

EFFICIENT SYNTHESIS OF 4'-CYCLOPROPYLATED CARBOVIR ANALOGUES WITH USE OF RING-CLOSING METATHESIS FROM GLYCOLATE

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 \Box The first synthetic route of novel 4-cyclopropylated carbovir analgues is described. The construction of cyclopropylated quaternary carbon at 4-position of carbocyclic nucleosides was successfully made via sequential Johnson's orthoester rearrangement and ring-closing metathesis (RCM) starting from ethyl glycolate. Synthesized compounds **15** and **16** showed moderate antiviral activity without any cytotoxicity up to 100 μ mol.

Keywords Carbocyclic nucleoside; antiviral agents; ring-closing metathesis; Claisen rearrangement

INTRODUCTION

The finding that thymidine analogue with 4'-azido^[1] and 4'-cyano group^[2] show significant inhibitory activity against HIV proliferation has stimulated the synthesis of 4'-substituted nucleoside analogues. Recently, 4'-homologated stavudine^[3] thiostavudine^[4] analogue, especially ethenyl and ethynyl, are molecules of considerable interest. One of reasons for this prominence arises from the notable biological activities as antiviral and antitumor agents.

Carbocyclic nucleosides^[5] are a group of compounds structurally similar to natural nucleosides in which the furanose oxygen is replaced by a methylene group. Replacement of the furanose ring oxygen by carbon is of particular interest since the resulting carbocyclic nucleosides possess greater metabolic stability to the phosphorylase,^[6] which cleave the glycosidic bond

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FIGURE 1 Structure of potent carbocyclic nucleosides.

of nucleosides. The recent discovery of 2',3'-olefinic carbocyclic nucleosides, such as carbovir^[7] and abacavir,^[8] which are potent anti-HIV agents, have increased interests in the search for novel nucleosides in this class of compounds (Figure 1).

Stimulated by these interesting molecular structures and antiviral activity relationship, we have determined to synthesize novel classes of nucleoside comprising 4'-alkylated carbocyclic nucleoside with an additional cyclopropyl group which has a similar electron density as those of double or triple bond.

In this context, we describe a very convenient and general synthetic procedure for nucleosides using reiterative three step sequences ([3,3]-sigmatropic rearrangement,^[9] RCM,^[10] and Pd(0)-catalyzed allylic alkylation^[11]). As shown in Scheme 1, we envisioned that ring-closing metathesis of proper divinyls **10**, which could be readily synthesized via sequential [3,3]-sigmatropic rearrangement and carbonyl addition starting from ethyl glycolate **1**, would produce cyclopropylated cyclopentene **11** β .

Silyl protection of the alcohol of commercially available starting material 1 followed by hydrolysis gave carboxylic acid derivative 3, which was transformed to Weinreb amide 4 by the treatment of DCC and DMAP coupling reagent.^[12] Conversion of the amide **4** to cyclopropyl ketone derivative **5** turned out to be successful under the usual carbonyl addition condition (cyclopropylMgBr, THF, -78°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 Johnson's orthoester Claisen 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 CH₉=CHMgBr to yield inseparable diastereomeric mixture 10 by a non-stereoselective manner.



SCHEME 1 Synthesis route of aldehyde intermediate 9.

Without separation, divinyl **10** was subjected to standard RCM condition using second generation Grubbs catalyst [(Im)Cl₂PCy₃RuCHPh]^[14] to provide cyclopentenol **11** α and **11** β , respectively. The relative stereochemical assignments were readily made based on NMR studies. Upon the irradiation of *C*₁-H, different NOE pattern was observed at the protons of compound **11** β [*methyloxy*-H (0.1%) & *cyclopropyl*-H (0.5)], from those of compound **11** α [*methyloxy*-H (0.6%) & *cyclopropyl*-H (0.2)] (Figure 2).



FIGURE 2 NOE comparisons of compound 11α and 11β .

