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PREPARATION OF 2',3'-EPIMINO-CARBOCYCLIC NUCLEOSIDES BASED ON 2-AZABICYCLO[2.2.1]HEPT-5-EN-3-ONE

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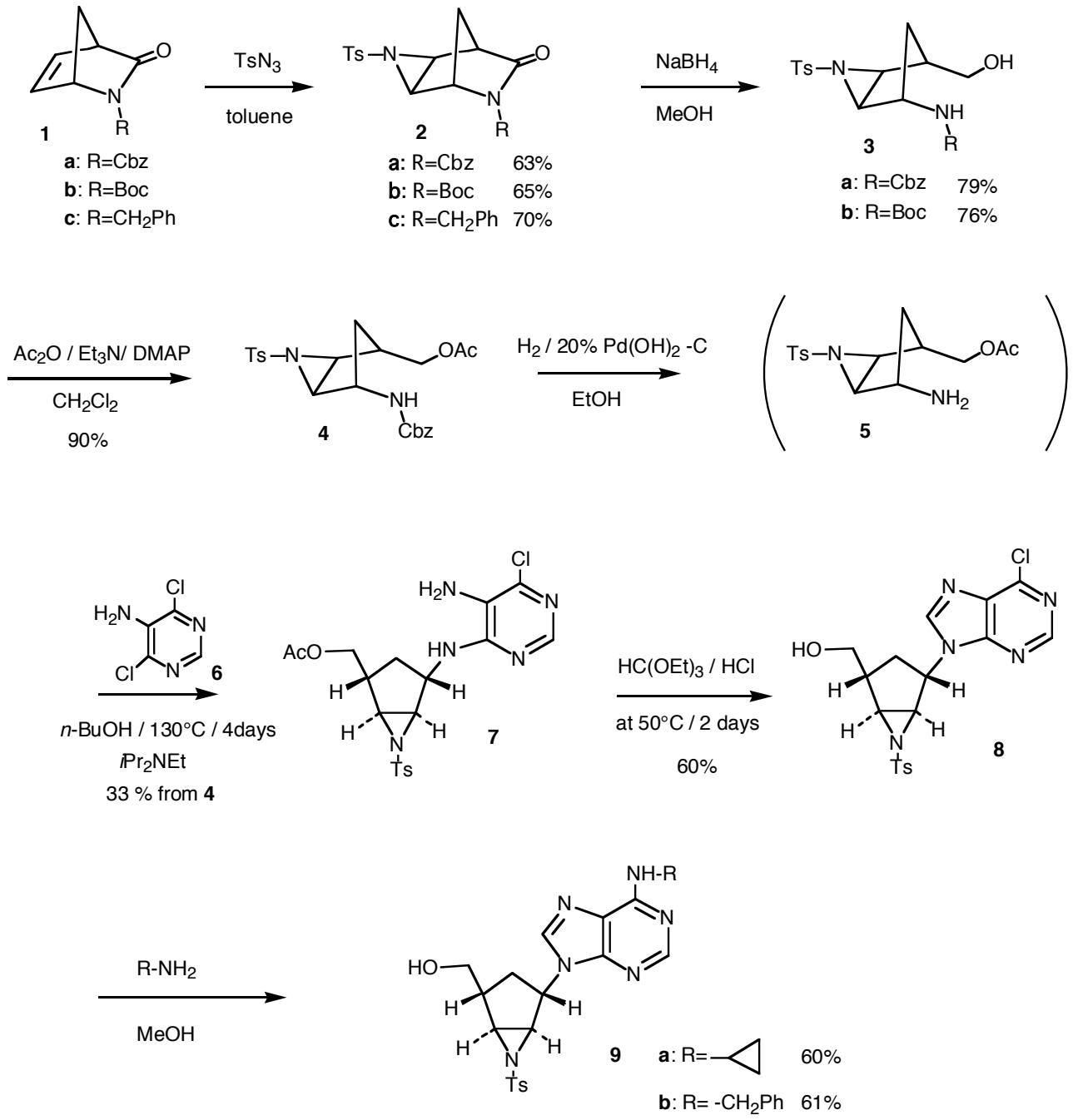
Abstract – The thermal reaction of *N*-substituted 2-azabicyclo[2.2.1]hept-5-en-3-one (ABH) (**1**) with tosyl azide, which allowed the stereoselective introduction of an aziridine moiety into ABH (**1**), led to the facile construction of 6-azabicyclo[3.1.0]hexane (**3**). Successful conversion of **3** to the hitherto unknown 2',3'-epimino-carbocyclic nucleosides (**8**) could be attained through a series of steps.

