Selective Synthesis of 1'(α),2'(β)-C-Dimethyl Carbocyclic Adenosine Analogue as Potential anti-HCV Agent

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As a part of an ongoing effort to discover inhibitors of the Hepatitis C Virus RNA replication, we describe here the first synthetic route of 1'(α),2'(β)-C-dimethyl carbocyclic adenine analogue. The key intermediate cyclopentenyl alcohol **8(α)** was prepared from aldehyde **4** using ring-closing metathesis (RCM) as a key reaction. Coupling of **8(α)** with nucleosidic base via the regioselective Mitsunobu reaction followed by stereoselective dihydoxylation and deprotection afforded the target carbocyclic adenine analogue **12**.

Key Words: Mitsunobu reaction, Dihydroxylation, Carbodine, anti-HCV agents

Introduction

Hepatitis C virus (HCV) is the pathogen associated with the majority of sporadic and transfusion related non-A and non-B hepatitis infections. Although HCV is often asymptomatic, it is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals.[1] The current standard of care for chronic hepatitis C is combination therapy with an interferon-α/ribavirin than that with unpegylated interferon-α.[2]

The nonstructural protein NS5B has been characterized as an RNA-dependent RNA polymerase (RdRp) that is required for viral replication. This polymerase is considered to be an essential component in the HCV replication complex and therefore is an ideal target for drug discovery.[3] Since nucleoside analogues have been used as a drug of choice in curing viral infection including, a number of nucleoside analogues have been synthesized and evaluated for anti-HCV agent.[4] Generally, nucleosides are prodrugs, and their biological activity is exerted by their 5'-triphosphate derivatives. Intracellular phosphorylation is required to convert a nucleoside drug to its active 5'-triphosphate in order to be incorporated into a viral DNA. The sequential phosphorylation is normally executed by three viral or cellular kinases, including nucleoside kinase, nucleoside monophosphate kinase, and nucleoside diphosphate kinase.[5] Once incorporated into an elongating viral DNA chain, the nucleotide inhibitor functions as a terminator to abort viral DNA synthesis.

Nucleoside chain terminators comprise a major class of drugs that target a viral polymerase.[6] For example replacement of the 2'-hydrogen of natural ribonucleosides with a methyl group yields compounds with excellent chain-terminating properties. Among them, 2'-C-methyladenosine[7] **1**, (EC_{50} = 0.3 μM) and 2'-C-methyl-7-deazaadenosine[8] **2** (Figure 1) were found as the most potent inhibitors of HCV RNA replication without significant toxicity.

Carbocyclic nucleosides are derivatives in which the endocyclic oxygen of the nucleoside sugar ring has been replaced by a methylene group.[9] These analogues display remarkable metabolic stability since they are unaffected by phosphorylase and hydrolase that cleave the glycosidic bond of natural nucleosides.[10] They are also recognized by the same enzymes that recognize normal nucleosides displaying, correspondingly, a wide range of biological properties.[11]

On the basis of these findings that the methyl group of 2'-position could impose northern (2'-exo/3'-endo) conformation which shows favorable steric as well as electronic effect on the interaction with HCV polymerase, we have determined to synthesize novel class of carbocyclic nucleoside comprising 1'(α),2'(β)-C-dimethylated carbodine analogue, which has an additional methyl group in the 1'-position in order to take the same northern (2'-exo/3'-endo) conformation as lead compounds **1** and **2**.[12]

