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PREPARATION OF 2',3'-METHANO-CARBOCYCLIC NUCLEOSIDES THROUGH THE ADDITION OF DIAZO-METHANE TO 2-AZABICYCLO[2.2.1]HEPT-5-EN-3-ONE

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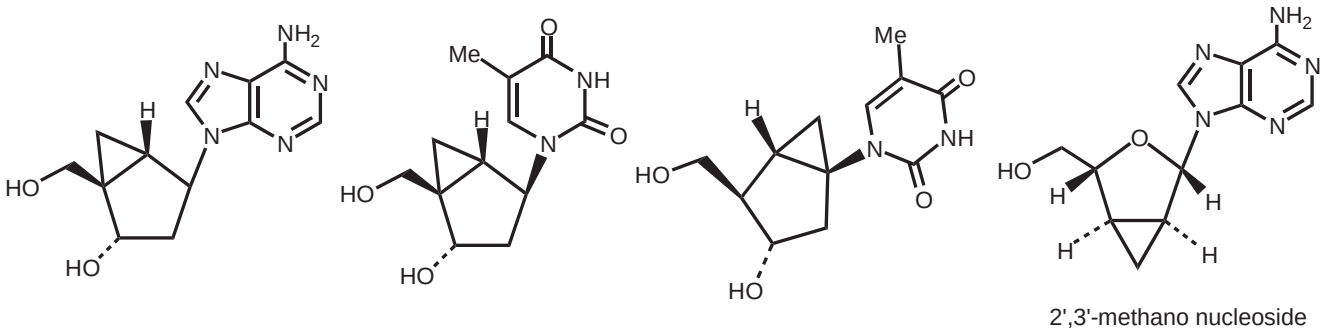
Abstract – The preparation of 2',3'-methano-carbocyclic analogues of adenosine is reported. The addition of diazomethane to *N*-substituted 2-azabicylo[2.2.1]-hept-5-en-3-one (ABH) (**1**) provided cyclopropane-fused ABH (**3**), which was converted to 2',3'-methano carbocyclic nucleosides (**8**).

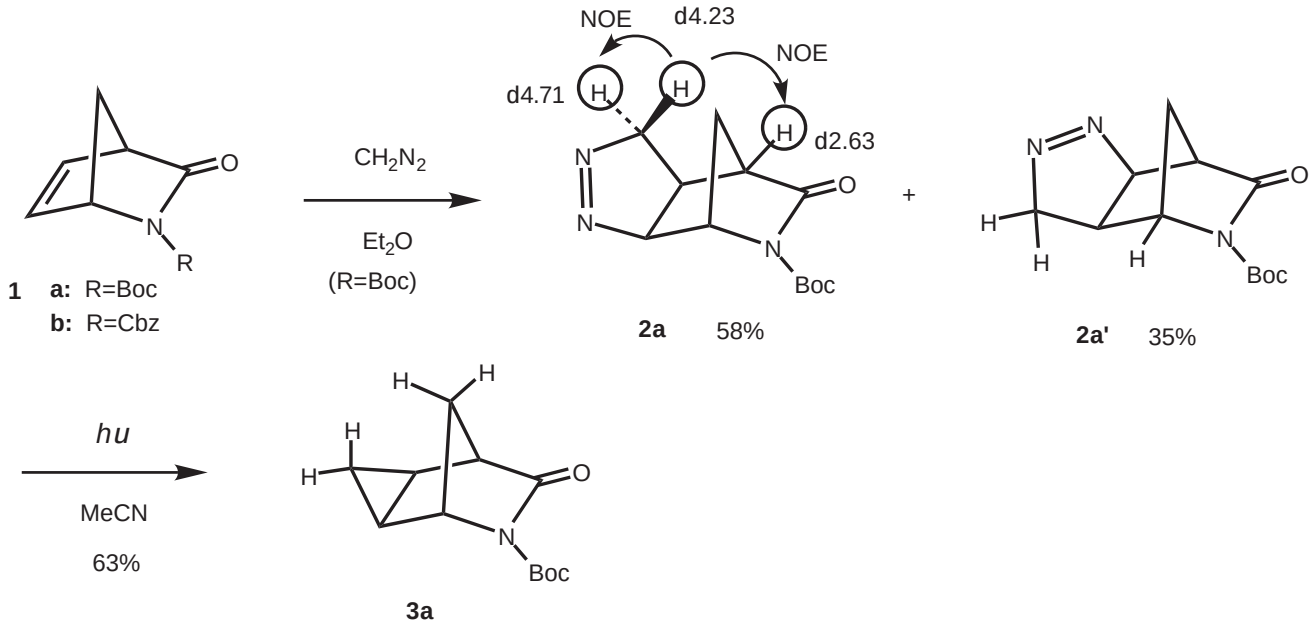
Intensive efforts to develop potent antiviral agents have resulted in the discovery of various nucleoside derivatives.[1] During these studies, "methanocarba" nucleoside modification of the ribose ring (1',6'- and 4',6'-methano carbocyclic nucleosides)[2] has been introduced in order to develop a new type of nucleoside analogue, in which the fused three-membered ring has a profound impact on fixing the conformation and the puckering of the cyclopentane ring. In connection with our studies to develop new carbocyclic nucleosides,[3] we have been interested in the preparation of a hitherto unknown 2',3'-methano carbocyclic nucleoside,[4] in which bicyclo[3.1.0]hexane (**5**), available from the introduction of cyclopropane ring into *N*-substituted 2-azabicylo[2.2.1]hept-5-en-3-one (ABH) (**1**), may serve as a key intermediate for the further transformation to methano-carbocyclic nucleoside, and these results are reported in this paper.[5]



