Synthesis of Methyl-substituted Bicyclic Carbanucleoside Analogs as Potential Antiherpetic Agents†

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Novel bicyclo[3.1.0]hexanyl purine nucleoside analogues were synthesized as potential antiherpetic agents *via* a bicyclo[3.1.0]hexanol (±)-**8**, which was prepared using a highly efficient carbenoid cycloaddition reaction. A highly diastereoselective reduction of ketone and a Mitsunobu reaction for the condensation of glycosyl donor (±)-**12** with 6-chloropurine were employed.

Key Words : Bicyclo[3.1.0]hexanone, Intramolecular carbenoid cycloaddition, Mitsunobu reaction, Diastereoselective reduction, *North* conformation

Introduction

Since the discovery of acyclovir[1] which has been the drug of choice for the treatment of HSV-1 and 2 (herpes simplex virus type 1 and 2) and VZV (varicella-zoster virus) infections as a potent and selective inhibitor, acyclic nucleosides have attracted interest of medicinal chemists as well as biologists (Figure 1). In efforts in search of new chemotherapeutic agents with better antiviral activity, ganciclovir[2] which has become a drug of choice for the treatment of HCMV (human cytomegalovirus) infections, particularly HCMV retinitis which causes blindness in AIDS patients and penciclovir[3] with a broad antiviral spectrum such as anti-HSV-1 and 2, anti-HBV and anti-VZV activities were found. It is known that these acyclic nucleosides are efficiently phosphorylated by viral TK (thymidine kinases) to the corresponding monophosphates and further phosphorylated by cellular kinases to the corresponding triphosphates.

Marquez and coworkers reported that methanocarba-nucleoside analogues exhibited anti-HSV and anti-HCMV activity.[4] Especially methanocarba-thymine nucleoside showed superior activity to acyclovir against HSV-1 and 2. Methanocarba-nucleosides have a rigid sugar template with a *north* conformation in pseudorational cycle.[5] It was reported that nucleosides bearing a sugar template fixed with a *north* conformation can not be phosphorylated by cellular kinases to the corresponding monophosphates.[6] However, although bicyclo[3.1.0]hexenyl nucleosides, previously reported by the author *et al.* keep *north* conformations, the thymine nucleoside analog showed very potent anti-AIDS activity. They make their conformations to be more plane than bicyclo[3.1.0]hexanyl nucleosides do. Maybe, the property of bicyclo[3.1.0]hexenyl nucleosides related to their structural planarity might give them a proper structural conformation for phosphorylation. Judged from showing potent anti-HSV activity, methanocarba-nucleosides are probably phosphorylated by viral TK as acyclovir, ganciclovir and penciclovir are done.

Although methanocarba-nucleosides have shown highly potent anti-HSV and anti-HCMV activities, the study on a structure-activity relationship has not been conducted, presumably due to the synthetic difficulties of bicyclo[3.1.0]-hexane template.[4,7] In addition, there is no study on an ability of kinases to accommodate methyl substituent at 4" position (normal nucleoside's numbering). Therefore, we wish to report extremely efficient synthesis of novel methanocarba-nucleoside analogs having purine nucleobases for the study of structure-activity relationship from commer-

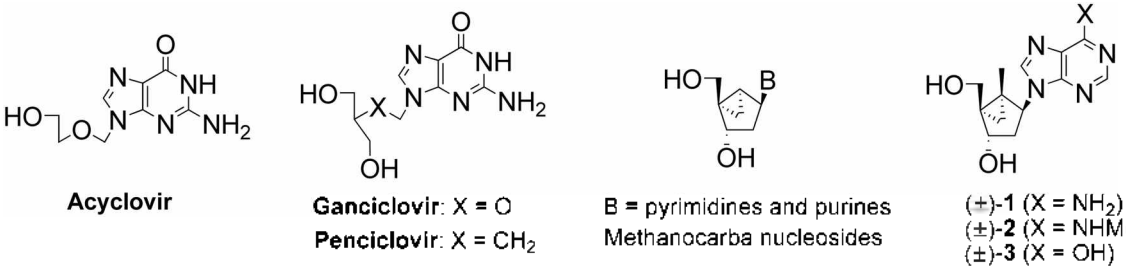

Figure 1. Nucleosides showing antiherpetic activity and target compounds.

