Efficient Construction of Quaternary Carbon: Stereocontrolled Synthesis of Novel Abacavir Analogue

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This paper discusses the racemic and stereoselective synthetic route for novel 4'α-methyl and 6'α-methyl analogues of abacavir. The quaternary carbon at the 4'-position of carbocyclic nucleoside was installed successfully *via* a Claisen rearrangement. The stereocontrolled construction of a methyl group in the 6'α-position was directed through the Felkin-Anh rule. A Bis-vinyl compound **9** was cyclized successfully using Grubbs' catalyst II to provide a carbocycle nucleus for the target compound. The synthesized compound **15** showed moderate anti-HIV activity (EC_{50} = 10.67 μM, MT-4 cell lines).

Key Words : Quaternary carbon, Abacavir, Claisen rearrangement, Ring-closing metathesis

Introduction

Emerging drug-resistant virus strains and toxicity are major problems in antiviral chemotherapy, and a number of structurally modified nucleosides have been synthesized to overcome these drawbacks. More fundamental modifications to the pentofuranose moiety, such as carbocyclic nucleosides, have been reported to be compatible with their antiviral activity. Carbocyclic nucleosides[1] are a group of compounds that are structurally similar to the natural nucleosides where the furanose oxygen is replaced by a methylene group. The replacement of the oxygen on the furanose ring by carbon is of particular interest because the resulting carbocyclic nucleosides have a greater metabolic stability to phosphorylase,[2] which cleaves the glycosidic bond of nucleosides. Since the cyclopentane ring of the carbocyclic nucleosides can emulate the furanose moiety, a number of these compounds exhibit interesting biological activities, particularly in the areas of antiviral and anticancer chemotherapy. The recent discovery of olefinic carbocyclic nucleosides, such as abacavir **1**[3] and entecavir,[4] as potential antiviral agents has attracted considerable research attention in the search for novel nucleosides in this class of compound. Recently, several branched nucleosides were synthesized and evaluated as potent antitumor or antiviral agents. Among them, the 4'α-ethenyl compound[5] and 4'α-ethynyl compound[6] were shown potent antiviral and antitumor activity. Furthermore, 6'α-hydroxymethyl carbovir **2**[7] and 6'α-methyl-carbothymidine **3**[8] also showed significant antiviral and antitumor activity (Figure 1). Based on these interesting findings of branched nucleosides, a novel class of nucleosides comprising 4'α-quaternary carbocyclic nucleosides with an additional methyl group at the 6'-position was synthesized.

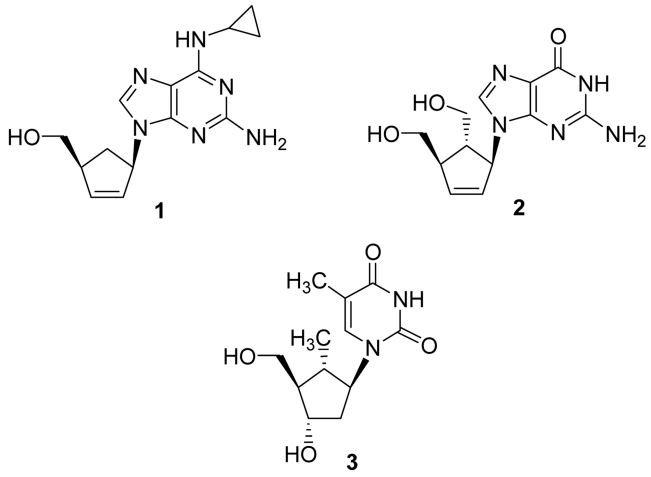


Figure 1. Antiviral carbonucleosides.

Results and Discussion

The quaternary carbon of γ,δ-unsaturated ester **5** was constructed successfully using a previously reported procedure.[9] The stereocontrolled introduction of a methyl group in **5** using an ester enolate alkylation (LiHMDS/CH3I) provided compounds **6a** (57%) and **6b** (21%) as diastereomeric mixtures, respectively. Each diastereomer was separated by column chromatography and assigned its stereochemistry by various NMR technique. The relative stereochemical determinations for these compounds would be discussed in the cyclopentenols (**10** and **11**), which was readily be assigned through the NOE comparison between the proximal protons in the cyclopentenol structures. First, the direct reduction of the ester in toluene solvent at –78 °C gave aldehyde **8** in low yield (36%). On the other hand, the addition of DIBALH to a solution of the ester **5** in CH_2Cl_2 at 0 °C gave the alcohol derivative **6**, which was subjected to oxidation conditions using PCC to give the aldehyde **8** in a 76% two step yields.

