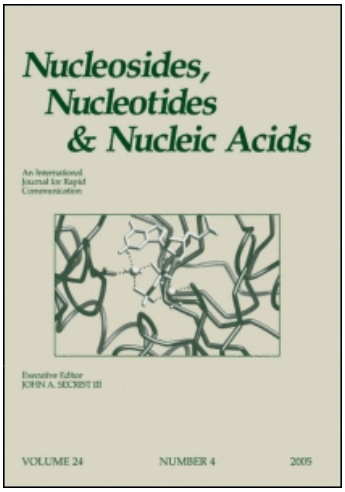

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Synthesis and Anti-Hepatitis C Virus Activity of 2'(β)-Hydroxyethyl and 4'(α)-Hydroxymethyl Carbodine Analogues

Lian Jin Liu[a]; Joon Hee Hong[a]
[a] BK21-Project Team, College of Pharmacy, Chosun University, Kwangju, Republic of Korea

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SYNTHESIS AND ANTI-HEPATITIS C VIRUS ACTIVITY OF 2′(β)-HYDROXYETHYL AND 4′(α)-HYDROXYMETHYL CARBODINE ANALOGUES

Lian Jin Liu and Joon Hee Hong

BK21-Project Team, College of Pharmacy, Chosun University, Kwangju, Republic of Korea

□ *2′(β)-Hydroxyethylated adenosine is a potent and selective inhibitor of hepatitis C virus (HCV) replication targeting the RNA-dependent RNA polymerase of HCV, NS5B. The synthesis and anti-HCV evaluation of carbodine analogues are described. The cyclopentene intermediate* ***10*** *was successfully made via sequential Johnson-Claisen orthoester rearrangement and ring-closing metathesis. Coupling of bases via a Pd(0) catalyst, selective dihydroxylation, and desilylation yielded the target carbodine analogues. Cytosine analogue* ***17*** *weakly inhibited the replication of the HCV replicon in Hua-7 cells by 50% at 21.1 μM.*

Keyword Carbodine; anti-HCV agent; substituted carbocyclic nucleoside

INTRODUCTION

Hepatitis C virus (HCV) infection[1] is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals. Once infected, about 20% of people clear the virus, but the rest can harbor HCV the rest of their life. About 10–20% of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. Current therapy based on pegylated interferon and ribavirin is often poorly tolerated and effective in only 50% of patients.[2] Moreover, there is no established vaccine for HCV, and there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection. The nonstructural protein NS5B is an RNA-dependent RNA polymerase that is required for viral replication. This polymerase is an essential component in the HCV replication complex and therefore is an ideal target for drug discovery.[3]

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Address correspondence to Joon Hee Hong, College of Pharmacy, Chosun University, Kwangju 501-759, Republic of Korea. E-mail: hongjh@mail.chosun.ac.kr

