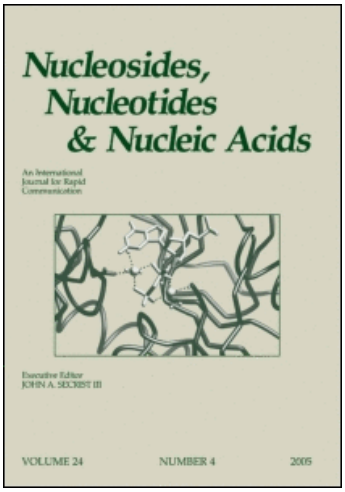

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Jae Young Lee[a]; Chang Hyun Oh[b]; Ok Hyun Ko[a]; Joon Hee Hong[a]
[a] College of Pharmacy, Chosun University, Kwangju, South Korea [b] Medicinal Chemistry Research Center, Korea Institute of Science and Technology, Seoul, South Korea

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SYNTHESIS AND ANTI-HCMV ACTIVITY OF NOVEL ACYCLIC NUCLEOSIDES

Jae Young Lee,[1] Chang Hyun Oh,[2] Ok Hyun Ko,[1] and Joon Hee Hong[1,*]

[1]College of Pharmacy, Chosun University, Kwangju 501-759, South Korea
[2]Medicinal Chemistry Research Center, Korea Institute of Science and Technology, Seoul 130-650, South Korea

ABSTRACT

A series of novel acyclic nucleosides **10**, **11**, **21**, and **22** were synthesized efficiently starting from D-lactose. The condensation of the mesylate **5** and **16** with an adenine and cytosine base under standard nucleophilic substitution conditions (K_2CO_3, 18-*Crown*-6, DMF) afforded a series of acyclic novel nucleosides. Compound **21** displayed moderate anti-HCMV activity in the AD-169 cells ($EC_{50} = 18.5\,\mu g/mL$) without exhibiting any cytotoxicity up to $100\,\mu M$.

INTRODUCTION

The discovery of acyclovir[1] as an antiherpes agent ignited the search for new antiviral nucleosides with a disconnected chain resulting from the omission of bonds from the pentose or cyclopentane rings. During the past twenty years, many new synthetic schemes for various acyclic nucleoside[2] analogues have been discovered and many of these molecules have shown

*Corresponding author. E-mail: hongjh@mail.chosun.ac.kr

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promising antiviral activities.[3] Among them, deciclovir,[4] ganciclovir,[5] penciclovir,[6] famciclovir[7] have exhibited potent antiviral activity against HBV, HIV, and the herpes virus. It may be assumed that the potent antiviral activity originates from the flexible acyclic sugar mimicking moiety.

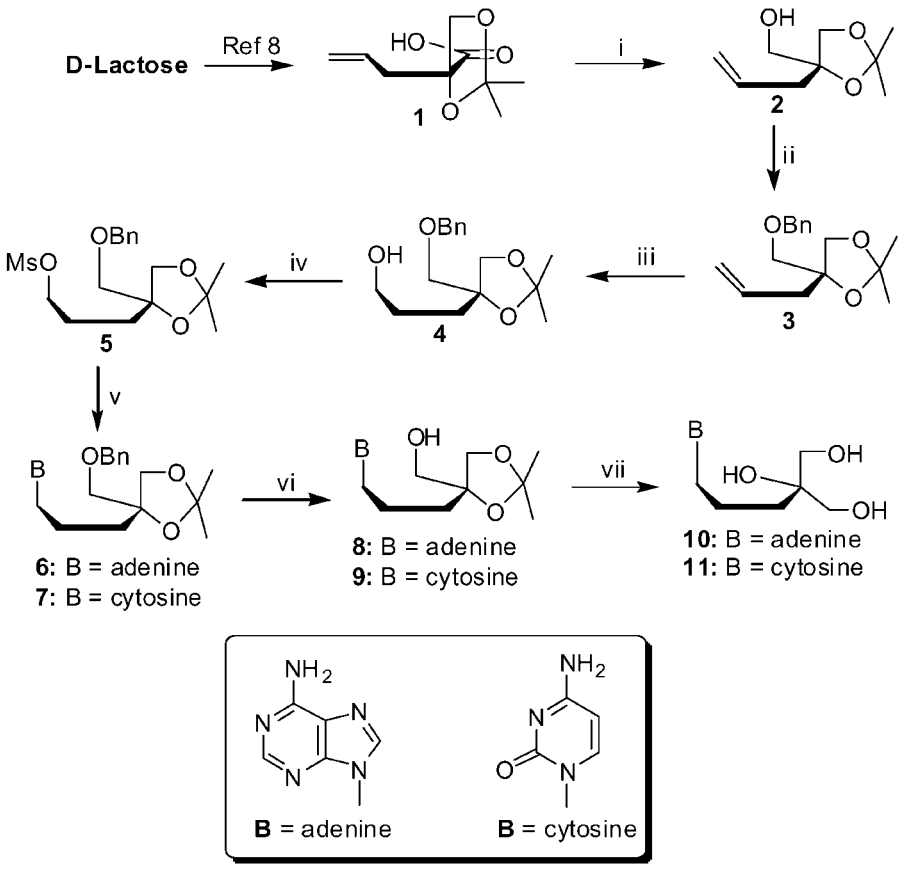
Nevertheless, the utility of these drugs is limited due to their toxicity and side effects, as well as the emergence of drug resistant viral strains. Therefore, it is essential to search for less toxic and more effective antiviral agents, which do not have a cross-resistance with the existing drugs. To the best of the authors' knowledge, no attempts to synthesize and screen novel acyclic nucleosides containing both a tertiary hydroxyl group and a two-bond disconnection have yet been made.

