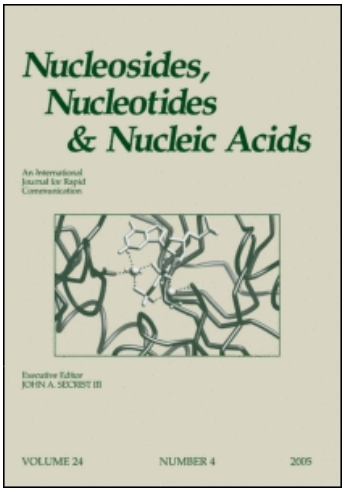

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Synthesis and anti-HIV Study of Novel Acyclic Guanine Derivatives

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SYNTHESIS AND ANTI-HIV STUDY OF NOVEL ACYCLIC GUANINE DERIVATIVES

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□ *This paper reports a new method for synthesizing an acyclic version of 6′-methylene and 6′(α)-methylated carbovir analogues. The introduction of a methylene group to the requisite 6′-position was carried out employing a Mannich type reaction using Eshenmoser's salt (methylene-N,N-dimethylammonium iodide). Carbonyl enolate alkylation (LiHMDS, CH_3I) was used to introduce a methyl group to the 6′(α)-position. The guanine analogues were successfully synthesized from the bromide compound **8** and **14** via a S_N2 type reaction and deprotection. When the synthesized compounds **11** and **17** were tested against HIV-1, they showed toxicity that was not related to any anti-HIV activity.*

Keywords Carbovir; alkylation; Eschenmoser salt; acyclic nucleoside

INTRODUCTION

Emerging drug-resistant virus strains and toxicity are major problems with antiviral chemotherapy. A number of structurally modified nucleosides have been synthesized in an attempt to overcome these drawbacks. Fundamental modifications of the classical pentofuranose moiety, such as carbocyclic nucleosides[1–3] have been designed and synthesized, and shown to have excellent antiviral or antitumor activity. Among the synthesized carbocyclic nucleosides tested, abacavir (**1**)[4] was found to be active against HIV-1 without any apparent cytotoxicity. Furthermore, carbocyclic nucleosides with exocyclic methylene in place of a furanose oxygen were synthesized and evaluated for their antiviral activity. Of these derivatives, the guanine derivative entecavir (**2**)[5] was found to be quite active against HBV, and was 100 times more potent than the clinically available drug, lamivudine[6] (Figure 1). In general, carbocyclic nucleosides are more

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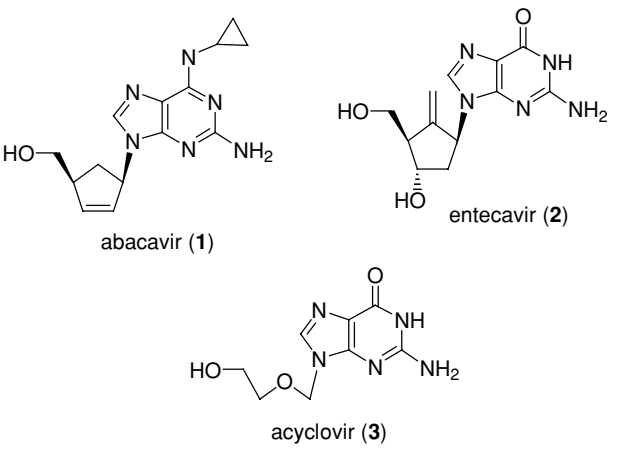


FIGURE 1 Rational design of target guanine nucleoside.