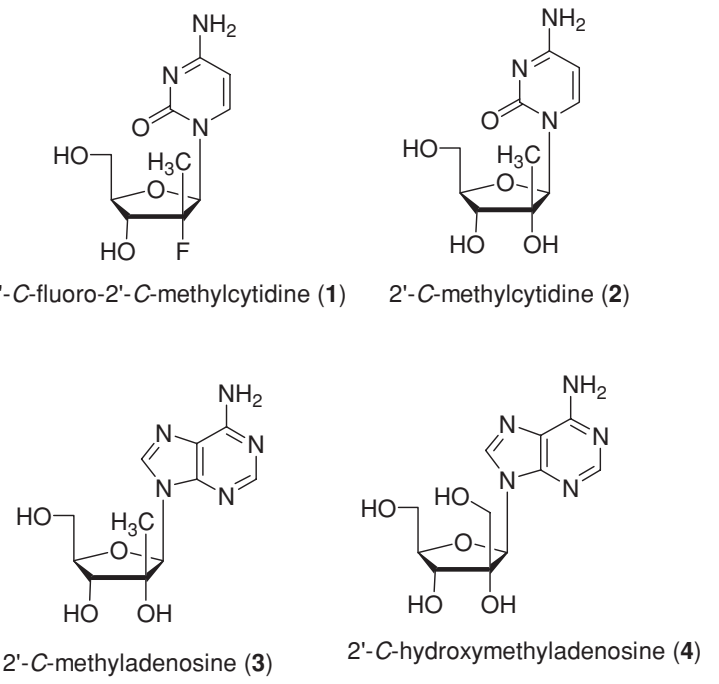


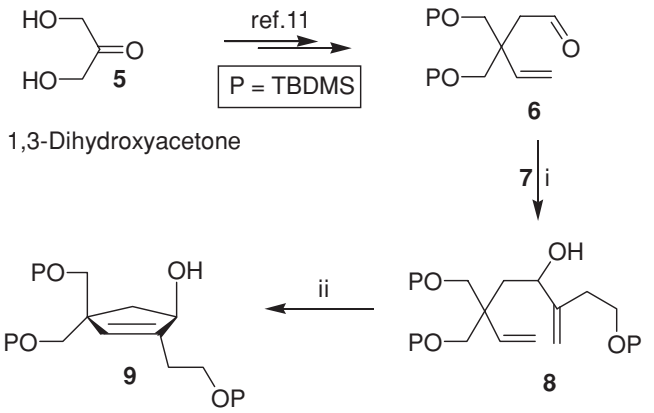
FIGURE 1 Structure of potent nucleoside anti-HCV agents.

Nucleoside analogues are the drugs of choice in curing viral infection, and were synthesized and evaluated for anti-HCV activity.[4] These nucleosides are incorporated into proviral RNA and act as chain terminators.[5] Recently, several 2′-modified nucleoside analogues with potent inhibitory activity against the HCV NS5B polymerase have been identified.[6] Among the most potent compound in this class, 2′-deoxy-2′-fluoro-2′-*C*-methyl cytidine[7] **1**, 2′-*C*-methylcytidine[8] **2**, and 2′-*C*-methyladenosine[8] **3** are potent anti-HCV agents (Figure 1).

Recently, Jeong et al. reported a synthetic procedure and potent anti-HCV activity of 2′-*C*-hydroxymethyl adenosine **4**.[9] Based on these findings, we designed and synthesized novel carbocyclic classes of nucleosides comprising 2′-*C*-hydroxyethylated carbodine analogues as potent anti-HCV agents.

RESULTS AND DISCUSSION

For the synthesis of target carbocyclic nucleoside analogues, cyclopentene derivative **10** was chosen as the key intermediate prepared from aldehyde **6** as starting material.[10] The aldehyde was condensed with the lithium reagent prepared from three equivalents of 3-bromo-but-3-enyloxy-*t*-butyldimethylsilane **7** and 2.5 equivalents of butyl lithium in THF at

