Synthesis of 3'(β)-*C*-methyl Carbodine Analogues as Potential Anti-HCV Agents

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The synthetic route of novel 3'-*C*-methyl carbodine analogue is described. The construction of tertiary alcohol at 3'-position of carbodine analogues was successfully made via sequential [3,3]-sigmatropic rearrangement, ring-closing metathesis (RCM) and stereoselective dihydroxylation reactions starting from ethyl glycolate.

Key Words: Carbodine, Anti-HCV agents, Ring-closing metathesis, Vicinal dihydroxylation

Introduction

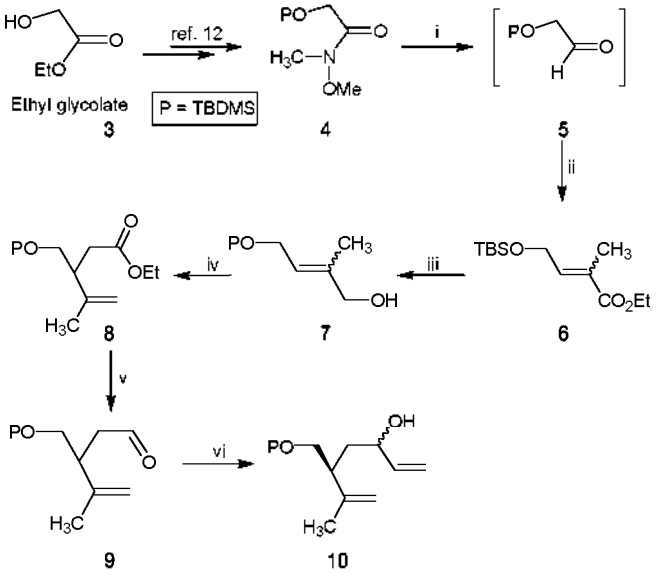
Hepatitis C virus (HCV) infection is a leading cause of chronic hepatitis, liver cirrhosis and hepatoma carcinoma.[1] However, there is no effective chemotherapy for the treatment of HCV-infected people except immunotherapy using ribavirin in combination with interferon-α, which leads to a sustained virological response in only about half of the patients treated.[2]

Recent advances in the molecular virology HCV have led to the identification of a number of antiviral molecular targets, including the NS5B RNA-dependent RNA polymerase. Inhibition of this enzyme results in the inhibition of the replication of HCV, making this enzyme crucial target for the development of new anti-HCV agent.[3] Since nucleoside analogues have been used as a drug of choice in curing viral infection, a number of nucleoside analogues have been synthesized and evaluated for anti-HCV agent.[4] These nucleosides are incorporated into proviral RNA like a substrate after being converted to their corresponding triphosphates and act as chain terminators. Modification in the vicinity of the 2'-hydroxy of the ribose in natural ribonucleosides can produce effective RNA chain terminator.[5] For example, 2'-methyl-ribonucleosides yield compounds with excellent chain-terminating properties. Among them, 2'-*C*-methyladenosine[6] **1** and 2'-*C*-methylcytidine[7] **2** were discovered as potent anti-HCV agents and are in clinical trials.

Natural as well as synthetic carbocyclic nucleosides[8] are well known for their interesting biological activities, including antitumor and antiviral activities against a wide variety of RNA and DNA viruses. Carbocyclic nucleosides are chemically more stable and are subject to the action of the enzymes that cleave the glycosyl linkage in conventional nucleosides.

On the basis of these findings that the methyl group of 2'-position could impose favorable steric as well as electronic effect on the interaction with HCV polymerase, we have determined to synthesize novel classes of nucleosides comprising 3'(β)-*C*-methylated carbodine analogues, which transpose the methyl group from 2'- to 3'-position.

