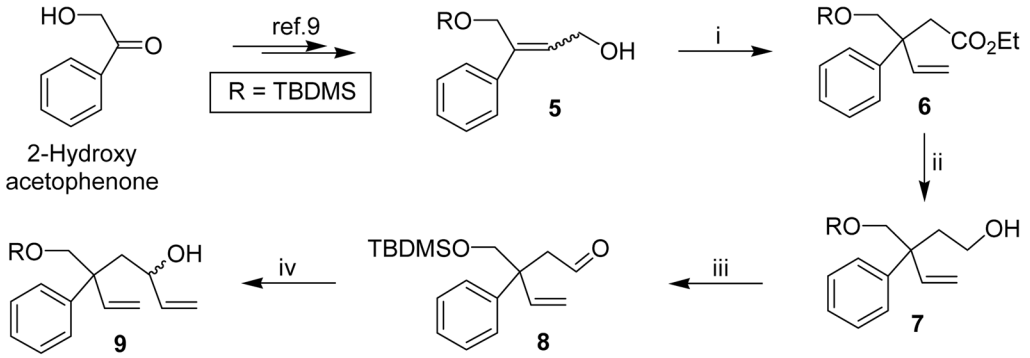


Figure 1. Synthesis rationable of the target nucleoside.

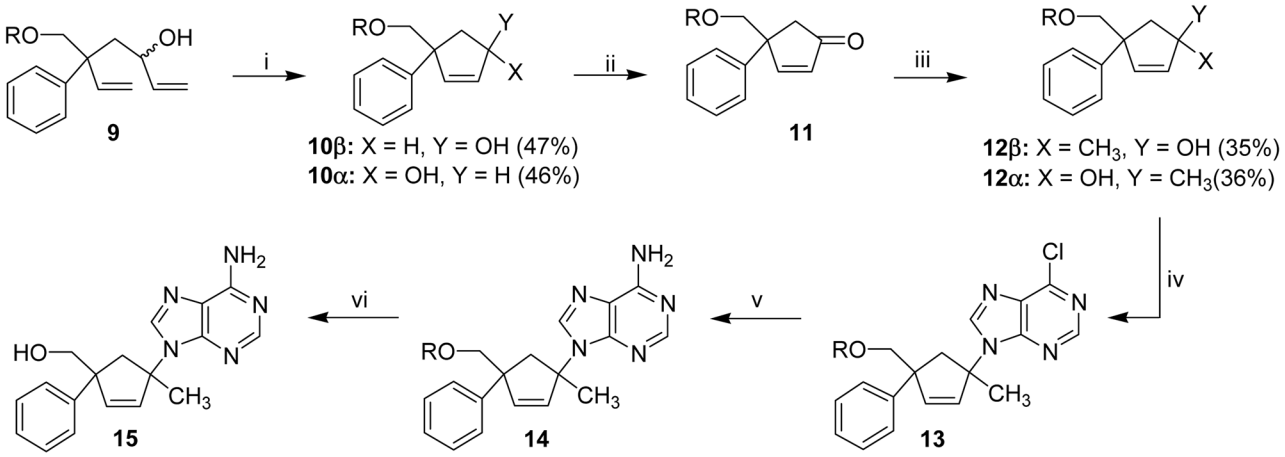
Based on the stimulating results of branched nucleosides as well as the carbocyclic nucleosides, and as part of an ongoing investigation into the discovery of less toxic and more effective antiviral agents, we synthesized 4'-phenyl and 1'-methyl branched carbocyclic nucleoside.

Results and Discussion

As shown in Scheme 1, allylic alcohol **5**, which is readily synthesized from 2-hydroxy acetophenone using previously reported method,[9] was subjected to the [3,3]-sigmatropic rearrangement reaction to give compound **6**. The ester derivative **6** was sequentially reduced and oxidized to provide aldehyde **8**, which was subjected to Grignard addition using vinylmagnesium bromide to give a divinyl **9** as an



Scheme 1. Synthesis of divinyl intermediate **9**. Reagents: i) Triethylorthoacetate, Propionic acid; ii) DIBAL-H, CH_2Cl_2; iii) PCC, 4A-MS, CH_2Cl_2; iv) CH_2=CHMgBr, THF.



