Synthesis of N^6-[*endo*-2′-(*endo*-5′-Hydroxy)norbornyl]-8-(*N*-methylisopropylamino)-9-methyladenine (WRC-0571): A Potent and Selective Adenosine A1 Receptor Antagonist

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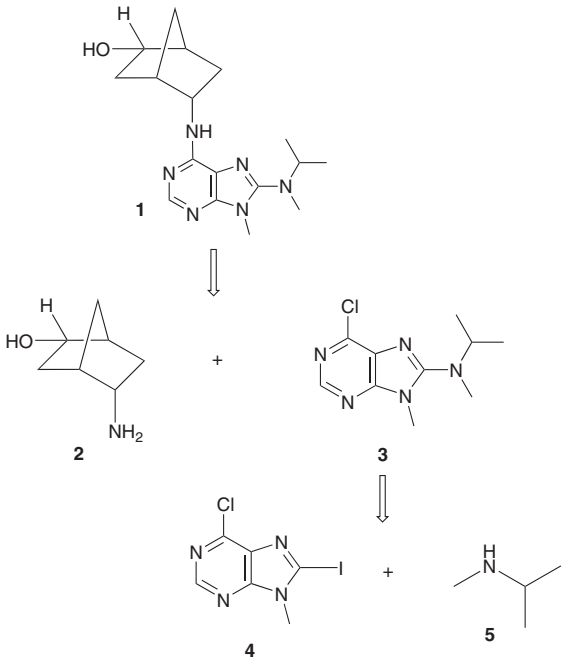
Abstract: A new versatile synthesis of N^6-[*endo*-2′-(*endo*-5′-hydroxy)norbornyl]-8-(*N*-methylisopropylamino)-9-methyladenine (WRC-0571), a highly potent and selective antagonist for adenosine A_1 receptor, is presented. The overall yield is 14%. The key step involved the stereoselective reduction of *endo*-2-(diphenylmethylamino)norbornan-5-one to generate the *endo*-5-hydroxy substituent using the Luche reagent ($NaBH_4$–$CeCl_3$) at –40 °C.

Key words: WRC-0571, Luche reduction, palladium-catalyzed amination

Adenosine is a purine nucleoside that is widely distributed throughout the body and exerts a variety of physiological functions through interactions with extracellular receptors.[1] Adenosine mediates a large variety of effects, e.g. on the cardiovascular, immune, and central nervous systems. To date, four distinct subclasses of adenosine receptors (A_1, A_{2a}, A_{2b} and A_3) have been cloned and characterized pharmacologically. Numerous adenosine receptor ligands have been synthesized and studied as adenosine receptor agonists and antagonists, which have many potential uses including cardiac imaging and in the treatment of cardiac arrhythmia, edema and depression.[2,3]

In 1996, Martin and co-workers reported N^6-[*endo*-2′-(*endo*-5′-hydroxy)norbornyl]-8-(*N*-methylisopropylamino)-9-methyladenine (WRC-0571) to be one of the most potent and selective antagonists for adenosine A_1 receptor both in vitro and in vivo.[4] WRC-0571 inhibited [^{3}H]-N^6-cyclohexyladenosine (CHA) binding to guinea pig A_1 receptor with a K_i value of 1.1 nM and was 200-fold less potent at inhibiting [^{3}H]-5′-*N*-ethylcarboxamidoadenosine binding to bovine A_{2a} receptor. In human adenosine receptors, WRC-0571 is 62-fold selective for the A_1 vs. A_{2a} and 4670-fold selective for the A_1 vs. A_3 receptors. The synthesis of WRC-0571, a nine-step linear synthetic sequence, was first reported in a patent by Peck et al.[5] However, their synthesis had several steps with low yields, especially the key $NaBH_4$ reduction of N^6-[*endo*-2′-(5′-oxo)norbornyl]-9-methyladenine to generate the corresponding *endo*-5′-hydroxy substituent (51% yield). In addition, experimental details of the last two steps, halogenation of N^6-[*endo*-2′-(*endo*-5′-hydroxy)norbornyl]-9-methyladenine and subsequent coupling with *N*-methylisopropylamine, were not reported. As a part of an ongoing research program, gram quantities of WRC-0571 were needed. In this paper, we report a new versatile synthetic approach to WRC-0571 in 14% overall yield.

