Articles

Stereoselective Synthesis of a Novel Cyclohexene Version of Carbovir

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This paper describes a racemic and stereoselective synthetic route for a novel cyclohexenyl carbocyclic adenine analogue. The required stereochemistry of the target compound was controlled using a stereoselective glycolate Claisen rearrangement followed by α-chelated carbonyl addition. The introduction of 6-chloropurine was achieved using Mitsunobu conditions, and further modifications of the corresponding heterocycle gave the target cyclohexenyl nucleoside.

Key Words : Carbovir, Glycolate Claisen rearrangement, α-Chelation

Introduction

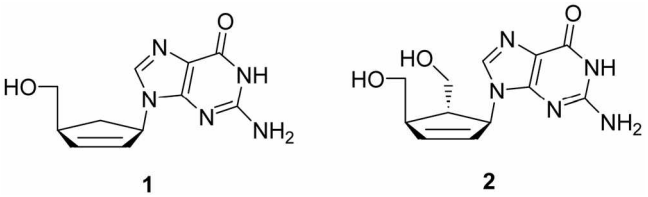
Carbocyclic nucleosides are pharmaceutically important compounds that have significant antiviral activity. The discovery of olefinic carbocyclic nucleosides such as carbovir **1**[1] and 6-hydroxymethyl carbovir **2**[2] are of particular interest because they represent a new class of compounds that exhibit significant anti-HIV activity. However, the toxicity[3] and emerging drug-resistant virus strands[4] are factors limiting their therapeutic applications. Recently, the fundamental modification of the pentofuranose moiety such as cyclohexenyl carbocyclic nucleosides[5,6] were reported to be compatible with their antiviral activity.[7] The presence of a double bond induces flexibility in the six-membered ring that is similar to the flexibility of a furanose ring.[8] Furthermore, the conformational adaptability of a cyclohexenyl nucleoside to external agents was demonstrated by observing that its conformation is different when incorporated in different double-stranded DNA sequences.[9] Cyclohexenyl nucleic acid hybridizes with both DNA and RNA, even though this effect is sequence-dependent.[10] Therefore, a deoxy cyclohexenyl nucleoside can be considered a constitutional mimic of a natural deoxynucleoside.

Stimulated by the interesting antiviral activity of cyclohexenyl nucleosides as well as the particular curiosity of the regulation of gene expression by small interfering RNAs, this study designed and synthesized novel cyclohexene nucleoside in which the heterocycle and hydroxymethyl moiety were placed in the 1,3-position. This paper reports its stereocontrolled synthesis procedure using an α-chelation controlled glycolate Claisen rearrangement and an α-chelation controlled Grignard addition reaction as the key reactions.

Results and Discussion

The α,β-unsaturated methyl ester **3**, which is readily obtained using a well-known procedure,[11] was reduced by DIBALH in CH_2Cl_2 to give the allylic alcohol **4**. This was protected with *t*-butyldimethylsilyl chloride (TBDMSCl) to give compound **5**. The isopropylidene protecting group of compound **5** was hydrolyzed by 70% acetic acid to provide the diol **6**. The selective mono-silylation of the diol **6** with TBDMSCl at −10 °C gave compound **7**, which was then converted to the benzyloxymethyl-protected allylic glycolate ester **8** under DCC and DMAP conditions.[12]

In this study, the chelation-controlled modification of the Ireland's ester enolate Claisen rearrangement (LHMDS, TMSCl/TEA)[13] was used to convert the allylic glycolate ester **8** to a γ,δ-unsaturated glycolate **9**, possibly through a chelation-controlled chair-like transition state, to give the crude acid (Figure 2). The crude acid was treated directly with CH_3I, in the presence of Triton-B, which produced the desired product **9** in a highly stereoselective manner. A notable increase in the diastereoselectivity resulted from the introduction of an α-substituent in the allylic system. A single diastereomer could be obtained with the majority of α-benzyloxy substrates.



1 **2**

Figure 1. Structures of potent carbovir analogues.