While searching for improved nucleosides with potent *anti*-viral activities, the studies of the conformational restriction of nucleoside and nucleotide molecules that may adopt a range of conformations were used to define the role of sugar puckering in stabilizing the active form, and a methano-carba approach was adopted to constrain the sugar ring of nucleosides.[1] In connection with our recent interest in developing novel carbocyclic nucleosides based on 2-azabicyclo[2.2.1]hept-5-en-3-one (ABH) (**1**; R=H), we have recently reported the first preparation of 2',3'-methano-carbocyclic nucleosides based on *exo*-selective cycloaddition of diazomethane to *N*-substituted ABH (**1**) as key feature.[2] The stereoselectivity in the introduction of the cyclopropane moiety encouraged us to diverse a common route to novel carbocyclic nucleosides fused with a three-membered ring. Since only a few epimino-nucleosides appear in the literature and there are not known epimino-carbocyclic nucleosides,[3] we have become attracted to the preparation of novel 2',3'-epimino-carbocycilc nucleosides in which the ring oxygen is replaced with a methylene group and the cyclopentane ring would be expected to exist in a puckered conformation by the fusion of an aziridine moiety at the 2' and 3' positions. These results are described in this paper.[4]

As depicted in Scheme, our synthetic plan includes the stereoselective introduction of an aziridine moiety into **1** in the intial step, and the coupling of amine (**5**) with dichloropyrimidine in a later step. Thus, our

initial interest was the preparation of 6-azabicyclo[3.1.0]hexane (**3**), which may serve as a key intermediate for the construction of 2',3'-epimino-carbocyclic nucleosides (**9**). We have previously reported the formation of aziridine-fused ABH through high-pressure promoted 1,3-dipolar cycloaddition



Scheme

of azides, followed by photolysis of the resulting triazoline derivatives;[5] however, their instability did not permit further transformations. During these studies, TsN_3 was found to be a prominent nitrene precursor whose reaction with **1** under thermal conditions allowed the facile formation of **2**. The reaction of **1** with TsN_3 in toluene at 120°C smoothly led to aziridine-fused ABH (**2**) as a single isomer *via* the *exo*-

addition of nitrene to the double bond of **1**.[6] The structures of **2a** and **2c** were deduced based on NOE experiments as shown in Figure, in which there was detected no NOE between H-4 and H-8.