The addition of vinylmagnesium bromide to the resulting carbonyl compound **8** yielded a bisolefin **9** as a diastereomeric mixture, which was not readily separable by conventional column chromatography. The diastereomeric mixture of **9** was not separated but instead subjected to standard ring-closing metathesis conditions using a second-generation Grubbs' catalyst [(Im)Cl_2PCy_3RuCHPh][10] to predominantly

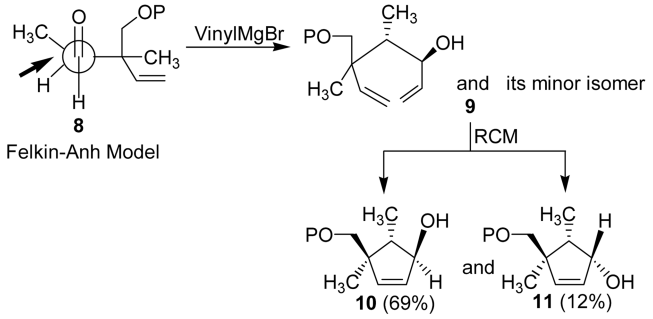
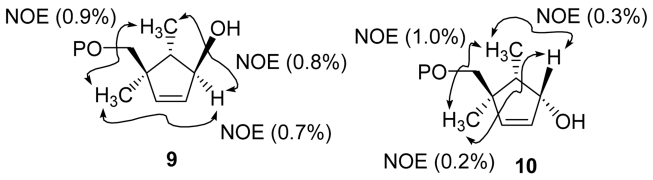


Figure 2. Stereocontrolled addition of nucleophile to aldehyde **8**.



Figur 3. Relative stereochemistry determination based on NOE comparisons of compound **9** and **10**.

provide the required cyclopentenol **10** (76%) along with compound **11** (11%) as a minor isomer. The stereochemistry of the cyclized products (**10** and **11**) was determined by employing the NOE experiment between the corresponding hydrogen atoms. Upon the irradiation of C_1-H, a relatively strong NOE was observed at the methyl protons of compound **9** [C_4-H (0.7%) & C_6-H (0.8)], but not at the methyl protons of compound **10** [C_4-H (0.2%) & C_6-H (0.3)] (Figure 3). The major stereochemical outcome of compounds **9** and **10** was reasonably explained by a mechanistic rational of the favored π-facial selection based on the Felkin-Anh rule[11] depicted in Figure 2, which shows that the stereochemical assignment of the cyclopentenols **10** and **11** was correct. This rule states that the bulkiest of the α ligand (L) is placed in a perpendicular relationship to the plane of the carbonyl group anti to the incoming nucleophile, and the sterically next most bulky α substituent (M) is placed gauche to the carbonyl function. The correct configuration of compound **8** could be assigned based on spectroscopic comparisons observed in compounds **10** and **11**.

The abacavir analogue was synthesized by activating the cyclopentenol **10** to the ethoxycarbonyl derivative **12** using ethyl chloroformate. Compound **12** was coupled with the 2-amino-6-chloropurine anions generated by NaH/DMSO with the [tris(dibenzylodene-acetone)-dipalladium(0)-chloroform][12] adduct to give the compound **13** (Scheme 2). The required β-stereochemistry of the nucleosides **13** was controlled successfully from the β-configuration of compound **10** *via* a Pd(0) catalyzed π-allyl complex mechanism. Compound **13** were desilylated by treating them with tetrabutylammonium fluoride (TBAF) to give the nucleoside **14**. Therefore, the exposure of compound **14** to cyclopropylamine in EtOH under reflux provided the desired nucleoside **15**.