†Dedicated to Prof. Moon Woo Chun on the occasion of his 65th birthday and for his many contributions to the field of nucleoside chemistry.
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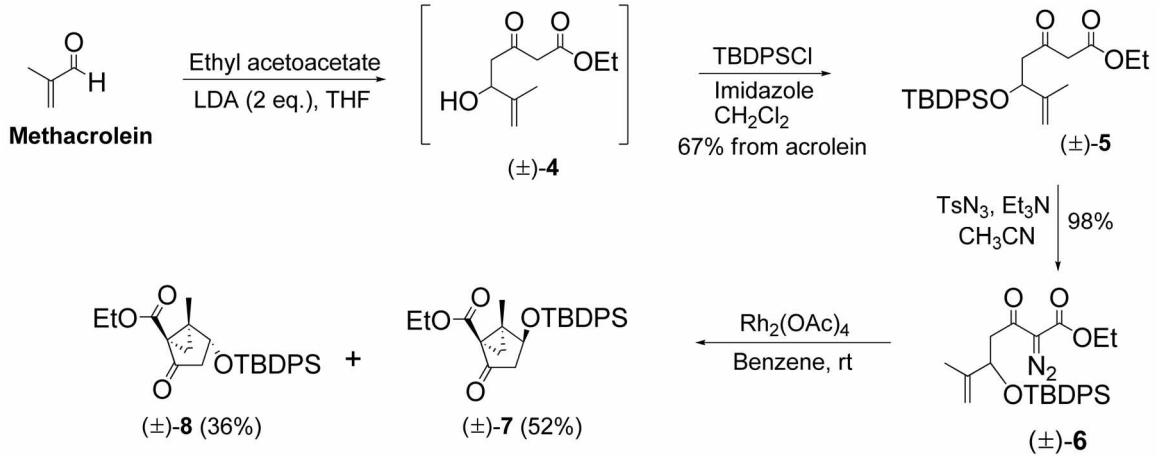
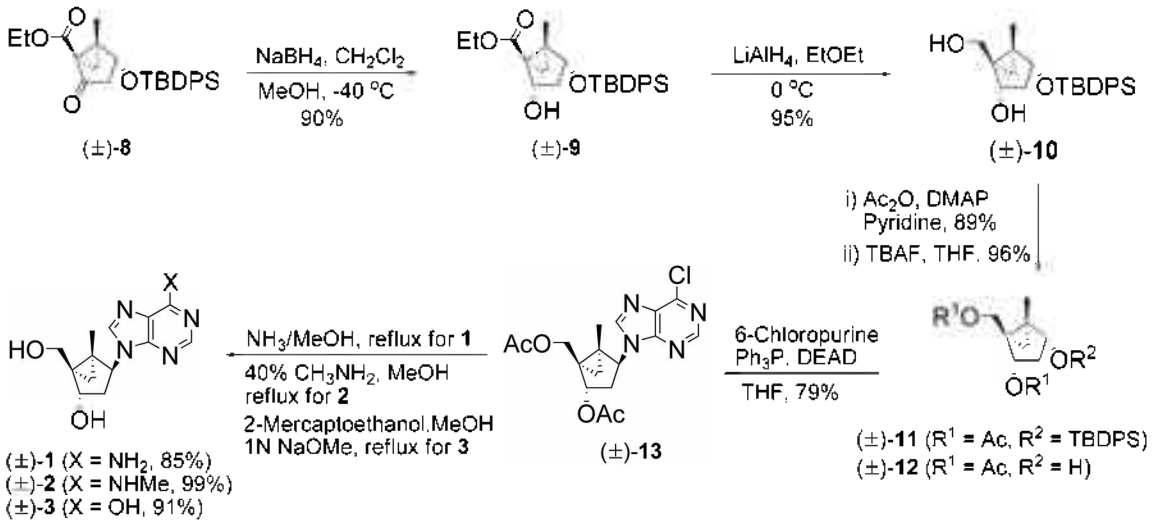


Scheme 1. Synthesis of bicyclo[3.1.0]hexanone template using a carbenoid insertion reaction into an intramolecular double bond.



Scheme 2. Synthesis of glycosyl donor and bicyclic carbanucleoside analogs.

cially available starting materials, methacrolein and ethyl acetoacetate. The key intermediate, bicyclo[3.1.0]hexane template was successfully constructed *via* an intramolecular carbenoid cycloaddition to a double bond in the presence of metal catalyst, which was previously developed by the author *et al.*[7b]