The allylic functionalization using palladium(0)-catalyzed reactions have been the central role in synthetic organic chemistry. We have successfully applied this methodology to the synthesis of desired nucleoside. Cyclopentenol 11β was transformed to 12 using ethyl chloroformate, which was coupled with 2-amino-6-chloropurine anions generated by NaH/DMSO with use of catalyst [tris(dibenzylidene-acetone)-dipalladium (0)-chloroform] adduct to provide nucleoside analogue 13. Based on ${}^{1}H$ NMR integration study, the product mixtures indicated no N7 isomer (less than 5%) formed in the reaction of 12. The analysis of the N7 and N9 coupling products is readily accomplished by ¹H NMR. Since the proton at the 8-position of the purine is well separated and readily distinguished in the two region-isomers. The C-8 isomers proton of the N9 isomer is typically upfield of the the N7 isomer.^[15] Removal of silyl protection group of 13 was preformed by the treatment of tetrabutylammonium fluoride (TBAF) to give nucleoside 14, which was treated with cyclopropylamine in EtOH under reflux to provide the desired 4'-cyclopropylated abacavir analogue 15. Treatment of compound 14 with 2-mercaptoethanol and sodium methoxide in methanol, followed by hydrolysis with acetic acid gave the desired acyclic nucleoside 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. As shown in Table 1, compound **15** and **16** exhibited moderate antiviral activity against HCMV in the Davis cell without any cytotoxicity up to 100 μ mol.^[16] It is believed that the arrangement between the 4'-branched carbocyclic nucleoside analogues may be conformationally similar to natural nucleosides containing ribose. Hence, the presence of cyclopropyl group at the 4'-position of nucleosides could be supposed to enhance the level of phosphorylation by kinase to produce the active monophosphate form.

In summary, an efficient synthetic method of 4'-cyclopropylated carbocyclic nucleoside from ethyl glycolate was developed. On the basis of this

	$ ext{HIV-1}\ ext{EC}_{50}\left(\mu ext{M} ight)$	HSV-1 EC ₅₀ (μ M)	HSV-2 EC ₅₀ (μ M)	$\mathrm{HCMV}\ \mathrm{EC}_{50}(\mu\mathrm{M})$	Cytotoxicity $CC_{50}(\mu M)$
15	56.2	77.3	99	12.7	99
16	44.7	99	99	20.1	99
AZT	0.008	ND	ND	ND	2.25
GCV	ND	ND	ND	0.55	>10
ACV	ND	0.3	ND	ND	>100

TABLE 1 The antiviral activity of the synthesized compounds

AZT: Azidothymidine; GCV: Ganciclovir; ACV: Acyclovir.

ND: Not Determined.

 $EC_{50}(\mu M)$: Concentration required to inhibit 50% of the virus induced cytopathicity.

 $CC_{50}(\mu M)$: Concentration required to reduce the cell viability by 50%.



SCHEME 2 Synthesis route of taregt nucleosides.

strategy, the syntheses of other nucleosides such as vinylated or acetylated carbocyclic nucleosides with different nucleobases are in progress.

EXPERIMENTAL SECTION

The melting points were determined on a Mel-temp II laboratory device and are uncorrected. The NMR spectra were recorded on a JEOL 300 Fourier transform spectrometer (JEOL, Tokyo, Japan). 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 elemental analyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. (Newark, DE, USA). Unless specified otherwise, all reactions were carried out in a N₂ atmosphere. Dry dichloromethane, benzene and pyridine were obtained by distillation from CaH₂. Dry THF was obtained by distillation from Na and benzophenone immediately before use. (tert-Butyldimethylsilyloxy)-acetic acid ethyl ester (2): To a solution of ethyl glycolate 1 (10 g, 0.096 mol) and imidazole (8.8 g, 0.144 mol) in CH₂Cl₂ (200 mL), TBDMSCl (15.97 g, 0.106 mol) was added slowly at 0°C, and stirred for 5 hours at the same temperature. The reaction solvent was evaporated under reduced pressure. The residue was extracted twice with diethyl ether and water. The combined organic layer was dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **2** (19.9 g, 95%) as a colorless oil: ¹H NMR (CDCl₃, 300 MHz) δ 4.12 (s, 2H), 4.08 (q, J = 6.9 Hz, 2H), 1.17 (t, J = 6.9 Hz, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ¹³C NMR (CDCl₃) δ 171.61.80, 60.66, 25.69, 18.35, 14.12, -5.50;

