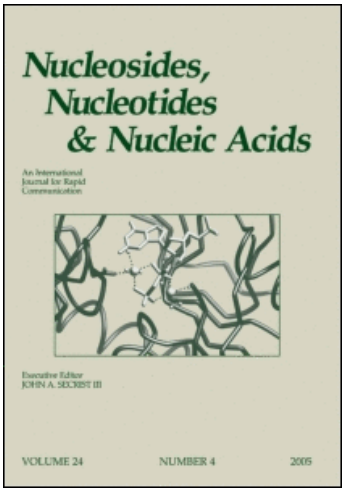


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# Synthesis and Antiviral Activity of Novel 2′,4′-Doubly Branched Carbocyclic Nucleosides

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## ABSTRACT

A series of 2′ and 4′-doubly branched carbocyclic nucleosides **15**, **16**, **17** and **18** were synthesized starting from simple acyclic ketone derivatives. The required 4′-quaternary carbon was constructed using Claisen rearrangement. In addition, the installation of a methyl group in the 2′-position was accomplished using a Grignard carbonyl addition of isopropenylmagnesium bromide. Bis-vinyl was successfully cyclized using a Grubbs' catalyst II. Natural bases (adenine, cytosine) were efficiently coupled by using Pd(0) catalyst.

*Key Words:* Branched carbocyclic nucleosides; Claisen rearrangement; Grignard addition; Antiviral agents.

## INTRODUCTION

Since the discovery of 3′-azido-and 3′-deoxythymidine (AZT) as antiviral agents for the treatment of acquired immunodeficiency syndrome (AIDS), much attention has been focused on nucleosides as reverse transcriptase inhibitors in search for more active and less toxic compounds. Currently, seven nucleoside reverse transcriptase inhibitors such as AZT,[1] ddC,[2] ddI,[3] d4T,[4] 3TC,[5] viread,[6] and abacavir[7] are available for

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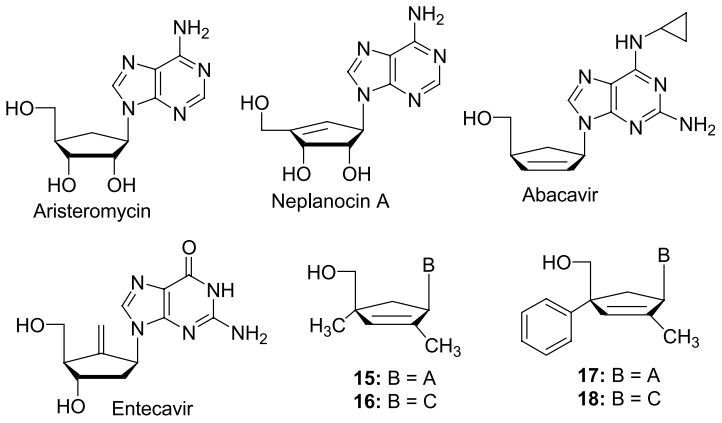
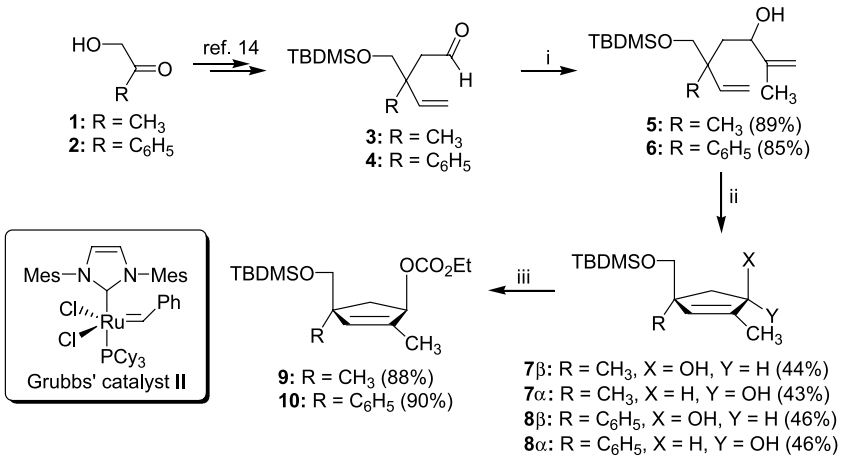


