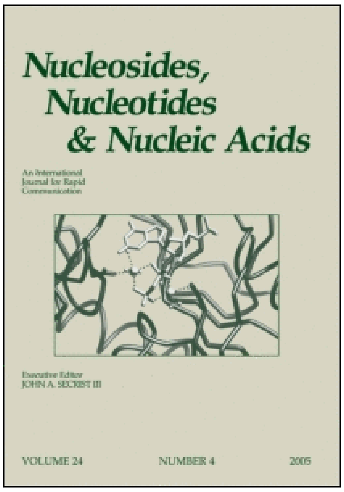

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Synthesis and Anti-HCMV Activity of Novel 2',3',4'-Trimethyl Branched Carbocyclic Nucleosides

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SYNTHESIS AND ANTI-HCMV ACTIVITY OF NOVEL 2′,3′,4′-TRIMETHYL BRANCHED CARBOCYCLIC NUCLEOSIDES

Aihong Kim and Joon Hee Hong ▫ *College of Pharmacy, Chosun University, Kwangju, Republic of Korea*

▫ *This article reports the synthesis of novel 2′,3′,4′-trimethyl branched carbocyclic nucleosides. The introduction of a methyl group in the 2′ and 3′-position was accomplished by sequential Horner-Wadsworth-Emmons reaction and isopropenyl magnesiumbromide addition, respectively. The construction of the 4′-quaternary carbon needed was carried out using a [3,3]-sigmatropic rearrangement. Bis-vinyls were successfully cyclized using a Grubbs catalyst II. The natural bases (adenine, cytosine) were efficiently coupled with the use of a Pd(0) catalyst.*

Keywords Antiviral agents, Triply branched carbocyclic nucleosides, [3,3]-Sigmatropic rearrangement

INTRODUCTION

The synthesis rationale of carbocyclic nucleosides[1–3] in which the ring oxygen of furanose nucleosides is substituted by a methylene group is to stabilize the hydrolytically and enzymatically[4] scissile glycosyl bond with minimal structural disturbances. However, the fact that most conventional carbocyclic nucleosides have generally exhibited poorer biological potencies than the corresponding furanose nucleosides would suggest that the conformational differences between furanose and cyclopentane rings might be partially responsible for the observed differences in biological potency. During a large search for new antiviral agents, carbocyclic nucleosides such as carbovir **1**,[5] abacavir **2**,[6] and entecavir **3**[7] (Figure 1) have been synthesized and have shown interesting antiviral activities against human immunodeficiency virus (HIV)[8,9] and hepatitis B virus,[10] respectively. 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.[11,12] The inhibition of the

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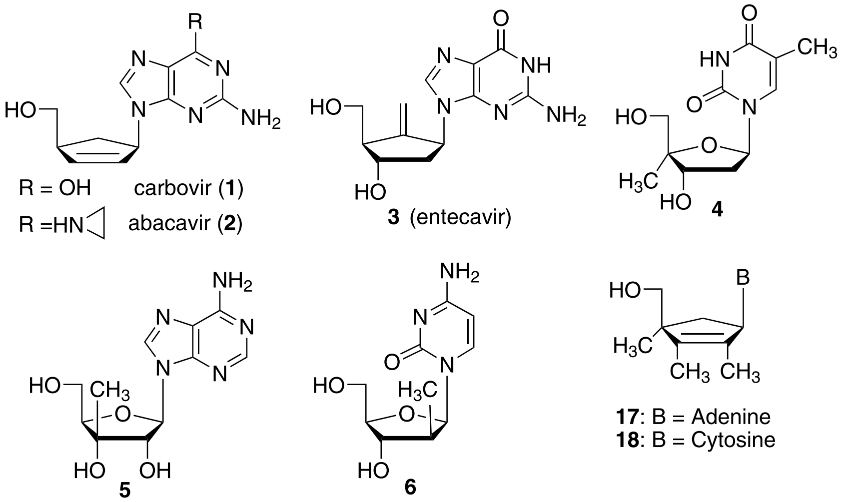


