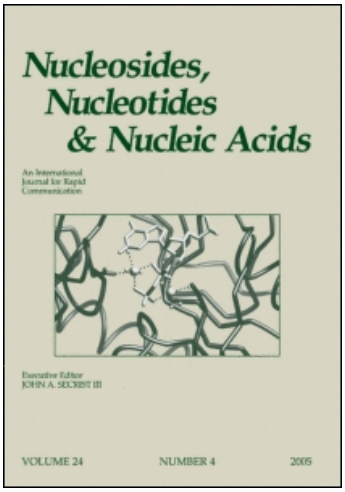

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Oh, Chang Hyun , Liu, Lian Jin and Hong, Joon Hee(2008) 'First Synthesis and Anti-HIV Evaluation of 4'-Methyl-Cyclopentanyl 9-Deazaadenosine', Nucleosides, Nucleotides and Nucleic Acids, 27: 10, 1144 — 1152
To link to this Article: DOI: 10.1080/15257770802341392
URL: http://dx.doi.org/10.1080/15257770802341392

Nucleosides, Nucleotides and Nucleic Acids, 27:1144–1152, 2008

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770802341392

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FIRST SYNTHESIS AND ANTI-HIV EVALUATION OF 4′-METHYL-CYCLOPENTANYL 9-DEAZAADENOSINE

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□ *The first synthesis of a 4′-methylated carbocyclic* C*-nucleoside* ***16*** *was achieved via the mesylate intermediate* ***10****, which was prepared using ring-closing metathesis and* S_N2 *alkylation from acetol* ***5****. When antiviral evaluation of synthesized compound* ***16*** *was performed against various viruses such as HIV, HSV-1, HSV-2, and HCMV, it showed moderate anti-HIV activity in MT-4 cell line* ($EC_{50} = 14.7\,\mu mol$).

Key words Carbocyclic *C*-nucleoside; antiviral agents; S_N2 alkylation

INTRODUCTION

Carbocyclic *C*-nucleoside[1] is unique class of nucleosides in which the heterocycle is connected to a sugar moiety by a $C-C$ bond instead of the $C-N$ bond of the natural nucleosides. *C*-Nucleosides have received considerable attention due not only to the chemical stability but also to the interesting biological activities of naturally occurring compounds such as showdomycin[2] and oxazinomycin.[3] Although several biologically active synthetic furanose *C*-nucleosides such as pseudoisocytidine,[4] thiazofurin,[5] and 9-deazaadenosine **1**[6] have been reported, only a few examples of synthetic carbocyclic *C*-nucleosides[7] have been synthesized, probably due to the synthetic difficulties of these nucleosides. In recent studies along this line, carbocyclic 9-deazaadenosine **2** have been shown to be promising anti-HIV agents.[8]

Also, the finding that thymidine bearing 4′-azido **3**[9] and 4′-cyano group **4**[10] shows significant inhibitory activity against HIV proliferation

Received January 9, 2008; accepted June 19, 2008.
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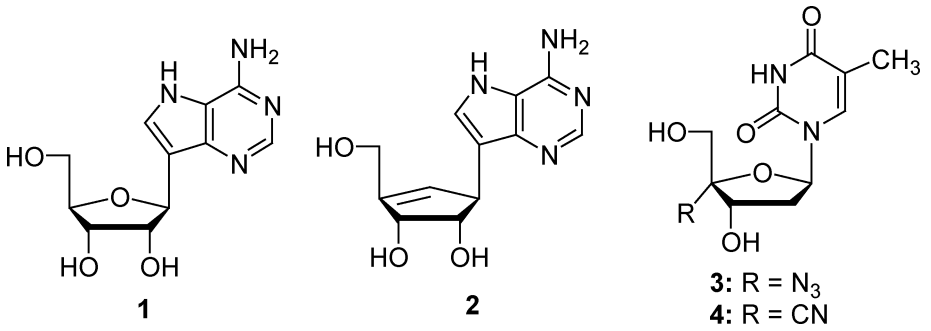