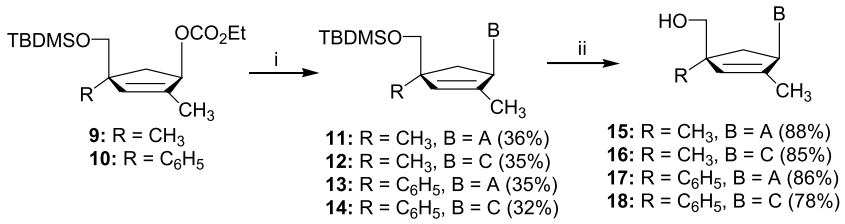

***Figure 1.*** Structures of biologically active carbocyclic nucleosides and target compounds.



the treatment of AIDS. However, toxicities[8,9] and side effects as well as the emergence of the drug resistant viral strains[10,11] limit the usefulness of the currently available nucleosides as anti-HIV agents. Furthermore, the disadvantage of normal nucleosides and their analogs is that susceptible glycosidic bond to enzymatic hydrolysis by phosphorylase.[12] Various strategies have been employed in attempts to overcome the latter problem, among which are carbocyclic nucleoside analogs.[13,14] For example, abacavir (Fig. 1) has been approved by the Food and Drug Administration as an anti-HIV agent.[7] A carbocyclic nucleoside with an exomethylene double bond,




***Scheme 1.*** Synthesis of 2,4-disubstituted cyclopentene systems.




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

***Scheme 2.*** Construction of final doubly branched nucleosides.

entecavir, is also currently undergoing phase III clinical trials for the treatment of chronic hepatitis B virus infection.[15]

Furthermore, various carbocyclic nucleosides such as aristeromycin and neplanocin A (Fig. 1) are considered as potent inhibitors of the cellular enzyme, *S*-adenosyl-*L*-homocysteine (AdoHcy) hydrolase,[16,17] which catalyze the reversible hydrolysis of *S*-adenosyl-*L*-homocysteine to adenosine and homocysteine. AdoHcy hydrolase is very important in regulating *S*-adenosyl methionine (SAM) dependent methylation reactions. Methyl transferases are necessary for the maturation of the mRNA. Inhibition of methyl transferase *via* blocking the metabolism of AdoHcy can therefore, disrupt viral mRNA maturation. AdoHcy inhibitors usually display broad-spectrum of antiviral activities. Moreover, this mechanism might be exploited in combination therapies in association with the nucleosides with a different mechanism of action. In view of these interesting mechanisms and antiviral activities of carbocyclic nucleosides, we have synthesized and assayed 2′ and 4′-doubly branched novel carbocyclic nucleosides as potential antiviral agents.

## RESULTS AND DISCUSSIONS

For the synthesis of target nucleosides, aldehyde derivatives **3** and **4** were selected as starting materials, which were readily prepared from acetol and 2-hydroxyacetophenone, respectively, following the reported procedure.[18] The carbonyl addition by $CH_2 = C(CH_3)MgBr$ yielded the bis-olefins **5** and **6** as stereoisomeric mixtures (Scheme 1). Without purificarion, the stereomeric mixture of **5** and **6** are subjected to the standard ring-closing metathesis (RCM) conditions using a Grubbs' catalyst II [$(Im)Cl_2PCy_3RuCHPh$] to provide the cyclopentenols **7β**, **7α**, **8β** and **8α**, respectively.[a] The stereochemistry of compounds **7β** and **7α** was unambiguously determined on the basis of NOE correlations between the proximal hydrogen and methyl group (H-1, vs. $CH_3$-4). The stereochemistry of **8β** and **8α** was also assigned by the similar NMR studies.

[a]This metathesis did not progress with the Grubbs' catalyst I.

***Table 1.*** The antiviral activity of the synthesized compounds.

| Compounds | HIV-1 $EC_{50}$(μg/mL) | HSV-1 $EC_{50}$(μg/mL) | HCMV $EC_{50}$(μg/mL) | CoxB3 $EC_{50}$(μg/mL) | Cytotoxicity $IC_{50}$(μg/mL) |
|---|---|---|---|---|---|
| **15** | > 100 | > 100 | 56.6 | > 100 | > 100 |
| **16** | > 100 | > 100 | > 100 | 27.4 | > 100 |
| **17** | > 100 | > 100 | > 100 | > 100 | > 100 |
| **18** | > 100 | > 100 | > 100 | 35.4 | > 100 |
| AZT | 0.0005 | ND | ND | ND | 0.5 |
| Ganciclovir | ND | 1.35 | ND | ND | > 10 |
| Ribavirin | ND | ND | ND | 30.25 | > 300 |

ND: Not Determined.