2',3'-methano nucleoside

Initially, experiments to introduce a cyclopropane ring to ABH (**1**) were carried out based on the reaction of *N*-Boc-ABH (**1a**) with diazomethane. The simple treatment of **1a** with an excess of diazomethane in ether at room temperature smoothly provided two isomeric 1,3-dipolar adducts (**2a** and **2a'**), which were separated by silica gel column chromatography (Scheme 1). The structure of **2a** was assigned on the basis of NOE experiments. Subsequently, a mixture of **2a** and **2a'** was subjected to photolysis with a

high-pressure mercuric lamp, giving rise to cyclopropane-fused ABH (**3a**).



Scheme 1

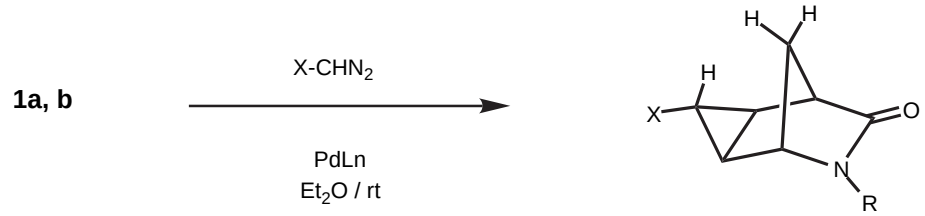
Our next objective was to find a more convergent way to **3** from **1**, and, thus, the palladium-catalyzed cycloaddition of diazomethane to **1** was examined (Scheme 2).[6] An ethereal solution of diazomethane was added dropwise to a solution of **1a** and a catalytic amount of palladium complex in ether at room temperature under an argon atmosphere, affording **3a** as a single isomer in an *exo*-selective manner.[7] Successful results were secured by the very slow addition of an ethereal solution of diazomethane. The similar treatment of **1a**, **b** with diazomethane and trimethylsilyldiazomethane in the presence of a palladium complex proceeded smoothly to give **3b-d**, respectively.

Reductive cleavage of the amide (N-CO) bond in **3c**,**d** with $NaBH_4$ provided alcohols (**4a**,**b**), respectively. Removal of the *N*-Cbz group in **4** by catalytic hydrogenation produced amines (**5**), which were subjected to condensation with 5-amino-4,6-dichloropyrimidine in *n*-butyl alcohol without purification to give pyrimidines (**6a**,**b**). The conversion of **6a**,**b** to purine (**7a**,**b**) was effected conventionally by the treatment of **6** with ethyl orthoformate under an acidic condition, or heating **6** with diethoxymethyl acetate. The introduction of an amino group to the purine ring in **7a** through the treatment with ammonia and cyclopropylamine produced adenosine analogues (**8a**,**b**), respectively.

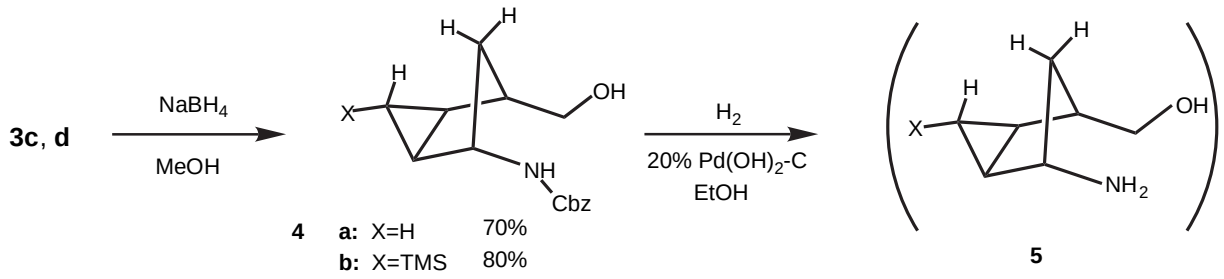
In summary, we have prepared 2',3'-methano-carbocyclic adenosine analogues (**8**) *via* a cyclopropanation reaction for the addition of diazomethane to ABH (**1**), and **8** were tested separately for *anti*-viral (HIV, HSV-1, VZV, RSV) and *anti*-tumor activities (MT-4, HeLa), but these compounds were not active in any of the tests performed.