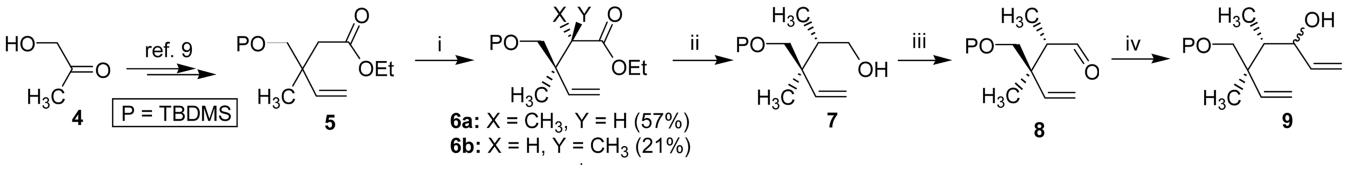
Based on an extensive literature search, compound **15** appears to be a novel nucleoside. The antiviral evaluations against various viruses such as HIV-1, HSV-1, HSV-2 and HCMV were performed. The synthesized compound **15** showed moderate anti-HIV activity (EC_{50} = 10.67 μM, MT-4 cell lines)[13] without any cytotoxicity up to 100 μM.

In summary, an efficient synthetic method was developed for the synthesis of 4' and 6'-dimethylated carbocyclic nucleosides from a simple acetol. This procedure focuses on the simplicity of installing a quaternary carbon and the stereoselectivity in the methylation at cyclopentene ring systems.

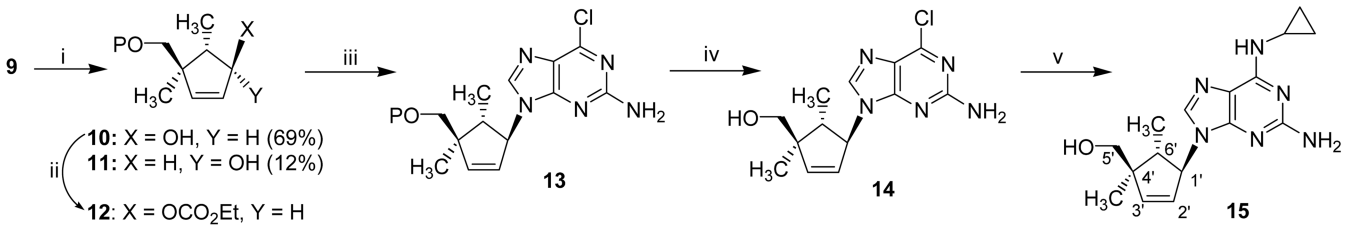
Experimental Section

All chemicals were reagent grade and were used as purchased. All the moisture-sensitive reactions were performed in either a N_2 or Ar atmosphere using distilled dry solvents. Elemental analysis was performed using an Elemental Analyzer System (EA1112). The NMR spectra were recorded on a JEOL JNM-LA 300 spectrometer.

(*rel*)-(2*S*,3*S*)-3-(*t*-Butyldimethylsilyloxymethyl)-3-meth-



Scheme 1. Synthesis of divinyl intermediate **9**. Reaents: i) LiHMDS, CH_3I, THF, −78 °C; ii) DIBALH, CH_2Cl_2, 0 °C; iv) PCC, 4A MS, CH_2Cl_2, 4 h, rt; iv) CH_2=CHMgBr, THF.



Scheme 2. Synthesis of abacavir analogue. Reagents: i) 2nd-Generation Grubbs' catalyst, CH_2Cl_2, reflux, overnight; ii) $ClCO_2Et$, DMAP, pyridine, rt, overnight; iii) 2-amino-6-chloropurine, $Pd_2(dba)_3{\cdot}CHCl_3$, P(O-*i*-Pr)$_3$, NaH, THF/DMSO, reflux, overnight; iv) TBAF, THF, rt; v) cyclopropylamine, EtOH, Reflux.