(tert-Butyldimethylsilyloxy) acetic acid (3): A solution of KOH (2.57 g, 59.53 mmol) in EtOH (20 mL) was slowly added to a solution of **2** (10 g, 45.79 mmol) in EtOH (200 mL) at 0°C. The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was dissolved in water (200 mL) and carefully neutralized with *c*-HCl solution to pH 3~4. The solution was extracted with EtOAc two times. The organic layer was washed with brine and dried over anhydrous MgSO₄, filtered and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give **3** (7.84 g, 90%) as a colorless oil: ¹H NMR (CDCl₃, 300 MHz) δ 4.12 (s, 2H), 0.82 (s, 9H), 0.01 (s, 6H); ¹³C NMR (CDCl₃) δ 171.02, 61.90, 25.55, 18.71, -5.57.

2-(tert-Butyldimethylsilyloxy)-*N***-methoxy-***N***-methylacetamide (4):** To solution of acid derivative **3** (5.0 g, 26.27 mmol) in a anhydrous CH₂Cl₂ (150 mL), *N*,*O*-dimethylhydroxylamine hydrochloride (3.06 g, 31.44 mmol), DMAP (317 mg, 2.6 mmol), DCC (6.48 g, 31.4 mmol), and triethylamine (3.18 g, 31.44 mmol) was sequentially added to reaction mixture. The solution was stirred overnight at room temperature. After addition of methanol (5 mL) and acetic acid (5 mL), the mixture was stirred for 1 hour and neutralized with saturated aqueous NaHCO₃ solution. The resulting solid was filtered off through a short pad of Celite and the filtrate was concentrated in vacuum. The resulting residue was purified by silica gel column chromatography (EtOAc/hexane, 1:1.5) to give Weinreb amide **4** (5.21g, 85%) as a colorless oil: ¹H NMR (CDCl₃, 300 MHz) δ 4.48 (s, 2H), 3.57 (s, 3H), 3.05 (s, 3H), 0.80 (s, 9H), 0.02 (s, 6H); ¹³C NMR (CDCl₃) δ 171.63, 61.00, 60.56, 52.63, 31.67, 25.54, 18.49, -5.61.

2-(tert-Butyldimethylsilyloxy)-1-cyclopropyl-ethanone (5): To a solution of Weinreb amide **4** (2.5 g, 10.71 mmol) in dry THF (60 mL) was slowly added cyclopropylmagnesium bromide (25.70 mL, 0.5 M solution in THF) at 0°C. After 4 hours, saturated NH₄Cl solution (16 mL) was added, and the reaction mixture was slowly warmed to room temperature. The mixture was extracted with EtOAc (2 × 60 mL). The combined organic layer was dried over MgSO₄, filtered, and evaporated. The residue was purified by

silica gel column chromatography (EtOAc/hexane, 1:10) to give **5** (1.65 g, 72%) as colorless oil: ¹H NMR (CDCl₃, 300 MHz) δ 4.21 (s, 2H), 2.18-2.10 (m, 1H), 1.17 (m, 2H), 0.97 (m, 2H), 0.82 (s, 9H), 0.02 (s, 6H); ¹³C NMR (CDCl₃) δ 210.41, 69.61, 25.76, 18.34, 16.11, 11.27, -5.46; Anal. Calcd. for C₁₁H₂₂O₂Si · 0.5 EtOAc: C, 60.41; H, 10.14. Found: C, 60.49; H, 10.01.