Scheme 2. Synthesis of target nucleoside. Reagents: i) Grubbs' catalyst II, CH_2Cl_2, reflux, overnight; ii) PCC, 4A-MS, CH_2Cl_2; iii) CH_3MgBr, THF; iv) 6-chloropurine, DIAD, PPh_3, dioxane/DMF; v) NH_3/MeOH, steel bomb; vi) TBAF, THF.

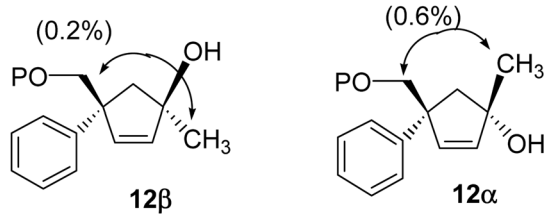


Figure 2. NOE comparisons of compound **12**α and **12**β.

inseparable diastereomeric mixture. The divinyl **9** was cyclized under ring-closing metathesis conditions using a 2nd generation Grubbs' catalyst [(Im)$Cl_2PCy_3RuCHPh$[10] to afford the cyclopentenols **10**α and **10**β, respectively (Scheme 2). The stereochemical assignments were accomplished based on the NOE experiments. Without separation, mixture of **10**α and **10**β was oxidized to ketone derivative **11**, which was also subjected to addition reaction of methylmagnesium bromide to yield **12**α and **12**β, respectively. Upon the irradiation of C_1-CH_3, a relatively strong NOE (0.6%) was observed at the methylene protons of compound **12**α, but weak NOE (0.2%) was observed at the methylene protons of **12**β (Figure 2).

The Mitsunobu reactions were used to couple the cyclopentenol with the nucleosidic base.[11] This methodology has been successfully used to synthesize the target nucleosides with the desired β-configuration. The required β-configurations of nucleoside **13** was successfully controlled from the α-configuration of compound **12**α. The success of the Mitsunobu reactions in the synthesis of the nucleoside analogue depends on the conditions. The appropriate choice of solvent system, temperature and procedure are essential for the regioselectivity as well as for the yield. In purine synthesis, a 2 : 1 mixture of dioxane and DMF were used as the solvent for the coupling of the cyclopentenol **12**α with 6-chloropurine instead of THF. The heterocyclic bases had a better solubility in the dioxane-DMF mixture resulting in better yields. The slow addition of diisopropylazodicarboxylate (DIAD) to a mixture of cyclopentenol **12**α, triphenylphosphine and the corresponding purine base in an anhydrous solvent gave a yellow solution, which was then stirred for 2 hours at –20 °C to give the protected 6-chloropurine analogue **13**. The 6-chloropurine **13** was converted to a protected adenosine analogue **14** by treating it with a saturated solution of metahnolic ammonia in a steel bomb at 90-95 °C overnight. The final nucleoside **15** was obtained from the corresponding protected nucleoside by treating them with tetrabutylammonium fluoride (TBAF).

In summary, the first synthetic method for 4' phenyl and 1' methyl doubly branched carbocyclic nucleoside from a α-hydroxy acetophenone was developed. The synthesized compounds were tested against several viruses such as HIV (MT-4 cells), HSV-1,2 (CCL18 cells) and HCMV (AD-169). However, none of these compounds had any significant activity up to 100 μM. The lack of antiviral activity of these compounds is presumably associated with their unfavorable conformations for the phosphorylation occurring during the nucleotide activation process. However, the information obtained in the present study will be useful for the development of novel nucleoside antiviral agents.

Experimentals and Methods

The melting points were determined on a Mel-tem II laboratory device and were uncorrected. The NMR spectra were recorded on a JEOL JNM-LA 300 spectrometer. The chemical shifts are reported as 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 (EA 1112). TLC was performed on Uniplates (silica gel) that were purchased from Analtech Co. Unless otherwise specified, all the reactions were carried out in a N_2 atmosphere. Dry dichloromethane, benzene and pyridine were obtained by distillation from CaH_2. The dry THF was obtained by distillation from Na and benzophenone immediately before use.

(±)-3-(*t*-Butyldimethylsilyloxymethyl)-3-phenyl-pent-4-enoic acid ethyl ester (6): A solution of allylic alcohol **5** (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 **6** (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.