In order to couple the cyclopentenols with the bases (A = adenine, C = cytosine) using a simple and convenient nucleophilic substitution type reaction, **7α** and **8α** were subjected to a mesylation reaction (MsCl, TEA, $CH_2Cl_2$). Unexpectedly, the reactions resulted in a very low yield (10–15%) and were irreproducible. Therefore, attention was turned to palladium(0) catalyzed reactions[19] for the purpose of base coupling.

The cyclopentenols **7β** and **8β** were activated to compounds **9** and **10** using ethyl chloroformate in a high yield (88–90%), which were coupled with an adenine anion generated by NaH/DMSO using the well-known coupling catalyst [tris(dibenzylidene-acetone)-dipalladium(0)-chloroform] adduct to give compounds ***11***, ***12***, ***13*** and ***14***. The required stereochemistry of the nucleosides ***11***, ***12***, ***13*** and ***14*** were successfully controlled from the β-configuration of compounds ***9*** and ***10*** through a double inversion mechanism *via* a Pd(0) catalyzed π–allyl complex. The regioisomer of *N*-7 adenine nucleoside (ratio *N*-9/*N*-7 = 3/1) was readily separable by normal chromatography. The desilylations of compounds ***11***, ***12***, ***13*** and ***14*** were performed by a treatment with tetrabutylammonium fluoride (TBAF) to give the final nucleosides ***15***, ***16***, ***17*** and ***18*** in a 78–88% yield (Scheme 2).

The antiviral assays against the HIV-1, HSV-1, HCMV and CoxB3 were performed. As shown in Table 1, cytosine analogues **16** and **18** showed moderate activity against CoxB3 without significant cytotoxicity to the host cell. In addition, adenine analogue **15** showed weak antiviral activity against the HCMV.

In summary, a concise synthetic method for synthesizing 2′ and 4′-doubly branched carbocyclic nucleosides from simple α-hydroxyketone derivatives were developed. This procedure highlights the simplicity and efficiency in constructing the double alkyl branches in the cyclopentene ring systems of nucleosides. Extensions of the current strategy to prepare other systems, which may represent novel class of nucleosides, are under investigation in our laboratory.

## EXPERIMENTAL SECTION

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



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Ar using distilled dry solvents. The NMR spectra were recorded on a bruker 300 Fourier transform spectrometer. Elemental analyses were performed using an Elemental Analyzer System (Profile HV-3).

**(rel)-(3R and 3S,5S)-5-(t-Butyldimethylsilyloxymethyl)-2,6-dimethyl-hepta-1,6-dien-3-ol (5):** To a cooled (− 20 °C) solution of compound **3** (5.0 g, 20.6 mmol) in dry THF (80 mL) isopropenylmagnesium bromide (22.7 mL, 1.0 M solution in THF) was added slowly. After 3 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 x 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 diastereomeric mixture **5** (5.2 g, 89%) as a colorless oil: as diastereomeric mixture for $^1$H NMR ($CDCl_3$, 300 MHz) δ 5.89 (dd, $J$ = 17.7, 11.4 Hz, 1H), 5.72 (dd, $J$ = 17.4, 6.9 Hz, 1H), 5.05–4.89 (m, 2H), 4.70 (s, 1H), 4.10 (d, $J$ = 8.1 Hz, 1H), 4.64 (s, 1H), 3.51–3.32 (m, 2H), 1.65 (s, 3H), 1.59–1.53 (m, 2H), 1.00 (s, 3H), 0.83 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 148.42, 148.23, 145.33, 143.84, 113.42, 112.31, 109.85, 109.76, 72.23, 71.87, 70.63, 70.37, 45.28, 45.06, 41.29, 41.18, 25.83, 22.85, 20.61, 18.25, 18.17, 18.01, − 5.49; Anal calc for $C_{16}H_{32}O_2Si$: C, 67.54; H, 11.34. Found: C, 67.60; H, 11.45.