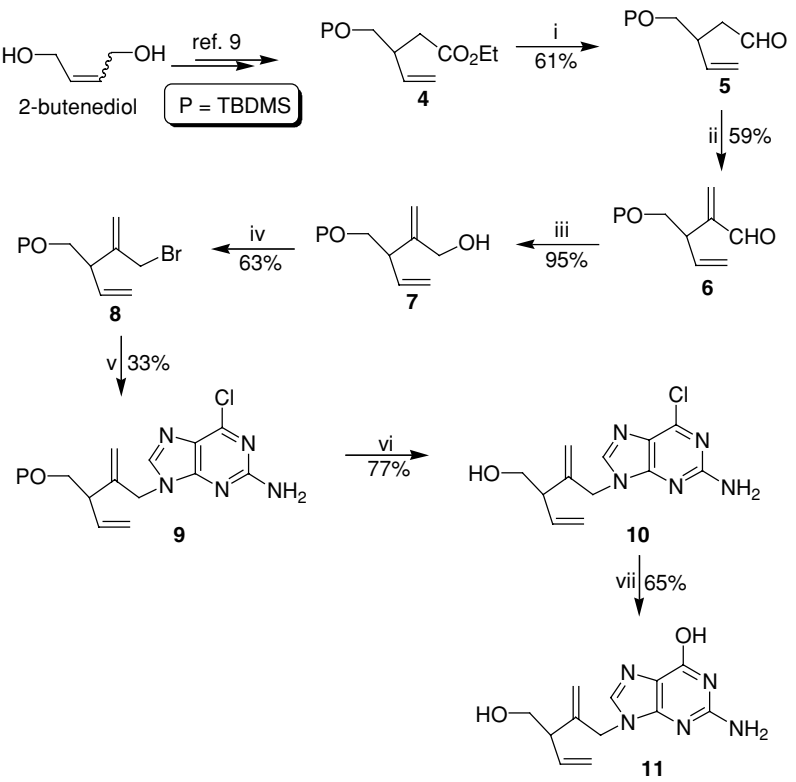
resistant to enzymatic hydrolysis and degradation than classical furanose nucleosides, and this property has potential in the search for new therapeutic agents.[7]

Once the significance of the early reports of the selective anti-herpetic activity of acyclovir (**3**)[8] became known, a worldwide effort was triggered to synthesize analogues of acyclic nucleosides. Although modifications to the heterocyclic moiety have been attempted, the guanine analogues have proven to be the most interesting from a biological point of view.

Therefore, the aim of this study was to synthesize hybrid guanine analogues that contain both a potent acyclic nucleoside moiety and the aforementioned olefinic carbocyclic nucleoside. Such hybridization was performed to obtain synergistic chemotherapeutic activity with higher selectivity and less toxicity.

RESULT AND DISCUSSION

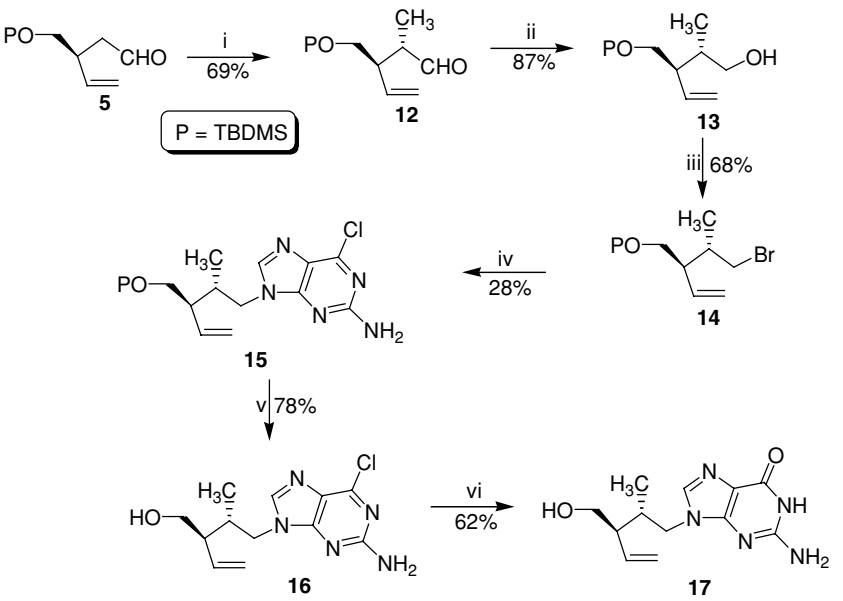
As shown in Scheme 1, the γ,δ-unsaturated ester **4** was readily synthesized from the commercially available 2-butene-1,4-diol using the reported procedure.[9] The addition of one equivalent of DIBALH to a solution of the ester **4** in anhydrous toluene at $-78^{\circ}C$ gave the reduced aldehyde derivative **5**. The treatment of carbonyl **5** with the Eschenmoser salt (methylene-*N*,*N*-dimethylammonium iodide)[10,11] gave α-methylenated aldehyde derivative **6**, which was subjected to the Luche reduction procedure ($NaBH_4/CeCl_3{\cdot}7H_2O$)[12,13] using sodium borohydride in the presence of cerium chloride to provide the allylic alcohol **7**. The conversion of the allylic alcohol **7** to the bromide derivative **8** was accomplished by the sequential addition of NBS to a solution of the alcohol and triphenylphosphine in CH_2Cl_2 in a high yield. The exo-methylene acyclic guanine