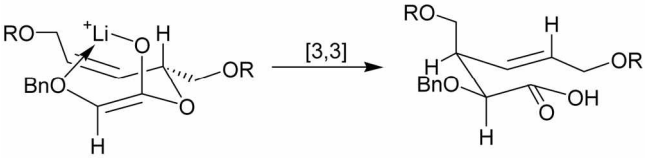


Figure 2. α-chelation controlled [3,3]-sigmatropic rearrangment.

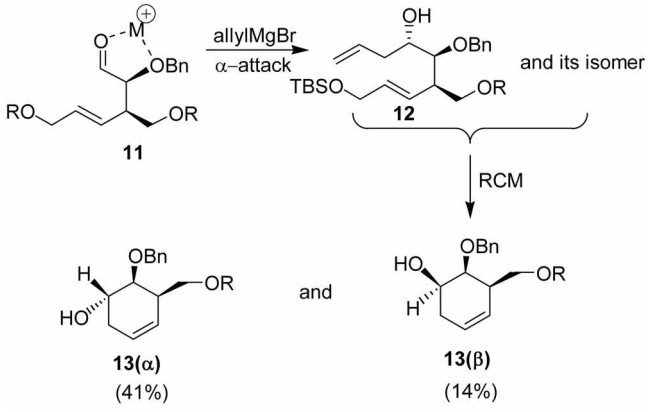


Figure 3. α-chelation controlled carbonyl addition.

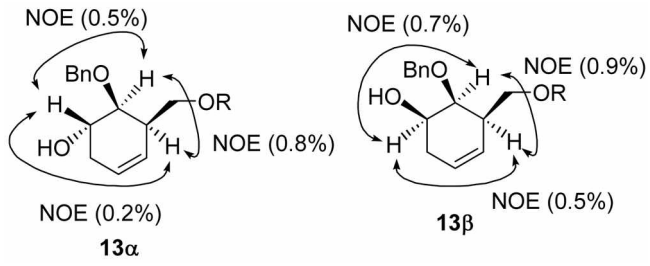


Figure 4. NOE comparisons of compound **13**α and **13**β.

The addition of DIBALH to a solution of ester **9** in CH_2Cl_2 at –20 °C followed by PCC oxidation of the corresponding alcohol **10** gave the aldehyde **11**, which underwent an α-chelation controlled carbonyl addition[14] by allyl magnesium bromide to provide a mixture of the divinyl **12** (Figure 3). The relative stereochemical study was performed in the subsequent reaction, because the mixture was difficult to separate at this stage.

The diastereomeric mixture **12** was subjected to the ring closing metathesis[15,16] conditions using a 2nd-generation Grubbs catalyst to provided the cyclopentenols **13**(β) and **13**(α) in 14% and 41% yield, respectively. These were readily separated by column silica gel chromatography. The relative stereochemistry of compounds **13**(β) and **13**(α) were determined unambiguously by NOE correlation studies between the proximal hydrogens (Figure 4).

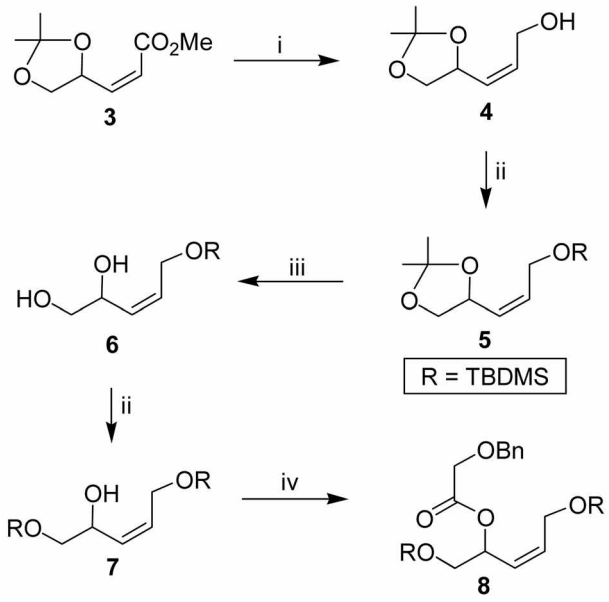
For coupling with a nucleobase, the hydroxyl group can be activated mesylate for nucleophilic substitution. However, the yield of mesylation was very low and its product was unstable during work-up or storage. Alternatively, the alkylation of adenine was attempted under Mitsunobu conditions using DIAD (diisopropylazodicarboxylate) and PPh_3 under a dioxane/THF solvent. Unfortunately, the direct coupling of adenine with alcohol **13**(α) failed. A nucleobase precursor such as 6-chloropurine was coupled under Mitsunobu conditions to give compound **14** in 71% yield. Transformation of 6-chloropurine to adenine was also readily performed by treating it with ammonia in methanol in a steel bomb at 95-100 °C. The silyl protection group of compound **15** was readily removed by treating it with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) to give compound **16**. The Birch-type reaction condition was used to remove the benzyl group. Treating compounds **16** with sodium metal in liquid ammonia/THF at –78 °C provided the desired cyclohexenyl adenine nucleoside **17**.