FIGURE 1 Structures of olefinic carbocyclic nucleosides, branched furanose nucleosides, and target nucleosides.

enzyme on intact cellular systems results in the accumulation of AdoHcy; higher concentration of AdoHcy suppresses the enzyme activity by acting as a product inhibitor of the AdoMet-dependent methylation reaction.[13,14] Methyltransferases are essential for the maturation of mRNA. Therefore, inhibiting the methyl transferases by blocking the AdoHcy metabolism can disrupt viral mRNA maturation. AdoHcy inhibitors usually display a broad-spectrum of antiviral activity. Moreover, this mechanism might be exploited in a combination therapy in association with the nucleosides with a different mechanism of action. Recently, the branched furanose nucleosides, particularly the alkyl branches (Figure 1), have been of considerable interest. One of reasons for this interest arises from their notable biological activities as antiviral and antitumor agents, as illustrated by 4′-*C*-methyl-thymidine **4**,[15] 3′-*C* methyladenosine **5**,[16] and 2′-*C*-methyl-2′-deoxycytidine **6**[17] (Figure 2).

With regard to these interesting mechanisms of carbocyclic nucleosides, as well as the biological activity of branched furanose nucleosides, this study synthesized and assayed novel 2′,3′,4′- triply branched carbocyclic nucleosides.

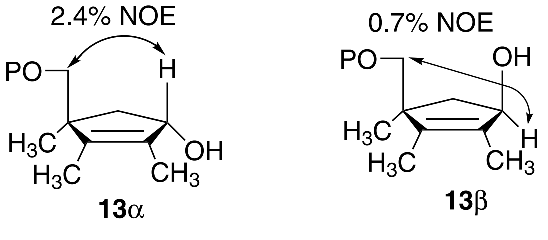
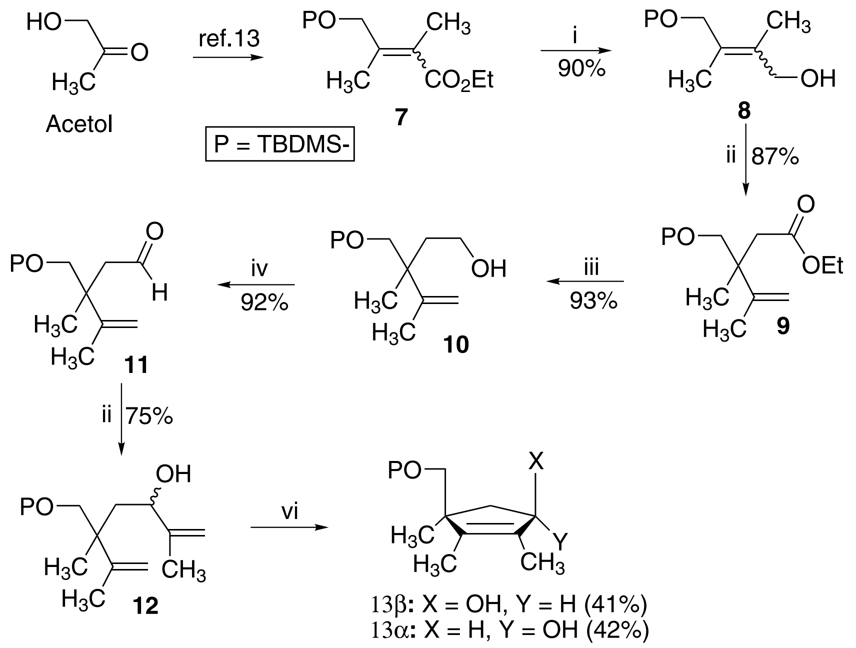


FIGURE 2 NOE study of compound **13β** and **13α**.



Reagents: i) Dibal-H, CH_2Cl_2, –50°C; ii) triethylorthoacetate, propionic acid, 140°C; iii) dibal-H, CH_2Cl_2, 0°C; iv) PCC, 4A MS, CH_2Cl_2, 4 h rt: v) $CH_2{=}C(CH_3)MgBr$, THF, –78°C; vi) Grubbs' catalyst II benzene, reflux, overnight.