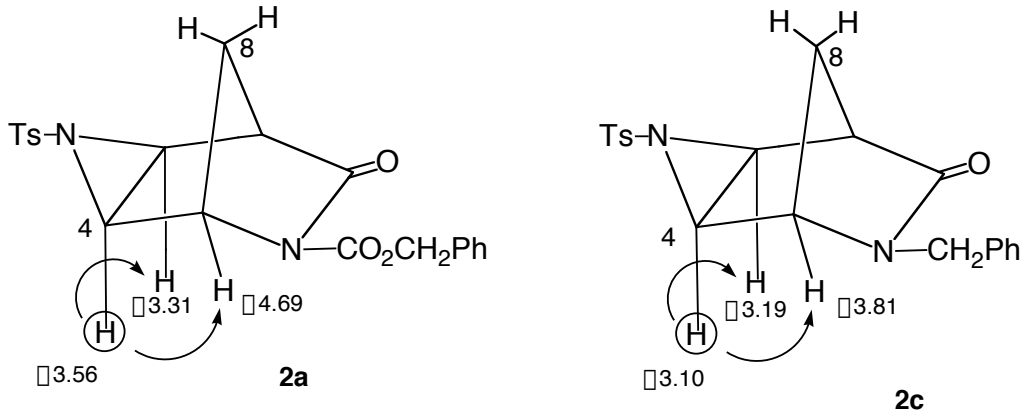


Figure NOE correlations of **2**

Reductive cleavage of the amide bond (N-CO) in **2** with $NaBH_4$ in MeOH afforded **3**. Because of ready availability of amine (**5**), **3a** was subjected to subsequent transformations. Acetylation of **3a** with acetic anhydride successively afforded acetate (**4**), and amine (**5**), readily available from the catalytic hydrogenation of **4**, could be coupled with dichloropyrimidine (**6**) in *n*-BuOH at 130°C for 4 days to produce **7** in 33 % yield. Treatment of **7** with excess amounts of ethyl orthoformate at 50°C in the presence of HCl provided **8** in 60% yield, and subsequent treatment with amines afforded the novel 2',3'-epimino-carbocyclic nucleosides (**9**).

In summary, we have prepared novel 2',3-epimino-carbocyclic analogues of adenosine (**9**) *via* the stereoselective addition of tosylazide to *N*-substituted ABH (**1**) as the key feature, and **9** were evaluated in *anti*-viral (HIV, HSV, VZV, RSV) activities, failed to find any activities.

EXPERIMENTAL

Melting points were recorded on a Yamato MP21 and are uncorrected. MS and high-resolution MS spectra 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 (□) 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 solvents were purchased from Kanto Chemical Co. Inc.

Reaction of 1 with tosylazide; General procedure:
A mixture of **1** (20 mmol) and tosyl azide (5.9 g, 30 mmol) in toluene (60 mL) was heated at 120°C for 10 h, and the mixture was concentrated *in vacuo*. The residue was separated by MPLC with hexane: AcOEt=1:1 as an eluent to give **2**.

Benzyl *rel*-(1*S*,2*R*,4*S*,5*R*)-3-(4-Methylphenylsulfonyl)-7-oxo-3,6-diazatricyclo[3.2.1.$0^{2,4}$]octane-6-

carboxylate (2a): syrup. IR (neat): 1798, 1775, 1718 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.58 (d, 1H, *J*=10.6 Hz), 1.93 (d, 1H, *J*=10.6 Hz), 2.47 (s, 3H), 3.08 (t, 1H, *J*=1.4 Hz), 3.31 (d, 1H, *J*=5.8 Hz), 3.56 (d, 1H, *J*=5.8 Hz), 4.69 (t, 1H, *J*=1.5 Hz), 5.26 (s, 2H), 7.32-7.44 (m, 7H), 7.81 (d, 2H, *J*=8.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.7, 28.5, 38.1, 41.9, 47.1, 58.4, 68.5, 128.1, 128.2, 128.6, 128.7, 130.0, 134.0, 134.8, 145.3, 150.7, 171.5. HR-MS *m/z*: Calcd for $C_{21}H_{20}N_2O_5S$: 412.1093. Found: 412.1104.