The antiviral activity of the synthesized compound was evaluated against several viruses such as herpes simplex virus type 1 and 2, vaccinia virus, varicella-zoster virus, Cosackie virus and cytomegalovirus, respectively. However, synthesized compound **17** did not show any significant antiviral activity at concentrations up to 100 μM without showing cytotoxicity.

In summary, a stereoselective synthetic route for novel cyclohexenyl carbocyclic nucleoside was developed. The required relative stereochemistry was elaborated successfully using a glycolate sigmatropic rearrangement as well as α-chelation controlled carbonyl addition.

Experimental Section

All 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 obtained using a JEOL JNM-LA 300 MHz-NMR 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 using a Beckman DU-7 spectrophotometer. The elemental analyses were performed using an Elemental Analyzer System (Leco-932). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. The dry THF was obtained by distillation from Na and benzophenone when the



Scheme 1. Reagents: i) DIBALH, CH_2Cl_2, 0 °C; ii) TBDMSCl, imidazole, CH_2Cl_2; iii) 80% acetic acid; iv) $BnOCH_2CO_2H$, DCC, DMAP, $CH2Cl_2$.

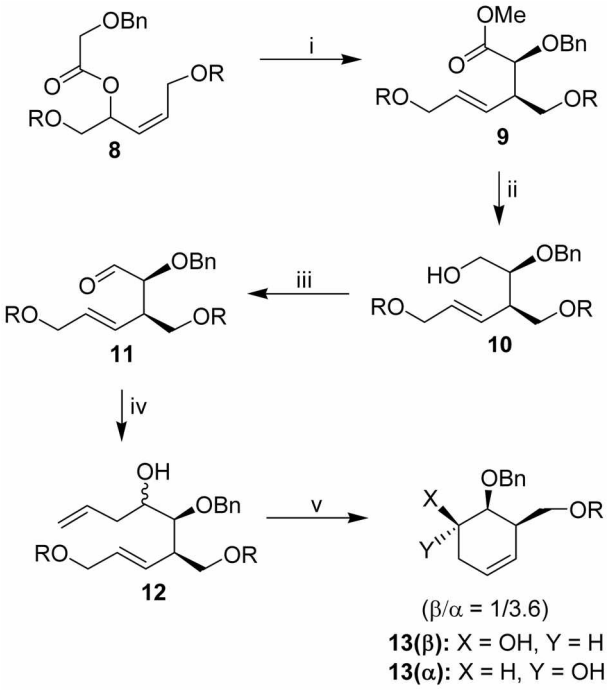
solution turned purple.

(±)-(*Z*)-4,5-(*O*-Isopropylidene)-pent-2-en-1-ol (4): DIBALH (73.3 mL, 1 M solution in hexane) was added slowly to the mixture of compound **3** (6.5 g, 34.9 mmol) in anhydrous CH_2Cl_2 (100 mL) at –20 °C and stirred for 1 h. The mixture was quenched by the slow addition of methanol (35 mL). The solution was stirred for 2 h at rt, and the resulting white solid was filtered through a Celite pad. The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give compound **4** (4.8 g, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.79-5.73 (m, 1H), 5.53-5.46 (m, 1H), 4.80 (dd, J = 14.4, 7.8 Hz, 1H), 4.24 (dd, J = 13.5, 7.2 Hz, 1H), 4.10 (dd, J = 12.6, 5.7 Hz, 1H), 4.03 (dd, J = 7.8, 6.0 Hz, 1H), 3.51 (t, J = 8.1 Hz, 1H), 1.37 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.23, 129.41, 109.47, 71.87, 69.50, 58.50, 26.70, 25.86.