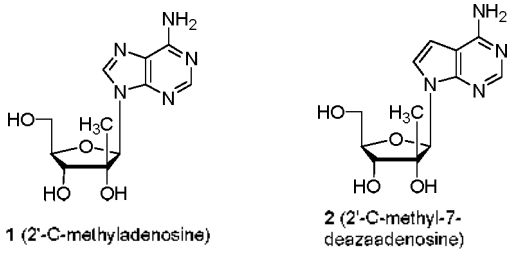
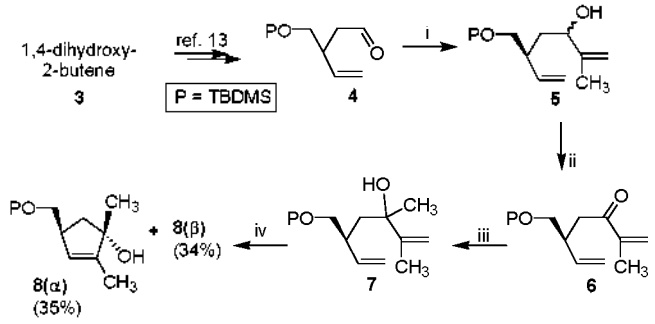


Figure 1. Synthesis rationale and structures of potent anti-HCV agents.



Reagents: i) isopropenylMgBr, THF; ii) MnO_2, CCl_4, 60 °C, overnight; iii) methylMgBr, THF; iv) 2nd Grubbs catalyst, benzene, reflux.

Scheme 1. Synthesis of cyclopentene intermediate

To reach the target molecule, we used an aldehyde **4** as starting material, which could be readily synthesized from 1,4-dihydroxy-2-butene as described in previous report.[13] The aldehyde **4** was subjected to carbonyl addition reaction by CH_2=C(CH_3)MgBr to yield an allylic alcohol derivative **5** as inseparable diastereomeric mixtures. Alcohol derivative **5** was oxidized using manganese dioxide (MnO_2) to give ketone derivative **6**, which again underwent Grignard addition by methyl magnesium bromide to provide a divinyl **7**. The divinyl **7** was subjected to standard ring-closing metathesis (RCM) condition using 2nd generation Grubbs catalyst[14] to provide cyclopentenols **8α** and **8β** with no stereoselectivity. As shown in Figure 2, the stereochemistries of **8α** and **8β** were unambiguously determined on the basis of the NOE correlations. On irradiation of C_4-H, relatively weak NOE was observed at C_1-H of **8**(α) (0.08%), but not at C_1-H of **8**(β) (0.27%).

First, attempt was made to couple the cyclopentenol **8α** with the base using convenient bimolecular nucleophilic substitution type (S_N2) reaction. The allylic alcohol **8α** was subjected to a mesylation condition (MsCl, TEA, CH_2Cl_2). Unexpectedly, the reaction was very complicated and was irreproducible. Therefore, our attention was turned to a Mitsunobu reaction to synthesize desired nucleoside. The success of Mitsunobu reactions in the synthesis of nucleoside analogues is known to depend on the condition employed. Appropriate choice of solvent system, temperature and procedure are critical for the regioselectivity as well as the yield. In purine synthesis, a 1:1 mixture of dioxane and DMF was used as solvent instead of only THF solvent for the coupling of the cyclopentenol **8α**

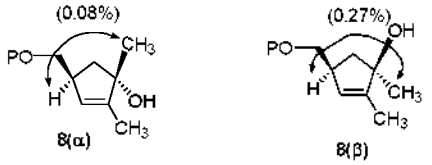
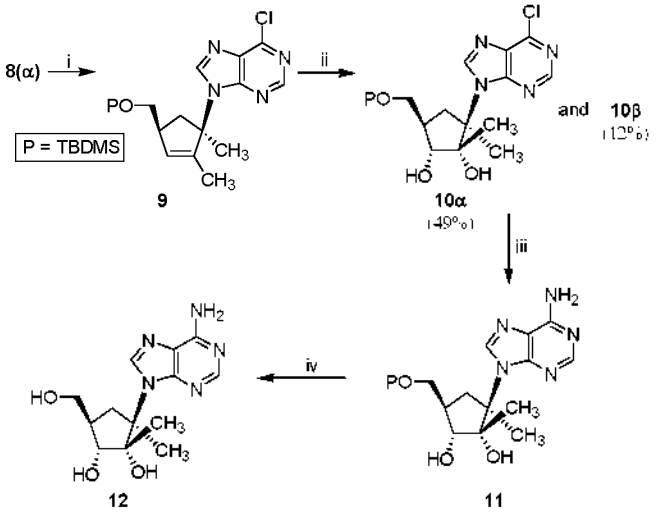


Figure 2. NOE data of compound **8**(α) and **8**(β).