***tert*-Butyl *rel*-(1*S*,2*R*,4*S*,5*R*)-3-(4-Methylphenylsulfonyl)-7-oxo-3,6-diazatricyclo[3.2.1.0^{2,4}]octane-6-carboxylate (2b):** mp 162-163 °C (hexane-AcOEt). IR ($CHCl_3$): 1788, 1746, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (s, 9H), 1.57 (d, 1H, *J*=10.7 Hz), 1.89 (d, 1H, *J*=10.7 Hz), 2.47 (s, 3H), 3.04 (s, 1H), 3.32 (d, 1H, *J*=6.0 Hz), 3.59 (d, 1H, *J*=6.0 Hz), 4.62 (s, 1H), 7.38 (d, 2H, *J*=8.3 Hz), 7.81 (d, 2H, *J*=7.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.7, 28.0, 28.4, 38.5, 42.1, 47.2, 57.8, 83.8, 128.0, 129.9, 134.2, 145.3, 149.3, 171.9. MS *m/z*: 378 (M^+). *Anal.* Calcd for $C_{18}H_{22}N_2O_5S$: C, 57.13; H, 5.86; N, 7.40. Found: C, 57.19; H, 5.90; N, 7.37.

***rel*-(1*S*,2*R*,4*S*,5*R*)-6-Benzyl-3-(4-methylphenylsulfonyl)-7-oxo-3,6-diazatricyclo[3.2.1.0^{2,4}]octane (2c):** mp 165-166°C (from AcOEt-hexane). IR ($CHCl_3$): 1702 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.51 (d, 1H, *J*=10.3 Hz),1.85 (d, 1H, *J*=10.3 Hz), 2.46 (s, 3H), 2.99 (s, 1H), 3.10 (d, 1H, *J*=5.7 Hz), 3.19 (d, 1H, *J*=5.7 Hz), 3.81 (s, 1H), 4.32 (d, 1H, *J*=14.3 Hz), 4.39 (d, 1H, *J*=14.3 Hz), 7.18-7.25 (m, 2H), 7.28-7.33 (m, 5H), 7.71 (d, 2H, *J*=8.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.7, 31.5, 40.3, 43.7, 45.9, 46.3, 58.5, 128.1, 128.2, 128.3, 129.0, 129.9, 134.3, 136.7, 145.0, 175.7. MS *m/z*: 368 (M^+). *Anal.* Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.20; H, 5.47; N, 7.60. Found: C, 65.19; H, 5.55; N, 7.62.

Reduction of 2 with $NaBH_4$; General procedure:

To a stirred solution of **2** (10 mmol) in MeOH (50 mL) and CH_2Cl_2 (6 mL), $NaBH_4$ (740 mg, 20 mmol) was added portionwise at 0°C. After the mixture was stirred at 0°C for 30 min, acetone (5 mL) was added to the mixture, and the mixture was concentrated *in vacuo*. The residue was diluted with AcOEt (200 mL), and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was separated by MPLC with hexane:AcOEt=1:1 as an eluent to give **3**.

Benzyl *rel*-(1*S*,2*R*,4*S*,5*R*)-*N*-[4-Hydroxymethy-6-(4-methylphenylsulfonyl)-6-azabicyclo[3.1.0]-hex-2-yl]carbamate (3a): mp 143-145°C (AcOEt-hexane). IR ($CHCl_3$): 3624, 3376, 3016, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (d, 1H, *J*=14.7 Hz),1.85 (br s,1H), 2.11-2.17 (m, 1H), 2.40-2.47 (m, 1H), 2.45 (s, 3H), 3.27 (d, 1H, *J*=4.4 Hz), 3.37 (br s, 1H), 3.63-3.68 (m, 1H), 3.89-3.96 (m, 1H), 4.18-4.25 (m, 1H), 5.07 (s, 2H), 6.20 (d, 1H, *J*=7.8 Hz), 7.33-7.34 (m, 7H), 7.80 (d, 2H, *J*=7.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.6, 34.1, 40.7, 48.0, 49.6, 50.8, 63.7, 66.6, 127.7, 128.1, 128.5, 129.8, 135.2, 136,5, 144.5, 155.7. MS *m/z*: 416 (M^+). *Anal.* Calcd for $C_{21}H_{24}N_2O_5S$: C, 60.56; H, 5.81; N, 6.73. Found: C, 60.59; H, 5.89; N, 6.72.