Retrosynthetic analysis of WRC-0571 (**1**) (Scheme 1) suggests two potential fragments: *endo*-2-amino-*endo*-5-hydroxynorbornane (**2**) and 6-chloro-8-(*N*-methylisopropylamino)-9-methylpurine (**3**). This new synthetic approach was designed to take advantage of the key intermediate **2** that has *endo* configurations on both C-2 and C-5 for the coupling reaction with purine. Further cleavage of the purine C-8–N bond in **3** provides 6-chloro-8-iodo-9-methylpurine (**4**) and *N*-methylisopropylamine (**5**) as potential precursors.



Scheme 1

The synthesis of *endo*-2-amino-*endo*-5-hydroxynorbornane (**2**) was first investigated (Scheme 2). *endo*-2-(Diphenylmethylamino)norbornan-5-one ethylene ketal (**9**) was prepared in 41% yield from commercial cyclopent-2-en-1-one ethylene ketal (**6**) following the reported

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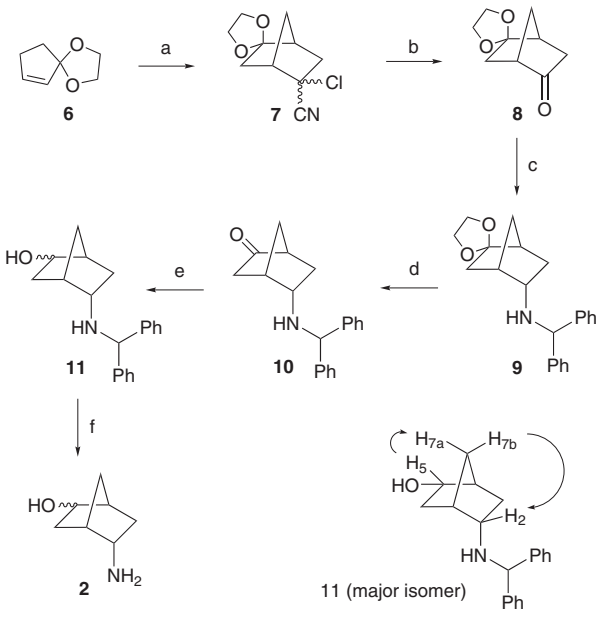
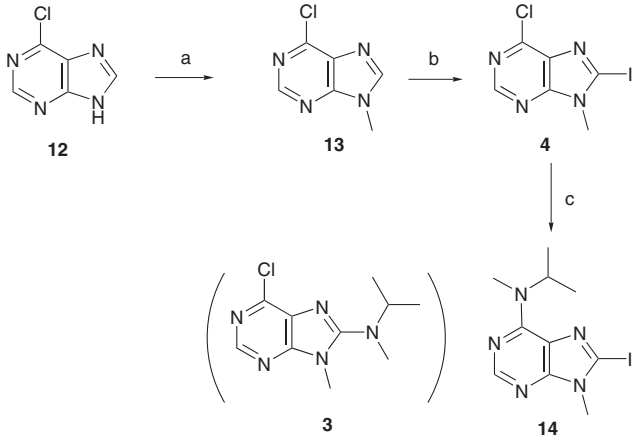
procedure.[5,6] Thus, treatment of **6** with 2-chloroacrylonitrile in refluxing acetonitrile gave the cycloaddition product **7**, which was readily hydrolyzed using potassium hydroxide to the ketone **8** in 44% yield. Reductive amination of **8** with aminodiphenylmethane provided *endo*-amine **9** in 93% yield.[7] Deketalization of **9** with HCl then led to *endo*-2-(diphenylmethylamino)norbornan-5-one (**10**) quantitatively. Reduction of ketone **10** to generate the *endo*-5-hydroxy substituent was first carried out using $NaBH_4$ in MeOH at 0 °C, yielding alcohol **11** as an 84:16 diastereoisomeric mixture as determined by ^1H NMR spectroscopy. Use of $LiAlH_4$ or the bulkier reducing agent 9-BBN did not give better results.[8] After extensive optimization, Luche reduction[9] using $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ in MeOH at –40 °C for three hours gave an approximately 95:5 diastereoisomeric mixture of **11** quantitatively. The major isomer was isolated by recrystallization from acetone–hexanes (major/minor >97:3) and the stereochemistry was determined by NMR studies.