(±)-(*Z*)-*tert*-Butyl-[3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-allyloxy]dimethylsilane (5): *t*-butyldimethylsilyl chloride (4.72 g, 31.29 mmol) at 0 °C was added to a stirred solution of the allylic alcohol **4** (4.5 g, 28.45 mmol) and imidazole (2.9 g, 42.67 mmol) in CH_2Cl_2 (150 mL). The mixture was stirred at room temperature for 6 h, and quenched by adding a $NaHCO_3$ solution (10 mL). The mixture was extracted using CH_2Cl_2 (200 mL), dried over $MgSO_4$, filtered and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **5** (6.74 g, 87%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.88 (m, 1H), 5.71 (dd, J = 9.6, 8.4 Hz, 1H), 4.99-4.89 (m, 2H), 4.14 (dd, J = 8.1, 6.3 Hz, 1H), 4.05 (dd, J = 8.2, 6.4 Hz, 1H), 3.60 (t, J = 7.5 Hz, 1H), 1.44 (s, 3H), 1.41 (s, 3H), 0.86 (s, 9H), 0.21 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.56, 129.77, 110.03, 72.31, 68.51, 59.43, 27.21, 26.34, 25.21, 18.67, –5.35.

(±)-(Z)-5-(*tert*-Butyldimethylsilanyloxy)-pent-3-ene-1,2-diol (6): A solution of compound **5** (4.4 g, 16.15 mmol) in a 70% aqueous acetic acid solution (150 mL) was stirred for 5 h at rt. The mixture was concentrated under reduced pressure and extracted with EtOAc/H_2O. The combined organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and purified by silica gel column chromatography (EtOAc/hexane, 3:1) to give the diol **6** (2.51 g, 67%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81-5.67 (m, 2H), 5.07 (dd, J = 12.3, 6.6 Hz, 1H), 4.83 (dd, J = 12.6, 5.7 Hz, 1H), 4.69 (m, 1H), 3.69-3.54 (m, 2H), 0.87 (s, 9H), 0.16 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.97, 128.58, 69.32, 67.45, 58.49, 25.21, 18.67, –5.35.

(±)-(*Z*)-1,5-Bis-(*tert*-butyldimethylsilanyloxy)-pent-3-en-2-ol (7): TBDMSCl (7.23 g, 52.8 mmol) dissolved in anhydrous CH_2Cl_2 (100 mL) was added slowly to a solution of the diol **6** (11.15 g, 48.01 mmol) and imidazole (4.9 g, 72.0 mol) in dry CH_2Cl_2 (250 mL) at –10 °C over 30 min. After stirring for 1 h at the same temperature, the reaction mixture was quenched using a saturated aqueous $NaHCO_3$ solution (40 mL). The solvent was extracted with CH_2Cl_2 (300 mL) and water (300 mL), and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered. The filtrate was concentrated under reduced pressure, and purified by silica gel column chromatography (EtOAc/hexane, 1:7) to give compound **7** (13.31 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.65-5.57 (m, 1H), 5.39-5.31 (m, 1H), 4.37 (m, 1H), 4.22-4.15 (m, 2H), 3.50 (dd, J = 9.9, 3.9 Hz, 1H), 3.36 (dd, J = 9.9, 8.1 Hz, 1H), 0.87 (s, 18H), 0.15 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.11, 128.99, 68.58, 66.77, 59.72, 25.91, 18.30, –5.23.