**(rel)-(3R and 3S,5S)-5-(t-Butyldimethylsilyloxymethyl)-2-methyl-6-phenyl-hepta-1,6-dien-3-ol (6):** Diastereomeric mixture **6** was prepared from compound **4** using the method described for compound **5**: yield 85%: as diastereomeric mixture for $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.48–7.32 (m, 5H), 6.09–6.03 (m, 1H), 5.44–4.23 (m, 4H), 4.25–3.53 (m, 3H), 2.138–2.19 (m, 2H), 1.86 (s, 3H), 0.96 (m, 9H), 0.10 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 148.19, 144.65, 143.17, 142.42, 128.10, 127.59, 127.42, 126.48, 115.23, 114.07, 109.99, 72.18, 72.02, 69.03, 67.90, 49.39, 43.04, 42.25, 25.79, 18.19, 17.83, − 5.52, − 5.78; Anal calc for $C_{21}H_{34}O_2Si$: C, 72.78; H, 9.89. Found: C, 72.44; H, 10.11.

**(rel)-(1R,4S)-4-(t-Butyldimethylsilyloxymethyl)-2,4-dimethyl-cyclopent-2-enol (7β); and (rel)-(1S,4S)-4-(t-Butyldimethylsilyloxymethyl)-2,4-dimethyl-cyclopent-2-enol (7α):** To a solution of compound **5** (1.8 g, 6.32 mmol) in dry $CH_2Cl_2$ (10 mL) Grubbs' catalyst II (263 mg 0.31 mmol) in dry $CH_2Cl_2$ (3 mL) was added slowly over a 10 minute period under $N_2$ atmosphere. The reaction mixture was refluxed overnight, and cooled to room temperature. The mixture was then concentrated under vacuum, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give the cyclopentenols, **7β** (713 mg, 44%) and **7α** (697 mg, 43%), respectively, as colorless oil. Compound **7β**: $^1$H NMR ($CDCl_3$, 300 MHz) δ 4.99 (s, 1H), 4.19 (dd, $J$ = 11.1, 7.5 Hz, 1H), 3.28 (dd, $J$ = 11.7, 2.1 Hz, 2H), 1.86 (dd, $J$ = 14.1, 7.2 Hz, 1H), 1.71 (s, 3H), 1.68 (d, $J$ = 14.1 Hz, 1H), 0.91 (s, 3H), 0.86 (s, 9H), 0.61 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 143.34, 133.75, 78.94, 69.82, 49.47, 46.07, 25.85, 23.60, 18.57, 13.85, − 5.45; Anal calc for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.38; H, 10.79: Compound **7α**: $^1$H NMR ($CDCl_3$, 300 MHz) δ 5.27 (s, 1H), 4.60 (t, $J$ = 6.6 Hz, 1H), 3.27 (t, $J$ = 9.9 Hz, 2H), 2.34 (dd, $J$ = 13.5, 7.5 Hz, 1H), 1.74 (s, 3H), 1.36 (dd, $J$ = 13.5, 4.8 Hz, 1H), 1.06 (s, 3H), 0.86 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR ($CDCl_3$,





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75 MHz) δ 141.58, 134.88, 79.69, 70.88, 48.99, 45.56, 25.85, 24.70, 18.24, 13.48, − 5.50; Anal calc for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.79; H, 10.73.