In view of the stimulating results of acyclic nucleosides and as part of our ongoing drug discovery efforts, this study aimed to synthesize novel acyclic nucleosides. This paper reports their synthetic routes from very cheap and commercially available D-lactose and their biological activities.

RESULTS AND DISCUSSIONS

Most methods used to synthesize acyclic nucleosides involve the alkylation of the acyclic chain by a suitable alkyl halide or a similar good leaving group. Thus, the requisite acyclic chain was prepared by starting with an acid derivative **1**, which was prepared from D-lactose in 5 steps using the procedure reported by Monneret et al.[8] Compound **1** was reduced to alcohol **2** by $LiAlH_4$ in an anhydrous THF solution, which was protected with benzyl bromide (BnBr) to give **3** in a 68.6% yield for the two steps (Sch. 1). Olefin **3** was hydroborated by stirring overnight with a BH_3/DMS complex in THF at room temperature. It was then oxidized by 30% H_2O_2 to provide the primary alcohol **4** in a 63% yield. The hydroxyl group of **4** was mesylated by treating it with methanesulfonyl chloride (MsCl) in an anhydrous CH_2Cl_2 solvent to give the key intermediate **5**, which was coupled with the nucleobases (adenine and cytosine) under well-known standard conditions (K_2CO_3, 18-*C*-6, DMF)[9] to give adenine and cytosine derivative **6** and **7** in 48–56% yield for the two steps. Removing the benzyl protecting groups of **6** and **7** was accomplished by the conditions[10] of 10% $Pd(OH)_2$ in methanol and a cyclohexene mixture system to furnish **8** and **9** in a 55–64% yield. The isopropylidene groups of nucleoside **8** and **9** could be readily removed by an acidic hydrolysis condition (80% AcOH, 80°C) to give **10** and **11** in 55–64% yield.

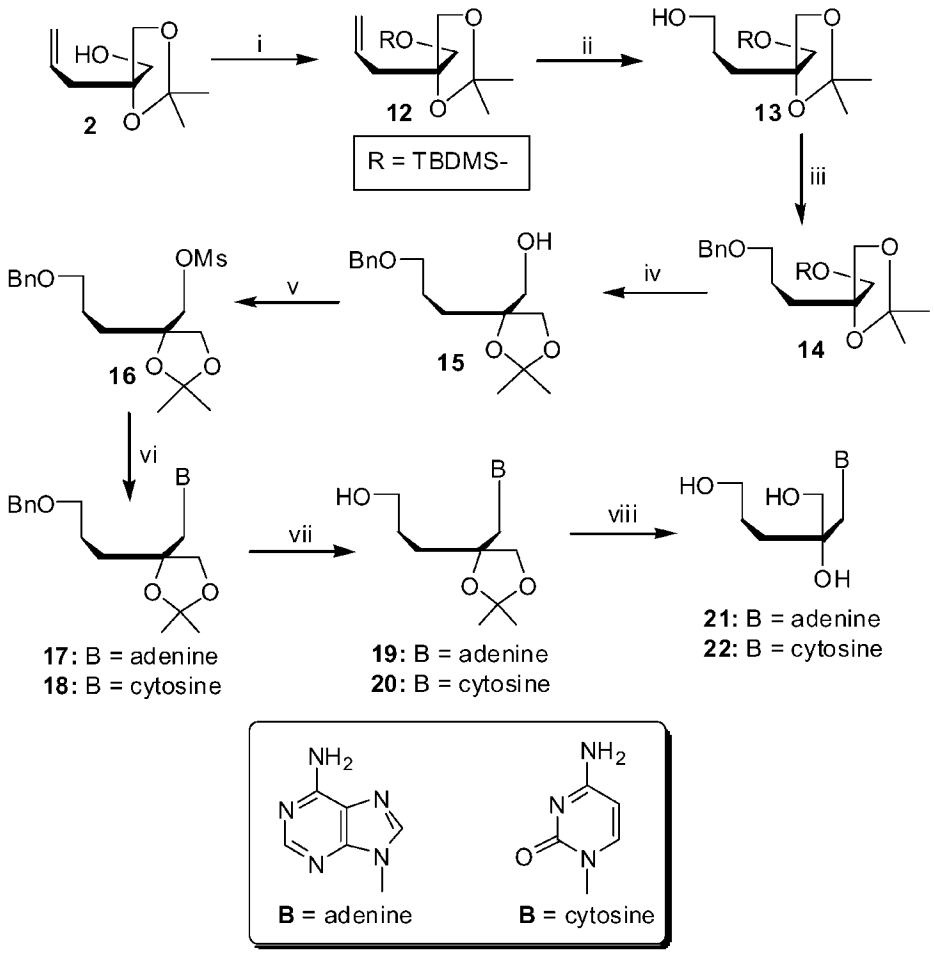
In order to synthesize the other type of diseco-nucleosides (two bond disconnection), the key intermediate **16** was made starting from **2** (Sch. 2). The choice of the hydroxyl protecting groups must be made to avoid the difficulties encountered with removing the benzyl groups during the subsequent step. Based on this consideration, the hydroxyl functional group of



Scheme 1. Reagents: i) $LiAlH_4$, THF, reflux, overnight, 88%; ii) BnBr, NaH, THF, rt, overnight, 78%; iii) BH_3/DMS, THF, $NaOH/H_2O_2$, 63%; iv) MsCl, TEA, 0°C, 1 h, 90%; v) adenine and cytosine, DMF, K_2CO_3, 18-C-6, 80°C, overnight, 48–56%; vi) $Pd(OH)_2$, MeOH, cyclohexene, reflux, overnight, 77–89%; vii) 80% AcOH, 80°C, overnight, 55–64%.