Scheme 2. Reagents: i) LHMDS, TMSCl/TEA, THF, –78 °C, 1 h, then rt, 2 h, (b) CH_3I, Triton-B, MeOH, overnight; ii) DIBALH, CH_2Cl_2; iii) PCC, CH_2Cl_2; iv) allylMgBr, THF, –78 °C; v) 2nd-generation Grubbs catalyst, CH_2Cl_2, reflux.

(±)-(*Z*)-Benzyloxy-acetic acid 4-(*tert*-butyldimethylsilanyloxy)-1-(*tert*-butyldimethylsilanyl oxymethyl)-but-2-enyl ester (8): DCC (3.39 g, 18.85 mmol) and DMAP (200 mg, 1.64 mmol) was added to a solution of compound **7** (5.69 g, 16.43 mmol) and benzyloxyacetic acid (3.0 g, 18.05 mmol) in dry CH_2Cl_2 (150 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give compound **8** (6.58 g, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41-7.30 (m, 5H), 5.94 (m, 1H), 5.75 (m, 1H), 5.58 (dd, J = 10.8, 9.4 Hz, 1H), 4.68 (s, 2H), 4.58 (s, 2H), 3.31 (dd, J = 8.6, 6.2 Hz, 2H), 3.78-3.70 (m, 2H), 0.88 (s, 18H), 0.18 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.14, 138.24, 133.43, 130.21, 128.87, 128.42, 128.01, 78.12, 72.43, 69.06, 66.42, 58.53, 25.72, 18.54, –5.67.

(±)-(2*R*,3*S*)-2-Benzyloxy-3-*tert*-butyldimethylsilyloxy-6-(*tert*-butyldimethylsilyloxy)-hex-4-enoic acid methyl ester (9): A solution of compound **8** (2.89 g, 5.84 mmol) and trimethylsilyl chloride/triethylamine (1/1 v/v, 15.2 mL)

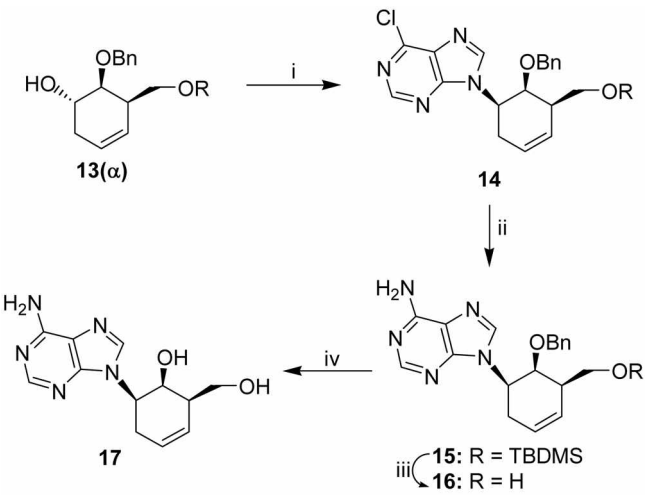
in dry THF (100 mL) was added slowly to a cooled solution of 1 M lithium bis(trimethylaily) amide in THF (46.4 mL, 46.4 mmol) at −78 °C. After stirring for 30 min at the same temperature, the reaction mixture was warmed to rt and stirred for a further 2 h. The reaction was then quenched with a 1 N NaOH solution (100 mL) in an ice bath. The resulting mixture was then stirred for 10 min at room temperature, and acidified to pH 4-5 using a 2 N HCl solution. The mixture was extracted with EtOAc (200 mL) and water (200 mL). The aqueous layer was extracted twice with EtOAc (200 mL), and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated under vacuum to give the crude acid. Without further purification, the crude acid was dissolved in THF (100 mL) and titrated with Triton-B (40% in methanol) using phenolphthalein as an indicator. After the solution turned violet, it was stirred at rt for 1 h, and CH_3I (1.44 mL, 23.1 mmol) was added slowly. The resulting mixture was stirred overnight at rt, and then diluted with hexane (100 mL) and filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **9** (2.29 g, 77%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.27 (m, 5H), 5.69 (m, 2H), 4.84 (d, J = 11.4 Hz, 1H), 4.53-4.33 (m, 5H), 3.72 (s, 3H), 3.66 (t, J = 9.6 Hz, 1H), 3.46 (dd, J = 9.6 Hz, 8.6 Hz, 1H), 0.90 (s, 18H), 0.21 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.21, 138.72, 132.54, 128.40, 128.12, 127.15, 79.54, 70.12, 64.65, 52.33, 46.50, 25.34, 18.67, −5.37; Anal calc for $C_{27}H_{48}O_5Si_2$: C, 63.73; H, 9.51. Found: C, 63.64; H, 9.40.