SCHEME 1 Synthesis of acyclic entecavir analogue **11**. Reagents: i) DIBAL, toluene, −78 °C; ii) methylene-*N*,*N*-dimethylammonium iodide, Et_3N, CH_2Cl_2, rt; iii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH; iv) NBS, PPh_3, CH_2Cl_2; v) 2-amino-6-chloropurine, NaH, DMF; vi) TBAF, THF; vii) (a) 2-mercaptoethanol, NaOMe, MeOH; (b) CH_3COOH.

derivative was synthesized by coupling the bromide **8** with the sodium salt of 2-amino-6-chloropurine, which was prepared by adding sodium hydride to 2-amino-6-chloropurine in DMF.[14] The silicon protection group of compound **9** was removed by a treatment with TBAF to produce compound **10**. Treatment of compound **10** with 2-mercaptoethanol and sodium methoxide in methanol, followed by hydrolysis with acetic acid gave the desired acyclic nucleoside **11** (Scheme 1).

The methylated acyclic guanine derivative **18** was synthesized using a similar reaction procedure described for synthesizing the exo-methylene guanine nucleoside **11**. First, an attempt was made to methylate the carbonyl derivative **5** using the well-known alkylation procedure (LiHMDS/CH_3I), which was previously developed in our laboratory obtaining **12**.[9] The carbonyl functional group of compound **12** was reduced using the Luche procedure to give the alcohol **13**. Compound **13** was subjected to similar reaction conditions as described above for compound **11** (bromination, purine base condensation, and deprotection) to provide the target nucleoside **17** (Scheme 2).



SCHEME 2 Synthesis of acyclic abacavir analogue **17**. Reagents: i) LiHMDS, CH_3I, THF, −78 °C; ii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH; iii) NBS, PPh_3, CH_2Cl_2; iv) 2-amino-6-chloropurine, NaH, DMF; v) TBAF, THF; vi) (a) 2-mecaptoethanol, NaOMe, MeOH, (b) CH_3COOH.

ANTI-HIV ACTIVITY STUDIES

The anti-HIV activity of the guanine analogues was evaluated in the human T-lymphoid cell lines MT-4. As shown in Table 1, compounds **11** and **17** exhibited potent anti-HIV-1 activities, but these inhibitory effects were associated with their nonspecific cytotoxicity to MT-4 cells.

In view of the outstanding cytotoxic effects of compounds **11** and **17** to the MT-4 cell line, the cytotoxic effects of both compounds were further examined in cancer cell lines. Therefore, based on the cytotoxicity of compounds **11** and **17** (50 μg/mL), their cytotoxic potential was evaluated in cultured human cells (as shown in Table 2). After treating Col2 (human

TABLE 1 The anti-HIV activity of the synthesized compounds

Compound	EC_{50} (μg/mL)[a]	CC_{50} (μg/mL)[b]
11	3.57	<3.57
17	5.02	<5.02
AZT	0.004	110

[a]Concentration required to inhibit HIV-1 induced cytopathic effect by 50% in MT-4 cells.

[b]Concentration required to reduce the viability of MT-4 cells by 50%.