2 was temporarily protected with *t*-butyldimethylsilyl chloride (TBDMSCl) to give **12** in a 95% yield. Olefin **12** was sequentially hydroborated with BH_3/DMS and oxidized by H_2O_2 to give **13** in a 56% yield. This time, the resulting hydroxyl group was protected by BnBr to give **14** in an 80% yield. The TBDMS protecting group of **14** was removed by a treatment with tetrabutyl-ammonium fluoride (TBAF) to furnish **15** in an 85% yield, which was mesylated with MsCl to give **16** in a 69% yield for the two steps.

The condensation of **16** with the nucleobases (adenine and cytosine) gave **17** and **18** in a 45–50% yield. A separate treatment of **17** and **18** with $Pd(OH)_2$ in the cyclohexene and methanol cosolvent system gave debenzylated nucleosides **19** and **20**, respectively. Removing the isopropylidene



Scheme 2. Reagents: i) TBDMSCl, imidazole, CH_2Cl_2, 0°C, 4 h, 95%; ii) BH_3/DMS, THF, H_2O_2, NaOH, 56%; iii) BnBr, NaH, THF, rt, overnight, 80%; iv) TBAF, THF, rt, 3 h, 85%; v) MsCl, TEA, CH_2Cl_2, 0°C, 87%; vi) adenine and cytosine, DMF, K_2CO_3, 18-C-6, 80°C, overnight, 45–60%; vii) $Pd(OH)_2$, MeOH, cyclohexene, reflux, overnight, 90–95%; viii) 80% AcOH, 80°C, overnight, 45–60%.

protecting group of **19** and **20** was readily made in an 80% AcOH solution at 80°C to afford **21** and **22**, respectively. The antiviral assays of the synthesized final nucleosides **10**, **11**, **20** and **21** against the human immunodeficiency virus 1 (HIV-1), the herpes simplex virus 1,2 (HSV-1, 2) and the human cytomegalovirus (HCMV) were performed. The compounds did not show any antiviral activity except for the adenine derivative **21**, which exhibited moderate anti-HCMV activity in AD-169 cells ($EC_{50} = 18.5\,\mu g/mL$) without any cytotoxicity up to 100 μM.

CONCLUSION

Novel acyclic nucleosides were successfully synthesized starting from D-lactose. The present synthetic method is highly efficient and convenient, and has the flexibility for further applications to the synthesis of geminally substituted novel acyclic nucleosides. Although the tested compounds did not display excellent antiviral activity, the adenine derivative **21** exhibited moderate anti-HCMV activity in AD-169 cells ($EC_{50} = 18.5\,\mu g/mL$). This result strongly suggests that this structure for the novel nucleosides (diseconucleoside) might be candidate for a new lead compound for developing new antiviral agents.

EXPERIMENTAL SECTION

The melting points were determined on a Mel-tem II laboratory device and were uncorrected. The NMR spectra were recorded on a Bruker 300 Fourier transform spectrometer. The chemical shifts are reported in parts per million (δ) and the signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). The UV spectra were obtained on a Beckman DU-7 spectrophotometer. The optical rotations were measured on an Autopol-IV digital polarimeter. The elemental analyses were performed in the Korea Basic Science Institute, Kwangju, Korea. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. All reactions were carried out under N_2 unless otherwise 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.

(2*R*)-2-Hydroxy-2-(hydroxymethyl)-2,2′-*O*-isopropylidene-pent-4-en-1-ol (2): To a solution of **1** (5 g, 26.8 mmol) in THF (20 mL), $LiAlH_4$ (1.6 g, 42.9 mmol) was added portionwise at 0°C. The mixture was stirred overnight under reflux, and then cooled to room temperature. To the mixture, water (1.48 mL), 15% NaOH solution (1.48 mL), and water (4.4 mL) sequentially added. The mixture was stirred at room temperature for 2 h, and the resulting solid was filtered through a Celeste pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 2:1) to give alcohol **2** (4.06 g, 88%) as a colorless oil: $[\alpha]_D^{25}$ −2.9° (*c* 3.0, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.86–5.72 (m, 1H, H-4), 5.16 (d, $J = 3.6$ Hz, 2H, H-5a), 5.11 (s, 1H, H-5b), 3.90 (d, $J = 8.7$ Hz, 1H, H-2′a), 3.84 (d, $J = 8.7$ Hz, 1H, H-2′b), 3.55 (d, $J = 12.3$ Hz, 2H, H-1), 2.41 (t, $J = 6.3$ Hz, 2H, H-3), 1.91 (s, 1H, OH), 1.42 (d, $J = 2.1$ Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$) δ 132.98, 118.70, 109.78, 82.98, 69.26, 65.22, 39.95, 27.09, 26.91; Anal. Calc. for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.68; H, 9.47.