yl-2-methyl-pent-4-enoic acid ethyl ester (6a) and (6b): A solution of compound **5** (1.23 g, 4.3 mmol) in tetrahydrofuran (7 mL) was added to a stirred solution of LiHMDS (8.6 mL, 1.0 M solution in THF) in tetrahydrofuran (25 mL) using a syringe at –78 °C. After stirring for 2 hr at the same temperature, the reaction mixture was warmed to –20 °C and stirred for an additional 1 hr at the same temperature. Methyl iodide (0.91 g, 6.45 mmol) was then added to this mixture at –78 °C and stirred for 3 h. The mixture was warmed to –25 °C and stirred for an additional 2 h. The reaction was quenched by adding a saturated ammonium chloride solution (7 mL). The resulting mixture was warmed to room temperature and partitioned between water (200 mL) and ethyl acetate (200 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (EtOAc/hexane, 1:35) to give compounds **6a** (735 mg, 57%) and **6b** (271 mg, 21%); compound for **6a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.02 (dd, *J* = 18.6, 10.8 Hz, 1H), 5.08 (dd, *J* = 10.8, 1.0 Hz, 1H), 5.00 (d, *J* = 18.6 Hz, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.39 (dd, *J* = 8.7, 5.1 Hz, 2H), 2.71 (q, *J* = 7.4 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H), 0.99 (s, 3H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.57, 142.28, 113.51, 68.99, 59.86, 43.74, 25.85, 18.26, 14.30, 12.62, –5.56; Anal calc for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73; Found: C, 64.16; H, 10.60; compound for **6b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.82 (dd, *J* = 18.4, 10.2 Hz, 1H), 5.09 (dd, *J* = 10.2, 0.9 Hz, 1H), 5.98 (d, *J* = 18.4 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.37 (d, *J* = 8.4 Hz, 2H), 2.68 (q, *J* = 7.5 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.97 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.54, 142.10, 113.74, 68.84, 59.78, 43.64, 25.81, 18.27, 14.27, 12.34, –5.60; Anal calc for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 63.84; H, 10.80.

(*rel*)-(2*S*,3*S*)-3-(*t*-Butyldimethylsilyloxymethyl)-3-methyl-2-methyl-pent-4-enol (7): DIBALH (28.35 mL, 1.0 M solution in hexane) was added slowly to a solution of compound **6a** (4.06 g, 13.5 mmol) in CH_2Cl_2 (200 mL) at 0 °C and stirred for 3 h at the same temperature. Methanol (28 mL) was then added to the mixture. The resulting mixture was stirred at room temperature for 3 h, and the 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, 1:24) to give compound **7** (3.21 g, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81 (dd, *J* = 18.8, 10.4 Hz, 1H), 5.01 (d, *J* = 18.8 Hz, 1H), 4.89 (d, *J* = 18.2 Hz, 1H), 3.42 (dd, *J* = 13.5, 2.4 Hz, 1H), 3.32 (dd, *J* = 9.9, 5.4 Hz, 1H), 1.72 (q, *J* = 6.8 Hz, 1H), 0.90 (s, 3H), 0.88 (d, *J* = 3.3 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.61, 113.00, 68.86, 64.72, 43.46, 41.14, 25.64, 18.20, 17.18, 12.29, –5.62; Anal calc for $C_{14}H_{30}O_2Si$: C, 65.06; H, 11.70. Found: C, 64.89; H, 11.58.

(*rel*)-(2*S*,3*S*)-3-(*t*-Butyldimethylsilyloxymethyl)-3-methyl-2-methyl-pent-4-enal (8): 4 Å molecular sieves (11.0 g) and PCC (9.0 g, 42 mmol) were added slowly to a solution of compound **7** (3.77 g, 14.58 mmol) in CH_2Cl_2 (110 mL), at 0 °C, and stirred overnight at room temperature. Excess diethyl ether (400 mL) was then added. The mixture was stirred vigorously for 4 h at the same temperature, and the resulting solid was filtered through a short silica gel column. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **8** (3.21 g, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.72 (s, 1H), 5.95 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.13 (d, *J* = 11.2 Hz, 1H), 5.08 (d, *J* = 17.7 Hz, 1H), 3.48 (dd, *J* = 9.9, 4.8 Hz, 2H), 2.48 (q, *J* = 6.8 Hz, 1H), 1.00 (d, *J* = 7.5 Hz, 3H), 0.98 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.04, 141.85, 114.25, 68.58, 50.75, 44.18, 25.77, 18.49, 18.20, 8.59, –5.68.

(*rel*)-(3*R* and 3*S*,4*S*,5*S*)-5-(*t*-Butyldimethylsilyloxymethyl)-5-methyl-4-methyl-hepta-1,6-dien-3-ol (9): Vinyl magnesium bromide (16.9 mL, 1.0 M solution in THF) was added slowly to a solution of compound **8** (3.62 g, 14.13 mmol) in dry THF (150 mL) at –78 °C. After 2 h, a saturated NH_4Cl solution (14 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, 1:25) to give the divinyl **9** (3.42 g, 85%) as a diastereomeric mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92 (dd, *J* = 18.1, 10.8 Hz, 1H), 5.75-5.69 (m, 1H), 5.04-4.83 (m, 2H), 3.59-3.27 (m, 3H), 1.54 (m, 1H), 1.02 (s, 3H), 0.91 (s, 3H), 0.82-0.79 (m, 12H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.82, 143.94, 141.32, 141.18, 113.53, 112.44, 71.31, 70.80, 67.84, 67.28, 45.84, 45.11, 44.12, 21.33, 20.64, 18.34, 7.13, –5.61; Anal calc for $C_{16}H_{32}O_2Si$: C, 67.54; H, 11.34. Found: C, 67.42; H, 11.25.