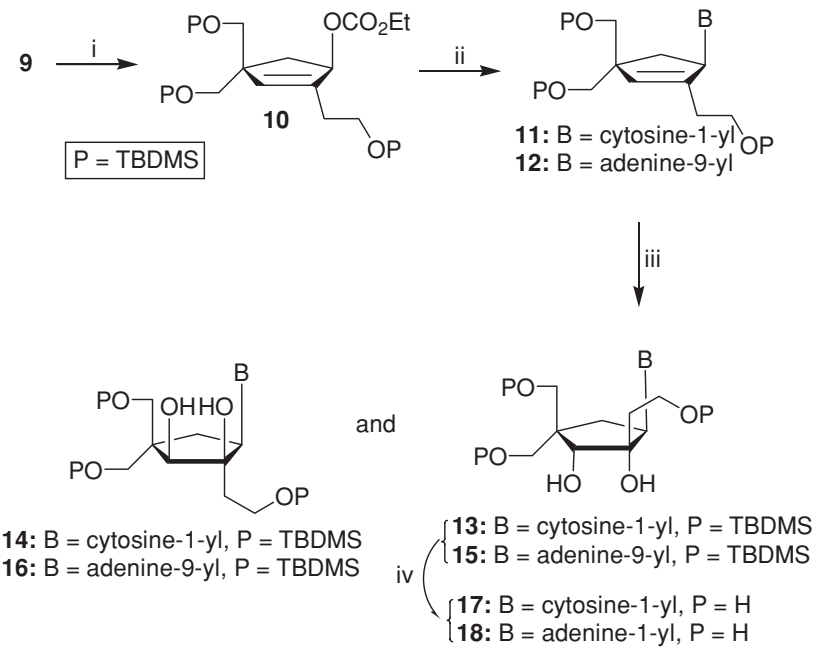


SCHEME 1 Synthesis of cyclopentenol intermediate **9**. Reagents: i) **7**, (3-Bromo-but-3-enyloxy)-*t*-butyldimethylsilane, butylithium, −110°C, THF; ii) second Grubbs catalysis, benzene.

−110°C to yield the diene analogue **8**.[11] The diene analogue **8** was subjected to ring-closing metathesis (RCM) conditions[12] using seconds-generation Grubbs catalysis to provide cyclopentenol **9** as a racemic mixture (Scheme 1).

Cyclopentenol **9** was transformed to the ethyl formate analogue **10** using ethyl chloroformate in pyridine solvent, and readily coupled with cytosine and adenine by allylic functionalization using a palladium catalyst adduct to generate nucleoside analogues **11** and **12**. Vicinal oxidations of olefin of the nucleoside analogues **11** and **12** gave carbodine-like nucleoside analogues **13** and **15** as major reaction products, with **14** and **16** as minor isomers. These stereochemical outcomes suggest that bulky groups such as silylated hydroxymethyl group and nucleosidic bases (cytosine and adenine) reinforce the steric hindrance of the β-faces. Furthermore, we hypothesize that the cyclopentene ring causes one of the protecting groups on the 4′-position to be in equatorial positions, which causes the other protecting group on 4′-substituent to be in the axial down position, making the dihydroxylation from the β-face more hindered. Their stereochemistries were readily determined by NOE experiments. For example, irradiation of 1′-*H* of compound **13** produced different NOE patterns at the proximal hydrogens such as 3′-*H* (0.29%), compared to 3′-*H* (0.45%) of compound **14** (Figure 2). Removal of the silyl protection groups of **13** and **15** was performed by tetrabutylammonium fluoride (TBAF) treatment to yield the desired carbodine analogues **17** and **18** (Scheme 2).

The synthesized nucleoside analogues were assayed for anti-HCV activity using an in vitro assay system. This system is composed of a human hepatocarcinoma cell line (Huh-7) supporting HCV replication. These cells contain an HCV subgenomic replicon RNA encoding a luciferase reporter gene as a marker. The antiviral potency of these analogues against the HCV



SCHEME 2 Synthesis of 2′-hydroxyethylated target compounds. Reagents: i) $ClCO_2Et$, pyrimidine, DMAP; ii) cytosine, adenosine, $Pd_2(dba)_3.CHCl_3$, P(O-*i*-pr)$_3$, NaH,vTHF/DMSO; iii) OsO_4, NMO; iv) TBAF, THF/CH_3CN, room temperature.

replicon is expressed as EC_{50}, which was quantified by a luciferase assay after a two-day incubation period with the compounds. To confirm the anti-HCV potency of compounds, subgenomic replicon RNA levels were quantified by real-time polymerase chain reaction (RT-PCR) analysis. In addition, the associated cytotoxicity was evaluated in a tetrazolium (XTT)-based assay. Cytosine analogue **17** weakly inhibited the replication of the replicon in Hua-7 cells by 50% at 21.1 μM.

In summary, on the basis of potent anti-HCV activity of 2′-modified nucleosides, we have designed and synthesized 2′-hydroxyethylated carbodine derivatives from 1,3-dihydroxy acetone. Synthesized cytosine analogue **17** exhibited weak anti-HCV activity.