Results and Discussion

A strategy for the synthesis of bicyclo[3.1.0]hexane template is outlined in Scheme 1. It was envisioned that diazo compound (±)-**6** derived from methacrolein could be a suitable intermediate to achieve a carbenoid cycloaddition into a double bond in a proper position of the molecule, resulting in the formation of bicyclic template. Aldol reaction of dianion of ethyl acetoacetate with methacrolein afforded an aldol adduct (±)-**4**, whose hydroxyl group was protected as a silyl ether to give (±)-**5** which existed in an equilibrium with its enol tautomer. *β*-Ketoester (±)-**5** was quantitatively converted to diazo compound (±)-**6** by treatment with *p*-toluenesulfonyl azide[8] and triethylamine. Intramolecular cycloaddition[7b] of compound (±)-**6** using rhodium(II) diacetate dimer as a metal catalyst generated a chromatographically separable mixture of the undesired product (±)-**7** (52%) and the desired product (±)-**8** (36%). Although the use of copper(II) sulfate instead of rhodium(II) diacetate dimer gave (±)-**7** and (±)-**8** in a 1:1 ratio, many by-products were generated and the yield was also very low. Assignment of relative stereochemistry of (±)-**7** and (±)-**8** was unambiguously determined from splitting patterns of peaks of their protons at 4-positon in ^{1}H NMR spectra. The peak of proton at 4-position of (±)-**8** should be a multiplet (doublets of doublet or triplet) whereas that of the undesired one (±)-**7** should be a doublet because the dihedral angle between H_4 and $H_{3\text{-exo}}$ hydrogen in the rigid bicyclo[3.1.0]-hexanone scaffold of (±)-**7** is close to 90°, resulting in a $J_{4,3exo}$ coupling near zero.[9] It is noteworthy that the desired relative stereochemistry of three chiral centers was obtained from only one-step reaction, carbenoid cycloaddition reaction.

Synthesis of bicyclo[3.1.0]hexanyl purine nucleosides (±)-**1-3** was described in Scheme 2. In order to convert (±)-**8** into

an appropriate glycosyl donor (±)-**12**, ketone functionality was first reduced with $NaBH_4$[10] to afford (±)-**9** as a sole diastereoisomer, maybe resulting from attack of the hydride from the convex face. Treatment of (±)-**9** with $LiAlH_4$ gave diol (±)-**10**, in which the two hydroxyl groups were protected as acetyl esters to give (±)-**11**. Desilylation of (±)-**11** with TBAF gave glycosyl donor (±)-**12**, which was ready for the condensation with nucleobase. Coupling of (±)-**12** with 6-chloropurine under Mitsunobu conditions[11] afforded protected 6-chloropurine nucleoside (±)-**13** in 79% yield. The final compounds, (±)-**1**, (±)-**2** and (±)-**3**, were obtained in 85-99% yield by treatment of (±)-**13** with methanolic ammonia, 40% methylamine and 2-mercaptoethanol in the presence of NaOMe, respectively.

The antiviral activity of the synthesized compounds (±)-**1**-**3** was evaluated against HIV-1 and 2, HSV-1 and 2, EMCV, Coxackie B4 virus and influenza viruses. However, all of them did not show significant antiviral activity and cytotoxicity up to 100 μM.

In summary, simple synthesis of bicyclo[3.1.0]hexanyl nucleoside analogs as potential antiherpetic agents was achieved using a highly efficient carbenoid cycloaddition reaction, which afforded bicyclo[3.1.0]hexanone (±)-**8** having three contiguous chiral centers. Reduction of ketone with $NaBH_4$ proceeded with high diastereoselectivity and a Mitsunobu reaction of bicyclo[3.1.0]hexanol (±)-**12** with 6-chloropurine provided nucleoside analog in a good yield.

Experiments

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Varian Unity INOVA 400 and Varian Unity AS 500 instruments. Chemical shifts are reported with reference to the respective residual solvent or deuteriated peaks (δ_H 3.30 and δ_C 49.0 for CD_3OD, δ_H 7.27 and δ_C 77.0 for $CDCl_3$). Coupling constants are reported in hertz. The abbreviations used are as follows: s (singlet), d (doublet), m (multiplet), t (triplet), dd (doublet of doublet), br s (broad singlet). All the reactions described below were performed under argon or nitrogen atmosphere and monitored by TLC. All anhydrous solvents were distilled over CaH_2 or Na/benzophenone prior to use.