**(rel)-(1R,4S)-4-(t-Butyldimethylsilyloxymethyl)-2-methyl-4-phenyl-cyclopent-2-enol (8β); and (rel)-(1S,4S)-4-(t-Butyldimethylsilyloxymethyl)-2-methyl-4-phenyl-cyclopent-2-enol (8α):** Compound **8β** and **8α** were prepared from compound **6** using the method described for compounds **7β** and **7α**: yield for **8β**, 46%, yield for **8α**, 46%; Compound **8β**: $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.26–7.11 (m, 5H), 5.55 (s, 1H), 4.26 (dd, ***J*** = 11.4 Hz, 1H), 3.62 (d, ***J*** = 9.3 Hz, 1H), 3.44 (d, ***J*** = 9.3 Hz, 1H), 2.35 (dd, ***J*** = 13.8, 6.9 Hz, 1H), 2.10 (d, ***J*** = 13.8 Hz, 1H), 1.81 (s, 3H), 0.81 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 145.61, 144.98, 129.79, 128.38, 126.47, 78.24, 70.25, 58.05, 46.45, 25.97, 18.59, 14.07, − 5.42; Anal calc for $C_{19}H_{30}O_2Si$: C, 71.64; H, 9.49. Found: C, 71.48; H, 9.54: Compound **8α**: $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.23 (m, 5H), 5.83 (s, 1H), 4.75 (d, ***J*** = 6.6 Hz, 1H), 3.69 (d, ***J*** = 9.6 Hz, 1H), 3.62 (d, ***J*** = 9.6 Hz, 1H), 2.86 (dd, ***J*** = 13.2, 7.5 Hz, 1H), 1.95 (dd, ***J*** = 13.2, 5.7 Hz, 1H), 1.91 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 146.60, 143.49, 131.13, 128.12, 126.55, 126.07, 79.38, 71.19, 56.62, 46.12, 25.79, 18.16, 13.71, − 5.62; Anal calc for $C_{19}H_{30}O_2Si$: C, 71.64; H, 9.49. Found: C, 71.89; H, 9.12.

**(rel)-(1R,4S)-1-Ethoxycarbonyloxy-4-(t-butyldimethylsilyloxymethyl)-2,4-dimethyl-cyclopent-2-ene (9):** To a solution of compound **7β** (3.5 g, 13.6 mmol) in anhydrous pyridine (15 mL) ethyl chloroformate (1.95 mL, 20.5 mmol) and DMAP (170 mg, 1.4 mmol) were added. The reaction mixture was stirred overnight at room temperature, and the reaction mixture was quenched using a saturated $NaHCO_3$ solution (1.5 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, 1:40) to give compound **9** (3.93 g, 88%) as a colorless syrup: $^1$H NMR ($CDCl_3$, 300 MHz) δ 5.45 (m, 2H), 4.18 (q, ***J*** = 7.5 Hz, 2H), 3.35 (s, 2H), 2.02 (dd, ***J*** = 15.0, 7.5 Hz, 1H), 1.77 (dd, ***J*** = 15.0, 3.9 Hz, 1H), 1.70 (s, 3H), 1.29 (t, ***J*** = 7.5 Hz, 3H), 1.02 (s, 3H), 0.86 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.31, 138.47, 136.87, 85.32, 71.03, 63.71, 49.31, 41.56, 25.89, 23.70, 18.29, 14.30, 13.81, − 5.48; Anal calc for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found: C, 61.87; H, 9.74.

**(rel)-(1R,4S)-1-Ethoxycarbonyloxy-4-(t-butyldimethylsilyloxymethyl)-2-methyl-4-phenyl-cyclopent-2-ene (10):** Compound **10** was prepared from compound **8β** using the method described for compound **9**: Yield 90%: $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.25 (m, 5H), 6.09 (s, 1H), 5.57 (t, ***J*** = 3.6 Hz, 1H), 4.32 (q, ***J*** = 6.9 Hz, 2H), 3.80 (dd, ***J*** = 12.9, 9.3 Hz, 2H), 2.69 (dd, ***J*** = 14.4, 7.8 Hz, 1H), 2.37 (dd, ***J*** = 14.4, 3.6 Hz, 1H), 1.93 (s, 3H), 1.42 (t, ***J*** = 6.9 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.30, 145.79, 138.61, 135.55, 127.93, 126.94, 126.05, 84.70, 71.39, 63.80, 57.25, 41.82, 25.77, 18.19, 14.31, 13.98, − 5.60; Anal calc for $C_{22}H_{34}O_4Si$: C, 67.65; H, 8.77. Found: C, 67.38; H, 8.60.