(±)-3-(*t*-Butyl-dimethyl-silanyloxymethyl)-3-phenylpent-4-en-1-ol (7): To a solution of **6** (4.5 g, 12.9 mmol) in toluene (100 mL), DIBALH (28.4 mL, 1.0 M solution in hexane) was added slowly at −78 °C, and stirred for 1 h at the same temperature. To the mixture, methanol (30 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 : 12) to give **7** (3.48 g, 88%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.25 (m, 5H), 6.12 (dd, J = 17.2, 10.3 Hz, 1H), 5.21 (d, J = 17.2 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 4.12 (t, J = 6.2 Hz, 2H), 3.96 (s, 2H), 1.82 (t, J = 6.2 Hz, 2H), 0.89 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 142.45, 140.75, 128.55, 127.30, 113.21, 69.45, 57.64, 45.32, 38.76, 25.89, 18.27, −5.74.

(±)-3-(*t*-Butyldimethylsilyloxymethyl)-3-phenyl-pent-4-enal (8): To a solution of compound **7** (3.58 g, 11.68 mmol) in CH_2Cl_2 (50 mL), 4 Å molecular sieves (8.25 g) and PCC (6.75 g, 31.5 mmol) were added slowly at 0 °C, and stirred overnight at room temperature. To the mixture, excess diethyl ether (400 mL) was then added. The mixture was stirred vigorously for 3 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 : 30) to give compound **8** (3.09 g, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.63 (s, 1H), 7.34-7.26 (m, 5H), 6.09 (dd, J = 17.7, 11.1 Hz, 1H), 5.34 (d, J = 11.1 Hz, 1H), 5.16 (d, J = 17.4 Hz, 1H), 3.86 (s, 2H), 2.97 (dq, J = 16.2, 3.0), 0.88 (s, 9H), −0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 202.86, 142.38, 141.49, 128.38, 127.33, 126.83, 115.70, 69.28, 49.01, 25.76, 18.19, −5.74.

(*rel*)-(3*R* and 3*S*,5*S*)-5-(*t*-Butyldimethylsilyloxymethyl)-5-phenyl-hepta-1,6-dien-3-ol (9): To a cooled (−78 °C) solution of **8** (7.0 g, 23.1 mmol) in dry THF (120 mL) vinylmagnesium bromide (27.7 mL, 1.0 M solution in THF) was added slowly. After 2 h, a saturated NH_4Cl solution (23 mL) was added, and the reaction mixture was warmed slowly to room temperature. The mixture was extracted with EtOAc (2 × 150 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 **9** (6.4 g, 84%) as a diastereomeric mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.21 (m, 5H), 6.02-5.96 (m, 2H), 5.21-4.96 (m, 4H), 4.11-3.89 (m, 2H), 2.21-2.07 (m, 2H), 0.88 (m, 9H), 0.04 (m, 6H).

(*rel*)-(1*R*,4*S*)-4-(*t*-Butyldimethylsilyloxymethyl)-4-phenyl-cyclopent-2-enol (10β); and (*rel*)-(1*S*,4*S*)-4-(*t*-Butyldimethylsilyloxymethyl)-4-phenyl-cyclopent-2-enol (10α): To a solution of **9** (3.1 g, 9.24 mmol) in dry CH_2Cl_2 (20 mL) second generation Grubbs catalyst (0.781 mg 0.92 mmol) in dry CH_2Cl_2 (20 mL) was added under a N_2 atmosphere. 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 : 5) to give the cyclopentenol **10β** (1.32 g, 47%) and **10α** (1.3 g, 46%), as colorless oils, respectively. Only for the characterizations, separation by column chromatography was accomplished. Compound **10β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28-7.12 (m, 5H), 6.03-5.97 (m, 2H), 4.60-4.53 (m, 1H), 3.65 (d, J = 9.6 Hz, 1H), 3.50 (d, J = 9.6 Hz, 1H), 2.33 (dd, J = 13.8, 6.9 Hz, 1H), 2.12 (dd, J = 8.1, 6.9 Hz, 1H), 0.81 (s, 9H), 0.01 (s, 6H): ^{13}C NMR ($CDCl_3$) δ 145.04, 136.44, 135.53, 128.46, 126.61, 75.62, 69.77, 58.70, 45.73, 26.00, 18.62, −5.41; Anal calc for $C_{18}H_{28}O_2Si$: C, 71.00; H, 9.27. Found: C, 70.73; H, 9.08. Compound **10α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24-7.19 (m, 5H), 6.12 (d, J = 4.8 Hz, 1H), 5.93 (dd, J = 6.0, 2.1 Hz,