(4*R*)-5-Benzyloxy-4-hydroxy-4-(hydroxymethyl)-4,4′-*O*-isopropylidene-pent-1-ene (3): To a stirred suspension of NaH (2 g, 50 mmol, 60%) in THF (100 mL), a solution of **2** (8.7 g, 33.3 mmol) in THF was slowly added at 0°C, and stirred at room temperature for 1 h. The mixture was cooled to 0°C, and benzyl bromide (6.8 g, 39.9 mmol) was then slowly added. The mixture was stirred overnight at room temperature, and quenched by adding a saturated ammonium chloride solution (10 mL). The mixture was extracted with EtOAc (200 mL) and water (200 mL), and the organic layer was washed with brine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give **3** (6.8 g, 78%) as a colorless oil: $[\alpha]_D^{25}$ −22.49° (*c* 1.52, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.25 (m, 5H, Ar), 5.89–5.75 (m, 1H, H-2), 5.13 (dd, $J = 13.5$, 1.8 Hz, 2H, H-1), 4.54 (s, 2H, CH_2-Ar), 3.95 (d, $J = 8.3$ Hz, 1H, H-4′a), 3.79 (d, $J = 8.3$ Hz, 1H, H-4′b), 3.40 (d, $J = 4.8$ Hz, 2H, H-5), 2.45 (d, $J = 7.5$ Hz, 2H, H-3), 1.40 (d, $J = 3.6$ Hz, 6H, $2CH_3$); Anal. Calc. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.38; H, 8.49.

(4*R*)-5-Benzyloxy-4-hydroxy-4-(hydroxymethyl)-4,4′-*O*-isopropylidene-pentan-1-ol (4): To a solution of olefin **3** (2.5 g, 9.5 mmol) in dry THF (10 mL), 1.0 M BH_3/DMS (in tetrahydrofuran, 11.4 mL) was added dropwise with a syringe at 0°C. The mixture was stirred overnight at room temperature, and then cooled to 0°C. A 2 N NaOH solution (10 mL, 20 mmol) was added followed by the careful addition of a 30% hydrogen peroxide solution (6.0 mL, 51.3 mmol). The reaction mixture was stirred at room temperature for 2 h. The mixture was then diluted with brine (10 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:1) to give **4** (1.67 g, 63%) as a colorless oil: $[\alpha]_D^{25}$ −10.81° (*c* 1.22, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.26 (m, 5H, Ar), 4.53 (s, 2H, CH_2-Ar), 4.03 (d, $J = 8.4$ Hz, 1H, H-4′a), 3.76 (d, $J = 8.4$ Hz, 1H, H-4′b), 3.67 (m, 2H, H-5), 3.45 (dd, $J = 13.8$, 9.3 Hz, 2H, H-1), 2.04–1.58 (m, 4H, H-2 and 3), 1.38 (s, 6H, $2CH_3$); Anal. Calc. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.50; H, 8.51.

(4*R*)-1-*O*-Mesyl-5-benzyloxy-4-hydroxy-4-(hydroxymethyl)-4,4′-*O*-isopropylidene-pentane (5): To a solution of alcohol **4** (3.6 g, 12.8 mmol) in anhydrous CH_2Cl_2, anhydrous triethyl amine (1 mL) and MsCl (1.76 g, 15.4 mmol) was added at 0°C. The mixture was stirred at the same temperature for 1 h, and quenched by cold water (2 mL). The mixture was extracted with methylene chloride (100 mL) and water (50 mL). The organic layer was dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under vacuum, and the residue was purified by silica gel

column chromatography (EtOAc/hexane, 1:1.5) to give **5** (4.13 g, 90%) as a colorless oil: $[\alpha]_D^{25}$ +1.65° (*c* 1.16, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.26 (m, 5H, Ar), 4.53 (d, $J = 3.0$ Hz, 2H, CH_2-Ar), 4.23 (t, $J = 5.7$ Hz, 2H, H-1), 4.12 (d, $J = 7.2$ Hz, 1H, H-4′a), 4.00 (d, $J = 7.2$ Hz, 1H, H-4′b), 3.38 (s, 2H, H-5), 2.97 (s, 3H, CH_3S), 1.84–1.63 (m, 4H, H-2 and 3), 1.37 (s, 6H, $2CH_3$); Anal. Calc. for $C_{17}H_{26}O_6S$: C, 56.96; H, 7.31. Found: C, 56.88; H, 7.33.

(4′*R*)-9-[5-Benzyloxy-4-hydroxy-4-(hydroxymethyl)-4,4′-*O*-isopropylidene-pentan-1-yl] adenine (6): A solution of mesylate **5** (56.4 mg, 0.157 mmol), K_2CO_3 (43.39 mg, 0.314 mmol), 18–crown-6 (62.66 mg, 0.24 mmol), adenine (42.43 mg, 0.314 mmol) in dry DMF (1.5 mL) was stirred overnight at 80°C. The mixture was cooled to room temperature and concentrated under vacuum. The residue was diluted with brine (10 mL) and extracted with CH_2Cl_2 (10 mL × 4). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:10) to give **6** (41.3 mg, 48%) as a white solid: mp 178–182°C; UV (MeOH) λ_{max} 262 nm; $[\alpha]_D^{25}$ +1.26° (*c* 2.05, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.36 (s, 1H, H-8), 7.77 (s, 1H, H-2), 7.35–7.24 (m, 5H, Ar), 6.26 (s, 2H, D_2O exchangeable, -NH_2), 4.50 (d, $J = 4.8$ Hz, 2H, CH_2-Ar), 4.23 (dd, $J = 11.4$, 7.2 Hz, 2H, H-5′), 3.97 (d, $J = 9.0$ Hz, 1H, H-4″a), 3.69 (d, $J = 9.0$ Hz, 1H, H-4″b), 3.37 (dd, $J = 10.5$, 9.6 Hz, 2H, H-1′), 1.97–1.54 (m, 4H, H-2′ and 3′), 1.36 (s, 3H, CH_3), 1.4 (s, 3H, CH_3); Anal. Calc. for $C_{21}H_{27}N_5O_3$: C, 63.46; H, 6.85; N, 17.62. Found: C, 63.38; H, 6.88; N, 17.54.