A two dimensional ROESY NMR spectrum was obtained on the major isomer of **11**. Strong correlations were observed between H-2 and H-7b and between H-5 and H-7a, indicating that these respective pairs of protons were proximal (Scheme 2). This observation is best explained by the *endo* configurations of both the 2-diphenylmethylamino and 5-hydroxy groups in the major isomer of **11**. Subsequent hydrogenolysis of **11** (diastereoisomeric mixture) with palladium hydroxide gave **2** in 98% yield.



Scheme 2 *Reagents and conditions*: (a) 2-chloroacrylonitrile, 2,6-dimethylpyridine, MeCN, reflux, 66%; (b) KOH, DMSO, 55 °C, 67%; (c) aminodiphenylmethane, PtO_2, H_2, 45 psi, 93%; (d) 3 N HCl, MeOH, reflux, ~100%; (e) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, –40 °C, 99%; (f) H_2, $Pd(OH)_2$, 45 psi, 98%.

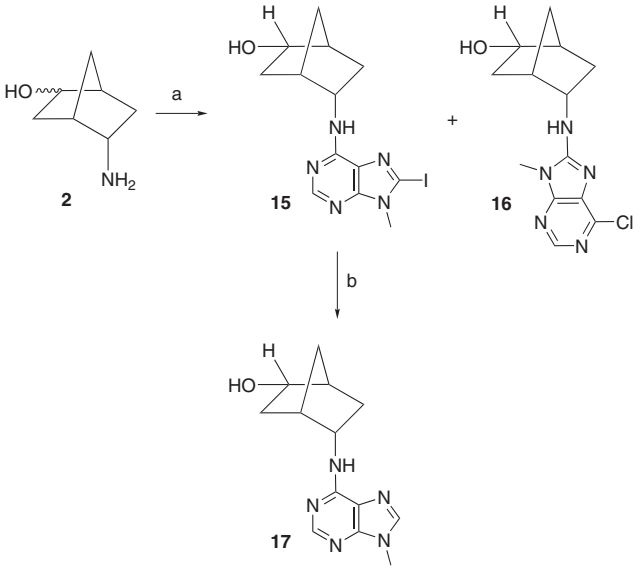
The synthesis of **3** was attempted following the route outlined in Scheme 3. N-Methylation of commercially available 6-chloropurine (**12**) using sodium hydride and iodomethane afforded 6-chloro-9-methylpurine (**13**)[10] in 68% yield. Treatment of **13** with *N*-iodosuccinimide[11] (NIS) in refluxing THF provided 6-chloro-8-iodo-9-methylpurine (**4**) in 63% yield. Palladium-catalyzed coupling reactions between 6,8-dihalopurines and organometallic reagents have been reported to give 8-substituted purines with good yields and high selectivity.[11,12] However, this facile palladium-catalyzed reaction has not been investigated on the selective amination of 6,8-dihalopurines. Palladium-catalyzed amination of aryl and heteroaryl halides has been shown to be a general method for the formation of aromatic carbon–nitrogen bonds.[13] Unfortunately, treatment of **4** with *N*-methylisopropylamine (**5**) using Buchwald's conditions for aryl iodides[14] [$Pd_2(dba)_3$, P(*o*-tolyl)$_3$, *t*-BuONa, 18-C-6, THF, r.t.] led to decomposition. The desired product **3** was not detected by ^1H NMR or MS analysis of the crude product mixture. Recently, Meyers et al.[15] reported regioselective palladium-catalyzed aminations of 2-chloro-3-iodopyridine with anilines on the 3-position using the mild base Cs_2CO_3. However, reaction of **4** with **5** using Meyers' conditions [$Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, reflux] also did not produce **3**. Instead **14**, a substitution product on the 6-position, was isolated in 36% yield[16] (Scheme 3). We believe that the formation of **14** was through a nucleophilic aromatic substitution reaction and the Pd catalyst was simply a spectator.