(±)-Ethyl 5-[(*tert*-butyldiphenylsilyl)oxy]-6-methyl-3-oxohept-6-enoate ((±)-5): A stirred solution of LDA (2.0 M in THF, 131 mL, 262.0 mmol) in anhydrous THF (350 mL) was treated dropwise with ethyl acetoacetate (13.3 mL, 104.6 mmol) at 0 °C. After 20 min the reaction mixture was cooled to −78 °C, and methacrolein (10 mL, 148.6 mmol) was added while stirring continued for 20 min at −78 °C. Following quenched with saturated NH_4Cl solution (40 mL), the reaction mixture was extracted with diethyl ether (3 × 150 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated under vacuum to give a crude product (±)-**4** (29.96 g), which was used in the next step without further purification. A stirred solution of this product and imidazole (11.76 g, 172.68 mmol) in methylene chloride (250 mL) was maintained at 0 °C and treated with TBDPSCl (22.5 mL, 86.34 mmol). After stirred for 6 h and allowed the temperature of the bath to reach ambient temperature, water (120 mL) and methylene chloride (250 mL) were added. The organic layer was separated, washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (18:1) as the eluent to give (±)-**5** (22.97 g, 67%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 11.81 (s, 1H, enolic proton, minor), 7.70-7.35 (m, 20H, 4*Ar, major and minor), 4.89 (s, 1H, 2-H, minor), 4.84 (m, 1H, C=C*H*H, major), 4.76-4.71 (m, 3H, C=CH*H*, C=CH_2, major and minor), 4.63 (t, 1H, J = 6.0 Hz, 5-CH, major), 4.50 (t, 1H, J = 6.5 Hz, 5-CH, minor), 4.20-4.13 (m, 4H, OCH_2CH$_3$, major and minor), 3.30 (s, 2H, 2-CH_2, major), 2.74 (dd, 1H, J = 6.0, 14.5 Hz, 4-C*H*H, major), 2.70 (dd, 1H, J = 6.0, 15.0 Hz, 4-CH*H*, major), 2.42 (dd, 1H, J = 7.0, 14.0 Hz, 4-C*H*H, minor), 2.33 (dd, 1H, J = 7.0, 13.5 Hz, 4-CH*H*, minor), 1.72 (br s, 3H, 6-CH_3, minor), 1.69 (br s, 3H, 6-CH_3, major), 1.29 (t, 3H, J = 7.0 Hz, OCH_2CH_3, minor), 1.26 (t, 3H, J = 7.0 Hz, OCH_2CH_3, major), 1.09 (s, 9H, *tert*-butyl, major), 1.08 (s, 9H, *tert*-butyl, minor); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.37 (major), 174.81 (minor), 172.37 (minor), 166.95 (major), 145.35 (minor), 145.14 (major), 136.00 (minor), 135.94 (major), 135.91 (minor), 135.89 (major), 133.91 (minor), 133.68 (major), 133.64 (minor), 133.30 (major), 129.77 (major), 129.70 (major), 129.56 (minor), 129.55 (minor), 127.59 (major), 127.45 (major), 127.42 (minor), 127.33 (minor), 112.61 (major), 112.49 (minor), 91.23 (minor), 74.97 (minor), 73.44 (major), 61.20 (major), 59.84 (minor), 50.07 (major), 49.53 (major), 42.57 (minor), 26.97 (major), 26.95 (minor), 19.33 (minor), 19.30 (major), 17.29 (major), 16.86 (minor), 14.24 (minor), 14.05 (major); LRMS (FAB+) m/z 381 $(M+H-t\text{-}Bu)^+$, 461 $(M+Na)^+$.

(±)-Ethyl 2-diazo-5-[(*tert*-butyldiphenylsilyl)oxy]-6-methyl-3-oxohept-6-enoate ((±)-6): A stirred solution of β-keto ester (±)-**5** (22.97 g, 52.37 mmol) and *p*-tosyl azide (10.33 g, 52.38 mmol) in CH_3CN (105 mL) was treated with triethylamine (14.59 mL, 104.68 mmol) at 0 °C. After 2 h of stirring at 0 °C, the reaction mixture was to reach room temperature and stirring was continued for 21 h. Diethyl ether (350 mL) and 2 N aqueous NaOH solution (350 mL) were added. After 10 min of stirring, the organic layer was separated, washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (11:1) as an eluent to give diazo compound (±)-**6** (23.8 g, 98%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.66-7.33 (m, 10H, 2*Ar), 4.78 (m, 1H, CH_3C=C*H*H), 4.75 (dd, 1H, J = 5.0, 8.0 Hz, 5-CH), 4.71 (m, 1H, CH_3C=CH*H*), 4.24 (m, 2H, OCH_2CH_3), 3.21 (dd, 1H, J = 8.0, 14.5 Hz, COC*H*H), 2.97 (dd, 1H, J = 5.0, 15.0 Hz, COCH*H*), 1.74 (s, 3H, CH_2=CCH_3), 1.31 (t, 3H, J = 7.3 Hz, OCH_2CH_3), 1.05 (s, 9H, *tert*-butyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.88, 161.08, 146.06, 136.06, 135.97, 134.02, 133.68, 129.49, 129.45, 127.30, 127.26, 112.21, 74.02, 61.25, 46.76, 26.95, 19.34, 17.10, 14.32; LRMS

(FAB+) m/z 407 $(M-t\text{-}Bu)^+$, 465 $(M+H)^+$, 487 $(M+Na)^+$.

