Synthesis and Antiviral Activity of 2'(β)-Hydroxymethylated Carbodine Analogues Against Hepatitis C Virus

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2'(β)-Hydroxymethylated adenosine is a potent and selective inhibitor of hepatitis C virus (HCV) replication. It targets the RNA-dependent RNA polymerase of HCV, NS5B. Synthesis and antiviral evaluation of carbocyclic versions are described. The cyclopentene intermediate (**9β**) was successfully synthesized through sequential Johnson-Claisen orthoester rearrangement and ring-closing metathesis (RCM). Coupling of bases *via* a Pd(0) catalyst, selective dihydroxylation, and desilylation yielded the target nucleoside analogues. The compounds **17** and **18** were assayed for their ability to inhibit HCV RNA replication in a subgenomic replicon Huh7 cell line and showed moderate antiviral activity with toxicity up to 20.0 and 24.7 μg/mL, respectively.

Key Words: Carbodine, Anti-HCV agent, Substituted carbocyclic nucleoside

Introduction

Hepatitis C virus (HCV)[1-3] is a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. Current therapy based on pegylated interferon and ribavirin is often poorly tolerated and effective in only 50% of patients. More effective therapeutic agents against HCV are needed.

Nucleoside analogues are the drugs of choice in the treatment of viral infection, and were synthesized and evaluated for anti-HCV activity.[4-6] These nucleosides are incorporated into proviral RNA and act as chain terminators.[7] Modification around the 2'-hydroxy group of the ribose in natural ribonucleosides can produce effective RNA chain termination.[8] For example, 2'-*C*-methylcytidine (**1**)[9] and 2'-*C*-methyladenosine (**2**)[10] are potent anti-HCV agents in clinical trials.

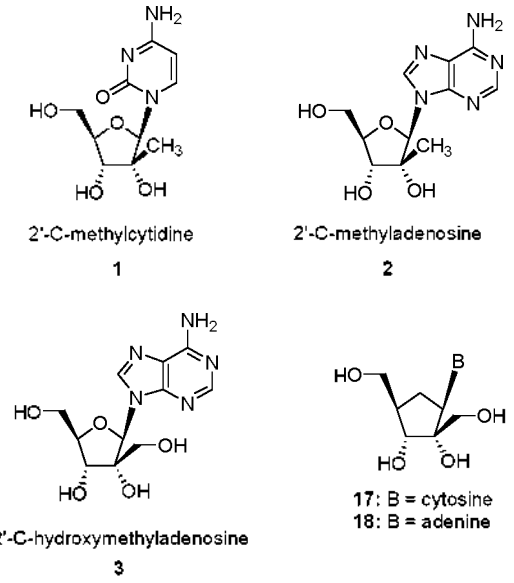


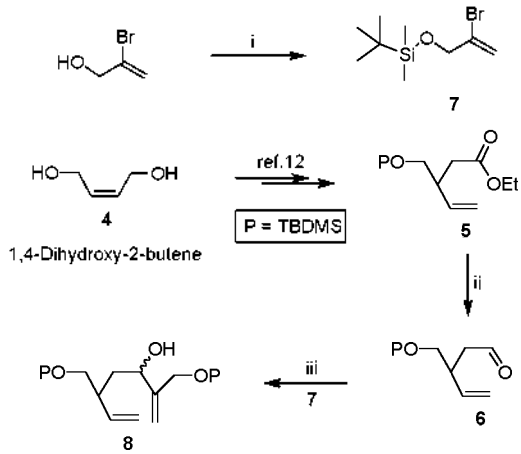
Figure 1. Structures of potent anti-HCV agents and 2'(β)-carbodine analogues (**17** and **18**).

In 2006, Yoo *et al.* reported the synthetic procedure and potent anti-HCV activity of 2'-*C*-hydroxymethyladenosine (**3**).[11] Based on these findings, we designed and synthesized novel carbocyclic classes of nucleosides comprising 2'-*C*-hydroxymethylated carbodine analogues (Fig. 1).

Results and Discussion

Chemistry. The γ,δ-unsaturated ethyl ester **5** was readily synthesized from the commercially available 2-butene-1,4-diol (**4**) using the reported procedure.[12] The ester **5** was reduced to the corresponding aldehyde **6** using DIBAL-H in toluene at −78 °C. The condensation of **6** with the lithium reagent prepared from 3 equivalents of 2-bromo-allyloxy-*tert*-butyldimethylsilane **7** and 2.5 equivalents of butyllithium in THF at −110 °C yielded diene analogue **8**[13] (Scheme 1).