(±)-(2*R*,3*S*)-2-Benzyloxy-3-*tert*-butyldimethylsilyloxy-6-(*tert*-butyldimethylsilyloxy)-hex-4-enol (10): DIBALH (10.22 mL, 1.0 M solution in hexane) was added slowly to a solution of compound **9** (2.6 g, 5.11 mmol) in CH_2Cl_2 (80 mL) at −20 °C, and stirred for 2 h at the same temperature. Methanol (10 mL) was then added to the resulting mixture. The mixture was stirred at room temperature for 3 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum, and purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **10** (2.18 g, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29-7.19 (m, 5H), 5.64 (m, 2H), 4.38 (s, 2H), 3.69-3.50 (m, 7H), 2.61 (m, 1H), 0.84 (s, 18H), 0.19 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.33, 132.14, 128.30, 127.78, 127.59, 127.54, 79.60, 72.36, 70.43, 63.61, 62.17, 44.55, 25.89, 18.34, −5.18.

(±)-(2*R*,3*S*)-2-Benzyloxy-3-*tert*-butyldimethylsilyloxy-6-(*tert*-butyldimethylsilyloxy)-hex-4-enal (11): 4 Å molecular sieves (8.4 g) and PCC (7.75 g, 36.26 mmol) were added slowly to a solution of compound **10** (6.92 g, 14.4 mmol) in CH_2Cl_2 (150 mL) at 0 °C, and stirred overnight at rt. An excess of diethyl ether (500 mL) was then added to the mixture. The mixture was stirred vigorously for 2 h at the same temperature, and the resulting solid was filtered through a short silica gel column. The filtrate was concentrated under vacuum and purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **11** (5.79 g, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.62 (s, 1H), 7.32-7.18 (m, 5H), 5.62 (m, 2H), 4.68 (d, J = 11.7 Hz, 1H), 4.50 (d, J = 11.7 Hz, 1H), 4.06 (d, J = 3.0 Hz, 2H), 3.79-3.77 (m, 2H), 3.63 (t, J = 9.0 Hz, 1H), 3.42 (dd, J = 9.0, 4.8 Hz, 1H), 2.96-2.87 (m, 1H), 0.85 (s, 18H), 0.09 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.29, 138.02, 132.83, 128.63, 128.04, 127.64, 126.97, 84.24, 73.24, 68.89, 63.28, 45.60, 25.90, 18.37, −5.19.

(±)-(4*S*,5*R*,6*S*)-5-Benzyloxy-9-(*tert*-butyl-dimethyl-silanyloxy)-6-(*tert*-butyl-dimethyl-silanyloxymethyl)-nona-1,7-dien-4-ol and (±)-(4*R*,5*R*,6*S*)-5-Benzyloxy-9-(*tert*-butyl-dimethyl-silanyloxy)-6-(*tert*-butyl-dimethyl-silanyloxymethyl)-nona-1,7-dien-4-ol (12): Allyl magnesium bromide (7.0 mL, 1 M solution in THF) was added slowly to a solution of compound **11** (2.83 g, 5.93 mmol) in anhydrous THF at −78 °C and stirred for 2 h at the same temperature. The mixture was quenched with a saturated ammonium chloride solution (60 mL), and elevated to room temperature. The mixture was extracted with EtOAc (150 mL) and water (150 mL), washed with brine, dried over anhydrous $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure, and purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give a mixture of compound **12** (2.16 g, 70%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.20 (m, 5H), 5.68-5.61 (m, 2H), 5.09-5.02 (m, 2H), 4.56 (dd, J = 19.2, 11.4 Hz, 2H), 4.08 (d, J = 4.2 Hz, 2H), 3.74-3.66 (m, 2H), 3.55-3.48 (m, 2H), 2.76-2.69 (m, 2H), 2.38 (m, 1H), 2.21 (m, 1H), 0.84 (s, 18H), 0.10 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.58, 131.53, 128.96, 128.38, 128.30, 127.68, 127.57, 117.41, 83.07, 73.29, 70.36, 63.65, 46.75, 37.27, 25.94, 18.37, −5.17.