Scheme 3 *Reagents and conditions*: (a) NaH, MeI, DMF, r.t., 68%; (b) NIS, THF, reflux, 63%; (c) Pd(0), *N*-methylisopropylamine (**5**).

Nucleophilic substitutions of 6,8-dichloropurines are well-documented in the literature.[17,18] However, the factors determining the regiochemistry of substitution reactions of 6,8-dihalopurines appear to be complex. The nucleophilic substitution of 6-chloro-8-iodo-9-methylpurine (**4**) with amine was also investigated. Treatment of **4** with amine **2** (97:3 diastereoisomeric mixture) and triethylamine in refluxing MeOH containing a catalytic amount of tetrabutylammonium iodide gave N^6-[*endo*-2′-(*endo*-5′-hydroxy)norbornyl]-8-iodo-9-methyladenine (**15**) in 73% yield as well as **16** in 7% yield (Scheme 4). Both **15** and **16** were isolated as single diastereoisomers. Unfortu-

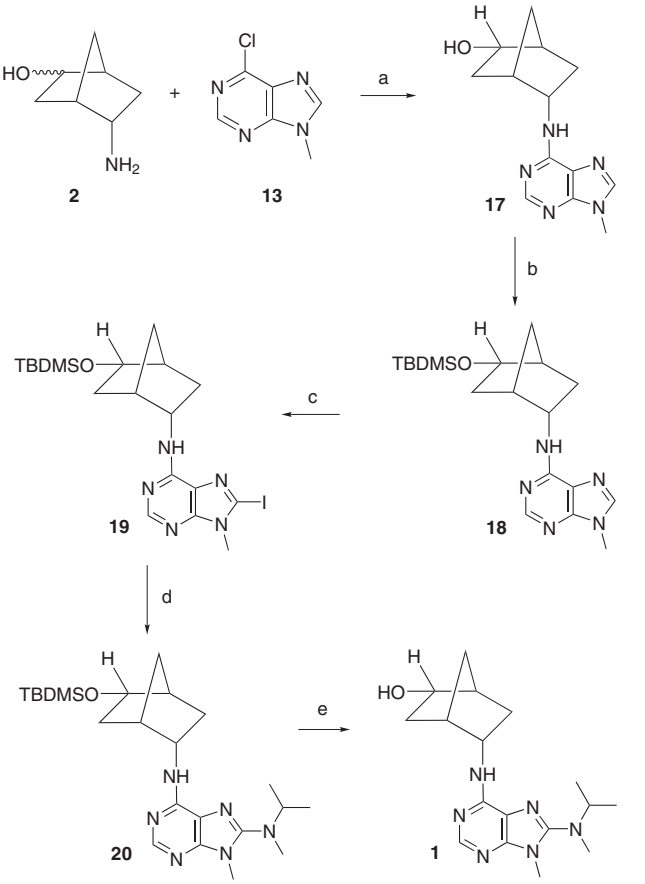
nately, subsequent reaction of **15** with *N*-methylisopropylamine (**5**) gave a 64% yield of the reductive product **17**. Only a small amount of the desired product **1** was detected by ^{1}H NMR and MS analyses.



Scheme 4 *Reagents and conditions*: (a) **4**, Bu_4NI, MeOH, Et_3N, reflux, **15**: 73%; **16**: 7%; (b) *N*-methylisopropylamine (**5**), DMSO, 130 °C, 64%.

In order to investigate the amination reaction of the 8-bromo or 8-chloro analogue of **15**, direct bromination or chlorination of **17** using Br_2 in $CHCl_3$,[19] Br_2 in Na_2HPO_4 and H_2O (pH 7),[20] or *N*-chlorosuccinimide (NCS)[19] was also tried but met with little success. In most cases, the oxidation product of the 5′-hydroxy group to the corresponding ketone was observed, suggesting that the 5′-hydroxy group needed to be masked for the halogenation and amination sequence (Scheme 5). Thus, the substitution reaction of **13** with amine **2** (93:7 diastereoisomeric mixture) was carried out in refluxing propan-1-ol to give **17** in 89% yield as a single diastereoisomer. The 5′-hydroxy group was then protected by treatment with *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in DMF to provide **18** in almost quantitative yield. Iodination[21] of **18** by lithiation of the C-8 position using three equivalents of LDA in THF followed by addition of iodine yielded **19**. Compound **19** was then treated with **5** in toluene at 155 °C in a steel bomb for three days to produce **20** in 40% yield. Recovered starting material **19** was then recycled to generate additional **20** (66% overall yield after two cycles). Subsequent deprotection of the 5′-*O*-*tert*-butyldimethylsilyl group using tetrabutylammonium fluoride (TBAF) in THF provided WRC-0571 (**1**) in 95% yield.