(4′*R*)-1-[5-Benzyloxy-4-hydroxy-4-(hydroxymethyl)-4,4′-*O*-isopropylidene-pentan-1-yl] cytosine (7): Compound **7** was synthesized according to the conditions used for synthesizing. Yield: 56%; mp 182–184°C; UV (MeOH) λ_{max} 272 nm; $[\alpha]_D^{25}$ −12.5° (*c* 0.3, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.55 (d, $J = 7.5$ Hz, 1H, H-6), 7.37–7.24 (m, 5H, Ar), 6.96 (br d, 2H, D_2O exchangeable, -NH_2), 5.61 (dd, $J = 7.2$, 1.5 Hz, 1H, H-5), 4.47 (s, 2H, CH_2-Ar), 3.83 (d, $J = 7.5$ Hz, 1H, H-4″a), 3.66 (d, $J = 7.5$ Hz, 1H, H-4″b), 3.61 (m, 4H, H-1′ and 5′), 1.65–1.51 (m, 4H, H-2′ and 3′), 1.25 (s, 6H, $2CH_3$); Anal. Calc. for $C_{20}H_{27}N_3O_4$: C, 64.34; H, 7.29; N, 11.25. Found: C, 64.27; H, 7.39; N, 11.41.

(4′*R*)-9-[4,5-Dihydroxy-4-(hydroxymethyl)-4,4′-*O*-isopropylidene-pentan-1-yl] adenine (8): To a solution of **6** (100 mg, 0.25 mmol), 10% $Pd(OH)_2$ (120 mg) in methanol (17 mL), anhydrous cyclohexene (6 mL) was added. The mixture was stirred overnight and cooled to room temperature, and filtered through a Celite pad. The filtrate was concentrated in vacuum, and the residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:8) to give **8** (59 mg, 77%) as a white solid: mp 185–188°C;

UV (MeOH) λ_{max} 262.5 nm; $[\alpha]_D^{25}$ +10.5° (*c* 0.19, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.34 (s, 1H, H-8), 7.73 (s, 1H, H-2), 6.23 (s, 2H, D_2O exchangeable, -NH_2), 4.23 (dd, $J = 11.4$, 7.2 Hz, 2H, H-1′), 3.91 (d, $J = 9.7$ Hz, 1H, H-4′a), 3.69 (d, $J = 9.0$ Hz, 1H, H-4′b), 3.31 (dd, $J = 10.5$, 9.6 Hz, 2H, H-5′), 1.97–1.54 (m, 4H, H-2′ and 3′), 1.36 (s, 3H, CH_3), 1.4 (s, 3H, CH_3); Anal. Calc. for $C_{14}H_{21}N_5O_3$: C, 54.71; H, 6.89; N, 22.79. Found: C, 54.55; H, 6.79; N, 22.75.

(4′*R*)-1-[4,5-Dihydroxy-4-(hydroxymethyl)-4,4′-*O*-isopropylidene-pentan-1-yl] cytosine (9): Compound **9** was synthesized according to the conditions used to synthesize **8**. Yield: 89%; mp 190–192°C; UV (MeOH) λ_{max} 273.5 nm; $[\alpha]_D^{25}$ −6.34° (*c* 1.04, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.65 (d, $J = 6.9$ Hz, 1H, H-6), 7.14 (br d, 2H, D_2O exchangeable, -NH_2), 5.71 (d, $J = 6.9$ Hz, 1H, H-5), 4.91 (t, $J = 5.6$ Hz, 1H, D_2O exchangeable, -OH), 3.90 (d, $J = 8.4$ Hz, 1H, H-1a′), 3.67 (m, 3H, H-1b′ and 5′), 1.68–1.51 (m, 4H, H-2′ and 3′), 1.33 (d, $J = 2.7$ Hz, 6H, $2CH_3$); Anal. Calc. for $C_{13}H_{21}N_3O_4$: C, 55.11; H, 7.47; N, 14.83. Found: C, 55.25; H, 7.49; N, 14.75.

9-[4,5-Dihydroxy-4-(hydroxymethyl)-pentan-1-yl] adenine (10): A solution of **8** (97 mg, 0.31 mmol) in 80% acetic acid solution was stirred for 5 h at 80°C. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The residue was coevaporated with toluene (10 mL) twice, and purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:9) to give **10** (63 mg, 77%) as a white solid: mp 180–182°C; UV (H_2O) λ_{max} 261 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.11 (s, 2H, H-8 and 2), 7.16 (br s, 2H, D_2O exchangeable, -NH_2), 4.38 (br s, 2H, -OH), 4.09 (t, $J = 6.9$ Hz, 2H, H-1′), 4.01 (s, 1H, -OH), 3.14 (m, 4H, H-5′ and H-4″), 1.88–1.78 (m, 2H, H-2′), 1.33–1.28 (m, 2H, H-3′); Anal. Calc. for $C_{11}H_{17}N_5O_3$: C, 49.43; H, 6.41; N, 26.20. Found: C, 49.51; H, 6.50; N, 26.25.