To this end, we describe a very convenient and general synthetic procedure for carbocyclic nucleosides using reiterative three step sequences ([3.3]-sigmatropic rearrangement[9], RCM[10] and vicinal dihydroxylation[11]). As shown in Scheme 1, we used the Weinreb amide **4** as starting material, which could be readily synthesized *via* silyl protection of the alcohol could be readily synthesized *via* silyl protection of the alcohol of commercially available starting material **3** followed by hydrolysis and amidation using DCC and DMAP coupling reagent as described in previous report.[12] Conversion of the amide **4** to aldehyde derivative **5** turned out to be successful under the usual carbonyl reduction condition (DIBALH, THF, 0 °C). Subjection of **5** to Horner-Wadsworth-Emmons (HWE) reaction condition[13] provided α,β-unsaturated ethyl ester **6** as *cis*/*trans* isomeric mixtures. It is unnecessary to separate the isomers, because they will be merged into one isomer in next reaction. Ester **6** was reduced to allylic alcohol **7** by using diisobutylaluminum hydride, which underwent regular [3,3]-sigmatropic rearrangement using triethyl orthoacetate to give γ,δ-unsaturated ester **8**. Direct conversion of the ester **8** to the aldehyde **9** was possible by slow addition of DIBALH in the toluene solvent system at -78 °C. The aldehyde **9** was subjected to carbonyl addition by CH_2=CHMgBr to yield divinyl **10** as inseparable diastereomeric mixtures.



Scheme 1. Synthesis of diene intermediate **10**. Reagents: i) DIBALTH, THF; ii) triethyl 2-phosphonopropionate, NaH, THF, 0 °C, 1 h, iii) DIBAL-H, CH_2Cl_2, 0 °C, iv) triethylorthoacetate, propionic acid, 140 °C; v) DIBAL-H, toluene, -78 °C; vi) vinylMgBr, THF.

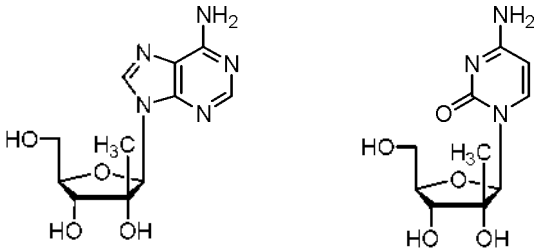


Figure 1. Structure of potent anti-HCV agents.

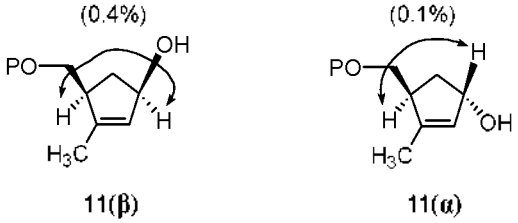


Figure 2. NOE results of compound **11(β)** and **11(α)**.

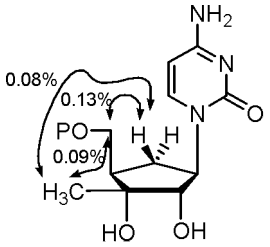
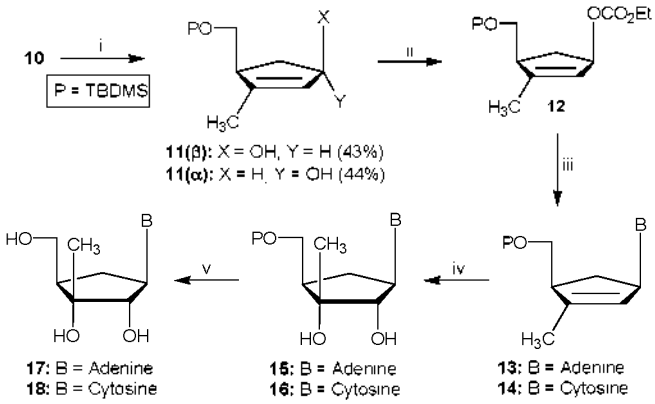


Figure 3. NOE result of compound **16**.

Without separation, divinyl **10** was subjected to standard RCM condition[14] using 2nd generation Grubbs catalyst [(Im)-$Cl_2PCy_3RuCHPh$] to provide cyclopentenol **11α** and **11β**, respectively. As shown in Figure 2, the stereochemistry was unambiguously assigned on the basis of the NOE correlations between the proximal hydrogens. On irradiation of C_4-H, relatively weak NOE was observed at C_1-H of **11(α)** (0.1% NOE), but not at C_1-H of **11(β)** (0.4% NOE).