(*E*) and (*Z*)-4-(tert-Butyldimethylsilyloxy)-3-cyclopropyl-but-2-enoic acid ethyl ester (6): To a suspension of sodium hydride (0.5 g, 20.8 mmol) in distilled THF (100 mL) was added drop wise triethyl phosphonoacetate (4.66 g, 20.8 mmol) at 0°C and the mixture was stirred at room temperature for 1 hour. The ketone **5** (4.46 g, 20.8 mmol) was added to this mixture and the mixture was for 2 hours. The solution was neutralized with AcOH (5 mL) and poured into H₂O (100 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous MgSO₄, filtered and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **6** (4.73 g, 80%) as a colorless oil: ¹H NMR (CDCl₃, 300 MHz) δ 5.96 (s, 1H), 4.15 (m, 4H), 2.21 (m, 1H), 1.19-1.09 (m, 2H), 0.97 (m, 2H), 0.83 (s, 9H), 0.02.

(*E*) and (*Z*)-4-(tert-Butyldimethylsilyloxy)-3-cyclopropyl-but-2-en-1-ol (7): To a solution of **6** (5.0 g, 17.57 mmol) in CH₂Cl₂ (100 mL), DIBALH (36.9 mL, 1.0 M solution in hexane) was added slowly at -20° C, and stirred for 1 hour at the same temperature. To the mixture, methanol (35 mL) was added. The mixture was stirred at room temperature for 2 hours, 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, 1:5) to give alcohol **7** (3.87 g, 91%) as a colorless oil: ¹H NMR (CDCl₃, 300 MHz) δ 5.69 (s, 1H), 4.19 (d, J= 6.8 Hz, 2H), 4.04 (s, 2H), 2.23 (m, 1H), 1.17-1.07 (m, 2H), 0.95 (m, 2H), 0.81 (m, 9H), 0.01 (m, 6H).

(±)-3-(t-Butyldimethylsilyloxymethyl)-3-cyclopropyl-pent-4-enoic acid ethyl ester (8): A solution of allylic alcohol 7 (8.4 g, 34.66 mmol) in triethyl orthoacetate (150 mL) and 0.3 mL of propionic acid was heated at 135–140°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 (8.66 g, 80%) as a colorless oil: ¹H NMR (CDCl₃, 300 MHz) δ 5.90 (d, *J* = 10.6 Hz, 1H), 5.87 (d, *J* = 11.2 Hz, 1H), 5.03 (d, *J* = 1.2 Hz, 1H), 5.03 (d, *J* = 7.6 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.44 (d, *J* = 9.4 Hz, 1H), 3.42 (d, *J* = 9.4 Hz, 1H), 2.42 (d, *J* = 3.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.82 (s, 9H), 0.46 (m, 1H), 0.28-0.21 (m, 4H), 0.01 (s, 6H); ¹³C NMR (CDCl₃) δ 171.96, 143.18, 114.04, 69.82, 60.07, 41.30, 25.82, 18.23, 14.56, 11.26, 8.46, -5.50; Anal. Calcd. for C₁₇H₃₂O₃Si: C, 65.33; H, 10.32. Found: C, 65.42; H, 10.27.

(±)-3-(t-Butyldimethylsilyloxymethyl)-3-cyclopropyl-pent-4-enal (9): To a solution of 8 (3.0 g, 9.6 mmol) in toluene (40 mL), DIBALH (7.1 mL, 1.5 M solution in toluene) was added slowly at -78° C, and stirred for 20 minutes at the same temperature. To the mixture, methanol (10 mL) was added. The mixture was stirred at room temperature for 1 hour, 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 (1.72 g, 67%) as a colorless oil: ¹H NMR (CDCl₃, 300 MHz) δ 9.78 (s, 1H), 5.92 (dd, J = 17.7, 11.1 Hz, 1H), 5.21 (d, J = 11.1 Hz, 1H), 5.14 (d, J = 17.7 Hz, 1H), 3.50 (d, J = 9.4 Hz, 1H), 3.32 (d, J = 9.4 Hz, 1H), 2.43-2.37 (m, 2H), 0.82 (s, 9H), 0.52 (m, 1H), 0.29 (m, 4H), 0.02 (s, 6H); ¹³C NMR (CDCl₃) δ 203.11, 142.32, 112.21, 69.86, 51.32, 42.54, 25.82, 18.45, 10.98, 6.72, -5.61; Anal. Calcd. for C₁₅H₂₈O₂Si · 1.0EtOAc: C, 63.99; H, 10.17. Found: C, 64.12; H, 9.98.