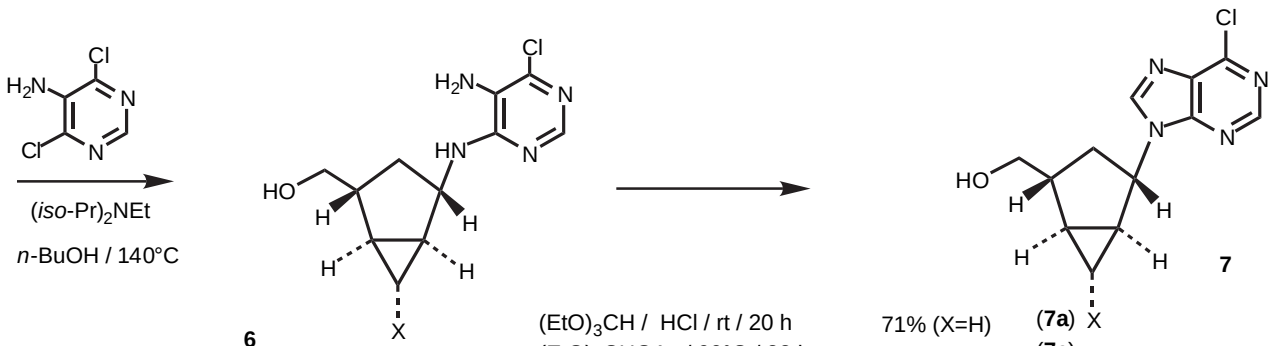
EXPERIMENTAL

Melting points were recorded on a Yamato MP21 and are uncorrected. MS and high-resolution MS



$Pd(OAc)_2$	83% (X=H)
$PdCl_2(PhCN)_2$	69% (X=H)
$Pd(OAc)_2$	85% (X=TMS)
$PdCl_2(PhCN)_2$	66% (X=TMS)





NH_3 / MeOH / 50°C / 15 h	72%	R= H	(**8a**)
H_2N / MeOH / 80°C / 15 h	65%	R=	(**8b**)

Scheme 2

were recorded on a Micromass AutoSpec 3100 mass spectrometer. IR spectra were measured on a Hitachi Model 270-30 spectrophotometer. The NMR experiments were performed with a JEOL JNM-LA300 or JNM-EX400 spectrometer, and chemical shifts are expressed in ppm (δ) with TMS as an internal reference. Medium-pressure liquid column chromatography (MPLC) and flash column chromatography were performed on silica gel (Silica gel 60N, Kanto Chemical Co., Inc.). Dehydrated THF was purchased from Kanto Chemical Co. Inc.

Reaction of 1a with diazomethane:

To a solution of **1a** (209 mg, 1 mmol) in ether (5 mL), excess amount of an ethereal solution of diazomethane was added under ice-cooling, and the mixture was then gradually warmed to rt and stirred for 15 h. After the solvent was removed, the residue was separated by MPLC with hexane:AcOEt=1:1 as an eluent to give **2a** (145 mg, 58 %) and **2a'** (87 mg, 35 %) .

***tert*-Butyl *rel*-(1*R*,2*R*,6*S*,7*S*)-4,5,8-Triaza-9-oxotricyclo[5.2.1.0^{2,6}]dec-4-ene-8-carboxylate (2a):**

mp 143-144°C (from AcOEt-hexane). IR ($CHCl_3$): 1788, 1756, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.88 (dt, 1H, *J*=11.7, 1.4 Hz), 1.58 (s, 9H), 1.85 (dt, 1H, *J*=11.7, 1.4 Hz), 2.50-2.60 (m, 1H), 2.63 (s, 1H), 4.23 (dt, 1H, *J*=19, 3.4 Hz), 4.71 (ddd, 1H, *J*=1.4, 9.8, 19 Hz), 5.06 (t, 1H, *J*=1.5 Hz), 5.29-5.34 (m, 1H). ^{13}C-NMR ($CDCl_3$): 28.0, 30.7, 34.0, 50.0, 59.6, 80.8, 83.7, 96.5, 148.9, 173.5. MS *m/z*: 223 (M^+-N_2). *Anal.* Calcd for $C_{12}H_{17}N_3O_3$: C, 56.03; H, 6.87; N, 16.34. Found: C, 56.28; H, 6.46; N, 16.49.