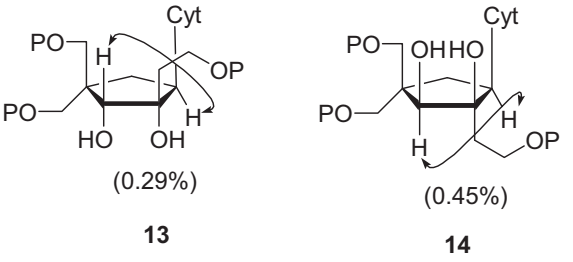


FIGURE 2 NOE comparisons of cytosine analogues **13** and **14**.

EXPERIMENTAL

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL 300 Fourier transform spectrometer (JEOL, Tokyo, Japan); chemical shifts are reported in parts per million (δ) and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublets). Ultraviolet (UV) spectra were obtained on a Beckman DU-7 spectrophotometer (Beckman, South Pasadena, CA, USA). The elemental analyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA). Thin layer chromatography (TLC) was performed on Uniplates (silica gel) purchased from Analtech Co. (7558, Newark, DE, USA). All reactions were performed under an atmosphere of nitrogen unless specified. Dry dichloromethane, benzene, and pyridine were obtained by distillation from CaH_2. Dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

(3-Bromo-but-3-enyloxy)-t-butyldimethylsilane (7): To a stirred solution of 3-bromo-but-3-en-1-ol (6.6 g, 43.8 mmol) and imidazole (4.62 g, 67.88 mmol) in CH_2Cl_2 (150 mL), *t*-butyldimethylsilyl chloride (7.26 g, 48.18 mmol) at 0°C was added. The mixture was stirred at room temperature for 6 hours and concentrated under vacuum. The residue was extracted using EtOAc (200 mL) and water (200 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:35) to give compound **7** (11 g, 95%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.59 (d, J = 5.8 Hz, 1H), 5.40 (d, J = 5.8 Hz, 1H), 3.79 (t, J = 7.2 Hz, 2H), 2.11 (t, J = 7.2 Hz, 2H), 0.81 (s, 9H), 0.1 (s, 6H).

(±)-2-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-5,5-bis-(tert-butyl-dimethyl-silanyloxymethyl)-hepta-1,6-dien-3-ol (8): To a solution of compound **7** (581 mg, 2.19 mmol) in dry THF (8 mL) cooled at −110°C (ether and liquid nitrogen), 1.6 M butyllithium in hexane (1.36 mL, 2.19 mmol) was slowly added for 5 minutes under an argon atmosphere. After stirring for 15 minutes at the same temperature, a solution of **6** (326 mg, 0.877 mmol) in dry THF (2 mL) was slowly added to the mixture over 5 minutes and stirred for 15 minutes at the same temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (3 mL) and warmed slowly to room temperature. The mixture was extracted with diethyl ether (50 mL) two times and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give a diastereomeric mixture of **8** (309 mg, 63%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.72 (dd, J = 5.6, 2.4 Hz, 1H), 5.08–4.97 (m, 4H), 3.92 (m, 1H), 3.81–3.72 (m, 4H), 3.61 (t, J = 7.0 Hz, 2H), 2.24 (t, J =

7.0 Hz, 1H), 1.45–1.39 (dd, $J = 6.8$, 2.8 Hz, 2H), 0.81 (m, 27H), 0.01 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.7, 148.3, 110.1, 108.7, 74.1, 70.7, 70.6, 65.1, 36.6, 35.2, 35.1, 25.4, 18.5, −5.6.

(±)-2-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-4,4-bis-(tert-butyl-dimethyl-silanyloxymethyl)-cyclopent-2-enol (9): To a solution of compound **8** (1.74 g, 3.12 mmol) in dry benzene (10 mL), a second-generation Grubbs' catalyst (21 mg, 0.0236 mmol) was added. The reaction mixture was refluxed overnight and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give the cyclopentenol **9** (1.32 mg, 80%) as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.47 (s, 1H), 4.10 (dd, $J = 5.4$, 1.2 Hz, 1H), 3.86 (t, $J = 7.2$ Hz, 2H), 3.77–3.69 (m, 4H), 2.12 (t, $J = 7.1$ Hz, 2H), 2.03 (dd, $J = 12.8$, 6.8 Hz, 1H), 1.89 (dd, $J = 12.8$, 5.4 Hz, 1H), 0.82 (m, 27H), 0.01 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.5, 133.2, 75.3, 70.7, 70.0, 64.2, 46.2, 36.1, 30.7, 25.5, 18.7, −5.4.