The diene analogue **8** diastereomeric mixture was subjected to ring-closing metathesis (RCM) conditions[14-18] to yield cyclo-



Scheme 1. Reagents and conditions: i) TBDMSCl, imidazole, CH_2Cl_2, 0 °C; ii) DIBAL-H, toluene, −78 °C; iii) **7**, 2-bromo-allyloxy-*tert*-butylmethysilane, n-butyllithium, −110 °C, THF.

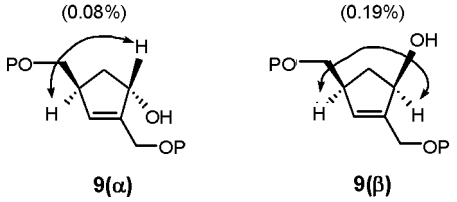


Figure 2. NOE comparison of compounds **9(α)** and **9(β)**.

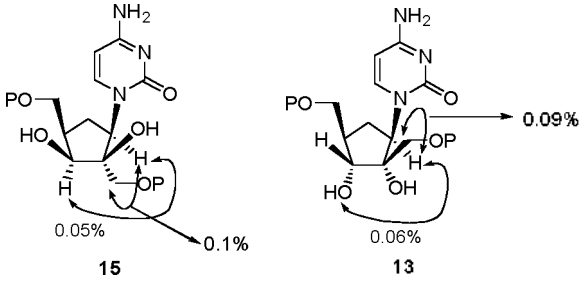
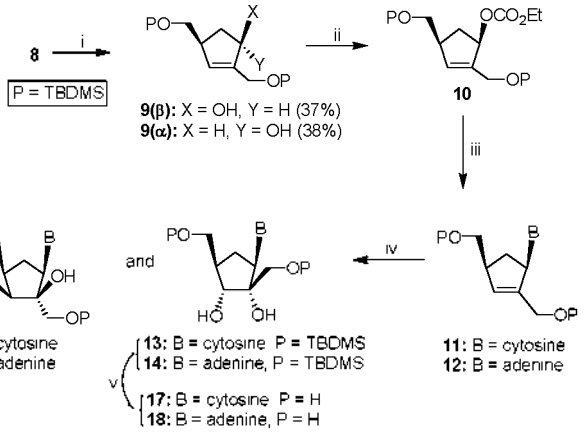


Figure 3. NOE comparison of compound **13** and **15**.

pentenol derivatives **9α** and **9β**. The stereochemical differences between the two isomers were determined by NOE comparisons. Irradiation of C_1-H, produced different NOE patterns at the proximal hydrogens of compound **9β** [*methyloxy*-H (0.19%)] compared to compound **9α** [*methyloxy*-H (0.08%)] (Fig. 2).

Compound **9β** was converted into **10** using ethyl chloroformate, and readily coupled with cytosine and adenine by allylic functionalization using a palladium catalyst adduct to generate nucleoside analogues **11** and **12**, respectively. Carbodine analogues were obtained by oxidation of the protected nucleosides **11** and **12** to yield dihydroxylated **13** and **14** as major reaction products with a small amount of **15** and **16**, respectively. Stereochemical differences were determined by NOE experiments. Irradiation of C_1-H of compound **15** produced different NOE patterns at the proximal hydrogens such as 2'-*methyloxy*-H (0.10%) and 3'-H (0.05%), compared with compound **13** 2'-*methyloxy*-H (0.09%) and 3'-*hydroxyl*-H (0.06%) (Fig. 3). Bulky groups such as silylated hydroxymethyl group and nucleosidic bases (adenine and cytosine) reinforce the steric hindrance of the β-faces.[19,20] Removal of the protecting silyl group of **13** and **14** was performed by treatment with tetrabutylammonium fluoride (TBAF) to yield target nucleosides **17** and **18**, respectively (Scheme 2).