FIGURE 1 Synthesis rationale of target compound.

has stimulated the synthesis of 4′-substituted nucleoside analogues (Figure 1).[11]

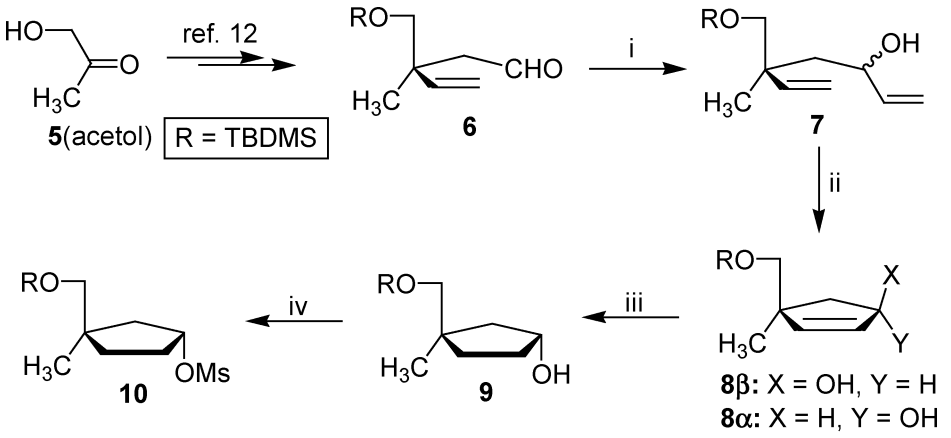
Based on these interesting chemical and biological properties of carbocyclic *C*-nucleosides and 4′-substituted nucleosides, we have determined to synthesize novel hybrid nucleosides, 4′-substituted carbocyclic *C*-nucleoside. Herein, we would like to report the first synthetic procedure of 4′-methylated carbocyclic *C*-nucleoside.

RESULTS AND DISCUSSION

To reach the target carbocyclic *C*-nucleosides, we utilized the aldehyde intermediate **6** as a starting material, which was readily prepared by previously reported procedure from commercially available acetol **5**.[12] Slow addition of CH_2=CHMgBr to aldehyde derivative **6** gave divinyl **7** as inseparable diastereomeric mixtures (Scheme 1). Without separation, each divinyl **7** was subjected to standard ring-closing metathesis[13] condition using second generation Grubbs catalyst to provide cyclopentenol **8**β and **8**α, which were readily separated by silica gel column chromatography. The relative stereochemical assignments were unequivocally made by NOE comparisons of **8**β and **8**α (Figure 2).

Cyclopentenol **8**α was reduced under the catalytic hydrogenation conditions (H_2, Pd/C) to give cyclopentanol **9** (Scheme 1). The hydroxyl group of **9** was methanesulfonylated in the condition of MsCl and TEA in anhydrous CH_2Cl_2 to provide key intermediate mesylates **10**, which was alkylated with ethyl acetonitrile by nucleophilic S_N2 substitution conditions to give the **11**.

The intermediate **11** was selectively reduced to the enol **12** by DIBALH, which was converted to enamine **13** by treatment of aminoacetonitrile monosulfate ($H_2NCH_2CN{\cdot}H_2SO_4$) and sodium acetate three hydrate ($NaOAc{\cdot}3H_2O$) in MeOH (Scheme 2). The pyrrole structure **14** was successfully achieved by sequential treatment of ethyl chloroformate and 1,8-diazabicyclo[5,4,0] undec-7-ene (DBU) in CH_2Cl_2 followed by Na_2CO_3.[14]



SCHEME 1 Synthesis of mesylate intermediate **10**.

Subjection of pyrrole analogue **14** to formidine acetate ($H_2NC{=}NH{\cdot}HOAc$) gave the protected 9-deazaadenosine derivative **15**, which was desilylated with tetrabutylammonium fluoride (TBAF) to give the target 4′-methyl cyclopentanyl 9-deazaadenosine **16** (Scheme 2).