(±)-2-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-4,4-bis-(tert-butyl-dimethyl-silanyloxymethyl)-cyclopent-2-enyl ethyl carbonate (10): To a solution of compound **9** (2.98 g, 5.61 mmol) in anhydrous pyridine (15 mL), ethyl chloroformate (656 mg, 6.05 mmol) and DMAP (60 mg, 0.49 mmol) were added. The reaction mixture was stirred overnight at 65°C. The reaction mixture was then quenched using a saturated $NaHCO_3$ solution (1.0 mL) and vacuum-concentrated. Water (150 mL) was poured into the residue and extracted with EtOAc (150 mL) two times. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **10** (2.6 g, 77%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.42 (s, 1H), 4.78 (t, $J = 6.2$, 4.8 Hz, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 3.85 (t, $J = 7.0$ Hz, 2H), 3.76–3.68 (m, 4H), 2.14 (t, $J = 7.0$ Hz, 2H), 2.08 (dd, $J = 12.8$, 7.0 Hz, 1H), 1.89 (dd, $J = 12.8$, 8.8 Hz, 1H), 1.29 (t, $J = 7.2$ Hz, 3H), 0.82 (m, 27H), 0.01 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.2, 140.7, 132.9, 83.5, 70.7, 70.1, 64.2, 63.2, 46.1, 36.3, 28.1, 25.4, 18.7, 13.7, −5.7.

(±)-1-[2-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-4,4-bis-(tert-butyl-dimethyl-silanyloxymethyl)-cyclopent-2-enyl] cytosine (11): To generate a nucleosidic base anion, cytosine (124 mg, 1.12 mmol) was added to hexane-washed NaH (26.8 mg, 1.12 mmol) in anhydrous DMSO (7.0 mL). The reaction mixture was stirred for 30 minutes at 50–55°C and cooled to room temperature. Simultaneously, P(O-*i*-Pr)$_3$ (93 mg, 0.448 mmol) was added to a solution of $Pd_2(dba)_3$ and $CHCl_3$ (60 mg, 5.76 μmol) in anhydrous THF (5.0 mL), which was stirred for 30 minutes. A catalyst solution of THF and **10** (603 mg, 1.0 mmol) dissolved in anhydrous THF (7.0 mL) was sequentially added to the cytosine solution of DMSO.

The reaction mixture was stirred overnight at refluxing temperature and quenched with water (3.0 mL). The reaction solvent was removed under vacuum. The residue was purified by silica gel column chromatography (MeOH/Hexane/EtOAc, 0.1:4:1) to yield **11** (200 mg, 32%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (d, J = 7.0 Hz, 1H), 5.38 (d, J = 7.0 Hz, 1H), 4.42 (dd, J = 6.6, 2.4 Hz, 1H), 3.84 (t, J = 6.8 Hz, 2H), 3.73–3.65 (m, 4H), 2.17 (t, J = 6.9 Hz, 1H), 2.16 (dd, J = 13.2, 6.8 Hz, 1H), 1.91 (dd, J = 13.2, 8.8 Hz, 1H), 0.82 (m, 27H), 0.02 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 165.3, 156.2, 146.6, 139.6, 132.8, 94.1, 69.8, 69.3, 64.0, 55.8, 46.7, 37.2, 27.5, 25.7, 18.5, −5.6.

(±)-9-[2-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-4,4-bis-(tert-butyl-dimethyl-silanyloxymethyl)-cyclopent-2-enyl] adenine (12): Adenine nucleoside analogue **12** (147 mg, 0.227 mmol) was synthesized from **10** (351 mg, 0.582 mmol) by a similar procedure as described for **11**: yield 39%; 8.31 (s, 1H), 8.19 (s, 1H), 5.40 (s, 1H), 4.72 (t, J = 6.0 Hz, 1H), 3.82 (t, J = 7.0 Hz, 2H), 3.74–3.65 (m, 4H), 2.27 (dd, J = 12.8, 7.0 Hz, 1H), J = 6.9 Hz, 1H), 2.14 (t, J = 7.0 Hz, 2H), 1.89 (dd, J = 12.9, 8.6 Hz, 1H), 0.81 (m, 27H), 0.01 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 154.9, 153.2, 146.9, 143.2, 138.9, 132.5, 127.4, 70.5, 70.2, 63.6, 58.9, 47.3, 37.5, 26.5, 25.6, 18.4, −5.7.