In conclusion, we have developed a new versatile synthetic approach to N^6-[*endo*-2′-(*endo*-5′-hydroxy)norbornyl]-8-(*N*-methylisopropylamino)-9-methyladenine (WRC-0571) in 14% overall yield from commercially available cyclopent-2-en-1-one ethylene ketal (**6**). The key step involved stereoselective reduction of *endo*-2-(diphenylmethylamino)norbornan-5-one (**10**) to generate the *endo*-5-hydroxy substituent **11** (90% de) quantitatively using the Luche reagent ($NaBH_4$-$CeCl_3$).



Scheme 5 *Reagents and conditions*: (a) Bu_4NI, propan-1-ol, Et_3N, reflux, 89%; (b) TBDMSCl, imidazole, DMF, r.t., 99%; (c) LDA, THF, –78 °C, then I_2, 65%; (d) *N*-methylisopropylamine (**5**), toluene, 155 °C, 66%; (e) TBAF, THF, r.t., 95%.

Melting points were determined on a MEL-TEMP II capillary melting point apparatus and are uncorrected. NMR (^{1}H, ^{13}C, COSY and ROESY) spectra were obtained using a Bruker Avance DPX-300 MHz or a Varian Unity Inova 500 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. HRMS were recorded on a Waters Autospec Ultima mass spectrometer and were performed at the University of Michigan, Ann Arbor, MI. Elemental analysis was done by Atlantic Microlab Inc., Norcross, GA. Analytical TLC was carried out using EMD silica gel 60 F_{254} TLC plates. Flash column chromatography was done on a CombiFlash Companion system using Isco prepacked silica gel columns. Reagents were obtained from Aldrich Chemical Company and used as received unless otherwise noted. THF was freshly distilled from sodium-benzophenone.

(*endo*,*exo*)-2-Carbonitrile-2-chlorononorbornan-5-one Ethylene Ketal (7)

A mixture of cyclopent-2-en-1-one ethylene ketal (**6**; 14.5 g, 115 mmol) and 2-chloroacrylonitrile (30.2 g, 345 mmol) in anhydrous MeCN (290 mL) containing 2,6-dimethylpyridine (2.00 g, 18.4 mmol) was heated at 75 °C under argon for 22 h. After cooling to r.t., the pale yellow solution was concentrated in vacuo. Chromatography (120 g Isco silica gel column) using 4% EtOAc–20% CH_2Cl_2–76% hexanes afforded **7** (16.3 g, 66%) as a mixture of diastereoisomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ (major isomer) = 1.85–2.12 (m, 3 H), 2.20–2.39 (m, 3 H), 2.40–2.60 (m, 1 H), 2.70–2.88 (m, 1 H), 3.77–4.06 (m, 4 H).

2-Oxonorbornan-5-one Ethylene Ketal (8)

To a stirred solution of **7** (15.0 g, 70.2 mmol) in DMSO (62.5 mL) was added a solution of KOH (13.9 g, 210 mmol) in H_2O (7.5 mL). The mixture was heated at 55 °C for 4 h. The resultant orange solution was poured into H_2O (300 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (3 × 50 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography (40 g Isco silica gel column) using 10% EtOAc–20% CH_2Cl_2–70% hexanes afforded **8** (7.90 g, 67%) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72–1.88 (m, 2 H), 1.82–2.08 (m, 2 H), 2.13 (dd, *J* = 14.1, 5.1 Hz, 1 H), 2.34 (dd, *J* = 18.2, 4.1 Hz, 1 H), 2.46–2.63 (m, 2 H), 3.80–4.08 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.2, 38.2, 38.8, 43.0, 49.4, 64.3, 64.7, 114.3, 215.7.