The antiviral assay against several viruses such as the human immunodeficiency virus 1 (HIV-1), herpes simplex virus-1,2 (HSV-1,2) and human cytomegalovirus (HCMV) was performed. Synthesized **16** exhibited moderate anti-HIV activity in the MT-4 cell (EC_{50} = 14.7 μmol) without any cytotoxicity up to 100 μmol.

This observation strongly suggests that this class of 4′-methylated carbocyclic *C*-nucleoside, which has no hydroxy group in the 3′-position, may be a novel structural template for the development of new antiviral agents.

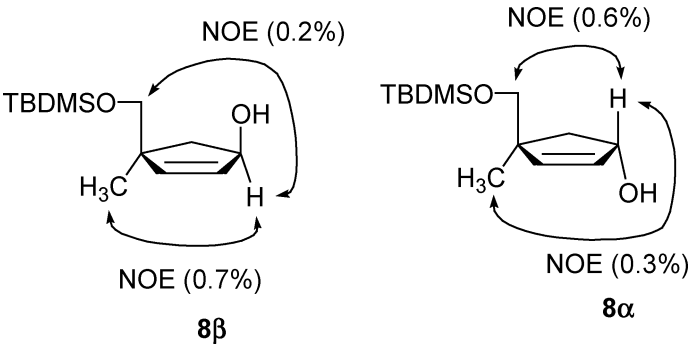
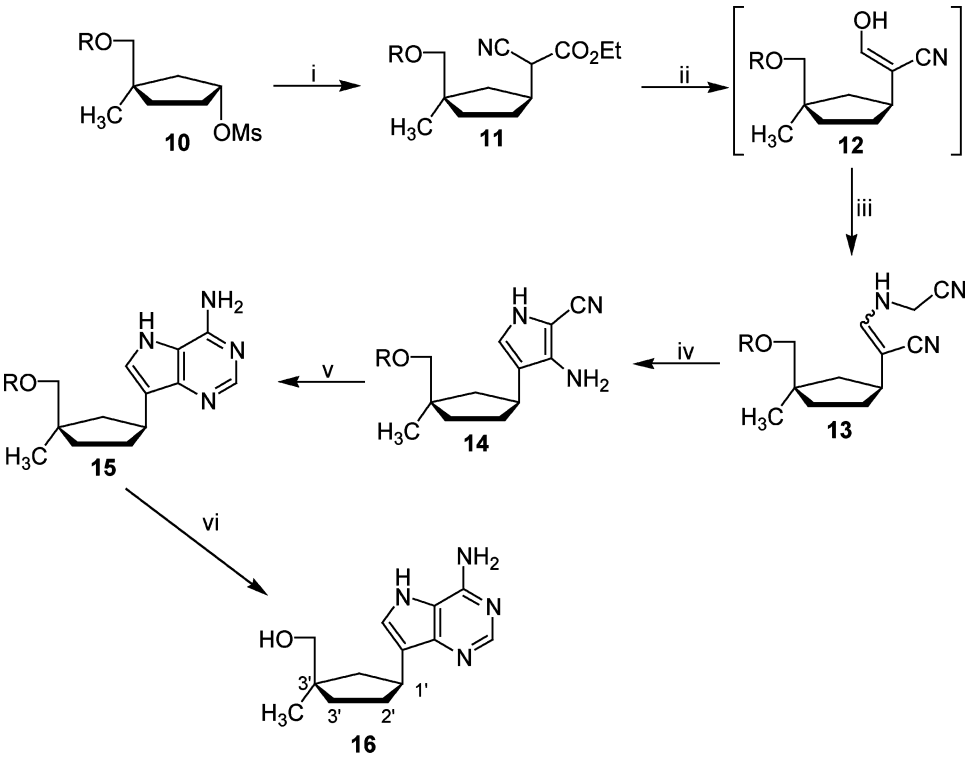


FIGURE 2 NOE comparisons of compound 8α and 8β.