TABLE 2 The cytotoxicity of compounds **11** and **17** in cultured human cancer cells

Compounds	Col2[a]	A549[b]
11	51.6[c]	56.1[c]
17	68.8[c]	56.3[c]

[a]Human colon carcinoma cells.
[b]Human lung carcinoma cells.
[c]% Survival compared with the control cultures at the test concentration of 50 μg/mL.

colon cancer) or A 549 (human lung cancer) cells with compound **11**, the relative cell viability of was decreased to 51.6% and 56.1% compared with the untreated cells, respectively. However, compound **17** showed different cytotoxicity patterns; 68.8% in colon cancer cells, and 56.3% survival compared to the control in lung cancer cells.

In summary, this study developed a novel method for synthesizing acyclic guanine analogues from simple 2,4-dihydroxy-2-butene. When the synthesized compounds were tested against HIV-1, they showed toxicity that was not related to any anti-HIV activity. Although no good anti-HIV agents were identified in this study, the finding of some anticancer activity in this series means that these compounds and their derivatives have potential as new anti-cancer agents.

EXPERIMENTS

All the chemicals were of reagent grade and were used as purchased. All the moisture-sensitive reactions were performed in an inert atmosphere of either N_2 or Ar using distilled dry solvents. The melting points were determined using a Mel-temp II laboratory device and were uncorrected. The NMR spectra were recorded on a JEOL JNM-LA 300 MHz-NMR spectrometer (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 UV spectra were obtained using a Beckman DU-7 spectrophotometer (South Pasadena, CA, USA). The elemental analyses were performed using an Elemental Analyzer System (Leco-932, Leco Corp., St. Joseph, MN, USA). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. The dry THF was obtained by distillation from Na and benzophenone when the solution turned purple.

(±)-3-(tert-Butyldimethylsilanyloxymethyl)-pent-4-enal(5): DIBALH (4.4 mL, 1.0 M solution in toluene) was added slowly to a solution of compound **4** (1.1 g, 4.04 mmol) in anhydrous toluene (10 mL) at –78°C, and stirred for 20 minutes. Methanol (5 mL) was then added. The temperature of the resulting mixture was slowly elevated to room temperature and stirred

for 3 hours, and the precipitated solid was filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/n-hexane, 1:35) to give compound **5** (563 mg, 61%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.59 (s, 1H), 5.65-5.57 (m, 1H), 5.06-5.01 (m, 2H), 3.68-3.51 (m, 2H), 2.60 (m, 1H), 2.42 (dd, J = 13.8, 5.6 Hz, 1H), 2.19 (dd, J = 13.8, 8.6 Hz, 1H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 203.96, 134.87, 116.43, 63.51, 46.67, 37.40, 25.65, 18.27, −5.53.

(±)-3-(tert-Butyldimethylsilanyloxymethyl)-2-methylene-pent-4-enal(6): Eschenmoser's salt, methylene-*N*,*N*-dimethylammonium iodide, (4.36 g, 23.64 mmol) was added to a solution of aldehyde **5** (2.7 g, 11.82 mmol) and triethylamine (4.92 mL, 35.46 mmol) in CH_2Cl_2 at room temperature. The mixture was stirred overnight at room temperature. After adding a saturated aq. $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/n-hexane, 1:35) to give compound **6** (1.67 g, 59%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.54 (s, 1H), 6.11 (d, J = 0.8 Hz, 1H), 5.82 (d, J = 0.7 Hz, 1H), 5.61-5.52 (m, 1H), 5.04–4.96 (m, 2H), 3.69 (d, J = 10.2 Hz, 1H), 3.50 (d, J = 10.2 Hz, 1H), 2.87 (m, 1H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 203.32, 150.21, 134.45, 130.72, 115.40, 64.53, 38.32, 25.56, 18.41, −5.57.