Cyclopentenol **11β** was transformed to **12** using ethyl chloroformate, which was coupled with cytosine or adenine anions generated by NaH/DMSO with use of catalyst [tris-(dibenzylidene-acetone)-dipalladium(0)-chloroform] adduct to provide nucleoside analogues **13** and **14**. In order to synthesize the 2',3'-dihydroxy nucleoside analogues **17** and **18**, the protected nucleosides **13** and **14** were subjected to a catalytic amount of OsO_4 and NMO to give the dihydroxylated **15** and **16** as the only reaction products. As shown in Figure 3, the stereochemistry was readily determined by NOE experiment. It is noteworthy that an unexpected higher stereoselectivity was observed in this study than what was reported in previously.[15] These stereochemical outcomes suggest that the bulky groups such as silylated hydroxymethyl group and nucleosidic base of **13** and **14** reinforce the steric hindrance of the β-faces.



Scheme 2. Synthesis of 3'-C-methyl carbocyclic nucleosides. Reagents: i) 2nd Grubbs catalyst, CH_2Cl_2; ii) ethylchloroformate, DMAP, pyridine, iii) nucleobases, $Pd_2(dba)_3$, $P(O\text{-}i\text{-}Pr)_3$, NaH, THF/DMSO, reflux, overnight, iv) OsO_4, NMO; v) TBAF, THF, rt.

Removals of silyl protection group of **15** and **16** were preformed by the treatment of tetrabutylammonium fluoride (TBAF) to give target nucleosides **17** and **18** (Scheme 2).

The synthesized nucleoside analogues mentioned above were assayed for their ability to inhibit HCV RNA replication in a subgenomic replicon Huh7 cell line (LucNeo#2). These cells contain an HCV subgenomic replicon RNA encoding a luciferase reporter gene as a marker. The antiviral potency of the analogues against the HCV replicon is expressed as EC_{50}, which was quantified by a luciferase assay after a two-day incubation period with the corresponding compound. In addition, the associated cytotoxicity was evaluated in a tetrazolium (XTT)-based assay according to the manufacturer's protocol.[16] However, the synthesized nucleosides neither showed any significant antiviral activity nor toxicity up to 100 μM.

In summary, an efficient synthetic method of 3'(β)-C-metylated carbodine analogues from ethyl glycolate was developed. We can conclude that the methyl group at 3'-position is responsible for the inability of the nucleoside kinase to catalyze the initial phosphorylation of the nucleosides to their monophosphates.

Experimental Section

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a JEOL 300 Fourier transform; chemical shifts are reported in parts per million (δ) and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). UV spectra were obtained on a Beckman DU-7 spectrophotometer. The elemental analyses were performed using an Elemental Analyzer System (EA1112). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. All reactions were carried out 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.

(*tert*-Butyldimethylsilanyloxy) acetaldehyde (5). To a solution of Weinreb amide **4** (3.0 g, 12.85 mmol) in dry THF (60

mL) was slowly added DIBALH (15.42 mL, 1.0 M solution in Hexane) at 0 °C. After 2 h, methanol (15 mL) was added, and the reaction mixture was slowly warmed to rt. 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 crude aldehyde **5** (1.77 g, 79%) as colorless oil. Without further purification, compound **5** was subject to next reaction.

(*E*) and (*Z*)-4-(*tert*-Butyldimethylsilanyloxy)-2-methyl-but-2-enoic acid ethyl ester (6). To a suspension of sodium hydride (400 mg, 9.98 mmol, 60% in dispersion of oil) in distilled THF (50 mL) was added drop wise triethyl 2-phosphonopropionate (2.38 g, 9.98 mmol) at 0 °C and the mixture was stirred at room temperature for 1 h. The aldehyde **5** (1.74 g, 9.98 mmol) was added to this mixture and the mixture was for 2 h. The solution was neutralized with AcOH (2.0 mL) and poured into H_2O (100 mL) and extracted with EtOAc (150 × 2). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **6** (1.8 g, 70%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.20 (dd, *J* = 4.2, 1.8 Hz, 1H), 4.49 (m, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 1.95 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 0.83 (m, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 168.4, 137.9, 127.3, 67.3, 60.2, 25.5, 18.4, 17.2, 12.9, -5.5.