***tert*-Butyl *rel*-(1*R*,2*R*,6*R*,7*S*)-3,4,8-Triaza-9-oxotricyclo[5.2.1.0^{2,6}]dec-3-ene-8-carboxylate (2a'):**

mp 138-139°C (from AcOEt-hexane). IR ($CHCl_3$): 1788, 1756, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.82 (dt, 1H, *J*=1, 11 Hz), 1.53 (s, 9H), 1.86 (ddd, 1H, *J*=1, 3, 11 Hz), 2.59 (m, 1H), 3.47 (br s, 1H), 4.23 (dt, 1H, *J*=3, 19 Hz), 4.29 (br s, 1H), 4.58 (ddd, 1H, *J*=1, 9, 19 Hz), 5.28 (m, 1H). ^{13}C-NMR ($CDCl_3$): 28.0, 31.1, 39.3, 50.0, 60.8, 79.4, 83.6, 92.3, 149.1, 171.9. MS *m/z*: 223 (M^+-N_2). *Anal.* Calcd for $C_{12}H_{17}N_3O_3$: C, 56.03; H, 6.87; N, 16.34. Found: C, 55.96; H, 7.09; N, 16.22.

Formation of 3a by photolysis of a mixture of 2a and 2a'; Typical procedure:

A mixture of **2a** and **2a'** (500 mg) in acetonitrile (100 mL) was irradiated with a high-pressure mercuric lamp under ice-cooling for 3 h. The solvent was removed, and the residue was separated by MPLC with hexane:AcOEt=5:1 as an eluent to give **3a** (280 mg, 63 %).

Formation of 3b by the palladium-catalyzed addition of trimethylsilyldiazomethane to 1a; Typical procedure:

To a solution of **1a** (209 mg, 1 mmol) and palladium acetate (11 mg, 0.05 mmol) in ether (10 mL), trimethylsilyldiazomethane (2M in hexane, 3 mmol) was added dropwise slowly over 2 h at rt and the mixture was then stirred for 15 h. After the solvent was removed, the residue was separated by MPLC with hexane:AcOEt=5:1 as an eluent to give **3b** (228mg, 83 %).

***tert*-Butyl *rel*-(1*R*,2*R*,4*S*,5*S*)-6-Aza-7-oxotricyclo[3.2.1.0^{2,4}]octane-6-carboxylate (3a):** mp 77°C (from AcOEt-hexane). IR ($CHCl_3$): 1778, 1750, 1704 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.76 (dd, 1H, *J*=7.3, 14 Hz), 1.15 (td, 1H, *J*=3.4, 6.8 Hz), 1.34 (d, 1H, *J*=11 Hz), 1.41-1.46 (m, 2H), 1.53 (s, 9H), 1.65-1.70 (m, 1H), 2.86 (t, 1H, *J*=1.5 Hz), 4.48 (s, 1H). ^{13}C-NMR ($CDCl_3$): 10.3, 13.0, 19.5, 25.9, 27.8, 454.9, 58.9, 82.0, 149.7, 176.8. MS *m/z*: 223 (M^+). *Anal.* Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C,

64.47; H, 7.66; N, 6.27.

***tert*-Butyl *rel*-(1*R*,2*S*,3*R*,4*S*,5*S*)-6-Aza-3-(1,1-dimethyl-1-silaethyl)-7-oxotricyclo[3.2.1.0^{2,4}]octane-6-carboxylate (3b):** mp 110°C (from AcOEt-hexane). IR ($CHCl_3$): 1778, 1748, 1702 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.00 (s, 9H), 0.55 (t, 1H, *J*=4.4 Hz), 1.26 (t, 1H, *J*=4.9 Hz), 1.40-1.55 (m, 3H), 1.51 (s, 9H), 2.79 (s, 1H), 4.43 (s, 1H). ^{13}C-NMR ($CDCl_3$): -2.4, 0.48, 11.1, 17.1, 23.6, 26.8, 28.1, 46.9, 59.8, 82.4, 150.3, 176.4. MS *m/z*: 275 (M^+). *Anal.* Calcd for $C_{15}H_{25}NO_3Si$: C, 60.98; H, 8.53; N, 4.74. Found: C, 60.90; H, 8.51; N, 4.73.