Reagents: i) 6-chloropurine, DIAD, PPh_3, Dioxane/DMF(1/1); ii) OsO_4, NMO; iii) NH_3/MeOH, 90 ~ 95 °C, steel bomb; iv) TBAF, THF/CH_3CN, rt.

Scheme 2. Synthesis of 1',2'-C-dimethyl carbocyclic adenine analogue

with 6-chloropurine, because the use of a dioxane-DMF mixture allowed better solubility of the heterocyclic base and better yield. Slow addition of diisopropylazodicarboxylate (DIAD) to a mixture of cyclopentenol **8α**, triphenylphosphine and the 6-chloropurine in anhydrous solvent gave a yellow solution which was stirred for 2 h at –20 °C to give protected purine analogue **9** (λ_{max} 264.0 nm). In order to synthesize the 2',3'-dihydroxy nucleoside analogue **10**, the protected nucleoside **9** was subjected to a catalytic amount of OsO_4 in the presence of stoichiometric amount of *N*-methylmorpholine *N*-oxide (NMO) to give the dihydroxylated **10α** (49%) as a major reaction product compared to **10β** (12%).[15] This stereochemical outcome suggested that the bulky groups such as silyloxymethyl group and purine base of **9** reinforce the steric hindrance of the β-face.[16]

The 6-chloropurine derivative **10α** was transformed to a protected adenosine analogue **11** by treatment with a saturated solution of ammonia in methanol in a steel bomb at 90 ~ 95 °C for overnight. Removal of silyl protection group of **11** was performed by the treatment of tetrabutylammonium fluoride (TBAF) in cosolvent system (THF/acetonitrile) to give target nucleoside **12** (Scheme 2).

The synthesized nucleoside analogue mentioned above was assayed for its ability to inhibit HCV RNA replication in a subgenomic replicon cell line (Huh-7 cell line).[17] However, the nucleoside failed to inhibit HCV RNA replication in the cell-based replicon assay.

In summary, structually related carbocyclic analogue of the active adenosine based inhibitor was synthesized in order to assess the effect of changes in stereo- and regiochemistry of the sugar moiety. The corresponding 1'(α),2'(β)-*C*-dimethylated carbocyclic adenine analogue **12** was found to be inactive against HCV NS5B (EC_{50} > 50 μM), indicating that the lack of cell based activity is at least in part due to the enzyme's inability to accept this modification. The importance of substitutions in the molecular structure was studied by the synthesis of 1'(α),2'(β)-*C*-dimethyladenosine analogue.

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). Perkin Elmer Spectrum 100 was used as FT-IR spectrometer. 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.

(*rel*)-(3*R* and 3*S*,5*R*)-5-(*t*-Butyldimethylsilyloxymethyl)-2-methyl-hepta-1,6-dien-3-ol (5). To a solution of compound **4** (4.0 g, 16.49 mmol) in dry THF (150 mL), isopropenyl magne-

sium bromide (19.78 mL, 1.0 M solution in THF) was added slowly at −78 °C. After 3 h, a saturated NH_4Cl solution (22 mL) was added, and the reaction mixture was warmed slowly to room temperature. The mixture was extracted with EtOAc (2 × 300 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give **5** (3.56 g, 80%) as a diastereomeric mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.72-5.60 (m, 1H), 5.03 (d, J = 8.4 Hz, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 4.78 (s, 1H), 4.11 (m, 1H), 3.56 (dd, J = 9.9, 4.8 Hz, 1H), 3.41 (dd, J = 9.9, 7.5 Hz, 1H), 2.40 (m, 1H), 1.81-1.73 (m, 1H), 1.66 (s, 3H), 1.58-1.49 (m, 1H), 0.84 (s, 12H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.03, 139.80, 115.79, 111.43, 73.87, 66.64, 43.05, 36.93, 25.89, 18.30, 17.50, −5.47.