SCHEME 1 Synthesis of 2,3,4-trimethyl-branched cyclopentene systems **13β** and **13α**.

RESULT AND DISCUSSION

As shown in Scheme 1, for the synthesis of the 2′,3′,4′-triply branched target nucleosides, α,β-unsaturated ester derivatives (**7**) was selected as the starting compound, which was readily synthesized from acetol by a previously reported method.[18] Without separation, the ester **7** was reduced using diisobutylaluminum hydride (DIBALH) and the resulting allylic alcohol **8** was subjected to a [3,3]-sigmatropic rearrangement using triethylorthoacetate to give the γ,δ-unsaturated esters (**9**) in a 62% two-step yield. The addition of DIBALH to a solution of the ester **9** in CH_2Cl_2 at −20°C gave the alcohol **10**, which was subjected to oxidation conditions using PCC. The resulting aldehyde **11** was subjected to a Grignard reaction by $CH_2 = C(CH_3)MgBr$ to yield the *bis*-olefin **12** as a stereoisomeric mixture (Scheme 2).

The *bis*-olefin **12** was subjected to the well-known ring-closing metathesis conditions[a] using a Grubbs' catalyst II [$(Im)Cl_2PCy_3RuCHPh$] to provide the stereoisomers, **13β** and **13α**, in equal amounts. The relative stereochemistry of compounds **13β** and **13α** was unambiguously determined based on the NOE

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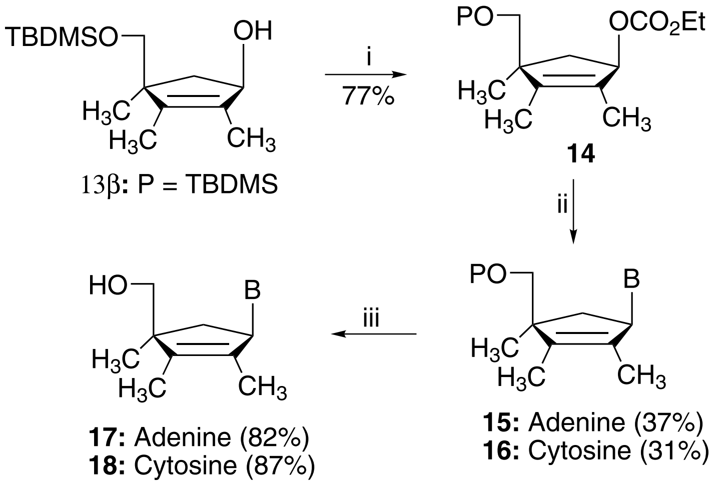
[a] For a review of RCM, see: Refs. [19–21].



Reagents: i) $ClCO_2ET$, DMAP, pyridine, rt, overnight;
ii) bases (A = adenine, C = cytosine), $Pd_2(dba)_3$ $CHCl_3$,
$P(O\text{-}i\text{-}Pr)_3$, NaH, THF/DMSO, reflux, overnight; iii) TBAF, THF, rt.

SCHEME 2 Synthesis of 2′,3′,4′-trimethyl-branched carbocyclic nucleosides **17** and **18**.

correlations between the proximal hydrogen and methylene group (H-1 vs. H-5). Unlike compound **13β**, the strong NOE correlation was observed between the H-1 vs. H-5 of compound **13α** (2.4% NOE).