**(rel)-(1′R,4′S)-9-[4-(t-Butyldimethylsilyloxymethyl)-2,4-dimethyl-cyclopent-2-en-1-yl] adenine (11):** Adenine (201 mg, 1.47 mmol) was added to pure NaH





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(35.1 mg, 1.47 mmol) in anhydrous DMSO (5.3 mL). The reaction mixture was stirred for 30 min at 50–55°C and cooled to room temperature. Simultaneously, $P(O\text{-}i\text{-}Pr)_3$ (0.288 mL, 0.66 mmol) was added to a solution of $Pd_2(dba)_3 \cdot CHCl_3$ (21 mg, 11.25 μmol) in anhydrous THF (5.0 mL), which was stirred for 40 min. The catalyst solution of THF and **9** (433.6 mg, 1.32 mmol) dissolved in anhydrous THF (3 mL) were added slowly to the adenine solution in DMSO. The reaction mixture was stirred overnight at a refluxing temperature and quenched with water (2 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 **11** (207 mg, 36%) as a white solid: mp 178–181°C; UV (MeOH) $\lambda_{max}$ 261.0 nm; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 8.37 (s, 1H), 7.91 (s, 1H), 5.66 (t, ***J*** = 7.8 Hz, 1H), 5.56 (d, ***J*** = 7.2 Hz, 1H), 3.51 (d, ***J*** = 9.6 Hz, 1H), 3.45 (d, ***J*** = 9.6 Hz, 1H), 2.34 (dd, ***J*** = 14.4, 9.3 Hz, 1H), 2.09 (dd, ***J*** = 14.4, 6.0 Hz, 1H), 1.64 (s, 3H), 1.09 (s, 3H), 0.89 (s, 9H), 0.02 (s, 6H); Anal calc for $C_{19}H_{31}N_5OSi$: C, 61.09; H, 8.36; N, 18.75. Found: C, 61.30; H, 8.51; N, 18.83.

**(rel)-(1′R,4′S)-1-[4-(t-Butyldimethylsilyloxymethyl)-2,4-dimethyl-cyclopent-2-en-1-yl] cytosine (12):** Compound **12** was prepared from compound **9** using the method described for compound **11**; Yield 35%; mp 160–161°C; UV (MeOH) $\lambda_{max}$ 271.0 nm; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, ***J*** = 6.6 Hz, 1H), 5.82 (d, ***J*** = 6.6 Hz, 1H), 5.78 (dd, ***J*** = 7.5, 3.9 Hz, 1H), 5.49 (s, 1H), 3.40 (dd, ***J*** = 10.5, 9.0 Hz, 2H), 2.14 (dd, ***J*** = 14.4, 7.8 Hz, 1H), 1.79 (dd, ***J*** = 14.4, 4.5 Hz, 1H), 1.76 (s, 3H), 1.06 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); Anal calc for $C_{18}H_{31}N_3O_2Si$: C, 61.85; H, 8.94; N, 12.02. Found: C, 61.69; H, 8.78; N, 12.23.

**(rel)-(1′R,4′S)-9-[4-(t-Butyldimethylsilyloxymethyl)-2-methyl-4-phenyl-cyclopent-2-en-1-yl] adenine (13):** Compound **13** was prepared from compound **10** using the method described for compound **11**: yield 35%; mp 198–200°C; UV (MeOH) $\lambda_{max}$ 261.5 nm; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H), 7.96 (s, 1H), 7.31–7.19 (m, 5H), 5.84 (s, 1H), 5.59 (dd, ***J*** = 8.4, 7.2 Hz, 1H), 3.75 (s, 2H), 2.85 (dd, ***J*** = 13.5, 8.7 Hz, 1H), 2.50 (dd, ***J*** = 13.5, 6.6 Hz, 1H), 1.59 (s, 3H), 0.84 (s, 9H), 0.02 (s, 6H); Anal calc for $C_{24}H_{33}N_5OSi$: C, 66.17; H, 7.64; N, 16.08. Found: C, 66.30; H, 7.50; N, 15.84.

**(rel)-(1′R,4′S)-1-[4-(t-Butyldimethylsilyloxymethyl)-2-methyl-4-phenyl-cyclopent-2-en-1-yl] cytosine (14):** Compound **14** was prepared from compound **10** using the method described for compound **11**: yield 32%; mp 180–182°C; UV (MeOH) $\lambda_{max}$ 271.5 nm; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 7.50 (d, ***J*** = 6.9 Hz, 1H), 7.30–7.22 (m, 5H), 5.94 (m, 2H), 5.57 (m, 1H), 3.79 (s, 2H), 2.91 (dd, ***J*** = 14.0, 8.6 Hz, 1H), 2.55 (dd, ***J*** = 14.0, 6.8 Hz, 1H), 1.62 (s, 3H), 0.86 (s, 9H), 0.05 (s, 6H); Anal calc for $C_{23}H_{33}N_3O_2Si$: C, 67.11; H, 8.08; N, 10.21. Found: C, 67.41; H, 7.92; N, 10.36.