1H), 4.87 (s, 1H), 3.55 (s, 2H), 2.70 (dd, J = 13.2, 7.2 Hz, 1H), 1.83 (dd, J = 18.0, 4.8 Hz, 1H), 0.75 (s, 9H), –0.13, 0.15 (s, 6H): ^{13}C NMR ($CDCl_3$) δ 144.98, 135.74, 135.03, 127.86, 125.51, 75.02, 68.12, 57.65, 43.23, 25.78, 18.14, –5.43; Anal calc for $C_{18}H_{28}O_2Si$: C, 71.00; H, 9.27. Found: C, 71.19; H, 9.11.

(±)-4-(*t*-Butyldimethylsilanyloxymethyl)-4-phenyl-cyclopent-2-enone (11): To a solution of diastereomeric mixture of **10**β and **10**α (1.77 g, 5.84 mmol) in CH_2Cl_2 (40 mL), 4 Å molecular sieves (4.12 g) and PCC (3.37 g, 15.75 mmol) were added slowly at 0 °C, and stirred overnight at room temperature. To the mixture, excess diethyl ether (200 mL) was then added. The mixture was stirred vigorously for 4 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 : 20) to give compound **11** (3.09 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (d, J = 6.0 Hz, 1H), 7.43-7.29 (m, 5H), 6.36 (d, J = 6.0 Hz, 1H), 3.87 (dd, J = 11.1, 9.6 Hz, 2H), 2.85 (d, J = 18.0 Hz, 1H), 2.57 (d, J = 18.0 Hz, 1H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 208.55, 166.68, 142.51, 134.09, 128.59, 126.99, 126.59, 54.83, 46.07, 25.64, 18.07, –5.69.

(*rel*)-(1*R*,4*S*)-4-(*t*-Butyl-dimethyl-silanyloxymethyl)-1-methyl-4-phenyl-cyclopent-2-enol (12β) and (*rel*)-(1*S*,4*S*)-4-(t-Butyl-dimethyl-silanyloxymethyl)-1-methyl-4-phenyl-cyclopent-2-enol (12α): To a solution of compound **11** (1.6 g, 5.3 mmol) in dry THF (20 mL), methylmagnesium bromide (6.36 mL, 1.0 M solution in THF) was added slowly at –78 °C. After 3 h, a saturated NH_4Cl solution (4 mL) was added, and the reaction mixture was warmed slowly to room temperature. The mixture was extracted with EtOAc (200 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and then evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 15) to give compound **12**β (590 mg, 35%) and **12**α (607 mg, 36%) as a syrup, respectively: Compound **12**β: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.25 (m, 5H), 5.85 (s, 2H), 3.67 (d, J = 9.6 Hz, 1H), 3.49 (d, J = 9.6 Hz, 1H), 2.31 (d, J = 14.1 Hz, 1H), 2.12 (d, J = 14.1 Hz, 1H), 1.55 (s, 3H), 0.87 (s, 9H), 0.15 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.30, 140.11, 133.80, 128.48, 126.61, 126.38, 81.00, 70.46, 59.00, 51.81, 26.16, 25.69, 18.64, –5.45; Compound **12**α: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42-7.30 (m, 5H), 6.25 (d, J = 5.4 Hz, 1H), 6.01 (d, J = 6.0 Hz, 1H), 3.82 (d J = 9.6 Hz, 1H), 3.73 (d, J = 9.6 Hz, 1H), 2.55 (d, J = 13.8 Hz, 1H), 2.35 (d, J = 13.8 Hz, 1H), 1.57 (s, 3H), 0.89 (s, 9H), 0.20 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 146.01, 140.72, 134.26, 128.01, 127.83, 126.14, 83.15, 70.60, 58.57, 50.29, 27.70, 25.77, 18.22, –5.65.