(±)-(1*S*,5*R*,6*S*)-6-Benzyloxy-5-(*tert*-butyldimethylsilanyloxymethyl)-cyclohex-3-enol (13β); and (±)-(1*R*,5*R*,6*S*)-6-Benzyloxy-5-(*tert*-butyldimethylsilanyloxymethyl)-cyclohex-3-enol (13α): 2nd generation Grubbs' catalyst (42 mg, 0.049 mmol) was added to a solution of compound **9**



Scheme 3. Reagents: i) 6-chloropurine, DIAD, PPh_3, dioxane/DMF; ii) NH_3/MeOH, steel bomb; iii) TBAF, THF; iv) Na, NH_3/THF, −78 °C, 15 min.

(3.60 g, 6.92 mmol) in dry CH_2Cl_2 (25 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 cyclopentenol **13**β (337 mg, 14%) and compound **13**α (989 mg, 41%); compound **13**β: Spectra for **13**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.25 (m, 5H), 5.86-5.57 (m, 2H), 4.61 (d, J = 11.4 Hz, 1H), 4.48 (d, J = 11.4 Hz, 1H), 4.17 (m, 1H), 3.68 (dd, J = 7.5, 2.1 Hz, 1H), 3.59-3.48 (m, 2H), 2.67-2.63 (m, 1H), 2.34 (m, 2H), 2.21 (d, J = 3.6 Hz, 1H), 0.87 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.35, 128.43, 127.91, 127.68, 127.12, 126.72, 77.36, 73.08, 70.38, 66.12, 38.82, 31.40, 25.87, 18.40, −5.26; Spectra for **13**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.24 (m, 5H), 5.66-5.53 (m, 3H), 4.68 (d, J = 11.4 Hz, 1H), 4.57 (d, J = 11.4 Hz, 1H), 3.87 (m, 1H), 3.59-3.49 (m, 3H), 2.48 (m, 2H), 2.19-2.15 (m, 1H), 0.85 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.10, 128.67, 128.55, 127.80, 127.86, 124.87, 81.48, 73.25, 70.67, 70.29, 43.75, 29.70, 25.65, 18.48, −5.41.

(±)-(1*R*,5*R*,6*S*)-9-[6-Benzyloxy-5-(*tert*-butyldimethylsilanyloxymethyl)-cyclohex-3-en-yl]-6-chloropurine (14): Triphenylphosphine (2.03 g, 3.88 mmol) and 6-chloropurine (499 mg, 3.21 mmol) in anhydrous dioxane (15 mL) and DMF (10 mL), diisopropyl azodicarboxylate (0.71 mL) was added dropwise to a solution containing compound **13**α (450 mg, 1.29 mmol) at −20 °C for 30 min. under nitrogen. The reaction mixture was stirred for 3 h at −20 °C under nitrogen. The solvent was concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc/hexane, 1:2) to give compound **14** (444 mg, 71%): UV (MeOH) λ_{max} 265.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (s, 1H), 7.59 (s, 1H), 7.41-7.36 (m, 5H), 5.71-5.65 (m, 2H), 4.54 (dd, J = 13.6, 8.8 Hz, 2H), 4.31 (m, 1H), 3.68 (dd, J = 9.0, 4.5 Hz, 1H), 2.71 (m, 1H), 2.62 (d, J = 4.6 Hz, 2H), 2.20 (d, J = 3.8 Hz, 1H), 0.86 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.27, 152.50, 148.80, 147.21, 138.43, 129.72, 128.68, 127.77, 127.32, 127.02, 121.71, 75.43, 71.48, 68.43, 50.34, 39.45, 32.45, 25.54, 18.48, −5.54; Anal calc for $C_{25}H_{33}ClN_4O_2Si$: C, 61.90; H, 6.86; N, 11.55. Found: C, 61.49; H, 6.49; N, 11.68.