(±)-5-(*tert*-Butyldimethylsilanyloxymethyl)-2-methyl-hepta-1,6-dien-3-one (6). A mixture of allylic alohol **5** (1.2 g, 4.45 mmol), manganese (IV) dioxide (1.08 g, 12.4 mmol) in CCl_4 (15 mL) was stirred at 60 °C. Additional manganese (IV) dioxide (180 mg, 2.06 mmol) was added per hour and the progress of the reaction was monitored by TLC (EtOAc/hexane, 1:25). The resultant mixture was filtered through a plug of celite, washed with ethyl acetate. The filtrate and washings were concentrated *in vacuo* to give a residue, which was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give α,β-unsaturated ketone derivative **6** (848 mg, 71%) as a coloress oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98-5.81 (m, 2H), 5.27-5.16 (m, 1H), 4.93 (s, 1H), 3.62 (dd, J = 12.2, 5.2 Hz, 1H), 3.43 (dd, J = 12.2, 7.6 Hz, 1H), 2.89-2.79 (m, 2H), 2.42 (m, 1H), 1.87 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.9, 147.4, 142.4, 122.6, 113.17, 68.7, 38.2, 36.2, 25.5, 18.3, 17.1, −5.4.

(*rel*)-(3*R* and 3*S*,5*S*)-5-(*tert*-Butyldimethylsilanyloxymethyl)-2,3-dimethyl-hepta-1,6-dien-3-ol (7). To a solution of **6** (1.77 g, 6.6 mmol) in dry THF (40 mL) was slowly added methylmagnesium bromide (7.92 mL, 1.0 M solution in THF) at −20 °C. After 4 h, saturated NH_4Cl solution (8 mL) was added, the reaction mixture was slowly warmed to rt and to the mixture water (150 mL) was poured. The mixture was extracted with EtOAc (150 mL) 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, 1:20) to give **7** (1.16 g, 62%) as a diastereomeric mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.76-5.66 (m, 2H), 5.12-5.01 (m, 2H), 3.56-3.48 (m, 2H), 2.27 (m, 1H), 1.52-1.46 (m, 2H), 1.38 (s, 3H), 0.81 (s, 9H), 0.01 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 148.2, 141.4, 118.6, 110.4, 78.1, 76.5, 43.6, 33.5, 26.2, 25.1, 18.2, 14.1, −5.5.

(*rel*)-(1*R*,4*S*)-4-(*t*-Butyldimethylsilyloxymethyl)-1,2-dimethyl-cyclopent-2-enol (8β) and (*rel*)-(1*S*,4*S*)-4-(*t*-butyldimethylsilyloxymethyl)-1,2-dimethyl-cyclopent-2-enol (8α). To a solution of **7** (1.76 g, 6.18 mmol) in dry benzene (8 mL) was added 2nd generation Grubbs catalyst (136 mg 0.16 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, 1:15) to give cyclopentenol **8β** (539 mg, 34%) and **8α** (555 mg, 35%) as colorless oils, respectively. Cyclopentenol **8β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.27 (dd, J = 8.2, 6.2 Hz, 1H), 3.70 (d, J = 12.2 Hz, 1H), 3.58 (d, J = 12.2 Hz, 1H), 2.83 (m, 1H), 2.42 (dd, J = 12.6, 4.8 Hz, 1H), 2.21 (dd, J = 12.6, 7.6 Hz, 1H), 1.73 (s, 3H), 1.32 (s, 3H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 143.2, 126.3, 82.1, 71.0, 39.4, 37.8, 25.9, 25.3, 18.5, 13.9, −5.5; Cyclopentenol **8α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.31 (m, 1H), 3.63 (dd, J = 14.2, 8.8 Hz, 2H), 2.87 (m, 1H), 2.38 (dd, J = 12.8, 6.8 Hz, 1H), 2.27 (dd, J = 12.7, 8.8 Hz, 1H), 1.82 (s, 3H), 1.39 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 142.9, 125.5, 81.8, 72.4, 40.1, 37.2, 26.1, 25.4, 18.6, 14.6, −5.7.