(*rel*)-(1'*R*,4'*S*)-9-[4-(*t*-Butyldimethylsilanyloxymethyl)-1-methyl-4-phenyl-cyclopent-2-enyl]-6-chloropurine (13): To a solution containing compound **12**α (344 mg, 1.08 mmol), triphenylphosphine (1.692 g, 3.24 mmol) and 6-chloropurine (416 mg, 2.68 mmol) in anhydrous dioxane (10 mL) and DMF (7 mL), diisopropyl azodicarboxylate (0.588 mL) was added dropwise at –20 °C for 30 min. under nitrogen. The reaction mixture was stirred for 2.5 h 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 : 4) to give compound **13** (137 mg, 28%): UV (MeOH) λ_{max} 266.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H), 7.89 (s, 1H), 7.34-7.26 (m, 5H), 6.53 (d, J = 5.4 Hz, 1H), 6.30 (d, J = 5.4 Hz, 1H), 3.75 (d, J = 6.9 Hz, 2H), 2.04 (dd, J = 12.6, 8.6 Hz, 2H), 1.57 (s, 3H), 0.90 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.56, 151.32, 150.93, 146.54, 141.97, 136.45, 132.88, 128.31, 126.61, 125.97, 71.51, 70.14, 59.23, 47.23, 27.16, 25.80, 18.45, –5.58; Anal calc for $C_{24}H_{31}ClN_4OSi$: C, 63.34; H, 6.87; N, 12.31. Found: C, 63.12; H, 6.90; N, 12.45.

(*rel*)-(1'*R*,4'*S*)-9-[4-(*t*-Butyldimethylsilanyloxymethyl)-1-methyl-4-phenyl-cyclopent-2-enyl]-adenine (14): Compound **13** (111.5 mg, 0.35 mmol) was dissolved in saturated methanolic ammonia (10 mL) and the resulting solution was stirred overnight at 95-100 °C in a steel bomb. After removing the reaction solvent, the residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 1 : 3 : 0.4) to give compound **14** (106.7 mg, 70%) as a solid: UV (MeOH) λ_{max} 261.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.50 (s, 1H), 8.11 (s, 1H), 7.30-7.22 (m, 5H), 6.21 (d, J = 5.4 Hz, 1H), 5.90 (d, J = 5.4 Hz, 1H), 3.66 (d, J = 10.6 Hz, 2H), 2.01 (d, J = 10.2 Hz, 1H), 1.75 (dd, J = 11.8, 8.6 Hz, 1H), 1.48 (s, 3H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.65, 152.56, 150.71, 146.67, 141.97, 137.66, 132.66 128.31, 127.65, 126.34, 118.34, 71.67, 69.23, 58.34, 46.89, 26.76, 25.76, 18.67, –5.71; Anal calc for $C_{24}H_{33}N_5OSi$: C, 66.17; H, 7.64; N, 16.08. Found: C, 66.04; H, 7.48; N, 15.77.

(*rel*)-(1'*R*,4'*S*)-9-[4-(Hydroxymethyl)-1-methyl-4-phenyl-cyclopent-2-enyl]-adenine (15): To a solution of compound **14** (152.4 mg, 0.35 mmol) in THF (10 mL) at 0 °C, TBAF (0.7 mL, 1.0 M solution in THF) 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 : 5) to give compound **15** (78.7 mg, 70%) as a white solid: mp 170-173 °C; UV (H_2O) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.42 (s, 1H), 8.07 (s, 1H), 7.32-7.21 (m, 5H), 6.25 (d, J = 5.6 Hz, 1H), 5.99 (d, J = 5.4 Hz, 1H), 4.99 (t, J = 5.4 Hz, 1H), 3.87 (d, J = 10.6 Hz, 1H), 3.65 (d, J = 10.6 Hz, 1H), 2.04 (d, J = 9.8 Hz, 1H), 1.80 (d, J = 9.8 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.97, 152.23, 149.65, 147.89, 142.54, 138.40, 133.45 128.67, 127.78, 127.12, 126.11, 119.20, 70.56, 68.91, 59.67, 46.72, 27.82; Anal calc for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.36; H, 6.10; N, 21.87.

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