1-[4,5-Dihydroxy-4-(hydroxymethyl)-pentan-1-yl] cytosine (11): Similar reaction conditions at those used for **10** was used to synthesize **11**. Yield: 89%; mp 190–192°C; UV (H_2O) λ_{max} 262 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.54 (d, $J = 6.9$ Hz, 1H, H-6), 6.98 (br d, 2H, D_2O exchangeable, -NH_2), 5.62 (d, $J = 6.9$ Hz, 1H, H-5), 4.66 (br s, 1H, D_2O exchangeable, -OH), 4.49 (br s, 1H, D_2O exchangeable, -OH), 3.92 (br s, 1H, D_2O exchangeable, -OH), 3.90 (d, $J = 13.8$ Hz, 1H, H-1′), 3.80 (d, $J = 13.8$ Hz, 1H, H-1′), 3.57 (m, $J = 6.9$ Hz, 4H, H-5′ and 4″), 1.57 (m, 2H, H-2′), 1.32 (m, 2H, H-3′); Anal. Calc. for $C_{10}H_{17}N_3O_4$: C, 49.37; H, 7.04; N, 17.27. Found: C, 49.46; H, 7.19; N, 17.35.

(4*S*)-5-(*t*-Butyldimethylsilyloxy)-4-hydroxy-4-(hydroxymethyl)-4,4′-*O*-isopropylidene-pent-1-ene (12): To a solution of **2** (10 g, 58 mmol) and

imidazole (3.9 g, 0.116 M) in anhydrous CH_2Cl_2 (300 mL) t-butyldimethylsilyl chloride (10.5 g, 69.6 mmol) was added at 0°C. The mixture was stirred for 2 h at room temperature, and quenched by water (10 mL). The mixture was extracted with CH_2Cl_2 (300 mL) and water (200 mL), and the organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give **12** (16.7 g, 95%) as a colorless oil: $[\alpha]_D^{25}$ −18.2° (*c* 1.42, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.55 (m, 1H, H-2), 5.08 (s, 1H, H-1a), 5.04 (d, $J = 7.5$ Hz, 1H, H-1b), 3.93 (d, $J = 10.2$ Hz, 1H, H-4′a), 3.68 (d, $J = 8.7$ Hz, 1H, H-4′b), 3.43 (d, $J = 1.2$ Hz, 2H, H-5), 2.32 (t, $J = 6.6$ Hz, 2H, H-3), 1.33 (s, 6H, $2CH_3$), 0.84 (s, 9H, t-Bu), −0.02 (s, 6H, $2SiCH_3$); Anal. Calc. for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55; O, 16.75. Found: C, 62.81; H, 10.61; O, 16.71.

(4*S*)-5-(*t*-Butyldimethylsilyloxy)-4-hydroxy-4-(hydroxymethyl)-4,4′-*O*-isopropylidene-pentan-1-ol (13): To a solution of olefin **12** (3 g, 10.47 mmol) and dry THF (15 mL) 1.0 M BH_3/DMS (in tetrahydrofuran, 12.5 mL) was added dropwise with a syringe at 0°C. The mixture was stirred overnight at room temperature, and cooled to 0°C. A 2 N NaOH solution (11 mL, 22 mmol) was added, which was followed by the careful addition of 30% hydrogen peroxide (7.3 mL, 62.3 mmol). The reaction mixture was stirred at room temperature for 2 h, and brine was then added. The mixture was extracted with ethyl acetate (100 mL × 3). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:4) to give **13** (1.78 g, 56%) as a colorless oil: $[\alpha]_D^{25}$ −7.7° (*c* 2.2, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.98 (d, $J = 8.4$ Hz, 1H, H-4′a), 3.6 (m, $J = 7.5$ Hz, 3H, H-4′b and H-1), 3.45 (m, 2H, H-5), 2.11 (br s, 1H, -OH), 1.75–1.51 (m, 4H, H-2 and 3), 1.33 (s, 6H, $2CH_3$), 0.82 (s, 9H, t-Bu), −0.02 (s, 6H, $2SiCH_3$); Anal. Calc. for $C_{15}H_{32}N_4Si$: C, 59.17; H, 10.59; O, 21.02. Found: C, 59.30; H, 10.63; O, 21.13.

(4*S*)-1-Benzyloxy-5-(*t*-butyldimethylsilyloxy)-4-hydroxy-4-(hydroxymethyl)-4,4′-*O*-isopropylidene pentane (14): To a stirred suspension of NaH (1.5 g, 37 mmol, 60%) in THF (70 mL) a solution of **13** (7.6 g, 24.9 mmol) in THF was slowly added at 0°C, and stirred at room temperature for 1 h. The mixture was cooled to 0°C, and benzyl bromide (5.1 g, 29.8 mmol) was added slowly. The mixture was stirred overnight at room temperature, and quenched by adding a saturated ammonium chloride solution (10 mL). The mixture was extracted with EtOAc (150 mL) and water (150 mL), and organic layer was washed with brine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **14** (7.86 g, 80%) as a colorless oil: $[\alpha]_D^{25}$ −12.44°

(*c* 3.51, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.22 (m, 5H, Ar), 4.45 (s, 2H, CH_2-Ar), 3.95 (d, $J = 8.4$ Hz, 1H, H-4′a), 3.63 (d, $J = 8.1$ Hz, 1H, H-4′b), 3.43 (m, 4H, H-1 and 5), 1.61 (m, 4H, H-2 and 3), 3.33 (d, $J = 2.7$ Hz, 6H, $2CH_3$), 0.84 (s, 9H, t-Bu), −0.03 (s, 6H, $2SiCH_3$); Anal. Calc. for $C_{22}H_{38}O_4Si$: C, 66.96; H, 9.71; O, 16.22. Found: C, 66.79; H, 9.80; O, 16.34.