***tert*-Butyl *rel*-(1*S*,2*R*,4*S*,5*R*)-*N*-[4-Hydroxymethy-6-(4-methylphenylsulfonyl)-6-azabicyclo[3.1.0]-hex-2-yl]carbamate (3b):** mp 133°C (AcOEt-hexane). IR ($CHCl_3$): 3650, 3495, 1702 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40-1.42 (m, 1H), 1.42 (s, 9H), 2.01-2.20 (m, 1H), 2.38-2.45 (m, 1H), 2.44 (s, 3H), 2.50 (br s, 1H), 3.26 (d, 1H, *J*=4.4 Hz), 3.37 (d, 1H, *J*=4.4 Hz), 3.63 (d, 1H, *J*=8.8 Hz), 3.89 (d, 1H, *J*=8.8 Hz), 4.15 (br s, 1H), 5.88 (d, 1H, *J*=9.3 Hz), 7.33 (d, 2H, *J*=7.8 Hz), 7.81(d, 2H, *J*=7.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.6, 28.4, 34.1, 40.9, 48.1, 49.8, 50.3, 63.7, 79.3, 127.7, 129.8, 135.2, 144.5, 155.2. MS *m/z*: 382 (M^+). *Anal.* Calcd for $C_{18}H_{26}N_2O_5S$: C, 56.52; H, 6.85; N, 7.32. Found: C, 56.39; H, 7.04; N, 7.25.

***rel*-(1*S*,2*R*,4*S*,5*R*)-4-Benzyloxycarbonylamino-6-(4-methylphenylsulfonyl)-6-azabicyclo[3.1.0]hex-2-ylmethyl Acetate (4):**

A mixture of **3a** (4.16 g, 10 mmol), triethylamine (2.8 mL, 20 mmol), 4-dimethylaminopyridine (610 mg, 5 mmol) and acetic anhydride (1.9 mL, 20 mmol) in CH_2Cl_2 (60 mL) was stirred at rt for 1 h. The mixture was concentrated in vacuo, and the residue was extracted with AcOEt. The extract was washed with 10% aq. NaOH and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by MPLC with hexane:AcOEt=1:1 as an eluent to give 4.1 g (90%) of **4** as crystrals. mp 129-130°C (AcOEt-hexane). IR ($CHCl_3$): 3448, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (d, 1H, *J*=14.6 Hz), 2.08 (s, 3H), 2.08-2.14 (m, 1H), 2.56-2.64 (m, 1H), 2.38 (s, 3H), 3.38 (s, 2H), 3.90 (dd, 1H, *J*=5.9, 11.2 Hz),

4.10-4.18 (m, 1H), 4.28 (dd, 1H, *J*=5.0, 11.2 Hz), 5.09 (s, 2H), 5.38 (br s, 1H), 7.30-7.40 (m, 7H), 7.81 (d, 2H, *J*=7.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 20.8, 21.6, 33.1, 38.7, 46.8, 48.7, 51.2, 65.3, 66.9, 127.7, 128.1, 128.4, 128.6, 129.8, 135.0, 136.2, 144.7, 155.4, 170.5. MS *m/z*: 458 (M^+). *Anal.* Calcd for $C_{23}H_{26}N_2O_6S$: C, 60.25; H, 5.72; N, 6.11. Found: C, 60.26; H, 5.75; N, 6.15.