Benzyl *rel*-(1*R*,2*R*,4*S*,5*S*)-6-Aza-7-oxotricyclo[3.2.1.0^{2,4}]octane-6-carboxylate (3c): mp 97°C (from AcOEt-hexane). IR ($CHCl_3$): 1788, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.77 (q, 1H, *J*=7.3 Hz), 1.10-1.18 (m, 1H), 1.36 (d, 1H, *J*=11.3 Hz), 1.40-1.45 (m, 1H), 1.46 (d, 1H, *J*=11.3 Hz), 1.66-1.72 (m, 1H), 2.90 (br s, 1H), 4.57 (br s, 1H), 5.26 (s, 2H), 7.30-7.40 (m, 3H), 7.41-7.45 (m, 2H). ^{13}C-NMR ($CDCl_3$): 10.5, 13.2, 19.7, 26.3, 46.1, 59.3, 67.7, 128.0, 128.3, 128.5, 135.5, 151.3, 175.8. MS *m/z*: 257 (M^+). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.87; N, 5.44. Found: C, 70.11; H, 5.93; N, 5.43.

Benzyl *rel*-(1*R*,2*S*,3*R*,4*S*,5*S*)-6-Aza-3-(1,1-dimethyl-1-silaethyl)-7-oxotricyclo[3.2.1.0^{2,4}]octane-6-carboxylate (3d): mp 71-72°C (from AcOEt-hexane). IR ($CHCl_3$): 1796, 1766, 1722 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.00 (s, 9H), 0.62 (t, 1H, *J*=4.4 Hz), 1.30-1.35 (m, 1H), 1.50-1.60 (m, 1H), 1.51 (br s, 2H), 2.88 (br s, 1H), 4.57 (br s, 1H), 5.30 (s, 2H), 7.31-7.42 (m, 3H), 7.43 (d, 2H, *J*=6.8 Hz). ^{13}C-NMR ($CDCl_3$): -2.3, 11.1, 17.0, 23.5, 26.8, 49.7, 60.0, 67.8, 128.0, 128.3, 128.5, 135.5, 151.5, 176.0. MS *m/z*: 329 (M^+). *Anal.* Calcd for $C_{18}H_{23}NO_3Si$: C, 65.62; H, 7.03; N, 4.25. Found: C, 65.70; H, 7.07; N, 4.25.

Reduction of 3 with $NaBH_4$; Typical procedure: To a solution of **3c** (150 mg, 0.58 mmol) in MeOH (10 mL), $NaBH_4$ (45 mg, 1.2 mmol) was added under ice-cooling, and the mixture was then stirred at rt for 1 h. After the mixture was concentrated on a rotary evaporator, the mixture was diluted with AcOEt (50 mL), washed with brine, and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was separated by MPLC with hexane:AcOEt= 2:1 as an eluent to give **4a** (108 mg, 71 %).

Benzyl *rel*-(1*S*,2*S*,4*R*,5*R*)-*N*-(4-Hydroxymethylbicyclo[3.1.0]hex-2-yl)carbamate (4a): syrup. IR (neat): 3670, 3020, 1706 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.17 (dd, 1H, *J*=4, 10 Hz), 0.52 (td, 1H, *J*=5, 10 Hz), 1.24-1.32 (m, 1H), 1.34-1.42 (m, 1H), 1.46 (d, 1H, *J*=14 Hz), 1.84 (td, 1H, *J*=7.8, 14 Hz), 2.17 (td, 1H, *J*=4, 8.3 Hz), 3.59 (dd, 1H, *J*=4, 10 Hz), 3.75 (dd, 1H, *J*=4, 10 Hz), 4.12 (d, 1H, *J*=7.3 Hz), 5.09 (s, 2H), 7.30-7.38 (m, 5H). ^{13}C-NMR ($CDCl_3$): 6.9, 20.2, 23.9, 33.7, 41.8, 52.7, 66.3, 66.7, 127.9, 128.0, 128.4, 136.9, 155.8. HR-MS *m/z*: Calcd for $C_{15}H_{19}NO$: 261.1365. Found: 261.1356.

Benzyl *rel*-(1*S*,2*S*,4*R*,5*R*,6*R*)-*N*-[6-(1,1-Dimethyl-1-silaethyl)-4-(hydroxymethyl)bicyclo[3.1.0]hex-2-yl]carbamate (4b): syrup. IR (neat): 3336, 1692 cm^{-1}. ^{1}H-NMR ($CDCl_3$): -0.69 (t, 1H, *J*=5 Hz), -0.07 (s, 9H), 1.23 (t, 1H, *J*=5 Hz), 1.33 (t, 1H, *J*=5 Hz), 1.50 (d, 1H, *J*=14 Hz), 1.80 (br s, 1H), 1.95-2.10 (m, 1H), 2.20-2.28 (m, 1H), 3.64 (dd, 1H, *J*=5, 10 Hz), 3.82 (dd, 1H, *J*=5, 10 Hz), 4.18 (d, 1H, *J*=7.3 Hz), 5.10 (s, 2H), 7.33-7.44 (m, 5H). ^{13}C-NMR ($CDCl_3$): -2.1, 6.9, 24.4, 28.1, 34.1, 42.5, 53.2, 66.3, 66.5, 127.9, 128.0, 128.4, 136.8, 155.8. HR-MS *m/z*: Calcd for $C_{18}H_{27}NO_3Si$: 333.1760. Found: 333.1757.