In order to couple the cyclopentenol with the bases (A = adenine, C = cytosine) using a simple nucleophilic substitution type reaction, compound **13a** was subjected to a mesylation reaction (MsCl, TEA, CH_2Cl_2). Unexpectedly, the reaction had a low yield and also was irreproducible. Therefore, attention was to turned to palladium(0) catalyzed reaction procedure.[22]

The cyclopentenol **13β** was transformed to the ethoxycarbonyl derivative **14** using ethyl chloroformate in a 77% high yield. Compound **14** was coupled with an adenine anion generated by NaH/DMSO with the [tris(dibenzylidene-acetone)-dipalladium(0)-chloroform] adduct to give the compounds **15** and **16**. Although a small amount of the *N*7-regioisomer of **15** (< 6%) was observed, the compound **15** and its *N*7-isomer could be easily separated and identified.[23] The required stereochemistry of the nucleosides **15** and **16** was successfully controlled from the β-configuration of compounds **14** *via* a Pd(0) catalyzed π−allyl complex mechanism. Compounds **15** and **16** were desilylated by treating the compounds with tetrabutylammonium fluoride (TBAF) to give the final nucleosides **17** and **18** in a high yield.

The synthesized compounds **17** and **18** 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). Interestingly, the adenosine analogue **17** exhibited good antiviral activity against the HCMV (8.8 μg/mL in Davis cell) without any cytotoxicity up to 100 μg/mL, indicating that this virus might allow the triply branched sugar moiety for phosphorylation as well as for DNA polymerase, which is unlike other viruses.

In summary, a concise synthetic method for synthesizing 2′,3′,4′-trimethyl branched carbocyclic nucleosides from simple acetol derivative was developed in this study. When the synthesized compounds were tested against several viruses such as the HIV-1, HSV-1, HSV-2, and HCMV, the adenosine analogue **17** exhibited good antiviral activity against the HCMV. The fact that 2′,3′,4′-triply branched carbocyclic nucleoside was active against HCMV suggests that the 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 with 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 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 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. Dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

(E) and (Z)-4-(t-Butyldimethylsilyloxy)-2,3-dimethyl-but-2-en-1-ol(8). To a solution of compound **7** (5 g, 18.35 mmol) in CH_2Cl_2 (100 mL), DIBALH (38.5 mL, 1.0 M solution in hexane) was added slowly at −50°C, and stirred for 2 h at the same temperature. Methanol (30 mL) was added to the resulting mixture. The mixture was stirred at room temperature for 5 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, 1:7) to give the allylic alcohol **8** (3.80 g, 90%) as a colorless oil: as an E/Z mixture for ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.21 (s, 2H), 4.19 (s, 2H), 4.03 (s, 2H), 1.77, 1.74 (s, s, 3H), 1.64, 1.62 (s, s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); Anal calc for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.61; H, 11.54.

(±)-3-(t-Butyldimethylsilyloxymethyl)-3,4-dimethyl-pent-4-enoic acid ethyl ester (9). A solution of the allylic alcohol **8** (10 g, 43.4 mmol) in triethyl orthoacetate (150 mL) and 1.0 mL of propionic acid was heated at 138–140°C overnight with constant stirring to allow for the removal of ethanol. An excess of triethylorthoacetate was removed by distillation, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **9** (11.34 g, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.85 (s, 1H), 4.65 (s, 1H), 4.05 (q, J = 7.2 Hz, 2H), 3.56 (dd, J = 9.3 Hz, 2H), 3.41 (d, J = 9.3 Hz, 2H), 2.42 (d, J = 3.2 Hz, 2H), 1.62 (s, 3H), 1.23 (t, J = 7.3 Hz, 3H), 1.12 (s, 3H), 0.91 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.96, 143.13, 113.02, 69.93, 59.84, 41.33, 25.81, 22.60, 20.70, 20, 45, 18.20, 14.26, −5.58; Anal calc for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 64.12; H, 10.60.