(*E*) and (*Z*)-3-(*tert*-Butyldimethylsilyloxymethyl)-2-methyl-but-2-en-1-ol (7). To a solution of **6** (2.7 g, 10.5 mmol) in CH_2Cl_2 (70 mL), DIBALH (23.1 mL, 1.0 M solution in hexane) was added slowly at -20 °C, and stirred for 1 h at the same temperature. To the mixture, methanol (23 mL) was added. The mixture was stirred at room temperature for 1 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, 1:10) to give alcohol **7** (2.04 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.62 (dd, *J* = 4.0, 1.6 Hz, 1H), 4.41-4.30 (m, 4H), 1.72 (s, 3H), 0.83 (m, 9H), 0.01 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 139.4, 122.2, 71.3, 65.3, 25.5, 18.4, 13.8, -5.6.

(±)-3-(*tert*-Butyldimethylsilyloxymethyl)-2-methyl-pent-4-enoic acid ethyl ester (8). A solution of allylic alcohol **7** (3.4 g, 15.8 mmol) in triethyl orthoacetate (60 mL) and 0.05 mL of propionic acid was heated at 140 °C overnight with stirring under condition for distillative removal of ethanol. The excess of triethyl orthoacetate was distilled off and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give **8** (3.62 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.63-5.55 (m, 2H), 4.09 (q, *J* = 7.0 Hz, 2H), 3.53 (d, *J* = 9.6 Hz, 1H), 3.42 (d, *J* = 9.6 Hz, 1H), 2.60 (dd, *J* = 14.0, 5.2 Hz, 1H), 2.36 (dd, *J* = 14.0, 8.6 Hz, 1H), 2.27 (m, 1H), 1.79 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 172.4, 139.4, 118.2, 66.4, 61.8, 45.9, 40.3, 25.7, 18.6, 17.4, 13.6, -5.6.

(±)-3-(*tert*-Butyldimethylsilyloxymethyl)-2-methyl-pent-4-enal (9). To a solution of **8** (3.0 g, 10.5 mmol) in toluene (50 mL), DIBALH (7.7 mL, 1.5 M solution in toluene) was added slowly at -78 °C, and stirred for 10 minutes at the same temperature. To the mixture, methanol (8 mL) was added. The mixture was stirred at room temperature for 1 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, 1:15) to give **9** (2.54 g, 63%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.71 (s, 1H), 5.60-5.53 (m, 2H), 3.62 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.45 (d, *J* = 9.6, 5.6 Hz, 1H), 2.70 (m, 1H), 2.61 (dd, *J* = 13.6, 5.4 Hz, 1H), 2.39 (dd, *J* = 13.6, 5.6 Hz, 1H), 1.76 (s, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 202.1, 140.7, 119.7, 69.5, 61.8, 46.1, 41.6, 25.7, 18.7, 17.9, -5.5.

(*rel*)-(*3R* and *3S*,*5S*)-5-(*tert*-Butyldimethylsilanyloxymethyl)-6-methyl-hepta-1,6-dien-3-ol (10). To a solution of **9** (1.86 g, 7.7 mmol) in dry THF (30 mL) was slowly added vinylmagnesium bromide (8.47 mL, 1.0 M solution in THF) at -78 °C. After 5 h, saturated NH_4Cl solution (9 mL) was added, and the reaction mixture was slowly warmed to rt. The mixture was extracted with EtOAc/water two times. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **10** (1.58 g, 76%) as a diastereomeric mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.71-5.63 (m, 2H), 5.30-5.18 (m, 4H), 4.11 (m, 1H), 3.56-3.40 (m, 2H), 2.37 (m, 1H), 2.22-1.78 (m, 1H), 1.66 (s, 3H), 1.58-1.49 (m, 1H), 0.82 (s, 9H), 0.01 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 147.1, 139.2, 139.1, 115.7, 115.6, 111.4, 73.8, 73.7, 66.5, 43.0, 27.3, 27.2, 25.8, 18.3, 17.3, -5.5.