Formation of 6 from 4: Typical procedure: The catalytic hydrogenation of **4a** (180 mg, 0.69 mmol)

was carried out using 20% Pd-C (18 mg) in EtOH (10 mL) under a hydrogen atmosphere. After the solvent and catalyst were removed, the residue was dissolved in *n*-BuOH (5 mL) and added to a solution of diisopropylethylamine (160 mg, 1.4 mmol) and 5-amino-4,6-dichloropyrimidine (250 mg, 1.4 mmol) in *n*-BuOH (10 mL). The whole mixture was heated at 140°C for 3 days. The mixture was diluted with AcOEt, washed with brine several times, and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was separated by MPLC with hexane-AcOEt=1:1 as an eluent to give **6a** (144 mg, 82 %).

***rel*-(1*S*,2*S*,4*R*,5*R*)-[4-(5-Amino-6-chloropyrimidin-4-ylamino)bicyclo[3.1.0]hex-2-yl]methanol (6a):** mp 104 °C (from AcOEt-hexane). IR ($CHCl_3$): 3624, 3368 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 013 (dd, 1H, *J*=4, 9 Hz), 0.59 (dt, 1H, *J*=5.4, 9 Hz), 1.29 (ddd, 1H, *J*=4.4, 5.4, 9 Hz), 1.46 (dt, 1H, *J*=8.3, 4.4 Hz), 1.55 (d, 1H, *J*=15 Hz), 2.00 (ddd, 1H, *J*=7.8, 8.3, 15 Hz), 2.28 (dt, 1H, *J*=9.3, 2.9 Hz), 3.43 (br s, 1H), 3.69 (dd, 1H, *J*=2.9, 10 Hz), 3.92 (dd, 1H, *J*=2.9, 10 Hz), 4.61 (t, 1H, *J*=7.8 Hz), 6.74 (br s, 2H), 8.04 (s, 1H). ^{13}C-NMR (DMSO-d_6): 7.0, 20.3, 20.4, 32.4, 42.5, 53.0, 65.5, 123.1, 137.8, 146.4, 151.8. MS *m/z*: 254 (M^+). *Anal.* Calcd for $C_{11}H_{15}N_4OCl$: C, 52.00; H, 6.02; N, 21.84. Found: C, 51.87; H, 5.94; N, 2.99.

***rel*-(1*S*,2*S*,4*R*,5*R*,6*R*)-[4-(5-Amino-6-chloropyrimidin-4-ylamino)-6-(1,1-dimethyl-1-silaethyl)-bicyclo[3.1.0]hex-2-yl]methanol (6b):** mp 159°C (from AcOEt-hexane). IR ($CHCl_3$): 3624, 3352 cm^{-1}. ^{1}H-NMR ($CDCl_3$): -0.53 (t, 1H, *J*=5 Hz), 0.00 (s, 9H), 1.25 (t, 1H, *J*=5 Hz), 1.38 (t, 1H, *J*=5 Hz), 1.56 (d, 1H, *J*=15 Hz), 2.17 (ddd, 1H, *J*=8. 9.2, 15 Hz), 2.31 (d, 1H, *J*=9.2 Hz), 3.73 (dd, 1H, *J*=2.9, 10 Hz), 3.96 (dd, 1H, *J*=2.9, 10 Hz), 4.70 (br s, 1H), 6.84 (br s, 1H), 8.06 (s, 1H). ^{13}C-NMR ($CDCl_3$): -2.1, 7.1, 24.4, 28.3, 34.4, 42.5, 52.7, 66.1, 122.2, 139.7, 148.6, 153.3. MS *m/z*: 326 (M^+). *Anal.* Calcd for $C_{14}H_{23}N_4OClSi$: C, 51.44; H, 7.09; N, 17.14. Found: C, 51.35; H, 6.96; N, 16.86.