(±)-3-(tert-Butyldimethylsilanyloxymethyl)-2-methylene-pent-4-enol(7): $NaBH_4$ (1.03 g, 27.4 mmol) and a solution of aldehyde **6** (2.2 g, 9.15 mmol) in MeOH (10 mL) were added successively to a solution of $CeCl_3 \cdot 7H_2O$ (6.86 g, 18.24 mmol) in MeOH (30 mL) at 0°C and stirred for 3 hours at room temperature. The mixture was quenched by adding a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic solvent layer washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/n-hexane, 1:20) to give compound **7** (2.1 g, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.63-5.54 (m, 1H), 5.01-4.92 (m, 3H), 4.81 (dd, J = 1.5, 2.0 Hz, 1H), 4.12 (d, J = 6.2 Hz, 2H), 3.74-3.66 (m, 2H), 2.92 (m, 1H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 149.21, 134.71, 114.21, 108.40, 65.82, 63.51, 36.46, 25.50, 18.64, −5.59; MS (EI) for $C_{13}H_{26}O_2Si$: m/z 242 $(M)^+$.

(±)-3-(tert-Butyldimethylsilanyloxymethyl)-2-methylene-pent-4-en-1-bromide(8): *N*-bromosuccinimide (729 mg, 4.1 mmol) and triphenylphosphine (1.07 g, 4.1 mmol) in CH_2Cl_2 (15 mL) was added to a solution of compound **7** (495 mg, 2.04 mmol) at 0°C. The mixture was stirred overnight at room temperature, and diluted with CH_2Cl_2 (20 mL). The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by quick flash

silica gel column chromatography (EtOAc/n-hexane, 1:20) to give the bromide **8** (392 mg, 63%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.60-5.41 (m, 1H), 5.00-4.89 (m, 4H), 3.78-3.69 (dd, J = 12.0, 8.8 Hz, 2H), 3.41 (d, J = 5.2 Hz, 2H), 2.88 (m, 1H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 149.47, 133.21, 115.81, 109.45, 66.51, 37.90, 34.11, 25.28, 18.60, −5.64; MS (EI) for $C_{13}H_{25}BrOSi$: m/z 306 $(M+1)^+$.

(±)-9-[3-(tert-Butyldimethylsilanyloxymethyl)-2-methylene-pent-4-en-1-yl] 2-amino-6-chloropurine(9): A solution of the 2-amino-6-chloropurine (496 mg, 2.92 mmol) and sodium hydride (81 mg, 3.4 mmol) in anhydrous DMF (16 mL) was stirred for 1 hour at room temperature. A solution of compound **8** (446 mg, 1.46 mmol) in DMF (10 mL) was then added to the mixture and stirred overnight at 80°C. The mixture was quenched by adding a saturated ammonium chloride solution (10 mL) and concentrated under reduced pressure. The residue was dissolved in water (100 mL) and extracted three times with CH_2Cl_2 (100 mL × 3). The combined organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (Hexane/EtOAc/MeOH, 1:2:0.1) to give compound **9** (190 mg, 33%) as a solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (s, 1H), 5.69-5.51 (m, 2H), 5.05-4.90 (m, 3H), 4.17 (d, J = 6.4 Hz, 2H), 3.61 (d, J = 10.4 Hz, 1H), 3.48 (d, J = 10.2 Hz, 1H), 3.11 (m, 1H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 159.21, 154.71, 151.44, 149.47, 143.88, 133.21, 124.67, 115.81, 109.45, 67.78, 47.90, 34.11, 25.47, 18.52, −5.39; Anal calc for $C_{18}H_{28}ClN_5OSi$: C, 54.87; H, 7.16; N, 17.78. Found: C, 54.69; H, 7.02; N, 17.87; MS (EI): m/z 395 $(M+1)^+$.

(±)-9-[3-(Hydroxymethyl)-2-methylene-pent-4-en-1-yl] 2-amino-6-chloropurine(10): A tetrabutylammonium fluoride (1.21 mL, 1.0 M solution in THF) was added to a solution of compound **9** (319 mg, 0.81 mmol) in tetrahydrofuran (10 mL) at 0°C, and stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 10:1) to give compound **10** (174 mg, 77%) as a colorless syrup: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.93 (s, 1H), 5.56-5.42 (m, 2H), 5.11-4.93 (m, 4H), 4.02 (d, J = 6.8 Hz, 2H), 3.72-3.64 (m, 2H), 2.95 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 159.78, 154.32, 151.07, 148.23, 142.36, 134.71, 125.77, 117.89, 108.19, 66.41, 48.32, 36.82; Anal calc for $C_{12}H_{14}ClN_5O$: C, 51.52; H, 5.04; N, 25.04. Found: C, 51.77; H, 4.92; N, 24.88; MS (EI): m/z 281 $(M+1)^+$.