(±)-3-(t-Butyldimethylsilyloxymethyl)-3,4-dimethyl-pent-4-en-1-ol (10). To a solution of compound **9** (6.0 g, 19.96 mmol) in CH_2Cl_2 (150 mL), DIBALH (41.92 mL, 1.0 M solution in hexane) was added slowly at −20°C, and stirred for 1 h at the same temperature. Methanol (40 mL) was then added to the 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, 1:20) to give compound **10** (4.79 g, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.79 (s,1H), 4.70 (s, 1H), 3.56 (t, J = 5.4 Hz, 2H), 3.52 (d, J = 9.6 Hz, 1H), 3.39 (d, J = 9.6 Hz, 1H), 1.73 (d, J = 4.2 Hz, 1H), 1.69 (s, 3H), 1.67 (d, J = 4.2 Hz, 1H), 1.00 (s, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.49, 111.10, 69.77, 59.60, 43.10, 38.95, 25.93, 21.55, 20.00, 18.22, −5.29; Anal calc for $C_{14}H_{30}O_2Si$: C, 65.06; H, 11.70. Found: C, 65.32; H, 11.59.

(±)-3-(t-Butyldimethylsilyloxymethyl)-3,4-dimethyl-pent-4-enal (11). To a solution of compound **10** (7.0 g, 27.08 mmol) in CH_2Cl_2 (150 mL), 4Å molecular sieves (15.7 g) and PCC (14.58 g, 67.64 mmol) were added slowly at 0°C and stirred for 4 h at room temperature. Excess diethyl ether (300 mL) was then added to the mixture. The mixture was stirred vigorously for 5 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 **11** (6.38 g, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.68 (m, 1H), 4.89 (s, 1H), 4.69 (s, 1H), 3.56 (d, J = 9.0 Hz, 1H), 3.42 (d, J = 9.0 Hz, 1H), .2.37 (d, J = 3.3 Hz, 2H), 1.75 (s, 3H), 1.13 (s, 3H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.35, 147.54, 112.23, 69.73, 49.53, 43.55, 25.81, 22.21, 20.03, 18.22, −5.61; Anal calc for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.69; H, 11.20.

(*rel*)-(3*R* and 3*S*,5*S*)-5-(t-Butyldimethylsilyloxymethyl)-2,5,6-trimethyl-hepta-1,6-dien-3-ol (12). To a solution of compound **10** (5.0 g, 19.49 mmol) in dry THF (150 mL) isopropenyl magnesiumbromide (23.39 mL, 1.0 M solution in THF) was added slowly at −78°C. After 4 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 × 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, 1:35) to give compound **12** (4.36 g, 75%) as a colorless oil: as a diastereomeric mixture for ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 4.89–4.68 (m, 4H), 4.05 (m, 1H), 3.65 (d, *J* = 9.6 Hz, 1H), 4.43 (dd, *J* = 9.9, 1.8 Hz, 1H), 3.34, 3.00 (s, s, 1H), 1.68 (d, *J* = 8.7 Hz, 6H), 1.04, 1.01 (s, s, 3H), 0.82 (s, 9H), 0.03, 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.50, 149.55, 148.45, 148.27, 111.71, 110.75, 109.89, 72.70, 72.18, 69.45, 43.68, 43.53, 43.27, 42.06, 25.82, 23.24, 21.21, 20.13, 18.22, 17.88, −5.54; Anal calc for $C_{17}H_{34}O_2Si$: C, 68.39; H, 11.48. Found: C, 68.50; H, 11.29.