Antiviral Activity. The newly synthesized nucleoside analogues were assayed for anti-HCV activity using an *in vitro* assay system that is suitable for monitoring anti-HCV activities of compounds. This system is composed of a human hepatocarcinoma cell line (Huh-7) supporting multiplication of a HCV replication, and the results are summarized in Table 1. These cells contain a HCV subgenomic replicon RNA encoding a luciferase reporter gene as a marker. The antiviral potency of the nucleoside analogues against the HCV replicon is expressed as EC_{50}, which was quantified by a luciferase assay after a two-days incubation period with the tested compound. To confirm the anti-HCV potency of compounds, subgenomic



Scheme 2. Reagents and conditions: i) Grubb's catalyst (II), benzene; ii) $ClCO_2Et$, pyridine DMAP; iii) cytosine, adenine, $Pd_2(dba)_3$-$CHCl_3$, $P(O\text{-}i\text{-}Pr)_3$, NaH, THF/DMSO; iv) OsO_4, NMO; v) TBAF, THF/CH_3CN, rt.

Table 1. Anti-HCV activity of the newly synthesized compounds **17** and **18**.

Compound No.	Anti-HCV EC_{50} (μg/mL)	Cytotoxicity CC_{50} (μg/mL)
17	11.7	20.0
18	18.2	24.7
2'-*C*-Me-*C*	3.7	> 50

2'-*C*-Me-C: 2'-*C*-Methylcytidine. EC_{50} (μg/mL): concentration required to inhibit 50% of the virus induced cytopathicity. CC_{50} (μg/mL): concentration required to reduce cell viability by 50%.

replicon RNA levels were quantified by real-time RT-PCR analysis. In addition, the associated cytotoxicity (expressed as CC_{50} in Table 1) was evaluated in a tetrazolium (XTT)-based assay. 2'-*C*-Methylcytidine (**1**) was selected as the reference standard due to its structure similarity to the newly synthesized compounds. Both compounds **17** and **18** inhibited the replication of the replicon in Huh-7 cells by 50% at concentrations of 11.7 μg/mL and 18.2 μg/mL, respectively.

In summary, on the basis of potent anti-HCV activity of 2'-*C*-hydroxymethyladenosine, we have accomplished the stereoselective synthesis of its carbodine derivatives starting from 2-butene-1,4-diol. Compounds **17** and **18** exhibited good anti-HCV activity, indicating that the hydroxymethyl group at 2'-position of carbodine system makes the conformation to be favorable for interaction with HCV polymerase.

Experimental Section

Melting points (mp) were measured on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded using a JEOL 300 Fourier transform spectrometer (JEOL, Tokyo, Japan). UV spectra were obtained using a Beckman DU-7 spectrophotometer (Beckman, South Pasadena, CA, USA). The elemental microanalyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA).

(±)-3-(*tert*-Butyldimethylsilanyloxymethyl)-pent-4-enal

(6). To a solution of **5** (2.5 g, 9.17 mmol) in toluene (60 mL), DIBAL-H (6.73 mL, 1.5 M solution in toluene, 10.10 mmol) was added slowly at −78 °C, and stirred for 15 min at the same temperature. Methanol (7 mL) was added and the reaction mixture was stirred at room temperature for 2 h. The resulting solid was filtered through celite. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate-hexanes 1:30 v/v) to yield compound **6** (1.44 g, 69%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.72 (s, 1H), 5.76-5.65 (m, 1H), 5.11-5.05 (m, 2H), 3.65 (dd, J = 9.8 and 4.8 Hz, 1H), 3.43 (dd, J = 9.8 and 2.6 Hz, 1H), 2.76 (m, 1H), 2.62-2.51 (m, 1H), 2.43-2.32 (m, 1H), 0.81 (s, 9H), 0.01 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.1, 137.7, 116.4, 65.8, 45.5, 41.1, 25.8, 18.3, -5.5.

(2-Bromoallyloxy)-*tert*-butyldimethylsilane (7). *tert*-Butylchlorodimethylsilane (6.05 g, 40.15 mmol) was added to a stirred solution of 2-bromoallyl alcohol (5.0 g, 36.5 mmol) and imidazole (3.85 g, 56.57 mmol) in CH_2Cl_2 (150 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h, and then evaporated under reduced pressure. The residue was partitioned between water and ethyl acetate and the organic layer was dried over $MgSO_4$ and filtered. After evaporation of the organic solvent, the residue was purified by column chromatography (silica gel, ethyl acetate-hexanes 1:40 v/v) to yield compound **7** (8.53 g, 93%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.61-5.55 (m, 2H), 4.61 (d, J = 0.6 Hz, 2H), 0.82 (s, 9H), 0.12 (s, 6H).