(*rel*)-Ethyl-(1*S*,4*S*,5*S*)-4-[(*tert*-butyldiphenylsilyl)oxy]-5-methyl-2-oxobicyclo[3.1.0]hexane-1-carboxylate ((±)-7) and (*rel*)-ethyl-(1*S*,4*R*,5*S*)-4-[(*tert*-butyldiphenylsilyl)-oxy]-5-methyl-2-oxobicyclo[3.1.0]hexane-1-carboxylate ((±)-8): To a stirred solution of diazo compound (±)-**6** (23.8 g, 51.22 mmol) in benzene (320 mL) was added rhodium (II) acetate dimer (5 mg, 0.01 mmol) at room temperature and stirred for 24 h. The reaction mixture was filtered through a pad of Celite, and washed with ethyl acetate. The organic solvent was concentrated under vacuum and the resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (10:1) as an eluent to give the desired bicyclic compound (±)-**8** (8.05 g, 36%) and its C-4 epimer (±)-**7** (11.55 g, 52%) as a colorless oil: compound (±)-**7**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.39 (m, 10H, 2*Ar), 4.47 (d, 1H, J = 5.5 Hz, 4-H), 4.38-4.24 (m, 2H, OCH_2CH_3), 2.21 (ddd, 1 H, J = 2.0, 5.0, 19.0 Hz, 3-CHH), 2.05 (d, 1H, J = 19.0 Hz, 3-CHH), 1.82 (dd, 1H, J = 2.0, 5.5 Hz, 6-CHH), 1.41 (s, 3H, 5-CH_3), 1.35 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 1.21 (d, 1H, J = 5.5 Hz, 6-CHH), 1.10 (s, 9H, *tert*-butyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.43, 167.05, 135.75, 133.33, 132.94, 129.86, 127.68, 71.61, 61.15, 45.41, 44.22, 43.83, 26.83, 24.75, 19.29, 14.27, 13.75; LRMS (FAB+) m/z 437 $(M+H)^+$, 459 $(M+Na)^+$; HRMS (FAB+) m/z $C_{26}H_{32}O_4SiNa$ $(M+Na)^+$ calcd 459.1968, obsd 459.1969; compound (±)-**8**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.39 (m, 10H, 2*Ar), 4.41 (t, 1H, J = 7.8 Hz, 4-H), 4.22-4.16 (m, 2H, OCH_2CH_3), 2.20 (dd, 1H, J = 8.5, 18.0 Hz, 3-CHH), 2.14 (dd, 1H, J = 7.5, 18.0 Hz, 3-CHH), 1.95 (d, 1H, J = 5.0 Hz, 6-CHH), 1.85 (d, 1H, J = 5.0 Hz, 6-CHH), 1.26 (s, 3H, 5-CH_3), 1.25 (t, 3H, J = 6.0 Hz, OCH_2CH_3), 1.11 (s, 9H, *tert*-butyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.65, 166.73, 136.02, 135.97, 133.51, 133.42, 130.29, 130.26, 128.04, 72.39, 61.58, 47.00, 44.58, 43.10, 27.14, 23.72, 19.49, 15.83, 14.45; LRMS (FAB+) m/z 437 $(M+H)^+$, 459 $(M+Na)^+$; HRMS (FAB+) m/z $C_{26}H_{32}O_4SiNa$ $(M+Na)^+$ calcd 459.1968, obsd 459.1951.

(*rel*)-Ethyl-(1*S*,2*S*,4*R*,5*S*)-4-[(*tert*-butyldiphenylsilyl)-oxy]-2-hydroxy-5-methylbicyclo[3.1.0]hexane-1-carboxylate ((±)-9): A stirred solution of bicyclic compound (±)-**8** (830 mg, 1.90 mmol) in methanol (7 mL) and methylene chloride (4 mL) was cooled to −40 °C and treated with $NaBH_4$ (86 mg, 2.28 mmol). After further stirred at −40 °C for 1.5 h, the reaction was quenched with acetic acid/MeOH solution. Methylene chloride was added and the organic layer was separated, washed with brine (12 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (5:1) as an eluent to give (±)-**9** (750 mg, 90%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.37 (m, 10H, 2*Ar), 4.57 (t, 1H, J = 8.5 Hz, 2-H), 4.21-4.10 (m, 2H, OCH_2CH_3), 4.03 (t, 1H, J = 8.5 Hz, 4-H), 2.06 (br s, 1H, OH), 1.95 (td, 1H, J = 7.5, 13.0 Hz, 3-CHH), 1.69 (d, 1H, J = 5.0 Hz, 6-CHH), 1.27-1.23 (m, 5H, OCH_2CH_3, 3-CHH, 6-CHH), 1.21 (s, 3H, 5-CH_3), 1.09 (s, 9H, *tert*-butyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.45, 136.15, 134.16, 134.05, 130.00, 127.87, 75.25, 68.92, 60.78, 40.48, 39.65, 36.63, 27.27, 19.58, 17.13, 15.74, 14.56; LRMS (FAB+) m/z 461 $(M+Na)^+$; HRMS (FAB+) m/z $C_{26}H_{34}O_4SiNa$ $(M+Na)^+$ calcd 461.2124, obsd 461.2132.