(*rel*)-(1′*R*,2′*R*,3′*R*)-1-[2-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-4,4-bis-(tert-butyl-dimethyl-silanyloxymethyl)-2,3-dihydroxy-cyclopentyl] cytosine (13); (*rel*)-(1′*R*,2′*S*,3′*S*)-1-[2-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-4,4-bis-(tert-butyl-dimethyl-silanyloxymethyl)-2,3-dihydroxy-cyclopentyl] cytosine (14): To a stirred solution of **11** (377 mg, 0.605 mmol) in cosolvent (7.0 mL, acetone/water = 5:1) was added *N*-methylmorpholine-*N*-oxide (NMO) (283 mg, 1.21 mmol) and OsO_4 (0.51 mL, 4% in water). The mixture was stirred overnight at room temperature and quenched with saturated Na_2SO_3 solution (5 mL). The resulting solid was removed by filtration through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:6) to give **13** (167 mg, 42% yield) and **14** (83 mg, 21% yield) as a white solid, respectively.

Compound for **13:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, J = 7.1 Hz, 1H), 5.32 (d, J = 7.0 Hz, 1H), 3.80 (t, J = 6.9 Hz, 2H), 3.72–3.64 (m, 5H), 3.28 (d, J = 6.0 Hz, 1H), 1.66–1.56 (m, 3H), 1.32 (dd, J = 13.0, 8.4 Hz, 1H), 0.81 (m, 27H), 0.02 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 164.9, 156.4, 145.7, 93.0, 76.8, 76.2, 64.7, 64.5, 58.4, 40.1, 34.3, 25.3, 18.7, 17.1, −5.7; Anal. Calc. for $C_{31}H_{63}N_3O_6Si_3$: C, 56.58; H, 9.65; N, 6.39. Found: C, 56.62; H, 9.58; N, 6.29.

Compound for **14:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (d, J = 7.0 Hz, 1H), 5.35 (d, J = 7.2 Hz, 1H), 3.85 (t, J = 7.0 Hz, 2H), 3.76–3.67 (m, 4H),

3.52 (dd, $J = 6.8$, 1.8 Hz, 1H), 3.31 (d, $J = 5.9$ Hz, 1H), 1.63–1.55 (m, 3H), 1.30 (dd, $J = 12.8$, 8.2 Hz, 1H), 0.82 (m, 27H), 0.01 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 164.6, 156.6, 146.0, 92.5, 76.2, 75.9, 64.3, 64.0, 59.1, 41.2, 33.9, 25.7, 18.6, 16.6, −5.6; Anal. Calc. for $C_{31}H_{63}N_3O_6Si_3$: C, 56.58; H, 9.65; N, 6.39. Found: C, 56.50; H, 9.71; N, 6.37.