(*rel*)-(1*R*,4*S*,6*S*)-4-(*t*-Butyldimethylsilyloxymethyl)-4-methyl-5-methyl-cyclopent-2-enol (10) and (*rel*)-(1*S*,4*S*,6*S*)-4-(t-Butyldimethylsilyloxymethyl)-4-methyl-5-methyl-cyclopent-2-enol (11): A 2nd generation Grubbs' catalyst (80 mg, 0.11 mmol) was added to a solution of compound **11** (3.3 g, 11.68 mmol) in dry CH_2Cl_2 (40 mL). The reaction mixture was refluxed overnight, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give the compounds **10** (2.1 g, 69%) and **11** (359 mg, 12%) as colorless oils: compound **10**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.82 (d, *J* = 5.8 Hz, 1H), 5.56 (d, *J* = 5.9 Hz, 1H), 4.49 (d, *J* = 6.5 Hz, 1H), 3.48 (d, *J* = 9.9 Hz, 1H), 3.28 (d, *J* = 9.9 Hz, 1H), 1.57 (q, *J* = 7.5 Hz, 1H), 1.14 (d, *J* = 7.2 Hz, 3H), 0.98 (s, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.84, 134.18, 84.10, 67.05, 53.46, 51.56, 25.95, 22.72, 18.11, 10.63, –5.57; Anal calc for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.47; H, 10.83; compound **11**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.80 (d, *J* = 6.0 Hz, 1H), 5.59 (d, *J* = 6.0 Hz, 1H), 4.50 (d, *J* = 6.6 Hz, 1H), 3.45 (d, *J* = 9.8 Hz, 1H), 3.26 (d, *J* = 9.8 Hz, 1H), 1.55 (q, *J* = 7.4 Hz, 1H), 1.16 (d, *J* = 7.3 Hz, 3H), 0.97 (s, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.12, 134.32, 83.98, 66.94, 53.32, 51.12, 25.62, 22.67, 18.49, 10.28, –5.53; Anal calc for $C_{14}H_{28}O_2Si$: C, 65.57; H,

11.00. Found: C, 65.68; H, 11.17.

(*rel*)-(1*R*,4*S*,6*S*)-1-Ethoxycarbonyloxy-4-(*t*-butyldimethylsilyloxymethyl)-4-methyl-5-methyl-cyclopent-2-ene (12): Ethyl chloroformate (1.44 mL, 10.1 mmol) and DMAP (100 mg, 0.72 mmol) were added to a solution of compound **10** (2.4 g, 9.36 mmol) in anhydrous pyridine (30 mL). The reaction mixture was stirred overnight at room temperature. The reaction was quenched using a saturated $NaHCO_3$ solution (2.5 mL) and concentrated under reduced pressure. The residue was extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give compound **12** (2.43 g, 79%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ5.83 (dd, J = 5.4, 1.4 Hz, 1H), 5.72 (dd, J = 5.4, 1.8 Hz, 1H), 5.21 (dt, J = 6.6, 1.5 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.37 (s, 2H), 2.06 (quint, J = 7.5 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 7.2 Hz, 3H), 0.90 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ155.30, 143.39, 127.96, 89.87, 89.46, 70.44, 63.76, 51.28, 43.88, 25.86, 18.15, 14.26, 13.01, 10.76, −5.54; Anal calc for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found: C, 62.05; H, 9.95.