(*rel*)-(1*R*,2*S*,4*R*,5*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-1-hydroxymethyl-5-methylbicyclo[3.1.0]hexan-2-ol ((±)-10): A stirred suspension of LAH (70.7 mg, 1.86 mmol) in diethyl ether (13.8 mL) was treated dropwise with a solution of crude (±)-**9** (545 mg, 1.24 mmol) in diethyl ether (2.8 mL) at 0 °C. After stirred for 10 min, water (0.08 mL), 15% NaOH (0.08 mL), and water (0.24 mL) were added dropwise successively at 0 °C. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under vacuum. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (1:1) as an eluent to give diol compound (±)-**10** (468 mg, 95%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73-7.36 (m, 10H, 2*Ar), 4.20 (t, 1H, J = 8.0 Hz, 2-H), 4.04 (t, 1H, J = 8.0 Hz, 4-H), 3.64 (d, 1H, J = 11.5 Hz, CHHOH), 3.62 (d, 1H, J = 11.5 Hz, CHHOH), 2.51 (br s, 2H, 2*OH), 1.92 (td, 1H, J = 7.5, 13.0 Hz, 3-CHH), 1.32 (d, 1H, J = 5.5 Hz, 6-CHH), 1.15 (td, 1H, J = 8.5, 13.5 Hz, 3-CHH), 1.09 (s, 9H, *tert*-butyl), 1.04 (s, 3H, 5-CH_3), 0.28 (d, 1H, J = 5.0 Hz, 6-CHH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.17, 136.14, 134.54, 134.43, 129.88, 129.87, 127.78, 76.16, 72.33, 64.89, 37.82, 37.79, 33.58, 27.27, 19.60, 16.32, 13.72; LRMS (FAB+) m/z 419 $(M+Na)^+$.

(*rel*)-(1*R*,2*S*,4*R*,5*S*)-2-Acetoxy-4-[(*tert*-butyldiphenylsilyl)oxy]-5-methylbicyclo[3.1.0]hexane-1-methyl acetate ((±)-11): A stirred solution of diol (±)-**10** (468 mg, 1.18 mmol) and DMAP (14.4 mg, 0.12 mmol) in pyridine was treated dropwise with acetic anhydride (0.33 mL, 3.54 mmol) at 0 °C. After 2 h of stirring at room temperature, the solvent was removed under reduced pressure and the residue was partitioned between methylene chloride (150 mL) and water (20 mL). The organic layer was washed with 0.5 N HCl (10 mL) and aqueous saturated $NaHCO_3$ solution (10 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using hexane and ethyl acetate (8:1) as an eluent to give the diacetate (±)-**11** (505 mg, 89%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.34 (m, 10H, 2*Ar), 5.07 (t, 1H, J = 8.0 Hz, 2-H), 4.27 (d, 1H, J = 12.0 Hz, AcOCHH), 4.09 (t, 1H, J = 8.0 Hz, 4-H), 3.70 (d, 1H, J = 12.4 Hz, AcOCHH), 2.13 (td, 1H, J = 7.6, 12.8 Hz, 3-CHH), 2.00 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$), 1.36 (d, 1H, J = 5.2 Hz, 6-CHH), 1.15 (td, 1H, J = 8.4, 13.2 Hz, 3-CHH), 1.04 (s, 9 H, *tert*-butyl), 0.98 (s, 3H, 5-CH_3), 0.37 (d, 1H, J = 5.6 Hz, 6-CHH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.27, 136.10, 136.07, 134.20, 134.17, 129.95, 129.92, 127.80, 75.96, 73.07, 64.50, 34.92, 33.31, 32.95, 27.18, 21.32, 21.11, 19.55, 16.21, 14.69; LRMS (FAB+) m/z 503 $(M+Na)^+$; HRMS (FAB+) m/z $C_{28}H_{36}O_5SiNa$ $(M+Na)^+$ calcd 503.2230, obsd 503.2238.