(*rel*)-(1*R*,4*R*)-4-(t-Butyldimethylsilyloxymethyl)-2,3,4-trimethyl-cyclopent-2-enol (13β) and (rel)-(1*S*,4*R*-4-(t-Butyldimethylsilyloxymethyl)-2,3,4-trimethyl-cyclopent-2-enol (13α). To a solution of compound **12** (3.0 g, 10.04 mmol) in dry benzene (10 mL), Grubbs' catalyst II (102 mg, 0.12 mmol) was added. The reaction mixture was refluxed overnight and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give the cyclopentenols **13β** (1.11 g, 41%) and **13α** (1.14 g, 42%) as colorless oil. **13β:**^1H NMR ($CDCl_3$, 300 MHz) δ 4.11 (dd, *J* = 11.4, 7.8 Hz, 1H), 3.37 (d, *J* = 9.3 Hz, 1H), 3.22 (d, *J* = 9.3 Hz, 1H), 1.83 (dd, *J* = 14.1, 7.5 Hz, 1H), 1.68 (s, 1H), 1.63 (s, 3H), 1.41 (s, 3H), 0.86 (s, 3H), 0.81 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.81, 136.21, 77.78, 67.68, 51.18, 45.62, 25.88, 22.10, 18.39, 11.77, 9.20, −5.56; Anal calc for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18. Found: C, 66.57; H, 11.05. **13α:**^1H NMR ($CDCl_3$, 300 MHz) δ 4.13 (m, 1H), 3.12 (s, 1H), 3.06 (s, 1H), 1.84 (dd, *J* = 13.8, 7.2 Hz, 1H), 1.69 (d, *J* = 13.8 Hz, 1H), 1.60 (s, 3H), 1.42 (s, 3H), 0.87 (s, 3H), 0.82 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.04, 134.48, 78.94, 69.07, 50.87, 45.36, 25.81, 22.73, 18.09, 11.23, 10.06, −5.61; Anal calc for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18. Found: C, 66.78; H, 10.95.

(*rel*)-(1*R*,4*R*)-1-ethoxycarbonyloxy-4-(t-butyldimethylsilyloxymethyl)-2,3,4-trimethyl-cyclopent-2-ene (14). To a solution of compound **13β** (4.0 g, 14.78 mmol) in anhydrous pyridine (30 mL) ethyl chloroformate (1.8 mL, 18.83 mmol) and DMAP (220 mg, 1.8 mmol) were added. The reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched using a saturated $NaHCO_3$ solution (2 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, 1:40) to give compound **14** (3.90 g, 77%) as a colorless syrup: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.44 (dd, *J* = 7.2, 4.5 Hz, 1H), 4.16 (q, *J* = 7.8 Hz, 2H), 3.27 (dd, *J* = 13.7, 6.7 Hz, 2H), 1.92 (dd, *J* = 14.2, 7.5 Hz, 1H), 1.70 (s, 1H), 1.65 (s, 3H), 1.41 (s, 3H), 1.30 (t, *J* = 7.8 Hz, 3H), 0.89 (s, 3H), 0.81 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.30, 136.81, 136.21, 85.03, 67.68, 65.93, 51.18, 45.62, 25.88, 22.10, 18.39, 13.92, 11.77, 9.20, −5.56; Anal calc for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.00. Found: C, 63.27; H, 10.05.

(*rel*)-(1′*R*,4′*R*)-9-[4-(t-Butyldimethylsilyloxymethyl)-2,3,4-trimethyl-cyclopent-2-en-1-yl] adenine (15). To pure NaH (46.8 mg, 1.96 mmol) in anhydrous DMSO (9.0 mL), adenine (268 mg, 1.96 mmol) was added. The reaction mixture was stirred for 30 min at 50–55°C and cooled to room temperature. Simultaneously, P(O-*i*-Pr)$_3$ (0.96 mL, 2.2 mmol) was added to a solution of Pd$_2$(dba)$_3$· CHCl$_3$ (46 mg, 25 μmol) in anhydrous THF (8.0 mL), which was stirred for 40 min. The catalyst solution of THF and compound **14** (602 mg, 1.76 mmol) dissolved in anhydrous THF (5 mL) were added slowly to the adenine solution in DMSO. The reaction mixture was stirred overnight at a refluxing temperature and quenched with water (5 mL). The reaction solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH$_2$Cl$_2$, 1:10) to give compound **15** (252 mg, 37%) as a white solid: mp 190–192°C; UV (MeOH) λ_{max} 261.0 nm; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.35 (s, 1H), 7.95 (s, 1H), 5.23 (br s, 1H), 3.38 (d, *J* = 9.6 Hz, 1H), 3.20 (d, *J* = 9.6 Hz, 1H), 1.92 (dd, *J* = 13.8, 7.6 Hz, 1H), 1.72 (d, *J* = 13.8 Hz, 1H), 1.69 (s, 3H), 1.40 (s, 3H), 0.85 (s, 3H), 0.82 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 155.36, 152.91, 150.27, 138.81, 135.21, 119.67, 67.68, 51.18, 45.62, 25.88, 22.10, 18.39, 11.77, 9.20, −5.56; Anal calc for C$_{20}$H$_{33}$N$_5$OSi: C, 61.98; H, 8.58; N, 18.07. Found: C, 61.77; H, 8.69; N, 17.89.