Reagents:i) $NCCH_2CO_2Et$, NaH, THF; ii) DIBALH, ether; iii) $NH_2CH_2CN.H_2SO_4$, $NaOAc.3H_2O$, MeOH; iv) (a) ethyl chloroformate, DBU, CH_2Cl_2; (b) DBU; (c) Na_2CO_3, MeOH; v) formidine acetate, EtOH; vi) TBAF, THF.

SCHEME 2 Synthesis of target 9-deazaadenine C-nucleoside.

EXPERIMENTS

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. 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). UV spectra were obtained on a Beckman DU-7 spectrophotometer (Beckman, South Pasadena, CA, USA). The elemental analyses were performed using an Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. (Newark, DE, USA). 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.

(±)-(3*R* and *3S*,5*S*)-5-(t-Butyldimethylsilyloxymethyl)-5-methyl-hepta-1,6-dien-3-ol (7). To a cooled (−78°C) solution of **6** (5.6 g, 23.1 mmol) in dry THF (70 mL) was slowly added vinylmagnesium bromide (27.7 mL, 1.0 M solution in THF). After 2 hours, saturated NH_4Cl solution (23 mL) was added, and the reaction mixture was slowly warmed to ambient temperature. The mixture was extracted with EtOAc (2 × 50 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give **7** (5.68 g, 91%) as colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.02–5.74 (m, 2H), 5.27–4.99 (m, 4H), 4.25 (br s, 1H), 3.56–3.40 (m, 2H), 1.70–1.56 (m, 2H), 1.08, 1.02 (s, s, 3H), 0. 91 (s, 9H), 0.08 (two s, 6H).

(±)-(1*R*,4*S*)-4-(t-Butyldimethylsilyloxymethyl)-4-methyl-cyclopent-2-enol (8β); and (±)-(1*S*,4*S*)-4-(t-Butyldimethylsilyloxymethyl)-4-methyl-cyclopent-2-enol (8α). To a solution of **7** (2.5 g, 9.24 mmol) in dry CH_2Cl_2 (10 mL) was added Grubbs catalyst (II) (280 mg, 0.33 mmol) in dry CH_2Cl_2 (10 mL) slowly over 10 minutes under N_2 atmosphere. 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, 1:5) to give cyclopentenol **8β** (0.98 g, 44%) and **8α** (1.0 g, 45%) as colorless oils, respectively. Cyclopentenol **8β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81 (dd, J = 5.4, 2.1 Hz, 1H), 5.45 (d, J = 5.7 Hz, 1H), 4.50 (t, J = 7.8 Hz, 1H), 3.32 (s, 2H), 1.83 (dd, J = 14.1, 6.9 Hz, 1H), 1.67 (d, J = 14.1 Hz, 1H), 0.95 (s, 3H), 0.82 (s, 9H), 0.01 (s, 6H); Anal. Calcd. for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.67; H, 10.74. Cyclopentenol **8α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.73 (m, 2H), 4.84 (t, J = 6.0 Hz, 1H), 3.32 (s, 2H), 2.29 (dd, J = 13.5, 7.5 Hz, 1H), 1.37 (dd, J = 13.5, 4.2 Hz, 1H), 1.11 (s, 3H), 0.87 (s, 9H), 0.00 (s, 6H); Anal. Calcd. for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.26; H, 10.70.

(±)-(1*R*,4*R*)-4-(tert-Butyldimethylsilyloxymethyl)4-methyl-cyclopent-1-anol (9). To a solution of **8α** (3.0 g, 12.37 mmol) in methanol (25 mL), Pd/C (10%, 250 mg) was added. The mixture was thoroughly deoxygenated, then stirred overnight under hydrogen gas using a rubber balloon. The charcoal was, then, removed by filtration through a short Celite pad, which was thoroughly washed with methanol. Evaporation of the solvent gave a crude product which was purified by column chromatography (EtOAc/hexane, 1:10) to yield 2.72 g (90%) of **9** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.32 (m, 1H), 3.27 (s, 2H), 1.97–1.83 (m, 2H), 1.69–1.43 (m, 3H), 1.30–1.24 (m, 1H), 1.06 (s, 3H), 0.88 (s, 9H), 0.02 (s, 6H); Anal. Calcd. for $C_{13}H_{28}O_2Si$: C, 63.87; H, 11.55. Found: C, 64.03; H, 11.65.