(*rel*)-(1*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-3-methyl-cyclopent-2-enol (11β); and (rel)-(1*S*,4*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-3-methyl-cyclopent-2-enol (11α). To a solution of **10** (2.78 g, 10.3 mmol) in dry CH_2Cl_2 (20 mL) was added 2nd generation Grubbs catalyst (152 mg, 0.18 mmol). The reaction mixture was refluxed overnight, and cooled to room temperature. The mixture was concentrated in vacuum, and residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give cyclopentenol **11β** (1.07 g, 43%) and **11α** (1.09 g, 44%) as colorless oils, respectively. Cyclopentenol **11β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.67 (dd, *J* = 5.4, 2.4 Hz, 1H), 4.52 (d, *J* = 4.8 Hz, 1H), 3.45 (dd, *J* = 13.8, 8.4 Hz, 2H), 2.88 (m, 1H), 1.98 (dd, *J* = 13.4, 6.8 Hz, 1H), 1.77 (dd, *J* = 13.4, 8.2 Hz, 1H), 1.40 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.7, 131.4, 77.1, 67.2, 47.4, 38.6, 25.3, 18.4, 14.5, -5.7. Cyclopentenol **11α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.60 (d, *J* = 5.2 Hz, 1H), 4.48 (m, 1H), 3.47 (d, *J* = 13.6 Hz, 1H), 3.33 (d, *J* = 13.6 Hz, 1H), 2.82 (m, 1H), 1.92 (dd, *J* = 13.6, 8.4 Hz, 1H), 1.71 (dd, *J* = 13.6, 7.2 Hz, 1H), 1.49 (s, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 143.6, 130.2, 76.3, 66.3, 47.2, 38.8, 25.5, 18.4, 14.2, -5.6.

(*rel*)-(1*R*,4*S*)-1-Ethoxy carbonyloxy-4-(*tert*-butyldimethylsilyloxymethyl)-3-methyl-cyclopent-2-ene (12). To a solution of **11β** (2.51 g, 10.38 mmol) in anhydrous pyridine (20 mL) was added ethyl chloroformate (2.25 g, 20.7 mmol) and DMAP (122 mg, 1.0 mmol). The reaction mixture was stirred overnight at 50 °C. The reaction mixture was quenched with saturated $NaHCO_3$ solution (5 mL), stirred for 10 minute and concentrated in reduced pressure. The residue was extracted with EtOAc/H_2O two times, and combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was

purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **12** (2.55 g, 78%) as colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92 (dd, J = 5.4 Hz, 1H), 5.72 (dd, J = 4.8, 1.4 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.40 (d, J = 13.2 Hz, 2H), 2.98 (m, 1H), 2.10-1.90 (m, 2H), 1.71 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.3, 138.5, 133.2, 85.7, 66.7, 63.5, 46.5, 35.3, 25.8, 18.3, 14.3, 12.8, -5.5.