(±)-9-[3-(Hydroxymethyl)-2-methylene-pent-4-en-1-yl] 2-amino-6-hydroxypurine(11): 2-Mercaptoethanol (0.09 mL, 1.29 mmol) and NaOMe (1.17 mL, 1.17 mmol, 1.0 M solution in MeOH) was added to a solution of compound **10** (61 mg, 0.22 mmol) in MeOH (8 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/CH_2Cl_2,

1:6) to give compound **11** (37 mg, 65%) as a solid: mp 188–190; UV (H_2O) λ_{max} 253.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.88 (s, 1H), 5.50-5.39 (m, 2H), 5.15-5.14 (m, 2H), 4. 92 (t, $J = 5.2$ Hz, 1H), 4.13 (d, $J = 6.6$ Hz, 2H), 3.65 (d, $J = 10.2$ Hz, 1H), 3.32 (d, $J = 10.2$ Hz, 1H), 2.95 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 159.31, 154.59, 150.37, 147.43, 141.55, 134.19, 126.32, 115.32, 109.16, 67.27, 47.29, 37.25; Anal calc for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.80. Found: C, 54.90; H, 5.72; N, 26.98; MS (EI): m/z 261 $(M)^+$.

(*rel*)-(2*S*,3*R*)-3-(tert-Butyldimethylsilanyloxymethyl)-2-methyl-pent-4-enal(12): Compound **5** (560 mg, 2.45 mmol) was dissolved in tetrahydrofuran (5 mL) and added to a stirred solution of LiHMDS (4.9 mL, 1.0 M solution in THF) in tetrahydrofuran (10 mL) at –78°C. After stirring for 1 hour at the same temperature, the reaction mixture was warmed to 0°C and stirred for an additional 1 hour at the same temperature. The mixture was cooled to –78°C and CH_3I (417 mg, 2.94 mmol) was then added. The mixture was stirred for 3 hours at the same temperature. The reaction was quenched by adding a saturated ammonium chloride solution (5 mL). The resulting mixture was warmed to room temperature, poured to water (150 mL), and extracted with ethyl acetate (150 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure and purified by column chromatography (EtOAc/hexane, 1:40) to give compound **12** (410 mg, 69%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.57 (s, 1H), 5.59-5.52 (m, 1H), 5.07-5.01 (m, 2H), 3.51 (m, 2H), 2.51 (m, 1H), 2.01 (m, 1H), 1.00 (d, $J = 6.8$ Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 203.96, 135.18, 116.83, 64.01, 47.27, 38.51, 25.36, 18.55, 13.84, −5.57.

(*rel*)-(2*S*,3*R*)-3-(tert-Butyldimethylsilanyloxymethyl)-2-methyl-pent-4-en-1-ol(13): The alcohol **13** was obtained from compound **12** using similar conditions for synthesizing compound **7**: yield 89%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.66-5.54 (m, 1H), 5.02-4.96 (m, 2H), 3.63-3.42 (m, 4H), 2.16 (m, 1H), 1.75 (m, 1H), 0.84 (s, 9H), 0.81 (d, $J = 5.1$ Hz, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 137.93, 116.71, 66.44, 65.19, 49.18, 37.18, 25.86, 18.25, 14.15, −5.52; MS (EI) for $C_{13}H_{28}O_2Si$: m/z 244 (M^+).