(±)-(1*R*,4*R*)-[4-(tert-Butyldimethylsilyloxymethyl)4-methyl-cyclopentan-1-yl]methane sulfonate (10). To a solution of the alcohol **9** (1.14 g, 4.68 mmol) in anhydrous CH_2Cl_2 (20 mL), anhydrous triethylamine (1.5 mL) and MsCl (0.64 g, 5.61 mmol) was added at 0°C. The mixture was stirred

at the same temperature for 4 hours, and quenched by a cold saturated $NaHCO_3$ solution (2.0 mL). The mixture was extracted with CH_2Cl_2 (150 mL)/water (150 mL) two times. The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give **10** (890 mg, 59%) as a colorless syrup:

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.45 (m, 1H), 3.29 (s, 2H), 3.02 (s, 3H), 2.01–1.89 (m, 2H), 1.73–1.45 (m, 3H), 1.33–1.27 (m, 1H), 1.07 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H); Anal. Calcd. for $C_{14}H_{30}O_4SSi$: C, 52.13; H, 9.38. Found: C, 52.30; H, 9.21.

(±)-(1*S*,4*R*)-4-(tert-Butyldimethylsilyloxymethyl)4-methyl-cyclopentanyl]isocyanoacetic acid ethyl ester (11). To a suspension of sodium hydride (222 mg, 9.25 mmol) in distilled THF (50 mL) was added dropwise ethyl cyanoacetate (1.05 g, 9.25 mmol) at 0°C and the mixture was stirred at room temperature for 1.5 hours. Compound **10** (3.98 g, 9.25 mmol) dissolved in THF (10 mL) was added to this mixture and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with H_2O (50 mL), and extracted with EtOAc (50 mL × 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, 1:10) to give **11**(1.5 g, 48%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.23 (q, $J = 6.9$ Hz, 2H), 3.35 (s, 2H), 3.07–3.02 (m, 2H), 2.90–2.74 (m, 2H), 2.53–2.47 (m, 1H), 1.91–1.86 (m, 1H), 1.59–1.22 (m, 2H), 1.30 (t, $J = 6.9$ Hz, 3H), 0.97 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); Anal. Calcd. for $C_{18}H_{33}NO_3Si$: C, 63.67; H, 9.80; N, 4.13. Found: C, 63.82; H, 9.99; N, 4.02.

(±)-(1*S*,4*R*)-3-(tert-Butyldimethylsilyloxymethyl)-4-methyl-cyclopentanyl] hydroxyacrylonitrile (12). DIBALH (2.65 mL, 1 M in hexane) was added to a solution of **11** (1.23 g, 3.64 mmol) in anhydrous ether at –78°C over 10 minutes. The resulting mixture was stirred for 10 minutes and quenched with MeOH (5 mL). The resulting white solid was filtered,and the filtrate was concentrated in reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give enol **12** (774 mg, 72%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.04 (s, 1H), 3.45 (s, 2H), 2.83 (m, 1H), 1.75–1.70 (m, 1H), 1.64–1.58 (m, 2H), 1.33–1.23 (m, 3H), 0.98 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H).

(±)-2-[(1′*S*,4′*R*)-4′-(tert-Butyldimethylsilyloxymethyl)4′-methyl-cyclopentanyl]3-(cyanomethylamino)acrylonitrile (13). Compound **12** (1.91 g, 6.48 mmol) was dissolved in MeOH (80 mL) followed by addition of aminoacetonitrile monosulfate (4.18 g, 27.15 mmol) and sodium acetate trihydrate (3.68 g, 27.05 mmol). The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (EtOAc/Hexane,

1:8) to give crude **13** (1.5 g, 70%) as a mixture *E/Z* diastereomers. The mixture was subjected directly to the next step.