(rel)-(3*R* and 3*S*,5*S*)-5-(t-Butyldimethylsilyloxymethyl)-5-cyclopropylhepta-1,6-dien-3-ol (10): To a solution of 9 (3.1 g, 11.55 mmol) in dry THF (50 mL) was slowly added vinyl magnesiumbromide (13.86 mL, 1.0 M solution in THF) at -78° C. After 3 hours, saturated NH₄Cl solution (10 mL) and water (50 mL) was sequentially added, and the reaction mixture was slowly warmed to room temperature. The mixture was extracted with EtOAc (2 × 50 mL). The combined organic layer was dried over MgSO₄, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give 10 (2.7 g, 79%) as colorless oil: ¹H NMR (CDCl₃, 300 MHz) δ 6.05-5.77 (m, 2H), 5.25-4.97 (m, 4H), 4.22 (m, 1H), 3.47 (m, 2H), 1.68-1.55 (m, 2H), 0.81 (s, 9H), 0.50 (m, 1H), 0.37-0.30 (m, 4H), 0.02 (m, 6H).

(*rel*)-(1*R*,4*S*)-4-(t-Butyldimethylsilyloxymethyl)-4-cyclopropyl-cyclopent-2-enol (11β); and (*rel*)-(1*S*,4*S*)-4-(t-Butyldimethylsilyloxymethyl)-4-cyclopropyl-cyclopent-2-enol (11α): To a solution of 10 (1.37 g, 4.62 mmol) in dry CH₂Cl₂ (10 mL) was added 2nd generation Grubbs catalyst (127 mg 0.15 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 (521 mg, 42%) and 11α (508 mg, 41%) as colorless oils, respectively. Cyclopentenol 11β: ¹H NMR (CDCl₃, 300 MHz) δ 5.86 (d, J = 5.4 Hz, 1H), 5.47 (d, J = 5.6 Hz, 1H), 4.52 (dd, J = 7.6, 1.2 Hz, 1H), 3.35 (s, 2H), 1.85 (dd, J = 14.2, 6.8 Hz, 1H), 1.68 (dd, J = 14.2, 2.4 Hz, 1H), 0.83 (s, 9H), 0.55 (m, 1H), 0.37-0.29 (m, 4H), 0.01 (s, 6H): ¹³C NMR (CDCl₃) δ 140.49, 133.98, 76.35, 68.99, 49.91, 44.78, 25.54,18.48, 12.54, 7.90, -5.57; Anal. Calcd. for C₁₈H₃₂O₄Si: C, 63.49; H, 9.47. Found: C, 63.36; H, 9.58.

Cyclopentenol 11 α : ¹H NMR (CDCl₃, 300 MHz) δ 5.78-5.69 (m, 2H), 4.80 (dd, J = 6.4, 1.2 Hz, 1H), 3.33 (s, 2H), 2.19 (dd, J = 13.6, 7.4 Hz, 1H), 1.32 (dd, J = 13.6, 4.4 Hz, 1H), 0.84 (s, 9H), 0.56 (m, 1H), 0.28-0.22 (m, 4H), 0.01 (s, 6H): 13 C NMR (CDCl₃) δ 140.95, 132.65, 76.78, 69.97, 51.21, 43.54, 25.58, 18.48, 10.58, 7.34, -5.48; Anal. Calcd. for C₁₈H₃₂O₄Si · 0.5 EtOAc: C, 65.33; H, 10.32. Found: C, 65.36; H, 10.41.