(±)-(1*R*,5*R*,6*S*)-9-[6-Benzyloxy-5-(*tert*-butyldimethylsilanyloxymethyl)-cyclohex-3-en-yl]-adenine (15): Compound **14** (228 mg, 0.47 mmol) was dissolved in saturated methanolic ammonia (15 mL) and the resulting solution was stirred overnight at 95-100 °C in a steel bomb. After removing the reaction solvent, the residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 1:2:0.1) to give compound **15** (148 mg, 68%): UV (MeOH) λ_{max} 260.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.50 (s, 1H), 8.11 (s, 1H), 7.38 (m, 5H), 5.68-5.62 (m, 2H), 4.57 (d, J = 8.8 Hz, 1H), 4.42 (d, J = 8.8 Hz, 1H), 4.28 (m, 1H), 3.65 (dd, J = 8.8, 4.6 Hz, 1H), 2.82-2.76 (m, 3H), 2.22 (s, 1H), 0.89 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.67, 152.81, 149.82, 142.32, 138.28, 130.43, 128.12, 127.76, 127.21, 126.71, 119.21, 75.51, 72.45, 68.65, 49.89, 38.32, 31.34, 25.67, 18.29, −5.50.

(±)-(1*R*,5*R*,6*S*)-9-[6-Benzyloxy-5-(Hydroxymethyl)-cyclohex-3-en-yl]-adenine (16): TBAF (0.6 mL, 1.0 M solution in THF) was added to a solution of compound **15** (186.2 mg, 0.40 mmol) in THF (8 mL) 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, 1:10) to give compound **16** (108 mg, 77%): UV (H_2O) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.40 (s, 1H), 8.11 (s, 1H), 7.43-7.38 (m, 5H), 5.65-5.59 (m, 2H), 4.87 (t, J = 5.2 Hz, 1H), 4.55 (dd, J = 13.4, 8.6 Hz, 2H), 4.33 (m, 1H), 3.66 (dd, J = 8.6, 5.0 Hz, 1H), 2.80-2.74 (m, 3H), 2.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.45, 152.21, 148.02, 141.45, 138.34, 128.76, 128.45, 127.80, 127.56, 126.99, 120.06, 74.56, 72.67, 69.21, 48.34, 38.65, 32.78.

(±)-(1*R*,5*R*,6*S*)-9-[6-Hydroxy-5-(hydroxymethyl)-cyclohex-3-en-yl]-adenine (17): Anhydrous ammonia gas was bubbled through a solution of compound **16** (102 mg, 0.29 mmol) in anhydrous THF (2 mL) at −78 °C until the total volume of the solution reached 6 mL. A small portion of Na metal was added to this mixture until a blue color persisted for 5 min. The mixture was quenched using a few drops of methanol and then warmed to room temperature. The residue was dissolved in 6 mL of methanol and neutralized with AcOH. The mixture was concentrated under vacuum, and purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:4) to give compound **17** (35 mg, 47%) as a white solid: mp 180-181 °C; UV (H_2O) λ_{max} 261 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.14 (s, 1H), 9.01 (s, 1H), 7.35 (br s, 2H), 5.60-5.54 (m, 2H), 5.02 (d, J = 5.4 Hz, 1H), 4.88 (t, J = 5.4 Hz, 1H), 4.59 (dd, J = 8.6 Hz, 1H), 4.40 (d, J = 8.6 Hz, 1H), 4.28 (m, 1H), 3.69 (dd, J = 8.8, 4.4 Hz, 1H), 2.82-2.75 (m, 3H), 2.22 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.72, 152.51, 148.21, 142.67, 138.63, 128.92, 119.39, 75.02, 72.32, 68.51, 49.45, 39.54, 32.28; Anal calc for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.80. Found: C, 54.95; H, 5.87; N, 26.67.

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