***rel*-(1*S*,2*R*,4*S*,5*R*)-4-(5-Amino-6-chloropyrimidin-4-ylamino)-6-(4-methylphenylsulfonyl)-6-azabicyclo[3.1.0]hex-2-ylmethyl Acetate (7):**
Acetate (**4**) (2.3g, 5mmol) was subjected to a catalytic hydrogenation on 20% $Pd(OH)_2$ on C (230 mg) in AcOEt (30 mL) under medium pressure of hydrogen (4 atm). The catalyst was removed by filtration, the solvent was removed to give **5**, which was subjected to further reaction without purification. A mixture of **5**, 5-amino-4,6-dichloropyrimidine (1.64g, 10 mmol) and diisopropylethylamine (1.7 mL, 10 mmol) in *n*-BuOH (30 mL) was heated at 130°C for 4 days. After the solvent was removed *in vacuo*, the residue was extracted with AcOEt, the extract was washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was separated by silica gel column chromatography with hexane:AcOEt=1:1 as an eluent to give 740 mg (33%) of **7** as crystals. mp 211-212°C (EtOH). IR (KBr): 3420, 3340, 3228, 1720 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 1.95 (s, 3H), 2.09 (dd, 1H, *J*=8.1, 13.8 Hz), 2.18 (s, 3H), 2.43 (d, 1H, *J*=13.8 Hz), 2.76 (s, 1H), 3.11 (d, 1H, *J*=10.3 Hz), 3.59 (br s, 1H), 3.80 (d, 1H, *J*=11.8 Hz), 5.05 (d, 1H, *J*=5.4 Hz), 5.27 (br s, 2H), 5.51 (s, 1H), 7.17 (d, 2H, *J*=6.8 Hz), 7.96 (d, 2H, *J*=6.8 Hz), 8.12 (s, 1H), 9.16 (s, 1H). ^{13}C-NMR (pyridine-d_5) δ: 20.9, 21.1, 34.3, 39.4, 52.8, 59.3, 61.1, 75.5, 125.9, 127.4, 129.9, 137.9, 143.3, 143.5, 146.8, 152.4, 171.7. MS *m/z*: 451 (M^+). HR-MS *m/z* Calcd for $C_{19}H_{22}N_5O_4ClS$: 451.1081. Found: 451.1080. *Anal.* Calcd for $C_{19}H_{22}N_5O_4ClS$: C, 50.50; H, 4.91; N, 15.50. Found: C, 50.40; H, 4.98; N, 15.37.

***rel*-(1*S*,2*R*,4*S*,5*R*)-4-(6-Chloropurin-9-yl-2-hydroxymethyl-6-(4-methylphenylsulfonyl)-6-azabicyclo[3.1.0]hexane (8):**
A mixture of **7** (100 mg, 0.22 mmol), ethyl orthoformate (10 mL), and one drop of conc-HCl was heated at 50°C for 48 h, and the mixture was concentrated *in vacuo*. To the residue, one drop of 1N HCl and THF (10 mL) were added, and the whole was heated at 50°C for 24 h. After the mixture was concentrated *in vacuo*, the residue was separated by flash column chromatography with AcOEt as an eluent to give 55 mg (60 %) of **8** as crystals. mp 162-163°C (acetone-hexane). IR (nujol): 3350 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.71 (dt, 1H, *J*=13.2, 2.3 Hz), 1.93 (dd, 1H, *J*=7.4, 13.2 Hz), 2.43 (s, 3H), 2.45 (s, 1H), 3.03 (s, 1H), 3.42-3.46 (m, 1H), 3.56 (s, 1H), 3.97 (d, 1H, *J*=6.9 Hz), 4.36 (s, 1H), 7.39 (d, 2H, *J*=8.0 Hz), 7.77 (d, 2H, *J*=8.0 Hz), 8.14 (s, 1H), 8.21 (s, 1H). ^{13}C-NMR (CD_3OD) δ: 20.2, 36.3, 40.2, 53.3, 58.9, 61.9, 71.7, 110.8, 126.9, 129.7, 137.5, 143.9, 155.3, 166.0. HR-MS *m/z*: Calcd for $C_{18}H_{18}N_5O_3ClS$ 419.0819. Found: 419.0817. *Anal.* Calcd for $C_{18}H_{18}N_5O_3SCl$: C, 51.49; H, 4.32; N, 16.68. Found: C, 51.36; H, 4.56; N, 16.49.