(2*R*)-5-Benzyloxy-2–hydroxy-2-(hydroxymethyl)-2,2′-*O*-isopropylidene pentan-1-ol (15): To a solution of **14** (3.6 g, 9.1 mmol) in THF (13 mL), tetrabutylammonium fluoride (10.9 mL, 1 M in THF solution) was added at 0°C. The mixture was stirred for 3 h at room temperature and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give **15** (2.16 g, 85%) as a colorless oil: $[\alpha]_D^{25}$ −2.4° (*c* 2.5, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.28 (m, 5H, Ar), 4.40 (s, 2H, CH_2-Ar), 3.92 (d, $J = 8.7$ Hz, 1H, H-2′a), 3.79 (d, $J = 8.7$ Hz, 1H, H-2′b), 3.59–3.46 (m, 4H, H-1 and 5), 1.74–1.61 (m, 4H, H-3 and 4), 1.41 (d, $J = 1.5$ Hz, 6H, $2CH_3$); Anal. Calc. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63; O, 22.83. Found: C, 68.50; H, 8.68; O, 22.74.

(2*R*)-1-*O*-Mesyl-5-benzyloxy-2-hydroxy-2-(hydroxymethyl)-2,2′-*O*-isopropylidene pentane (16): To a solution of **15** (5.0 g, 17.8 mmol) in anhydrous CH_2Cl_2 (50 mL), anhydrous triethyamine (3 mL) and methane sulfonyl chloride (2.4 g, 21.4 mmol) was added at 0°C. At the same temperature, the mixture was stirred for 1 h, and quenched by water (5 mL). The mixture was extracted with CH_2Cl_2 (100 mL) and water (100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:4) to give **16** (5.5 g, 87%) as a colorless oil: $[\alpha]_D^{25}$ −2.85° (*c* 1.05, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42–7.28 (m, 5H, Ar), 4.50 (s, 2H, CH_2-Ar), 4.11 (s, 2H, H-1), 3.98 (d, $J = 9.3$ Hz, 1H, H-4′a), 3.81 (d, $J = 9.3$ Hz, 1H, H-4′b), 3.49 (t, $J = 6.0$ Hz, 2H, H-5), 3.04 (s, 3H, CH_3S), 1.74 (m, 4H, H-3 and 4), 1.42 (d, $J = 12.6$ Hz, 6H, $2CH_3$); Anal. Calc. for $C_{17}H_{26}O_6S$: C, 56.96; H, 7.31; O, 26.78. Found: C, 56.88; H, 7.37; O, 26.75.

(2′*R*)-9-[5-Benzyloxy-2-hydroxy-2-(hydroxymethyl)-2,2′-*O*-isopropylidene-pentan-1-yl] adenine (17): A solution of mesylate **16** (222 mg, 0.61 mmol), K_2CO_3 (171 mg, 1.23 mmol), 18-crown-6 (247 mg, 0.93 mmol), adenine (167 mg, 1.24 mmol) in dry DMF (3 mL) was stirred overnight at 80°C. The mixture was cooled to room temperature and concentrated under vacuum. The residue was diluted with brine (20 mL) and extracted with CH_2Cl_2 (30 mL × 4). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:10) to give **17** (109 mg, 45%) as a white solid: mp 188–192°C; UV (MeOH) λ_{max} 261.5 nm; $[\alpha]_D^{25}$ −7.26° (*c* 1.07, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ

8.12 (s, 1H, H-8), 8.03 (s, 1H, H-2), 7.36–7.23 (m, 5H, Ar), 4.12 (s, 2H, CH_2-Ar), 3.92 (d, $J = 13.8$ Hz, 1H, H-2″a), 3.82 (dd, $J = 17.1$, 9.0 Hz, 2H, H-1′), 3.71 (d, $J = 13.8$ Hz, 1H, H-2″b), 3.39 (t, $J = 5.1$ Hz, 2H, H-5′), 1.56 (m, 4H, H-3′ and 4′), 1.28 (s, 3H, CH_3), 1.19 (s, 3H, CH_3); Anal. Calc. for $C_{21}H_{27}N_5O_3$: C, 63.46; H, 6.85; N, 17.62. Found: C, 63.49; H, 6.80; N, 17.66.

(2′*R*)-1-[5-Benzyloxy-4-hydroxy-2-(hydroxymethyl)-2,2′-*O*-isopropylidene-pentan-1-yl] cytosine (18): Compound **18** was synthesized according to the conditions used for **17**; Yield: 50%; UV (MeOH) λ_{max} 273 nm; $[\alpha]_D^{25}$ −78.5° (*c* 0.25, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.43 (d, $J = 6.9$ Hz, 1H, H-6), 7.36–7.23 (m, 5H, Ar), 7.06 (br d, 2H, D_2O exchangeable, -NH_2), 5.63 (d, $J = 7.2$ Hz, 1H, H-5), 4.09 (s, 2H, CH_2-Ar), 3.92–3.69 (m, 6H, H-1′, 5′, 2″a, and 2″b), 1.68–1.53 (m, 4H, H-3′ and 4′), 1.28 (s, 3H, CH_3), 1.15 (s, 3H, CH_3); Anal. Calc. for $C_{20}H_{27}N_3O_4$: C, 64.32; H, 7.29; N, 11.25. Found: C, 64.40; H, 7.38; N, 11.36.