(rel)-(1R,4S)-1-Ethoxy carbonyloxy-4-(t-butyldimethylsilyloxymethyl)-4cyclopropyl-cyclopent-2-ene (12): To a solution of 11β (1.94 g, 7.21 mmol) in anhydrous pyridine (8 mL) was added ethyl chloroformate (1.38 mL, 14.43 mmol) and DMAP (85 mg, 0.7 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with saturated NaHCO₃ solution (1 mL) and concentrated in vacuum. The residue was extracted with EtOAc, dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give 11 (1.77 g, 72%) as colorless syrup: ¹H NMR $(CDCl_3, 300 \text{ MHz}) \delta 5.88 \text{ (d, } I = 5.6 \text{ Hz}, 1\text{H}), 5.72 \text{ (dd, } I = 5.6, 2.4 \text{ Hz},$ 1H), 5.52 (m, 1H), 4.17 (q, I = 7.2 Hz, 2H), 3.31 (s, 2H), 1.89 (dd, I = 14.2, 7.6 Hz, 1H), 1.69 (dd, J = 14.2, 4.0 Hz, 1H), 1.25 (t. J = 7.2 Hz, 3H), 0.82 $(s, 9H), 0.58 (m, 1H), 0.30-0.23 (m, 4H), 0.01 (s, 6H): {}^{13}C NMR (CDCl_3) \delta$ 154.89, 144.90, 127.67, 83.41, 70.11, 63.21, 51.21, 40.56, 25.71, 18.48, 14.71, 11.98, 6.45, -5.58; Anal. Calcd. for C₁₈H₃₂O₄Si: C, 63.49; H, 9.47. Found: C, 63.36; H, 9.58.

(rel)-(1'R,4'S)-9-[4-(t-Butyldimethylsilyloxymethyl)-4-cyclopropyl-cyclopent-2-en-1-yl] 2-amino-6-chloropurine (13): To a pure NaH (12 mg, 0.49 mmol) in anhydrous DMSO (3.0 mL) was added 2-amino-6-chloropurine (83 mg, 0.49 mmol). The reaction mixture was stirred for 30 minutes at 50–55°C and cooled to room temperature. Simultaneously, $P(O-i-Pr)_3$ (0.048 mL, 0.11 mmol) was added to a solution of Pd₂(dba)₃.CHCl₃ $(2.3 \text{ mg}, 1.25 \ \mu\text{mol})$ in anhydrous THF (2.0 mL), which was stirred for 30 minutes. To the nucleosidic base solution of DMSO was sequentially added catalyst solution of THF and 12 (150 mg, 0.44 mmol) dissolved in anhydrous THF (2 mL). The reaction mixture was stirred overnight at refluxing temperature and quenched with water (1 mL). The reaction solvent was removed in vacuum. The residue was purified by silica gel column chromatography (MeOH/CH₂Cl₂, 1:15) to give 13 (78 mg, 42%) as a white solid. mp 168–171°C; ¹H NMR (CDCl₃, 300 MHz) δ 7.91 (s, 1H), 6.02 (d, I = 5.4 Hz, 1H), 5.80-5.71 (m, 2H), 5.30 (br s, 2H), 3.60 (d, I = 9.4Hz, 1H), 3.49 (d, *J* = 9.4 Hz, 1H), 2.32 (dd, *J* = 14.2, 8.8 Hz, 1H), 2.00 (dd, I = 14.2, 5.6 Hz 1H, 0.84 (s, 9H), 0.58 (m, 1H), 0.31-0.22 (m, 4H), 0.02 (s, 6H); ¹³C NMR (CDCl₃) δ 159.32, 154.34, 151.79, 144.36, 140.76, 133.73, 124.32, 70.42, 60.42, 52.54, 41.87, 25.45, 18.54, 13.01, 6.98, -5.65; Anal. Calcd. for C₂₀H₃₀ClN₅OSi · 0.8MeOH: C, 56.06; H, 7.51; N, 15.71. Found: C, 55.89; H, 7.64; N, 15.79.