***rel*-(3*R* and 3*S*,5*R*)-2,5-Bis-(*tert*-Butyldimethylsilanyloxymethyl)hepta-1,6-dien-3-ol (8).** To a solution of compound **7** (441 mg, 1.755 mmol) in dry THF (5 mL) cooled at −110 °C (ether and liquid nitrogen), butyllithium (0.91 mL, 1.6 M solution in hexanes, 1.46 mmol) was slowly added over 5 min under an argon atmosphere. After stirring for 15 min at the same temperature, a solution of **6** (133 mg, 0.585 mmol) in dry THF (0.5 mL) was slowly added to the reaction mixture over 5 min, and stirred for 15 min at the same temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (2 mL) and warmed slowly to room temperature. The mixture was extracted twice with diethyl ether (5 mL each) and the combined organic layer extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate-hexanes 1:30 v/v) to yield a diastereomeric mixture of **8** (157 mg, 67%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.71 (m, 1H), 5.25-5.14 (m, 4H), 3.92 (m, 1H), 3.73-3.67 (m, 2H), 3.51 (m, 2H), 2.27 (m, 1H), 1.52-1.47 (m, 2H), 0.82 (m, 18H), 0.01 (s, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.5, 143.6, 112.7, 107.4, 71.8, 70.2, 67.2, 39.8, 36.3, 25.6, 18.6, -5.4.

***rel*-(1*R*,4*S*)-2,4-Bis-(*tert*-butyldimethylsilanyloxymethyl)cyclopent-2-enol (9β) and *rel*-(1*S*,4*S*)-2,4-bis-(*tert*-butyldimethylsilanyloxymethyl)cyclopent-2-enol (9α).** To a solution of **8** (2.5 g, 6.24 mmol) in dry benzene (12 mL), second generation Grubbs' catalyst (40 mg, 0.0471 mmol) was added. The reaction mixture was refluxed overnight and then evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate-hexanes 1:25 v/v) to yield **9β** (860 mg, 37%) and **9α** (883 mg, 38%). Compound **9β**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.54 (d, J = 5.8 Hz, 1H), 4.45 (s, 2H), 4.09 (dd, J = 5.4 and 2.4 Hz, 1H), 3.72 (dd, J = 10.2 and 6.8 Hz, 1H), 3.59 (dd, J = 10.2 and 8.2 Hz, 1H), 2.48-2.40 (dd, J = 10.0 and 8.2 Hz, 1H), 2.02-1.95 (dd, J = 10.0 and 6.8 Hz, 1H), 0.82 (s, 18H), 0.02 (s, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.5, 126.2, 72.9, 69.9, 67.5, 41.1, 30.7, 25.7, 18.3, -5.7. Analysis for $C_{19}H_{40}O_3Si_2$ (514.91), Calcd.: C, 61.23; H, 10.82; Found: C, 61.34; H, 10.77. Compound **9β**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.57 (d, J = 6.2 Hz, 1H), 4.48 (d, J = 2.1 Hz, 2H), 4.01 (d, J = 5.0 Hz, 1H), 3.75 (dd, J = 9.8 and 6.2 Hz, 1H), 3.61 (dd, J = 9.8 and 8.0 Hz, 1H), 2.52-2.45 (dd, J = 10.2 and 7.8 Hz, 1H), 2.05-1.99 (dd, J = 10.0 and 8.2 Hz, 1H), 0.81 (m, 18H), 0.01 (s, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.7, 126.5, 71.8, 70.2, 68.2, 42.0, 31.4, 25.5, 18.7, -5.4. Analysis for $C_{19}H_{40}O_3Si_2$ (519.41), Calcd.: C, 61.23; H, 10.82; Found: C, 61.17; H, 10.90.