(2′*R*)-9-[2,5-Dihydroxy-2-(hydroxymethyl)-2,2′-*O*-isopropylidene-pentan-1-yl] adenine (19): To a solution of **17** (165.6 mg, 0.42 mmol), $Pd(OH)_2$ (197.7 mg) in methanol (29.6 mL), anhydrous cyclohexene (9.88 mL) was added. The mixture was stirred overnight and cooled to room temperature, and filtered through a Celite pad. The filtrate was concentrated under vacuum, and the residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:8) to give **19** (116 mg, 90%) as a white solid: mp 185–187°C; UV (MeOH) λ_{max} 261 nm; $[\alpha]_D^{25}$ +12.56° (*c* 1.37, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.13 (s, 1H, H-8), 8.00 (s, 1H, H-2), 7.24 (br s, 2H, D_2O exchangeable, -NH_2), 4.31 (d, $J = 14.7$ Hz, 1H, H-1″a), 4.21 (d, $J = 14.7$ Hz, H-1′b), 4.00 (d, $J = 9.0$ Hz, 1H, H-2″a), 3.79 (d, $J = 9.0$ Hz, 1H, H-2″b), 3.45 (s, 2H, H-5′), 1.51 (m, 4H, H-3′ and 4′), 1.27 (s, 3H), 1.08 (s,3H); Anal. Calc. for $C_{14}H_{21}N_5O_3$: C, 54.71; H, 6.89; N, 22.79. Found: C, 54.76; H, 6.80; N, 22.78.

(2′*R*)-1-[2,5-Dihydroxy-2-(hydroxymethyl)-2,2′-*O*-isopropylidene-pentan-1-yl] cytosine (20): Compound **20** was synthesized using similar reaction conditions as used for to **19**; Yield: 95%; UV (MeOH) λ_{max} 274 nm; $[\alpha]_D^{25}$ −100.9° (*c* 0.25, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.44 (d, $J = 7.5$ Hz, 1H, H-6), 7.11 (br d, 2H, D_2O exchangeable, -NH_2), 5.65 (d, $J = 6.9$ Hz, 1H, H-5), 4.40 (t, $J = 6.4$ Hz, 1H), D_2O exchangeable, OH), 3.94 (d, $J = 13.8$ Hz, 2H, H-1′), 3.81 (d, $J = 9.0$ Hz, 1H, H-2″a), 3.72 (d, $J = 3.9$ Hz, 1H, H-2″b), 3.67 (s, 2H, H-5′), 1.48 (m, 4H, H-3′ and 4′), 1.28 (s, 3H, CH_3), 1.14 (s, 3H, CH_3); Anal. Calc. for $C_{13}H_{21}N_3O_4$: C, 55.11; H, 7.47; N, 14.83. Found: C, 55.29; H, 7.50; N, 14.86.

(2′*R*)-9-[2,5-Dihydroxy-2-(hydroxymethyl)-pentan-1-yl] adenine (21): A solution of **19** (96 mg, 0.31 mmol) in 80% aqueous acetic acid solution (5 mL)

was stirred for 3 h at 80°C. The solution was concentrated under reduced pressure, and coevaporated with toluene three times. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:5) to give **21** (58 mg, 70%) as a white solid: mp 198–200°C; UV (MeOH) λ_{max} 261.5 nm; $[\alpha]_D^{25}$ −17.2° (*c* 0.45, MeOH); ^1H NMR (DMSO-d_6, 300 MHz) δ 8.13 (s, 1H, H-8), 8.02 (s, 1H, H-2), 7.35 (br s, 2H, D_2O exchangeable, -NH_2), 4.18 (d, $J = 14.4$ Hz, 1H, H-1′a), 4.11 (d, $J = 14.4$ Hz, 1H, H-1′b), 3.29 (br s, 2H, H-5′), 3.20 (d, $J = 11.1$ Hz, 1H, H-2″a), 3.09 (d, $J = 11.1$ Hz, 1H, H-2″b), 1.48–1.17 (m, 4H, H-3′ and 4′); Anal. Calc. for $C_{11}H_{17}N_5O_3$: C, 49.43; H, 6.41; N, 26.20. Found: C, 49.49; H, 6.55; N, 26.15.

(2′*R*)-1-[2,5-Dihydroxy-2-(hydroxymethyl)-pentan-1-yl] cytosine (22): Similar reaction condition as used for **21** was used to synthesize **22**. Yield: 60%; UV (MeOH) λ_{max} 273.5 nm; $[\alpha]_D^{25}$ −23.66° (*c* 0.24, MeOH); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.48 (d, $J = 6.9$ Hz, 1H, H-6), 7.20 (br d, 2H, D_2O exchangeable, -NH_2), 5.70 (d, $J = 7.2$ Hz, 1H, H-5), 4.12 (d, $J = 12.4$ Hz, 2H, H-1′), 3.85 (d, $J = 13.8$ Hz, 1H, H-2″a), 3.54 (d, $J = 13.8$ Hz, 1H, H-2″b), 3.06–2.96 (m, 2H, H-5′), 1.68–1.53 (m, 4H, H-3′ and 4′); Anal. Calc. for $C_{10}H_{17}N_3O_4$: C, 49.37; H, 7.04; N, 17.27. Found: C, 49.40; H, 7.12; N, 17.6.

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