(*rel*)-(1′*R*,2′*R*,3′*R*)-9-[2-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-4,4-bis-(tert-butyl-dimethyl-silanyloxymethyl)-2,3-dihydroxy-cyclopentyl] adenine (15); (*rel*)-(1′*R*,2′*S*,3′*S*)-9-[2-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-4,4-bis-(tert-butyl-dimethyl-silanyloxymethyl)-2,3-dihydroxy-cyclopentyl] adenine (16): The adenine nucleoside analogues **15** (113 mg, 0.166 mmol) and **16** (67 mg, 0.09 mmol) were synthesized from **12** (276 mg, 0.426 mmol) by a similar procedure as described for **13** and **14** as a white solid, respectively. Data for **15:** yield 39%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H), 8.18 (s, 1H), 3.79–3.70 (m, 3H), 3.70–3.62 (m 4H), 3.28 (s, 1H), 1.60 (t, $J = 7.0$ Hz, 2H), 1.89–1.80 (m, 2H), 0.81 (m, 27H), 0.01 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 154.9, 152.8, 147.6, 143.2, 127.8, 76.7, 76.4, 65.3, 65.1, 57.8, 56.9, 40.1, 34.7, 25.6, 18.7, 17.1, −5.5; Anal. Calc. for $C_{32}H_{63}N_5O_5Si_3$: C, 56.34; H, 9.31; N, 10.27. Found: C, 56.29; H, 9.33; N, 10.25. Data for **16**: yield 23%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (s, 1H), 8.21 (s, 1H), 3.78 (dd, $J = 5.2$, 1.2 Hz, 1H), 3.71–3.63 (m 6H), 3.26 (s, 1H), 1.62 (t, $J = 7.1$ Hz, 2H), 1.87–1.79 (m, 2H), 0.82 (m, 27H), 0.01 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 155.1, 153.1, 147.9, 143.6, 128.1, 76.9, 76.2, 65.8, 65.4, 57.2, 56.7, 41.2, 34.2, 25.7, 18.6, 16.9, −5.6; Anal. Calc. for $C_{32}H_{63}N_5O_5Si_3$: C, 56.34; H, 9.31; N, 10.27. Found: C, 56.46; H, 9.28; N, 10.31.

(*rel*)-(1′*R*,2′*R*,3′*R*)-1-[2-[2-(Hydroxy)-ethyl]-4,4-bis-(hydroxymethyl)-2,3-dihydroxy-cyclopentyl] cytosine (17). To a solution of **13** (178 mg, 0.27 mmol) in cosolvent (4.0 mL, THF/CH_3CN = 1:1) was added TBAF (1.35 mL, 1.0 M solution in THF) at 0°C. 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 **17** (64 mg, 76%) as a white solid: m.p. 202–204°C; UV (H_2O) λ_{max} 271.0 nm (ε 16,370, pH 7); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.47 (d, $J = 7.0$ Hz, 1H), 7.04 (br d, 2H), 5.37 (d, $J = 7.1$ Hz, 1H), 3.69 (d, $J = 6.2$ Hz, 1H), 3.54–3.35 (m, 6H), 1.66–1.57 (m, 3H), 1.35 (dd, $J = 12.8$, 6.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 165.2, 156.1, 145.5, 94.7, 75.9, 75.6, 62.5, 62.1, 55.4, 37.4, 34.1, 17.1; Anal. Calc. for $C_{13}H_{21}N_3O_6$ (+ 1.0 H_2O): C, 46.84; H, 6.95; N, 12.60. Found: C, 46.77; H, 7.02; N, 12.65.

(*rel*)-(1′*R*,2′*R*,3′*R*)-9-[2-[2-(Hydroxy)-ethyl]-4,4-bis-(hydroxymethyl)-2,3-dihydroxy-cyclopentyl] adenine (18): Adenine derivative **18** (68 mg, 0.2 mmol) was prepared from **15** (196 mg, 0.287 mmol) by the same procedure as described for **17**: yield 70%; m.p. 210–213°C; UV (H_2O) λ_{max} 265.5 nm

(ε 16,370, pH 7); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.50 (s, 1H), 8.21 (s, 1H), 6.23 (br s, 2H), 3.77 (d, J = 6.2, Hz, 1H), 3.52 (t, J = 7.1 Hz, 2H), 3.46–3.37 (m, 4H), 3.27 (s, 1H), 1.88–1.79 (dd, J = 13.0, 6.8 Hz, 1H), 1.60 (t, J = 7.1 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 154.9, 152.7, 147.3, 145.4, 128.5, 77.0, 76.8, 61.5, 61.2, 56.5, 54.7, 37.4, 34.5, 16.8; Anal. Calc. for $C_{14}H_{21}N_5O_5$ (+ 1.0 H_2O): C, 47.05; H, 6.49; N, 19.59. Found: C, 46.94; H, 6.52; N, 19.49.

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