(±)-3-Amino-4-[(1′*S*,4′*R*)-4′-(tert-butyldimethylsilyloxymethyl)-4′-methyl-cyclopentanyl]-1H-pyrrole-2-carbonitrile (14). To a solution of **13** (1.05 g, 3.15 mmol) in anhydrous CH_2Cl_2 (25 mL) was added 1,8-diazabicyclo[5,4,0] undec-7-ene (DBU, 0.75 mL, 6.28 mmol) and ethyl chloroformate (0.45 mL, 4.71 mmol). The mixture was stirred at 0°C for 3 hours and reaction temperature was elevated to room temperature. To the mixture was added DBU (0.75 mL, 6.28 mmol) and stirred overnight at the same temperature. After the reaction solvent was concentrated under reduced pressure and replaced with MeOH (15 mL). To the mixture was added solid Na_2CO_3 (33 mg, 0.315 mmol) and stirred for 3 hours. The reaction mixture was extracted with CH_2Cl_2/H_2O, and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (EtOAc/Hexane, 2.5:1) to give **14** (452 mg, 43%, 3 steps); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (br s, 1H), 6.47 (s, 1H), 3.55 (s, 2H), 3.04 (m, 1H), 2.45 (m, 1H), 2.30 (m, 1H), 1.79–1.67 (m, 4H), 0.98 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); Anal. calcd. for $C_{18}H_{31}N_3OSi \cdot 1.0$MeOH): C, 62.42; H, 9.65; N, 11.49. Found: C, 62.32; H, 9.54; N, 11.40.

(±)-7-{1′*S*,4′*R*)-[4′-(tert-Butyldimethylsilyloxymethyl)-4′-methyl-cyclopentanyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl˝amine} (15). To a solution of **14** (623 mg, 1.87 mmol) in EtOH (20 mL), formamidine acetate (975 mg, 9.39 mmol) was added and the reaction mixture was refluxed for overnight. The solvent was concentrated under reduced pressure to give the residue as a solid. To the residue, co-solvent of MeOH and CH_2Cl_2 (1:10) was added until the solid residue was completely dissolved and then solvent was slowly removed under reduced pressure to give oily residue. After carefully loaded, the residue was purified by silica gel column chromatography using elution solvent system (EtOAc/Hexane, 3:1) to provide **15** (492 mg, 73%) as a white solid: mp 160–162°C; UV (MeOH) λ_{max} 275.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (s, 1H), 7.19 (s, 1H), 3.42 (dd, J = 12.9, 6.3 Hz, 2H), 3.24 (dd, J = 9.3, 5.4 Hz, 1H), 2.55–2.43 (m, 2H), 1.72 (m, 2H), 0.97 (s, 3H), 0.88 (s, 9H), 0.01 (s, 6H); Anal. Calcd. for $C_{19}H_{32}N_4OSi \cdot 0.7$MeOH: C, 61.78; H, 9.16, N, 14.63. Found: C, 61.62; H, 9.14; N, 14.56.

(±)-[(1′*S*,4′*R*)-1′-[(4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-4′-methyl-cyclopentanyl]-methanol (16). To a solution of compound **15** (234 mg, 0.65 mmol) in THF (10 mL), tetrabutylammonium fluoride (TBAF, 1.0 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, 1:5) to give compound **16** (105 mg, 66%) as a white solid: mp 176–178°C; UV (H_2O) λ_{max} 275.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.78 (s, 1H, D_2O exchangeable), 8.02 (s, 1H), 7.27 (s, 1H), 6.75 (s, 2H, D_2O exchangeable), 5.01 (t, J = 5.4 Hz, 1H,

D_2O exchangeable), 4.99 (s, 1H, D_2O exchangeable), 3.37 (dd, J = 13.2, 6.2 Hz, 2H), 2.95 (m, 1H), 2.29 (dd, J = 9.6, 5.4 Hz, 2H), 1.97 (m, 2H), 1.81 (m, 2H), 0.99 (s, 3H); Anal. Calcd. for $C_{13}H_{18}N_4O$: C, 63.39; H, 7.37; N, 22.75. Found: C, 63.47; H, 7.43; N, 22.66.

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