**(rel)-(1′R,4′S)-9-[4-(Hydroxymethyl)-2,4-dimethyl-cyclopent-2-en-1-yl]adenine (15):** TBAF (0.48 mL, 1.0 M solution in THF) was added to a solution of compound **11** (150 mg, 0.401 mmol) in THF (3 mL) at 0°C. The mixture was stirred at room temperature for 4 h, and concentrated. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:4) to give compound **15** (91 mg, 88%) as a white solid: mp 181–183°C; UV ($H_2O$) $\lambda_{max}$ 262.5 nm; $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ

8.30 (s, 1H), 8.08 (s, 1H), 7.19 (br s, 2H), 5.50 (m, 2H), 3.33 (s, 2H), 2.07 (dd, ***J*** = 13.5, 6.3 Hz, 1H), 1.96 (dd, ***J*** = 13.5, 6.0 Hz, 1H), 1.41 (s, 3H), 1.03 (s, 3H); Anal calc for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.61; N, 27.01. Found: C, 60.57; H, 6.78; N, 26.80.

**(rel)-(1′R,4′S)-1-[4-(Hydroxymethyl)-2,4-dimethyl-cyclopent-2-en-1-yl]cytosine (16):** Compound **16** was prepared from compound **12** using the method described for compound **15**; Yield: 85%; mp 166–168°C; UV ($H_2O$) $\lambda_{max}$ 271.5 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 7.62 (d, ***J*** = 7.4 Hz, 1H), 5.97 (d, ***J*** = 7.4 Hz, 1H), 5.60 (s, 1H), 5.55 (br s, 1H), 3.47 (dd, ***J*** = 12.8, 4.5 Hz, 2H), 2.32 (dd, ***J*** = 13.0, 8.6 Hz, 1H), 2.03 (dd, ***J*** = 13.0, 6.0 Hz, 1H), 1.54 (s, 3H), 1.12 (s, 3H); Anal calc for $C_{12}H_{17}N_3O_2$: C, 61.26; H, 7.28; N, 17.86. Found: C, 61.33; H, 7.44; N, 17.81.

**(rel)-(1′R,4′S)-9-[4-(Hydroxymethyl)-2-methyl-4-phenyl-cyclopent-2-en-1-yl]adenine (17):** Compound **17** was prepared from compound **13** using the method described for compound **15**; Yield: 86%; mp 202–204°C; UV ($H_2O$) $\lambda_{max}$ 261.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.16 (s, 1H), 8.10 (s, 1H), 7.35–7.22 (m, 5H), 5.97 (s, 1H), 5.47 (br s, 1H), 3.65 (d, ***J*** = 3.9, Hz, 2H), 2.49 (dd, ***J*** = 14.0, 9.4 Hz, 1H), 2.01 (dd, ***J*** = 14.0, 6.0 Hz, 1H), 1.57 (s, 3H); Anal calc for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.38; H, 5.82; N, 21.90.

**(rel)-(1′R,4′S)-1-[4-(Hydroxymethyl)-2-methyl-4-phenyl-cyclopent-2-en-1-yl]cytosine (18):** Compound **18** was prepared from compound **14** using the method described for compound **15**; Yield: 78%; mp 179–181°C; UV ($H_2O$) $\lambda_{max}$ 271.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 7.48 (d, ***J*** = 7.2 Hz, 1H), 7.32–7.18 (m, 5H), 5.94 (s, 1H), 5.76 (d, ***J*** = 7.2 Hz, 1H), 5.46 (t, ***J*** = 7.5 Hz, 1H), 3.54 (d, ***J*** = 9.0 Hz, 2H), 3.15 (d, **J** = 9.0 Hz, 1H), 2.43 (dd, ***J*** = 13.5, 9.3 Hz, 1H), 2.01 (dd, ***J*** = 13.5, 6.6 Hz, 1H), 1.55 (s, 3H); Anal calc for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.55; H, 6.62; N, 14.15.



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