(*rel*)-(1'*R*,4'*S*,6'*S*)-9-[4-(*t*-Butyldimethylsilyloxymethyl)-4-methyl-6-methyl-cyclopent-2-en-1-yl] 2-amino-6-chloropurine (13): 2-Amino-6-chloropurine (383 mg, 2.26 mmol) was added to pure NaH (57.6 mg, 2.4 mmol) in anhydrous DMSO (9.0 mL). The reaction mixture was stirred for 40 min at 50-60 °C and then cooled to room temperature. For the preparation of the catalytic solution, P(O-*i*-Pr)$_3$ (10.08 mL, 2.26 mmol) was added to a solution of $Pd_2(dba)_3$·$CHCl_3$ (53.12 mg, 28.8 mmol) in anhydrous THF (15.0 mL), which was then stirred for 40 min. A catalyst solution of THF and formate starting material **12** (657 mg, 2.0 mmol) dissolved in anhydrous THF (15 mL) was then added slowly to the reaction mixture. The reaction mixture was stirred overnight under reflux and then quenched with water (7 mL). The reaction solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:10) to give compound **13** (261 mg, 32%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ7.95 (s, 1H), 5.82 (dd, J = 5.8, 1.8 Hz, 1H), 5.69 (dd, J = 6.0, 1.8 Hz, 1H), 5.39 (dd, J = 11.4, 2.0 Hz, 1H), 3.38 (dd, J = 9.9, 2.1 Hz, 2H), 2.29 (quint, J = 7.8 Hz, 1H), 1.01 (d, J = 7.6 Hz, 3H), 0.90 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ159.20, 154.27, 151.21, 143.11, 140.54, 134.67, 125.31, 68.81, 65.79, 52.91, 47.31, 25.71, 21.57, 18.22, 12.23, 10.93, −5.57; Anal calc for $C_{19}H_{30}ClN_5OSi$: C, 55.93; H, 7.41; N, 17.16. Found: C, 56.13; H, 7.55; N, 17.01.

(*rel*)-(1'*R*,4'*S*,6'*S*)-9-[4-(Hydroxymethyl)-4-methyl-6-methyl-cyclopent-2-en-1-yl] 2-amino-6-chloropurine (14): TBAF (0.57 mL, 1.0 M solution in THF) at 0 °C was added to a solution of compound **13** (111.6 mg, 0.38 mmol) in THF (10 mL). 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 **14** (79.25 mg, 71%) as a white solid: mp 178-180 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ7.95 (s, 1H), 5.81 (dd, J = 5.4, 2.1 Hz, 1H), 5.57 (dd, J = 6.0, 1.5 Hz, 1H), 5.07 (dt, J = 8.4, 1.8 Hz, 1H), 4.87 (t, J = 5.4 Hz, 1H), 3.29 (d, J = 10.5 Hz, 1H), 3.12 (d, J = 10.5 Hz, 1H), 1.98 (quint, J = 8.1 Hz, 1H), 0.98 (d, J = 7.2 Hz, 3H), 0.89 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 159.76, 154.81, 150.99, 142.84, 140.85, 135.01, 125.67.65, 65.42, 51.53, 40.33, 17.52, 12.47; Anal calc for $C_{13}H_{16}ClN_5O$: C, 53.15; H, 5.49; N, 23.84. Found: C, 53.27; H, 5.55; N, 23.73.

(*rel*)-(1'*R*,4'*S*,6'*S*)-9-[4-(Hydroxymethyl)-4-methyl-6-methyl-cyclopent-2-en-1-yl] 2-amino-6-cyclopropylpurine (15): Cyclopropyl amine (0.114 mL, 1.65 mmol) was added to a solution of compound **14** (96.9 mg, 0.33 mmol) in EtOH (12 mL) and refluxed for 5 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:5) to give compound **15** (62 mg, 68%) as a solid: mp 181-183; ^{1}H NMR (DMSO-d_6, 300 MHz) δ7.97 (s, 1H), 5.80 (dd, J = 5.6, 2.0 Hz, 1H), 5.65 (dd, J = 6.2, 2.0 Hz, 1H), 5.24 (dt, J = 8.2, 1.8 Hz, 1H), 4.89 (t, J = 5.2 Hz, 1H), 3.02 (m, 1H), 2.37 (d, J = 10.2 Hz, 1H), 2.29 (d, J = 10.5 Hz, 1H), 2.04 (quint, J = 8.0 Hz, 1H), 0.99 (d, J = 7.6 Hz, 3H), 0.92 (s, 3H), 0.57-0.71 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 158.98, 153.79, 150.21, 142.23, 141.47, 134.87, 125.14, 67.66, 64.18, 50.39, 41.32, 23.79, 16.99, 12.71, 6.43; Anal calc for $C_{16}H_{22}N_6O$: C, 61.13; H, 7.05; N, 26.73. Found: C, 60.90; H, 6.92; N, 26.68; MS (EI) m/z 315 $(M+1)^+$.

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