***rel*-(1*R*,4*S*)-1-Ethoxycarbonyloxy-2,4-bis-(*tert*-butyldimethylsilyloxymethyl)cyclopent-2-ene (10).** To a solution of compound **9β** (1.77 g, 4.68 mmol) in anhydrous pyridine (15 mL), ethyl chloroformate (547 mg, 5.04 mmol) and DMAP (49 mg, 0.4 mmol) were added. The reaction mixture was stirred overnight at 60 °C. The reaction mixture was then quenched using a saturated $NaHCO_3$ solution (0.5 mL) and evaporated under reduced pressure. The residue was partitioned between water and ethyl acetate and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layer extracts were washed with brine, dried over $MgSO_4$ and filtered. The organic solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, ethyl acetate-hexanes 1:25 v/v) to yield compound **10** (1.66 g, 80%) as a colorless syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.57 (d, J = 6.2 Hz, 1H), 4.85 (dd, J = 6.8 and 4.2 Hz, 1H), 4.48 (d, J = 1.8 Hz, 2H), 4.21 (t, J = 7.2 Hz, 2H), 3.69 (dd, J = 9.8 and 6.4 Hz, 1H), 3.46 (dd, J = 9.8 and 7.8 Hz, 1H), 2.78-2.69 (dd, J = 10.0 and 6.8 Hz, 1H), 2.02-1.94 (dd, J = 10.0 and 7.4 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H), 0.81 (m, 18H), 0.01 (m, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.1, 144.5, 127.8, 79.9, 71.6, 67.7, 64.3, 41.2, 32.6, 25.7, 18.6, 13.9, -5.6. Analysis for $C_{22}H_{44}O_5Si_2$ (444.75), Calcd.: C, 59.41; H, 9.97; Found: C, 59.55; H, 10.02.

***rel*-(1'*R*,4'*S*)-1-[2,4-Bis-(*tert*-butyldimethylsilyloxymethyl)cyclopent-2-en-1-yl]cytosine (11).** Cytosine (104 mg, 0.936 mmol) was added to a solution of hexane-washed NaH (22.4 mg, 0.936 mmol) in anhydrous DMSO (5.0 mL). The reaction mixture was stirred for 30 min at 50 - 55 °C and cooled to room temperature. Simultaneously, P(O-*i*-Pr)$_3$ (78 mg, 0.374 mmol) was added to a solution of $Pd_2(dba)_3$·$CHCl_3$ (50 mg, 4.8 μmol) in anhydrous THF (4.5 mL), which was stirred for 30 min. The catalyst solution in THF and **10** (373.6 mg, 0.84 mmol) dissolved in anhydrous THF (4.0 mL) was sequentially added to the cytosine solution in DMSO. The reaction mixture was refluxed overnight, and then cooled and quenched with water (2.0 mL). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, MeOH/Hexane/EtOAc, 0.1:3:1) to yield compound **11** (145 mg, 37%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (d, J = 6.8 Hz, 1H), 5.78 (d, J = 6.8 Hz, 1H), 4.57 (dd, J = 5.6 and 1.2 Hz, 1H), 4.42 (s, 2H), 3.53 (dd, J = 12.8

and 6.4 Hz, 2H), 2.40 (dd, J = 12.6 and 8.2 Hz, 1H), 2.32 (m, 1H), 2.01 (dd, J = 12.6 and 6.4 Hz, 1H), 0.82 (m, 18H), 0.01 (m, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.7, 156.8, 145.4, 143.4, 126.7, 91.8, 70.7, 67.4, 53.5, 42.3, 30.2, 25.6, 18.4, -5.7. Analysis for $C_{23}H_{43}N_3O_3Si_2$ (465.78). Calcd.: C, 59.31; H, 9.31; N, 9.02; Found: C, 59.24; H, 9.28; N, 8.95.

***rel*-(1'*R*,4'*S*)-9-[2,4-Bis-(*tert*-butyldimethylsilyloxymethyl) cyclopent-2-en-1-yl]adenine (12).** Adenine nucleoside analogue **12** was synthesized from **10** by a similar procedure as described for **11**. Compound **12**: yield 32%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.24 (s, 1H), 8.12 (s, 1H), 5.69 (d, J = 6.0 Hz, 1H), 4.64 (s, 2H), 4.51 (d, J = 5.8 Hz, 1H), 3.55 (dd, J = 9.8 and 4.8 Hz, 1H), 3.42 (dd, J = 9.8 and 6.8 Hz, 1H), 2.48 (dd, J = 12.4 and 8.0 Hz, 1H), 2.34 (m, 1H), 2.03 (dd, J = 12.4 and 6.8 Hz, 1H), 0.82 (s, 18H), 0.01 (s, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.6, 152.4, 150.9, 145.5, 143.6, 127.6, 117.9, 70.7, 68.3, 58.1, 41.8, 29.7, 25.6, 18.4, -5.5. Analysis for $C_{24}H_{43}N_5O_2Si_2$ (489.80). Calcd.: C, 58.85; H, 8.85; N, 14.30; Found: C, 58.74; H, 8.92; N, 14.26.