***endo*-2-(Diphenylmethylamino)norbornan-5-one Ethylene Ketal (9)**

A degassed mixture of **8** (7.80 g, 46.0 mmol), aminodiphenylmethane (7.92 mL, 46.0 mmol) and AcOH (3.97 mL, 69.0 mmol) in MeOH (59 mL) containing PtO_2 (281 mg) was hydrogenated at 45 psi for 6 h. The suspension was filtered through a short pad of Celite, washed with MeOH (3 × 10 mL) and the filtrate was concentrated in vacuo. Chromatography (120 g Isco silica gel column) using 0 → 50% EtOAc–hexanes afforded **9** (14.3 g, 93%) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.38 (m, 2 H), 1.58–1.76 (m, 3 H), 1.77–1.91 (m, 1 H), 1.94–2.10 (m, 2 H), 2.27 (br s, 1 H), 2.91–3.06 (m, 1 H), 3.71–3.96 (m, 4 H), 4.78 (s, 1 H), 7.11–7.46 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.0, 35.4, 37.2, 38.5, 44.2, 55.8, 63.9, 64.5, 65.6, 116.1, 127.0, 127.4, 127.5, 128.5, 144.0, 144.8.

***endo*-2-(Diphenylmethylamino)norbornan-5-one (10)**

To a stirred solution of **9** (3.35 g, 10.0 mmol) in MeOH (20 mL), was added 3 N HCl (20 mL). After refluxing for 1 h, the mixture was poured into aq sat. $NaHCO_3$ solution (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (3 × 30 mL) and dried (Na_2SO_4). Removal of solvent in vacuo afforded **10** (2.95 g, ~100%) as a white solid, which was used in the next step without further purification; mp 130–132 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (ddd, *J* = 13.5, 4.5, 3.0 Hz, 1 H), 1.54–1.60 (m, 1 H), 1.62 (br s, 1 H), 1.67–1.72 (m, 1 H), 1.94 (dd, *J* = 18.0, 4.5 Hz, 1 H), 2.13–2.02 (m, 1 H), 2.46–2.56 (m, 3 H), 3.22–3.26 (m, 1 H), 4.78 (s, 1 H), 7.18–7.38 (m, 10 H).

^{13}C NMR (125 MHz; $CDCl_3$): δ = 33.8, 37.0, 38.3, 38.6, 50.6, 55.8, 65.7, 127.4, 127.6, 127.7, 128.7, 128.8, 143.8, 144.3, 217.8.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{21}NO$ + Na: 314.1521; found: 314.1525.

***endo*-2-(Diphenylmethylamino)-(*endo*,*exo*)-5-hydroxynorbornane (11)**

To a stirred solution of **10** (2.95 g, 10.0 mmol) in MeOH (500 mL) at –40 °C was added $CeCl_3 \cdot 7H_2O$ (1.85 g, 5.00 mmol) followed by $NaBH_4$ (0.19 g, 5.00 mmol). After stirring at –40 °C for 3 h, the reaction was quenched by the addition of aq sat. NH_4Cl solution (20 mL). The MeOH was removed in vacuo and the resultant aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 extracts were washed with brine (3 × 50 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography (40 g Isco silica gel column) using 0 → 10% MeOH–CH_2Cl_2 afforded **11** (93:7 diastereoisomeric mixture, 2.90 g, 99%) as a white solid. The major isomer (major/minor >97:3) was isolated by recrystallization from acetone–hexanes; mp 113–116 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29–1.40 (m, 2 H), 1.47–1.54 (m, 2 H), 1.62–1.70 (m, 1 H), 1.72–1.80 (m, 1 H), 2.09 (br s, 2 H), 2.14–2.20 (m, 2 H), 3.00–3.60 (m, 1 H), 4.14–4.21 (m, 1 H), 4.74 (s, 1 H), 7.16–7.40 (m, 10 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.1, 32.0, 38.0, 40.3, 43.0, 56.3, 65.5, 72.7, 127.2, 127.4, 127.6, 127.7, 127.8, 128.7, 143.9, 144.6.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{23}NO$ + Na: 316.1677; found: 316.1666.