Formation of 7 from 6; Typical procedure:

Procedure A: To a mixture of **6a** (370 mg, 1.45 mmol) and triethyl orthoformate (10 mL), 30% hydrochloric acid (0.1 mL) was added, and the whole mixture was stirred at rt for 20 h. The reaction mixture was made alkaline with 10% NaOH (1 mL), and extracted with AcOEt (50 mL). The extract was washed with brine, and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was separated by flash column chromatography with AcOEt:hexane= 1:2 as an eluent to give **7a** (270 mg, 71 %).

Procedure B: A mixture of **6a** (100 mg, 0.39 mmol) and diethoxymethyl acetate (5 mL) was heated at 90°C for 38 h. The mixture was concentrated, and the residue was separated by flash column chromatography with AcOEt:hexane= 1:2 as an eluent to give **7a** (75 mg, 72 %).

***rel*-(1*S*,2*S*,4*R*,5*R*)-[{4-(6-Chloropurin-9-yl)bicyclo[3.1.0]hex-2-yl}methanol (7a):** mp 177°C (from MeOH). IR ($CHCl_3$): 3624 cm^{-1}. ^{1}H-NMR (pyridine-d_5): 0.35 (dd, 1H, *J*=3.9, 8.8 Hz), 0.77 (dt, 1H, *J*=5.4, 8.3 Hz), 1.82 (td, 1H, *J*=4.4, 8.3 Hz), 1.92 (td, 1H, *J*=4.4, 8.3 Hz), 2.10 (td, 1H, *J*=7.8, 15.6 Hz), 2.25 (d, 1H, *J*=15 Hz), 2.46 (dd, 1H, *J*=7.3, 15.4 Hz), 3.55 (dd, 1H, J=7.8, 10 Hz), 3.74 (dd, 1H, *J*=6.8, 10 Hz), 5.06 (d, 1H, *J*=7.3 Hz), 8.90 (s, 1H), 9.00 (s, 1H). ^{13}C-NMR ($CDCl_3$): 8.3, 21.4, 21.7, 33.1, 42.8, 57.7, 65.7, 132.0, 143.9, 150.8, 151.7. MS *m/z*: 264 (M^+). *Anal.* Calcd for $C_{12}H_{13}N_4OCl$: C, 54.45; H, 4.95; N, 21.16. Found: C, 54.47; H, 4.94; N, 21.15.

***rel*-(1*S*,2*S*,4*R*,5*R*,6*R*)-[4-(6-Chloropurin-9-yl)-6-(1,1-Dimethyl-1-silaethyl)bicyclo[3.1.0]hex-2-yl]-**

methanol (7b): mp 153°C (from AcOEt-hexane). IR ($CHCl_3$): 3624, 3392 cm^{-1}. ^{1}H-NMR ($CDCl_3$): -0.35 (t, 1H, *J*=4.8 Hz), 0.00 (s, 9H), 1.66 (t, 1H, *J*=5 Hz), 1.71 (t, 1H, *J*=5 Hz), 1.82 (br s, 1H), 1.88 (d, 1H, *J*=15 Hz), 2.24-2.42 (m, 2H), 3.47 (dd, 1H, *J*=6.3, 10 Hz), 3.53 (dd, 1H, *J*=6.3, 10 Hz), 5.10 (d, 1H, *J*=7.3 Hz), 8.48 (s, 1H), 8.70 (s, 1H). ^{13}C-NMR ($CDCl_3$): -2.2, 8.7, 25.7, 26.1, 34.0, 43.7, 58.2, 65.7, 96.1, 131.7, 144.3, 150.5, 151.6, 151.7. MS *m/z*: 336 (M^+). *Anal.* Calcd for $C_{15}H_{21}N_4OClSi$: C, 53.48; H, 6.28; N, 16.63. Found: C, 53.61; H, 6.13; N, 16.54.

Formation of 8a: A mixture of **7a** (100 mg, 0.38 mmol) and dry MeOH (10 mL) saturated with ammonia was heated at 50°C in a sealed tube for 15 h. The solvent was removed, and the residue was separated by flash column chromatography with CH_2Cl_2-MeOH=25:1 as an eluent to give **8a** (66 mg, 72 %).