(*rel*)-(1'*R*,4'*S*)-9-[4-(*t*-Butyldimethylsilyloxymethyl)-1,2-dimethyl-cyclopent-2-en-1-yl] 6-chloropurine (9). To a solution of compound **8α** (372 mg, 1.45 mmol), triphenylphosphine (1.13 g, 4.32 mmol) and 6-chloropurine (553 g, 3.58 mmol) in anhydrous dioxane (7 mL) and DMF (7 mL) was added diisopropyl azodicarboxylate (808 mg, 4.0 mmol) dropwise at −20 °C for 30 min under nitrogen. The reaction mixture was stirred for 2 h at −20 °C under nitrogen. The solvent was concentrated under reduced pressure and the residue was directly purified by silica gel column chromatography (EtOAc/hexane, 1:4) to give the compound **9** (382 mg, 62%) as a yellow solid; UV (MeOH) λ_{max} 264.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.71 (s, 1H), 8.18 (s, 1H), 5.41 (d, J = 5.2 Hz, 1H), 3.63 (d, J = 10.2 Hz, 1H), 3.40 (d, J = 10.3 Hz, 1H), 2.78 (m, 1H), 2.43 (dd, J = 12.4, 6.2 Hz, 1H), 2.19 (dd, J = 12.4, 8.4 Hz, 1H), 1.82 (s, 3H), 1.70 (s, 3H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.6, 165.7, 154.9, 144.2, 125.5, 120.35, 71.4, 66.4, 40.3, 33.5, 25.6, 22.4, 18.5, 14.3, -5.6; Anal calc for $C_{19}H_{29}ClN_4OSi$: C, 58.07; H, 7.44; N, 14.26. Found: C, 57.96; H, 7.41; N, 14.32.

(*rel*)-(1'*R*,2'*S*,3'*R*,4'*R*)-9-[4-(*t*-Butyldimethylsilyloxymethyl)-1,2-dimethyl-2,3-dihydroxy-cyclopentan-1-yl] 6-chloropurine (10α) and (*rel*)-(1'*R*,2'*R*,3'*S*,4'*R*)-9-[4-(*t*-butyldimethylsilyloxymethyl)-1,2-dimethyl-2,3-dihydroxy-cyclopentan-1-yl] 6-chloropurine (10β). To a stirred solution of **9** (393 mg, 1.0 mmol) in cosolvent (8.0 mL, acetone/water = 5/1) was added NMO (351 mg, 3.0 mmol), and OsO_4 (0.07 mL, 4% in water). The mixture was stirred overnight at 50 °C, and quenched with saturated Na_2SO_3 solution (8 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 **10α** (209 mg, 49%) and **10β** (51 mg, 12%) as a white solid: **10α**: mp 196 - 198 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.71 (s, 1H), 8.51 (s, 1H), 5.10 (s, 1H, D_2O exchangeable), 5.01 (d, J = 4.8 Hz, 1H, D_2O exchangeable), 3.81 (d, J = 10.8 Hz, 1H), 3.61-3.50 (m, 2H), 2.09-1.99 (m, 2H), 1.72-1.65 (m, 4H), 1.34 (s, 3H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 169.8, 165.4, 157.7, 137.5, 121.4, 87.3, 74.5, 67.7, 63.4, 30.4, 25.6, 23.7, 18.4, 15.3, 14.2, −5.4; Anal calc for $C_{19}H_{31}ClN_4O_3Si$ (+0.5 MeOH): C, 52.86; H, 7.50; N, 12.64. Found: C, 52.74; H, 7.42; N, 12.51; **10β**: mp 203 - 205 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.67 (s, 1H), 8.48 (s, 1H), 5.08 (s, 1H, D_2O exchangeable), 5.00 (d, J = 4.7 Hz, 1H, D_2O exchangeable), 3.79-3.70 (m, 2H), 3.42 (d, J = 7.2 Hz, 1H), 2.08 (dd, J = 8.6, 6.2 Hz, 1H), 1.75-1.67 (m, 2H), 1.53 (s, 3H), 1.32 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 169.1, 164.8,