(*rel*)-(1'*R*,4'*S*)-9-[4-(*tert*-Butyldimethylsilyloxymethyl)-3-methyl-cyclopent-2-en-1-yl] adenine (13). In order to generate nucleosidic base anion, adenine (162 mg, 0.94 mmol) was added to a pure NaH (25.2 mg, 1.05 mmol) in anhydrous DMSO (6.0 mL). The reaction mixture was stirred for 30 min at 50-55 °C and cooled to room temperature. Simultaneously, P(O-*i*-Pr)$_3$ (87 mg, 0.42 mmol) was added to a solution of $Pd_2(dba)_3$·$CHCl_3$ (55.6 mg, 5.37 μmol) in anhydrous THF (5.0 mL), which was stirred for 30 min. To the adenine solution of DMSO was sequentially added catalyst solution of THF and **12** (277 mg, 0.88 mmol) dissolved in anhydrous THF (5.0 mL). The reaction mixture was stirred overnight at refluxing temperature and quenched with water (3.0 mL). The reaction solvent was removed in vacuum. The residue was purified by silica gel column chromatography (MeOH/Hexane/EtOAc, 0.1:4:1) to give **13** (123.4 mg, 39%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H), 7.75 (s, 1H), 6.01 (s, 1H), 5.95 (br s, 2H), 5.60 (d, J = 5.2 Hz, 1H), 3.58 (d, J = 10.0 Hz, 2H), 3.15 (m, 1H), 2.39 (dd, J = 13.6, 8.2 Hz, 1H), 2.12-2.05 (m, 1H), 1.67 (s, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.3, 152.7, 150.7, 142.4, 140.1, 131.1, 119.5, 68.5, 63.2, 47.5, 34.5, 25.6, 18.4, 14.0, -5.5; Anal. Calcd. for $C_{18}H_{29}N_5OSi$: C, 60.13; H, 8.13; N, 19.48. Found: C, 60.32; H, 8.20; N, 19.50.

(*rel*)-(1'*R*,4'*S*)-1-[4-(*tert*-Butyldimethylsilyloxymethyl)-3-methyl-cyclopent-2-en-1-yl] cytosine(14). Cytosine nucleoside analogue **14** was synthesized from **12** by the similar procedure as described for **13**: yield 39%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14 (d, J = 7.2 Hz, 1H), 5.79 (s, 1H), 5.70 (d, J = 7.2 Hz, 1H), 3.46 (dd, J = 9.8, 7.8 Hz, 2H), 2.94 (m, 1H), 2.24-2.15 (m, 1H), 1.79 (dd, J = 10.2, 7.8 Hz, 1H), 1.62 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.2, 156.3, 140.1, 138.7, 131.1, 95.1, 67.9, 61.9, 47.1, 35.7, 25.7, 18.6, 13.8, -5.6; Anal. Calcd. for $C_{17}H_{29}N_3O_2Si$: C, 60.86; H, 8.71; N, 12.52. Found: C, 60.77; H, 8.80; N, 12.48.

(*rel*)-(1'*R*,2'*S*,3'*S*,4'*R*)-9-[4-(*tert*-Butyldimethylsilyloxymethyl)-3-methyl-2,3-dihydroxy-cyclopentan-1-yl] adenine (15). To a stirred solution of **13** (604 mg, 1.68 mmol) in cosolvent (6.0 mL, acetone:water/5:1) was added NMO (393 mg, 3.36 mmol), and OsO_4 (0.1 mL, 4% in water). The mixture was stirred overnight at 50 °C, and quenched with saturated Na_2SO_3 solution (6 mL). Resulting solid was removed by filtration through a pad of Celite, and filtrate was concentrated in reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:6) to give **15** (522 mg, 79%) as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.15 (s, 1H), 8.10 (s, 1H), 7.20 (br d, 2H, D_2O exchangeable), 5.18 (d, J = 4.8 Hz, 1H, D_2O exchangeable), 5.11 (s, 1H, D_2O exchangeable), 5.03 (m, 1H), 3.97 (d, J = 4.8 Hz, 1H), 3.46 (dd, J = 12.6, 7.2 Hz, 1H), 3.30 (dd, J = 12.6, 8.4 Hz, 1H), 2.44 (dd, J = 10.6, 3.8 Hz, 1H), 2.31 (dd, J = 10.6, 8.8 Hz, 1H), 1.60 (s, 3H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 155.7, 152.0, 149.7, 140.5, 119.4, 79.3, 69.7, 53.7, 41.5, 25.6, 18.4, 14.2, -5.8; Anal calc for $C_{18}H_{31}N_5O_3Si$: C, 54.93; H, 7.94; N, 17.80. Found: C, 54.85; H, 7.90; N, 17.74.