***rel*-(1*S*,2*S*,4*R*,5*R*)-[4-(6-Aminopurin-9-yl)bicyclo[3.1.0]hex-2-yl]methanol (8a):** mp 215-216°C (from MeOH). IR (KBr): 3332, 3164, 1664, 1604, 1566 cm^{-1}. ^{1}H-NMR (pyridine-d_5): 0.25-0.32 (m, 1H), 0.68 (td , 1H, *J*=8.3, 5.3 Hz), 1.80-1.87 (m, 2H), 2.07 (td, 1H, *J*=7.8, 15.6 Hz), 2.28 (d, 1H, *J*=15 Hz), 2.47 (q, 1H, *J*=7.8 Hz), 3.57 (dd, 1H, *J*=8.3, 10 Hz), 3.77(dd, 1H, *J*=7.3, 10 Hz), 5.06 (d, 1H, *J*=7.3 Hz), 5.20 (br s, 1H), 8.24 (br s, 2H), 8.51 (s, 1H), 8.74 (s, 1H). ^{13}C-NMR (DMSO-d_6): 7.3, 20.3, 20.8, 31.9, 42.9, 56.2, 64.4, 79.1, 119.3, 138.3, 149.4, 152.1, 155.9. MS *m/z*: 243 (M^+). *Anal.* Calcd for $C_{12}H_{13}N_5O$: C, 59.25; H, 5.39; N, 28.79. Found: C, 59.15; H, 5.50; N, 28.63.

Formation 8b: A mixture of **7a** (100 mg, 0.38 mmol) and cyclopropylamine (45 mg, 0.8 mmol) in anhydrous MeOH (10 mL) was heated in a sealed tube at 80°C for 15 h. The solvent was removed, and the residue was separated by flash column chromatography with CH_2Cl_2-MeOH=25:1 as an eluent to give **8b** (70 mg, 65 %).

***rel*-(1*S*,2*S*,4*R*,5*R*)-{[4-6-(Cyclopropylamino)purin-9-yl]bicyclo[3.1.0]hex-2-yl}methanol (8b):** mp 185°C (from MeOH). IR (KBr): 3292, 3028, 1628, 1578 cm^{-1}. ^{1}H-NMR (CD_3OD): 0.44 (dd, 1H, *J*=4, 9 Hz), 0.61-0.67 (m, 2H), 0.84-0.92 (m, 3H), 1.79 (dt, 1H, *J*=8.3, 4.4 Hz), 1.86 (d, 1H, *J*=15 Hz), 1.93 (dt, 1H, *J*=8.8, 4.4 Hz), 2.08 (dt, 1H, J=15, 7.4 Hz), 2.27 (q, 1H, *J*=8.3 Hz), 2.95 (br s, 1H), 3.15 (dd, 1H, *J*=7.8, 10 Hz), 3.36 (dd, 1H, *J*=7.3, 10 Hz), 4.93 (d, 1H, *J*=6.8 Hz), 8.29 (s, 1H), 8.32 (s, 1H). ^{13}C-NMR (CD_3OD): 7.6, 8.5, 21.7, 22.1, 24.4, 33.6, 44.2, 58.3, 66.3, 121.0, 139.9, 149.6, 153.3, 157.0. MS *m/z*: 285 (M^+). *Anal*. Calcd for $C_{15}H_{19}N_5O$: C, 63.14; H, 6.71; N, 24.54. Found: C, 62.97; H, 6.73; N, .24.50

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The structures of **3** were deduced from the structures of **7a** and **6b**, which were assigned based on NOE experiments (Figure).

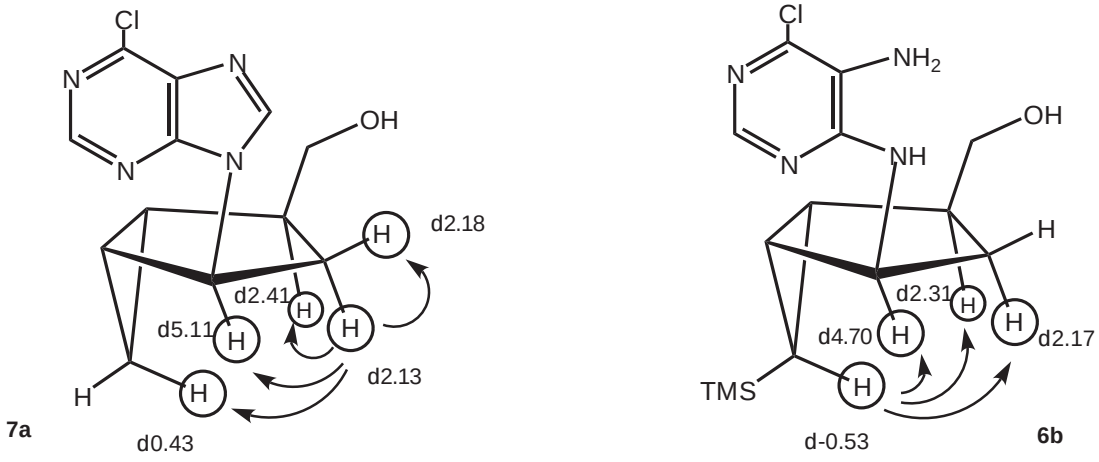

Figure NOE correlations of **6b** and **7a**