157.2, 136.8, 122.5, 88.9, 73.6, 66.2, 62.6, 31.3, 25.5, 22.9, 18.7, 14.6, 13.7, −5.6; Anal calc for $C_{19}H_{31}ClN_4O_3Si$: C, 53.44; H, 7.32; N, 13.12. Found: C, 53.53; H, 7.40; N, 13.07.

(*rel*)-(1'*R*,2'*S*,3'*R*,4'*R*)-9-[4-(*t*-Butyldimethylsilyloxymethyl)-1,2-dimethyl-2,3-dihydroxy-cyclopentan-1-yl] adenine (11). Compound **10α** (119 mg, 0.28 mmol) was dissolved in saturated methanolic ammonia (10 mL) and the resulting solution was stirred overnight at 90 - 95 °C in a steel bomb. After removal of reaction solvent, the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 10:1) to give the compound **11** (84 mg, 74%) as a white solid: mp 200 - 202 °C; UV (MeOH) λ_{max} 259.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.16 (s, 1H), 8.10 (s, 1H), 7.19 (br s, 1H, D_2O exchangeable), 5.17 (s, 1H, D_2O exchangeable), 5.05 (d, J = 4.8 Hz, 1H, D_2O exchangeable), 3.78 (d, J = 10.7 Hz, 1H), 3.50 (d, J = 10.6 Hz, 1H), 3.41 (dd, J = 8.4, 6.4 Hz, 1H), 2.02-1.93 (m, 2H), 1.80 (s, 3H), 1.67 (m, 1H), 1.32 (s, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 155.2, 152.5, 149.4, 138.7, 119.4, 85.3, 73.5, 67.3, 62.1, 32.5, 25.7, 24.2, 18.4, 14.8, 13.9, −5.5; Anal calc for $C_{19}H_{33}N_5O_3Si$ (+1.0 MeOH): C, 54.64; H, 8.48; N, 15.93. Found: C, 54.72; H, 8.41; N, 16.02.

(*rel*)-(1'*R*,2'*S*,3'*R*,4'*R*)-9-[4-(Hydroxymethyl)-1,2-dimethyl-2,3-dihydroxy-cyclopentan-1-yl] adenine (12). To a solution of **11** (159 mg, 0.39 mmol) in cosolvent (5.0 mL, THF: CH_3CN/1:1), TBAF (0.58 mL, 1.0 M solution in THF) was added 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 **12** (78 mg, 68%) as a white solid: mp 209 - 212 °C; UV (H_2O) λ_{max} 260.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.21 (s, 1H), 8.13 (s, 1), 7.21 (br s, 2H, D_2O exchangeable), 5.18 (s, 1H, D_2O exchangeable), 5.10 (d, J = 4.8 Hz, 1H, D_2O exchangeable), 4.81 (t, J = 4.6 Hz, 1H, D_2O exchangeable), 3.79 (d, J = 10.8 Hz, 1H), 3.49-3.38 (m, 2H), 2.02-1.93 (m, 2H), 1.78 (s, 3H), 1.63 (m, 1H), 1.30 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 155.6, 152.3, 148.2, 135.3, 118.8, 86.2, 72.9, 67.7, 61.9, 33.2, 24.7, 14.2, 13.4; Anal calc for $C_{13}H_{19}N_5O_3$(+1.0 H_2O): C, 51.65; H, 7.00; N, 23.16. Found: C, 51.54; H, 6.95; N, 23.22.

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