(*rel*)-(1'*R*,2'*S*,3'*S*,4'*R*)-1-[4-(*tert*-Butyldimethylsilyloxymethyl)-3-methyl-2,3-dihydroxy-cyclopentan-1-yl] cytosine (16). Cytosine nucleoside analogue **16** was synthesized from **14** by the similar procedure as described for **15**: yield 76%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.60 (d, J = 7.2 Hz, 1H), 7.06 (br d, 2H, D_2O exchangeable), 5.60 (d, J = 7.2 Hz, 1H), 5.12 (d, J = 4.6 Hz, 1H, D_2O exchangeable), 5.05 (s, 1H, D_2O exchangeable), 5.01 (m, 1H), 3.88 (d, J = 4.8 Hz, 1H), 3.49 (dd, J = 12.8, 6.8 Hz, 1H), 3.31 (dd, J = 12.8, 8.6 Hz, 1H), 3.02 (m, 1H), 2.21-1.97 (m, 2H), 1.59 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 165.0, 156.1, 145.2, 95.1, 76.5, 71.2, 52.1, 40.4, 25.3, 18.7, 13.9, -5.5; Anal. Calcd. for $C_{17}H_{31}N_3O_4Si$: C, 55.25; H, 8.64; N, 11.37. Found: C, 55.17; H, 8.76; N, 11.28.

(*rel*)-(1'*R*,2'*S*,3'*S*,4'*R*)-9-[4-(Hydroxymethyl)-3-methyl-2,3-dihydroxy-cyclopentan-1-yl] adenine (17). To a solution of **15** (138 mg, 0.35 mmol) in THF (5 mL) was TBAF (0.53 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, 1:5) to give **17** (76 mg, 78%) as a white solid: mp 195-197 °C; UV (H_2O) λ_{max} 259.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.17 (s, 1H), 8.09 (s, H1), 7.19 (br d, 2H, D_2O exchangeable), 5.21 (d, J = 4.6 Hz, 1H, D_2O exchangeable), 5.10 (s, 1H, D_2O exchangeable), 5.04 (m, 1H), 4.78 (t, J = 4.8 Hz, 1H, D_2O exchangeable), 3.91 (m, 1H), 3.48 (dd, J = 12.8, 7.4 Hz, 1H), 3.33 (dd, J = 12.8, 8.4 Hz, 1H), 2.44 (dd, J = 10.8, 4.0 Hz, 1H), 2.31 (dd, J = 10.8, 8.6 Hz, 1H), 1.61 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 155.7, 151.8, 148.5, 141.4, 118.3, 78.4, 68.6, 54.6, 42.6, 13.9; Anal calc for $C_{12}H_{17}N_5O_3$ · 1.0 MeOH: C, 50.15; H, 6.79; N, 22.49. Found: C, 50.22; H, 6.81; N, 22.45.

(*rel*)-(1'*R*,2'*S*,3'*S*,4'*R*)-1-[4-(Hydroxymethyl)-3-methyl-cyclopent-2-en-1-yl] cytosine (18). Cytosine nucleoside analogue **18** was synthesized from **16** by the similar condition as described for **17** as a white solid: yield 73%; mp 163-165 °C; UV (H_2O) λ_{max} 273.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.62 (d, J = 7.2 Hz, 1H), 7.07 (br d, 2H, D_2O exchangeable), 5.59 (d, J = 7.2 Hz, 1H), 5.12 (d, J = 4.8 Hz, 1H, D_2O exchangeable), 5.05 (s, 1H, D_2O exchangeable), 5.03 (m, 1H), 4.81 (t, J = 5.0 Hz, 1H), 3.91 (dd, J = 8.6, 4.4 Hz, 1H), 3.48 (dd, J = 12.4, 7.0 Hz, 1H), 3.32 (dd, J = 12.4, 8.2 Hz, 1H), 3.07 (m, 1H), 2.23-2.10 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 165.4, 156.3, 145.5, 96.6, 77.4, 69.2, 54.1, 42.3, 13.2; Anal. Calcd. for $C_{11}H_{17}N_3O_4$ · 1.0 H_2O: C, 48.34; H, 7.00; N, 15.38. Found: C, 48.27; H, 6.95; N, 15.42.

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