Reaction of 8 with amines; General procedure:
A mixture of **8** and amines (3 equiv.) in dioxane was heated in a sealed tube at 80°C overnight. The mixture was concentrated *in vacuo*, and the residue was separated by flash chromatography with AcOEt an an eluent to give **9**.

***rel*-(1*S*,2*R*,4*S*,5*R*)-4-(6-Cyclopropylaminopurin-9-yl-2-hydroxymethyl-6-(4-methylphenylsulfonyl)-6-azabicyclo[3.1.0]hexane (9a):** mp 167-168°C (MeOH). IR (nujol): 3288, 1686, 1666 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.47-0.51 (m, 2H), 0.71-0.76 (m, 2H), 1.67 (dd, 1H, *J*=2.5, 13.5 Hz), 1.88 (dd, 1H, *J*=7.4, 13.5 Hz), 2.38 (br s, 1H), 2.43 (s, 3H), 2.58-2.63 (m, 1H), 2.90 (d, 1H, *J*=9.7 Hz), 3.25-3.31 (m, 1H), 3.51 (s, 1H), 3.99 (d, 1H, *J*=7.4 Hz), 4.19 (s, 1H), 7.39 (d, 2H, *J*=8.0 Hz), 7.77 (d, 2H, *J*=8.0 Hz), 7.93 (s, 1H), 8.12 (s, 1H). ^{13}C-NMR (CD_3OD) δ: 7.4, 7.5, 21.2, 25.0, 37.4, 41.4, 54.3, 60.1, 62.4, 73.1, 94.2, 127.9, 138.0, 138.9, 144.9, 155.9, 157.9, 164.1. MS *m/z*: 440 (M^+). HR-MS *m/z*: Calcd for $C_{21}H_{24}N_6O_3S$: 440.1630. Found: 440.1637. *Anal.* Calcd for $C_{21}H_{24}N_6O_3S+H_2O+2/3CH_3OH$: C, 54.23; H, 6.02; N, 17.51. Found: C, 54.00; H, 5.94; N, 17.71.

***rel*-(1*S*,2*R*,4*S*,5*R*)-4-(6-Benzylaminopurin-9-yl-2-hydroxymethyl-6-(4-methylphenylsulfonyl)-6-**

azabicyclo[3.1.0]hexane (9b): mp 173-174°C (MeOH). IR (nujol): 3424, 3304, 1674 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.68 (d, 1H, *J*=13.7 Hz), 1.90 (dd, 1H, *J*=7.4, 13.7 Hz), 2.39 (br s, 1H), 2.44 (s, 3H), 2.93 (d, 1H, *J*=9.1 Hz), 3.48 (d, 1H, *J*=9.1 Hz), 3.53 (s, 1H), 4.00 (d, 1H, *J*=7.4 Hz), 4.19 (s, 1H), 4.53 (d, 1H, *J*=15.4 Hz), 4.59 (d, 1H, *J*=15.4 Hz), 7.15-7.19 (m, 1H), 7.25-7.28 (m, 4H), 7.40 (d, 2H, *J*=8.0 Hz), 7.77 (d, 2H, J=8.0 Hz), 7.84 (s, 1H), 8.19 (s, 1H). ^{13}C-NMR (CD_3OD) δ: 21.5, 37.4, 41.5, 45.0, 54.4, 60.2, 62.4, 73.1, 93.9, 127.6, 127.7, 128.0, 129.1, 130.7, 138.7, 140.7, 144.8, 156.4, 157.8, 160.8, 164.3. MS *m/z*: 490 (M^+). HR-MS *m/z*: Calcd for $C_{25}H_{26}N_6O_3S$: 490.1787. Found: 490.1787. *Anal.* Calcd for $C_{25}H_{26}N_6O_3S+CH_3OH+H_2O$: C, 57.76; H, 5.97; N, 15.54. Found: C, 57.81; H, 5.93; N, 15.72.

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