(*rel*)-(1*R*,2*S*,4*R*,5*S*)-2-Acetoxy-4-hydroxy-5-methylbicyclo[3.1.0]hexane-1-methyl acetate ((±)-12): A stirred solution of (±)-**11** (662 mg, 1.38 mmol) in THF (6 mL) was

treated dropwise with 1 N TBAF (2.1 mL, 2.10 mmol) at room temperature for 4 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography using hexane and ethyl acetate (2.5:1) as the eluent to give the glycosyl donor (±)-**12** (322 mg, 96%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (t, 1H, J = 8.0 Hz, 2-H), 4.38 (d, 1H, J = 12.0 Hz, AcOC*H*H), 4.17 (t, 1H, J = 8.5 Hz, 4-H), 3.82 (d, 1H, J = 12.0 Hz, AcOCH*H*), 2.51 (td, 1H, J = 7.5, 13.5 Hz, 3-C*H*H), 2.08 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 1.66 (br s, 1H, OH), 1.27 (d, 1H, J = 6.0 Hz, 6-C*H*H), 1.26 (s, 3H, 5-CH_3), 1.10 (td, 1H, J = 8.5, 13.5 Hz, 3-CH*H*), 0.42 (d, 1H, J = 6.0 Hz, 6-CH*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.33, 171.29, 74.93, 72.95, 64.37, 34.71, 33.51, 33.04, 21.28, 21.11, 15.83, 14.16; LRMS (FAB+) m/z 265 $(M+Na)^+$; HRMS (FAB+) m/z $C_{12}H_{18}O_5Na$ $(M+Na)^+$ calcd 265.1052, obsd 265.1064.

***(rel)*-(1*R*,2*S*,4*S*,5*S*)-2-Acetoxy-4-(6-chloro-9*H*-purin-9-yl)-5-methylbicyclo[3.1.0]hexane-1-methyl acetate ((±)-13):** To a stirred solution of (±)-**12** (609 mg, 2.51 mmol), triphenylphosphine (665 mg, 5.07 mmol), and 6-chloropurine (392 mg, 5.07 mmol) in anhydrous THF (15 mL) was added dropwise diethyl azodicarboxylate (0.40 mL, 5.07 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The volatiles were evaporated *in vacuo* and the resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (1:1) as an eluent to give the protected 6-chloropurine nucleoside (±)-**13** (628 mg, 79%) as a white solid: mp 159-160 °C; UV (MeOH) λ_{max} 264.0 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H, H-8), 8.33 (s, 1H, H-2), 5.92 (t, 1H, J = 8.5 Hz, 2-H), 5.32 (d, 1H, J = 8.0 Hz, 4-H), 4.65 (d, 1H, J = 12.5 Hz, AcOC*H*H), 3.91 (d, 1H, J = 13.0 Hz, AcOCH*H*), 2.38 (dd, 1H, J = 8.5, 16.0 Hz, 3-C*H*H), 2.19 (s, 3H, $COCH_3$), 2.11 (s, 3H, $COCH_3$), 1.94 (td, 1H, J = 8.0, 15.5 Hz, 3-CH*H*), 1.31 (d, 1H, J = 6.0 Hz, 6-C*H*H), 0.92 (s, 3H, 5-CH_3), 0.77 (d, 1 H, J = 6.0 Hz, 6-CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.18, 170.82, 152.35, 151.87, 151.57, 143.85, 131.60, 75.29, 63.84, 59.29, 35.50, 35.15, 31.00, 21.17, 21.09, 18.34, 14.36; LRMS (FAB+) m/z 379 $(M+H)^+$, 391 $(M+Na)^+$; HRMS (FAB+) m/z $C_{17}H_{20}ClN_4O_4$ $(M+H)^+$ calcd 379.1173, obsd 379.1165.

***(rel)*-(1*R*,2*S*,4*S*,5*S*)-4-(6-Amino-9*H*-purin-9-yl)-1-(hydroxymethyl)-5-methylbicyclo[3.1.0]hexan-2-ol ((±)-1):** A solution of (±)-**13** (157 mg, 0.41 mmol) and saturated methanolic ammonia (8 mL) was heated in a glass bomb at 80 °C for 5 h. The reaction mixture was evaporated in vacuo and purified by silica gel column chromatography using methylene chloride and methanol (8:1) as an eluent to give the adenine nucleoside (±)-**1** (97 mg, 85%) as a white solid: mp 132-134 °C; UV (MeOH) λ_{max} 262.0 nm; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.28 (s, 1H, H-8), 8.17 (s, 1H, H-2), 5.11 (t, 1H, J = 8.4 Hz, 2-H), 5.06 (d, 1H, J = 7.2 Hz, 4-H), 4.28 (d, 1H, J = 11.2 Hz, C*H*HOH), 3.35 (d, 1H, J = 12.0 Hz, CH*H*OH), 1.95 (dd, 1H, J = 8.4, 14.8 Hz, 3-C*H*H), 1.83 (td, 1H, J = 8.0, 14.8 Hz, 3-CH*H*), 1.16 (d, 1H, J = 5.6 Hz, 6-C*H*H), 0.95 (s, 3H, 5-CH_3), 0.46 (d, 1H, J = 5.6 Hz, 6-CH*H*); ^{13}C NMR (100 MHz, MeOH-d_4) δ 156.22, 152.37, 149.06, 140.79, 118.79, 71.28, 60.66, 59.88, 39.79, 37.49, 29.81, 16.20, 13.43; LRMS (FAB+) m/z 276 $(M+H)^+$; HRMS (FAB+) m/z $C_{13}H_{18}N_5O_2$ $(M+H)^+$ calcd 276.1460, obsd 276.1468.