(*rel*)-(1'R,4'R)-9-[4-(Hydroxymethyl)-4-cyclopropyl-cyclopent-2-en-1-yl] 2 -amino-6-chloropurine (14): To a solution of 13 (88 mg, 0.21 mmol) in THF (5 mL) was TBAF (0.31 mL, 1.0 M solution in THF) at 0°C. The mixture was stirred at room temperature for 5 hours, and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH₂Cl₂, 1:5) to give 14 (46 mg, 71%) as a white solid: mp 172–174°C; ¹H NMR (DMSO- d_6 , 300 MHz) δ 7.88 (s, 1H), 5.96 (d, J = 6.2 Hz, 1H), 5.71-5.60 (m, 2H), 4.97 (t, J = 5.4 Hz, 1H), 3.54 (d, J = 9.4 Hz, 1H), 3.42 (d, J = 9.4 Hz, 1H), 2.27 (dd, J = 14.0, 8.8 Hz, 1H), 1.98 (dd, J = 14.0, 5.4 Hz 1H), 0.56 (m, 1H), 0.30 (m, 4H); ¹³C NMR (DMSO- d_6) δ 159.42, 154.55, 150.48, 143.89, 141.76, 133.56, 124.78, 68.56, 61.42, 53.76, 42.28, 12.76, 6.39; Anal. Calcd. for C₁₄H₁₆ClN₅O \cdot 0.5MeOH: C, 54.12; H, 5.64; N, 21.76. Found: C, 53.98; H, 5.52; N, 21.82.

(*rel*)-(1′*R*,4′*R*)-9-[4-(Hydroxymethyl)-4-cyclopropyl-cyclopent-2-en-1-yl] 2 -amino-6-cyclopropylpurine (15): Cyclopropyl amine (0.173 mL, 1.98 mmol) was added to a solution of compound 14 (121 mg, 0.396 mmol) in EtOH (15 mL) and refluxed for 6 hours. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH₂Cl₂, 1:5) to give compound 15 (76 mg, 59%) as a solid: mp 186–188; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 7.90 (s, 1H), 5.87 (d, *J* = 6.2 Hz, 1H), 5.68 (d, *J* = 6.2 Hz, 1H), 5.30 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.99 (t, *J* = 5.4 Hz, 1H), 3.32 (d, *J* = 9.0 Hz, 1H), 3.21 (d, *J* = 9.2 Hz, 1H), 2.31 (dd, *J* = 14.2, 8.6 Hz, 1H), 2.04 (dd, *J* = 14.2, 5.2 Hz 1H), 0.71–0.59 (m, 2H), 0.32-0.17 (m, 8H); ¹³C NMR (DMSO-*d*₆) δ 159.21, 154.11, 150.40, 144.10, 141.45, 132.54, 125.02, 67.32, 62.54, 52.21, 42.22, 13.21, 12.79, 7.02, 6.32; Anal. Calcd. for C₁₇H₂₂N₆O · 1.0H₂O: C, 59.28; H, 7.02; N, 24.40. Found: C, 59.40; H, 6.90; N, 24.38.

(*rel*)-(1′*R*,4′*R*)-9-[4-(Hydroxymethyl)-4-cyclopropyl-cyclopent-2-en-1-yl]2amino-6-hydroxypurine (16): 2-Mercaptoethanol (0.135 mL, 1.935 mmol) and NaOMe (1.755 mL, 1.755 mmol, 1.0 M solution in MeOH) was added to a solution of compound 14 (101 mg, 0.33 mmol) in MeOH (13 mL), and heated overnight under reflux. After cooling, the reaction mixture was neutralized with a few drops of glacial AcOH and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH₂Cl₂, 1:6) to give compound 16 (65 mg, 69%) as a solid: mp 178–180; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 7.96 (s, 1H), 5.80 (d, *J* = 6.2 Hz, 1H), 5.39 (m, 2H), 4.94 (t, *J* = 5.4 Hz, 1H), 3.56 (d, *J* = 9.2 Hz, 1H), 3.45 (d, *J* = 9.2 Hz, 1H), 2.35 (dd, *J* = 14.0, 8.6 Hz, 1H), 1.96 (dd, *J* = 14.0, 5.6 Hz 1H), 0.53-0.57 (m, 1H), 0.29-0.33 (m, 4H); ¹³C NMR (DMSO-*d*₆) δ 160.19, 155.87, 150.91, 144.42, 142.28, 134.56, 125.11, 68.79, 62.08, 52.88, 44.00, 13.14, 6.97; Anal calc for C₁₄H₁₇N₅O₂ · 1.0MeOH: C, 56.41; H, 6.62; N, 21.93. Found: C, 56.32; H, 6.72; N, 22.07.

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