***rel*-(1'*R*,2'*S*,3'*S*,4'*R*)-1-[2,4-Bis-(*tert*-butyldimethylsilyl-oxymethyl)-2,3-dihydroxycyclo-pentan-1-yl]cytosine (13) and *rel*-(1'*R*,2'*R*,3'*R*,4'*R*)-1-[2,4-bis-(*tert*-butyldimethyl silyloxy-methyl)-2,3-dihydroxy-cyclopentan-1-yl]cytosine (15).** To a stirred solution of **12** (235 mg, 0.504 mmol) in cosolvent (4.0 mL, acetone/water = 5:1 v/v), NMO (236 mg, 1.01 mmol) and OsO_4 (0.42 mL, 4% aqueous solution) were added. The reaction mixture was stirred overnight at 50 °C, cooled, and then quenched with saturated Na_2SO_3 solution (2 mL). The resulting solid was removed by filtration through celite and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, MeOH/ CH_2Cl_2 1:7 v/v) to yield **13** (143 mg, 57%) and **15** (37 mg, 15%). Compound **13**: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.43 (d, J = 7.2 Hz, 1H), 7.01 (brd, 2H, D_2O exchangeable), 5.35 (s, 1H, D_2O exchangeable), 5.09 (d, J = 4.2 Hz, 1H, D_2O exchangeable), 3.99 (dd, J = 6.2 and 2.2 Hz, 1H), 3.71-3.60 (m, 4H), 3.32 (d, J = 6.2 Hz, 1H), 1.69-1.59 (m, 3H), 0.81 (m, 18H), 0.01 (m, 12H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 165.7, 155.8, 143.4, 93.9, 85.5, 71.0, 66.2, 65.2, 52.1, 32.2, 25.7, 18.6, 16.3, -5.54. Analysis for $C_{23}H_{45}N_3O_5Si_2$ (499.79). Calcd.: C, 55.27; H, 9.08; N, 8.41; Found: C, 55.40; H, 9.15; N, 8.53. Compound **15**: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.51 (d, J = 7.0 Hz, 1H), 7.03 (brd, 2H, D_2O exchangeable), 5.41 (brs, 1H, D_2O exchangeable), 5.10 (brs, 1H, D_2O exchangeable), 4.01 (d, J = 4.8 Hz, 1H), 3.69 (d, J = 10.6 Hz, 1H), 3.60-3.41 (m, 3H), 3.35 (d, J = 6.6 Hz, 1H), 1.67 (m, 1H), 1.59-1.51 (m, 2H), 0.82 (m, 18H), 0.02 (m, 12H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 165.5, 156.1, 146.3, 92.7, 86.1, 71.6, 67.1, 64.9, 53.6, 34.0, 25.1, 18.5, 17.9, -5.58. Analysis for $C_{23}H_{45}N_3O_5Si_2$ (499.79). Calcd.: C, 55.27; H, 9.08; N, 8.41; Found: C, 55.19; H, 8.99; N, 8.34.

***rel*-(1'*R*,2'*S*,3'*S*,4'*R*)-9-[2,4-Bis-(*tert*-butyldimethylsilyloxymethyl)-2,3-dihydroxy-cyclopentan-1-yl]adenine (14) and *rel*-(1'*R*,2'*S*,3'*S*,4'*R*)-9-[2,4-bis-(*tert*-butyldimethylsilyloxymethyl)-2,3-dihydroxy-cyclopentan-1-yl]adenine (16).** The adenine nucleoside analogues **14** and **16** were synthesized from **13** by the same procedure as described for the preparation of **13** and **15**. Compound **14**: yield 52%; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.21 (s, 1H), 8.13 (s, 1H), 7.22 (brs, 2H, D_2O exchangeable), 5.32 (brs, 1H, D_2O exchangeable), 5.08 (d, J = 4.2 Hz, 1H, D_2O exchangeable), 3.96 (dd, J = 6.2 and 4.0 Hz, 1H), 3.68-3.59 (m, 4H), 3.35 (d, J = 7.0 Hz, 1H), 1.76-1.68 (m, 2H), 1.68 (m, 1H), 0.81 (m, 18H), 0.02 (m, 12H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 155.8, 152.5, 149.8, 141.5, 119.7, 87.1, 71.5, 65.3, 64.2, 55.2, 33.7, 25.6, 18.4, 16.7, -5.6. Analysis for $C_{24}H_{45}N_5O_4Si_2$ (523.82). Calcd.: C, 55.03; H, 8.66; N, 13.37; Found: C, 54.93; H, 8.56; N, 13.44. Compound **16**: yield 16%; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.18 (s, 1H), 8.09 (s, 1H), 7.15 (brs, 2H, D_2O exchangeable), 5.38 (brs, 1H, D_2O exchangeable), 5.11 (d, J = 4.4 Hz, 1H, D_2O exchangeable), 3.89 (d, J = 6.0 Hz, 1H), 3.65-3.53 (m, 4H), 3.29 (d, J = 6.8 Hz, 1H), 1.69-1.61 (m, 3H), 0.82 (m, 18H), 0.01 (m, 12H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 155.6, 153.0, 148.9, 140.4, 118.2, 86.7, 70.8, 66.0, 65.2, 54.9, 32.8, 25.7, 18.7, 17.2, -5.8. Analysis for $C_{24}H_{45}N_5O_4Si_2$ (523.82). Calcd.: C, 55.03; H, 8.66; N, 13.37; Found: C, 55.12; H, 8.73; N, 13.27.