(*rel*)-(1′*R*,4′*R*)-1-[4-(t-Butyldimethylsilyloxymethyl)-2,3,4-trimethyl-cyclopent-2-en-1-yl] cytosine (16). Compound **16** was prepared from compound **14** using the method described for synthesizing compound **15**: yield 31%; mp 171–172°C; UV (MeOH) λ_{max} 272.0 nm; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.51 (d, *J* = 7.2 Hz, 1H), 5.83 (br s, 1H), 5.67 (d, *J* = 7.2 Hz, 1H), 3.40 (d, *J* = 8.6 Hz, 1H), 3.22 (d, *J* = 8.6 Hz, 1H), 2.12 (m, 1H), 1.79 (d, *J* = 8.8 Hz, 1H), 1.71 (s, 3H), 1.42 (s, 3H), 0.87 (s, 3H), 0.85 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 165.12, 155.98, 146.21, 143.78, 133.68, 93.88, 67.23, 51.18, 45.62, 25.88, 22.10, 18.39, 11.77, 9.20, −5.56; Anal calc for C$_{19}$H$_{33}$N$_3$O$_2$Si: C, 62.77; H, 9.15; N, 11.56. Found: C, 62.57; H, 9.31; N, 11.41.

(*rel*)-(1′*R*,4′*R*)-9-[4-(Hydroxymethyl)-2,3,4-trimethyl-cyclopent-2-en-1-yl] adenine (17). To a solution of compound **15** (150 mg, 0.387 mmol) in THF (5 mL), TBAF (0.58 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$_2$Cl$_2$, 1:4) to give compound **17** (86 mg, 82%) as a white solid: mp 196–198°C; UV (H$_2$O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.25 (s, 1H), 8.05 (s, 1H), 7.19 (br d, 2H, D$_2$O exchangeable), 5.61 (br t, 1H), 4.82 (br s, 1H, D$_2$O exchangeable), 3.77 (d, *J* = 8.6 Hz, 1H), 3.25 (d, *J* = 8.6 Hz, 1H), 2.21 (dd, *J* = 13.6, 8.2 Hz, 1H), 1.83 (s, 1H), 1.71 (s, 3H), 1.45 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.42, 153.12, 151.36, 141.81, 132.21, 119.98, 67.68, 51.18, 45.62, 22.10, 11.77, 9.20; Anal calc for C$_{14}$H$_{19}$N$_5$O: C, 61.52; H, 7.01; N, 25.62. Found: C, 61.38; H, 6.89; N, 25.44.

(*rel*)-(1′*R*,4′*R*)-1-[4-(Hydroxymethyl)-2,3,4-trimethyl-cyclopent-2-en-1-yl] cytosine (18). Compound **18** was prepared from compound

16 using the method described for synthesizing compound **17**: yield 87%; mp 170–172°C; UV (H_2O) λ_{max} 271.0 nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.41 (d, *J* = 7.2 Hz, 1H), 7.11 (br d, 2H, D_2O exchangeable), 5.85 (m, 1H), 5.65 (d, *J* = 7.2 Hz, 1H), 4.81 (br s, 1H, D_2O exchangeable), 3.72 (dd, *J* = 14.1, 8.2 Hz, 2H), 2.25 (dd, *J* = 13.4, 7.8 Hz, 1H), 1.76 (d, *J* = 7.8 Hz, 1H), 1.88 (s, 3H), 1.52 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.133, 155.78, 145.28, 141.45, 132.12, 95.23, 68.56, 51.34, 45.51, 22.82, 10.99, 8.81; Anal calc for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.43; H, 7.76; N, 16.69.

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