***(rel)*-(1*R*,2*S*,4*S*,5*S*)-1-(Hydroxymethyl)-5-methyl-4-[6-(methylamino)9*H*-purin-9-yl]bicyclo[3.1.0]hexan-2-ol ((±)-2):** A solution of (±)-**13** (61 mg, 0.16 mmol) and 40% methylamine (3 mL) in methanol (3 mL) was heated at 80 °C for 5 h, and the reaction mixture was evaporated *in vacuo*. The resulting residue was purified by silica gel column chromatography using methylene chloride and methanol (8:1) as the eluent to give the corresponding 6-methylamino purine nucleoside (±)-**2** (46 mg, 99%) as a white solid: mp 155-157 °C; UV (MeOH) λ_{max} 268.0 nm; ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.26 (s, 2H, H-2, H-8), 5.15 (t, 1H, J = 8.0 Hz, 2-H), 5.08 (d, 1H, J = 7.2 Hz, 4-H), 4.32 (d, 1H, J = 12.0 Hz, C*H*HOH), 3.38 (d, 1H, J = 11.5 Hz, CH*H*OH), 3.13 (br s, 3H, *N*-CH_3), 1.98 (dd, 1H, J = 8.0, 14.5 Hz, 3-C*H*H), 1.86 (td, 1H, J = 8.0, 14.5 Hz, 3-CH*H*), 1.15 (d, 1H, J = 5.5 Hz, 6-C*H*H), 0.99 (s, 3H, 5-CH_3), 0.50 (d, 1H, J = 5.0 Hz, 6-CH*H*); ^{13}C NMR (125 MHz, MeOH-d_4) δ 157.02, 153.75, 149.35, 141.61, 120.75, 72.69, 62.09, 61.30, 41.19, 38.94, 31.21, 27.99, 17.59, 14.77; LRMS (FAB+) m/z 289 $(M)^+$, 290 $(M+H)^+$; HRMS (FAB+) m/z $C_{14}H_{20}N_5O_2$ $(M+H)^+$ calcd 290.1617, obsd 290.1624.

***(rel)*-9-[(1*S*,2*S*,4*S*,5*R*)-4-Hydroxy-5-(hydroxymethyl)-1-methylbicyclo[3.1.0]hexan-2-yl]-1*H*-purin-6(9*H*)-one ((±)-3):** To a stirred solution of (±)-**13** (51 mg, 0.14 mmol) in methanol (3 mL) were added 2-mercaptoethanol (0.06 mL, 0.84 mmol) and 1 N NaOMe (1.35 mL, 1.4 mmol) and the mixture was stirred at 80 °C for 6 h. The reaction mixture was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography using methylene chloride and methanol (8:1) as an eluent to give the hypoxanthine nucleoside (±)-**3** (34 mg, 91%) as a white solid: mp 168-171 °C; UV (MeOH) λ_{max} 248.0 nm; ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.32 (s, 1H, H-8), 8.08 (s, 1H, H-2), 5.14 (d, 1H, J = 7.0 Hz, 2-H), 5.11 (t, 1H, J = 8.0 Hz, 4-H), 4.28 (d, 1H, J = 11.5 Hz, C*H*HOH), 3.39 (d, 1H, J = 11.5 Hz, CH*H*OH), 2.02 (dd, 1 H, J = 7.5, 14.5 Hz, 3-C*H*H), 1.85 (m, 1 H, 3-CH*H*), 1.16 (d, 1H, J = 5.5 Hz, 6-C*H*H), 0.97 (s, 3H, 5-CH_3), 0.50 (d, 1H, J = 5.5 Hz, 6-CH*H*); ^{13}C NMR (125 MHz, MeOH-d_4) δ 159.11, 150.10, 146.67, 141.24, 125.04, 72.69, 61.80, 61.01, 41.08, 38.63, 31.37, 17.50, 14.69; LRMS (FAB+) m/z 277 $(M+H)^+$, 299 $(M+Na)^+$; HRMS (FAB+) m/z $C_{13}H_{17}N_4O_3$ $(M+H)^+$ calcd 277.1301, obsd 277.1304.

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