***rel*-(1'*R*,2'*S*,3'*S*,4'*R*)-1-[2,4-Bis-(hydroxymethyl)-2,3-dihydroxy-cyclopentan-1-yl]cytosine (17).** TBAF (0.75 mL, 1.0 M solution in THF, 0.75 mmol) was added to a solution of **13** (125 mg, 0.25 mmol) in cosolvent (3.0 mL, THF/CH_3CN 1:1 v/v) at 0 °C. The mixture was stirred overnight at room temperature and then evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, MeOH/CH_2Cl_2 1:4 v/v) to yield **17** (55 mg, 81%) as a white solid: mp 195 - 197 °C; UV (H_2O): λ_{max} 270.5 nm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.43 (d, J = 6.9 Hz, 1H), 7.02 (brd, 2H, D_2O exchangeable), 5.59 (d, J = 7.0 Hz, 1H), 5.36 (brs, 1H, D_2O exchangeable), 5.14 (brs, 1H, D_2O exchangeable), 4.89 (t, J = 4.2 Hz, 1H, D_2O exchangeable), 4.80 (brs, 1H, D_2O exchangeable), 3.65-3.57 (m, 3H), 3.40-3.33 (m, 2H), 3.28 (d, J = 6.2 Hz, 1H), 1.69-1.62 (m, 2H), 1.53 (dd, J = 8.2 and 6.8 Hz, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 165.6, 155.4, 144.7, 94.4, 85.2, 70.6, 63.8, 61.2, 52.6, 32.3, 17.4. Analysis for $C_{11}H_{17}N_3O_5$ (+1.5 H_2O, 317.29). Calcd.: C, 44.29; H, 6.76; N, 14.08; Found: C, 44.27; H, 6.67; N, 13.96.

***rel*-(1'*R*,2'*S*,3'*S*,4'*R*)-9-[2,4-Bis-(hydroxymethyl)cyclopent-2-en-1-yl]adenine (18).** Adenine nucleoside analogue **18** was synthesized from **14** by the same procedure as described for the preparation of **17** as a white solid: yield 75%; mp 202 - 205 °C; UV (H_2O): λ_{max} 260.0 nm. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.17 (s, 1H), 8.05 (s, 1H), 7.12 (brd, 2H, D_2O exchangeable), 5.29 (brs, 1H, D_2O exchangeable), 5.12 (d, J = 4.6 Hz, 1H, D_2O exchangeable), 4.86 (t, J = 4.2 Hz, 1H, D_2O exchangeable), 4.79 (t, J = 4.0 Hz, 1H, D_2O exchangeable), 3.81 (dd, J = 10.8 and 6.8 Hz, 2H), 3.68-3.53 (m, 3H), 3.31 (d, J = 6.2 Hz, 1H), 1.89-1.80 (m, 2H), 1.69 (m, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 155.7, 152.6, 146.5, 143.2, 117.9, 84.9, 71.3, 63.6, 61.3, 52.9, 31.8, 16.9. Analysis for $C_{12}H_{17}N_5O_4$ (+0.5 MeOH, 311.31): C, 48.23; H, 6.15; N, 22.49; Found: C, 48.17; H, 6.09; N, 22.53.

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