(*rel*)-(2*S*,3*R*)-3-(tert-Butyldimethylsilanyloxymethyl)-2-methyl-pent-4-en-1-bromide(14): Compound **14** was synthesized from compound **13** using a similar procedure for synthesizing compound **8**: Yield 68%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.62-5.58 (m, 1H), 5.00 (s, 1H), 4.98-4.90 (m, 1H), 3.89 (m, 2H), 3.54 (dd, $J = 10.2$, 8.6 Hz, 2H), 2.23 (m, 1H), 1.89 (m, 1H), 0.85 (s, 9H), 0.80 (d, $J = 5.2$ Hz, 3H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 137.54, 117.13, 67.56, 48.32, 36.71, 33.46, 25.32, 18.67, 14.42, −5.57; MS (EI) for $C_{13}H_{27}BrOSi$: m/z 308 $(M+1)^+$.

(*rel*)-(2′*S*,3′*R*)-9-[3-(tert-Butyldimethylsilanyloxymethyl)-2-methyl-pent-4-en-1-yl]2-amino-6-chloropurine(15): The purine derivative **15** was synthesized from compound **14** using a similar procedure for synthesizing compound **9**: yield 28%;^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (s, 1H),

5.74-5.62 (m, 1H), 5.58 (s, 1H), 5.24-5.10 (m, 1H), 4.18-4.10 (m, 2H), 3.57 (d, J = 7.0 Hz, 2H), 2.67 (m, 1H), 2.19 (m, 1H), 0.86 (s, 9H), 0.82 (d, J = 6.2 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 159.19, 154.22, 151.04, 143.20, 137.51, 124.39, 116.34, 63.81, 49.04, 48.03, 32.81, 25.74, 18.11, 12.58, -5.57; Anal calc for $C_{18}H_{30}ClN_5OSi$: C, 54.59; H, 7.64; N, 17.69. Found: C, 54.38; H, 7.73; N, 17.56; MS (EI): m/z 397 $(M+1)^+$.

(*rel*)-(2′*S*,3′*R*)-9-[3-(Hydroxymethyl)-2-methyl-pent-4-en-1-yl]2-amino-6-chloropurine(16): Desilylation was performed using the similar procedure to that described for compound **10**: yield 78%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.89 (s, 1H), 6.02 (br s, 2H), 5.70-5.57 (m, 2H), 5.12 (m, 1H), 5.01 (t, J = 5.2 Hz, 1H), 4.22 (dd, J = 13.4, 6.8 Hz, 1H), 4.02 (dd, J = 13.4, 7.8 Hz, 1H), 3.63 (m, 2H), 2.59 (m, 1H), 2.18 (m, 1H), 0.89 (d, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 159.63, 154.65, 151.27, 143.66, 134.90, 124.39, 118.92, 63.98, 48.71, 47.99, 32.97, 12.42; Anal calc for $C_{12}H_{16}ClN_5O$: C, 51.16; H, 5.72; N, 24.86. Found: C, 51.09; H, 5.68; N, 24.99; MS (EI): m/z 283 $(M+1)^+$.

(*rel*)-(2′*S*,3′*R*)-9-[3-(Hydroxymethyl)-2-methyl-pent-4-en-1-yl] 2-amino-6-hydroxypurine(17): The guanine derivative **17** was synthesized from compound **16** using a similar procedure for synthesizing described for compound **11**: yield 62%; mp 180–182; UV (H_2O) λ_{max} 255.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.86 (s, 1H), 6.02 (br s, 2H), 5.78-5.66 (m, 1H), 5.30-5.15 (m, 2H), 4.99 (t, J = 5.4 Hz, 1H), 4.21 (dd, J = 13.8, 6.6 Hz, 1H), 4.05 (dd, J = 13.8, 7.8 Hz, 1H), 3.76-3.62 (m, 2H), 2.45 (m, 1H), 2.22 (m, 1H), 0.89 (d, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 159.45, 153.78, 150.23, 141.32, 134.32, 123.27, 117.78, 64.03, 48.69, 48.61, 33.67, 13.69; Anal calc for $C_{12}H_{17}N_5O_2$: C, 54.74; H, 6.51; N, 26.60. Found: C, 54.84; H, 6.45; N, 26.36; MS (EI): m/z 264 $(M+1)^+$.

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