***endo*-2-Amino-(*endo*,*exo*)-5-hydroxynorbornane Hydrochloride (2)**

A degassed mixture of **11** (93:7 diastereoisomeric mixture, 2.90 g, 10.0 mmol,) and $Pd(OH)_2$ (145 mg) in MeOH (60 mL) was hydrogenated at 45 psi for 28 h. The suspension was filtered through a short pad of Celite, washed with MeOH (3 × 10 mL) and the filtrate was concentrated in vacuo. The resultant residue was treated with 1 M HCl solution in Et_2O to give **2** (1.60 g, 98%) as a white solid, which was used in the next step without further purification; mp 164–167 °C.

^{1}H NMR (300 MHz, CD_3OD): δ (major isomer) = 1.26 (d, *J* = 14.4 Hz, 1 H), 1.59 (s, 2 H), 1.78–2.02 (m, 3 H), 2.31 (br t, 1 H), 2.41 (br t, 1 H), 3.52–3.63 (m, 1 H), 4.22–4.32 (m, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 26.4, 31.2, 38.1, 41.6, 44.2, 53.3, 72.1.

HRMS-EI: *m*/*z* [M]$^+$ calcd for $C_7H_{13}NO$: 127.0997; found: 127.0997.

***N*^{6}-[*endo*-2′-(*endo*-5′-Hydroxy)norbornyl]-9-methyladenine (17)**

A mixture of **2** (93:7 diastereoisomeric mixture, 1.20 g, 7.36 mmol), 6-chloro-9-methylpurine (**13**;[10] 1.21 g, 7.22 mmol), Bu_4NI (26.6 mg, 0.072 mmol) and Et_3N (4.03 mL, 28.9 mmol) in propan-1-ol (25 mL) was refluxed under argon for 20 h. After cooling to r.t., propan-1-ol was removed in vacuo. The resultant residue was dissolved in CH_2Cl_2 (200 mL), washed with brine (3 × 50 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography (40 g Isco silica gel column) using 0 → 10% MeOH–CH_2Cl_2 afforded **17** (single isomer, 1.66 g, 89%) as a white solid; mp 222–224 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 1.35–1.45 (m, 1 H), 1.52–1.70 (m, 2 H), 1.76–1.90 (m, 2 H), 1.92–2.07 (m, 1 H), 2.28 (br t, 1 H), 2.55 (br t, 1 H), 3.81 (s, 3 H), 4.20–4.30 (m, 1 H), 4.48 (br s, 1 H), 8.02 (s, 1 H), 8.24 (s, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 28.3, 30.3, 31.7, 37.9, 42.5, 44.2, 53.9, 73.3, 120.4, 142.9, 150.5, 153.8, 156.3.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}N_5O$ + H: 260.1511; found: 260.1508.

***N*^{6}-{*endo*-2′-[*endo*-5′-*O*-(*tert*-Butyldimethylsilyl)]norbornyl}-9-methyladenine (18)**

To a stirred solution of **17** (1.30 g, 5.02 mmol) in DMF (20 mL) at r.t. under N_2, was added imidazole (0.85 g, 12.6 mmol) followed by TBDMSCl (0.94 g, 6.02 mmol). After stirring at r.t. for 5 h, the mixture was poured into ice-water and extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 extracts were washed with brine (3 × 30 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography (40 g Isco silica gel column) using 0 → 3% MeOH–CH_2Cl_2 afforded **18** (1.85 g, 99%) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 3 H), 0.06 (s, 3 H), 0.90 (s, 9 H), 1.33–1.43 (m, 1 H), 1.44–1.51 (m, 1 H), 1.54–1.64 (m, 1 H), 1.65–1.86 (m, 2 H), 1.87–2.00 (m, 1 H), 2.21 (br t, 1 H), 2.55 (br t, 1 H), 3.77 (s, 3 H), 4.18–4.28 (m, 1 H), 4.56 (br s, 1 H), 5.93 (br s, 1 H), 7.68 (s, 1 H), 8.36 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = –4.9, –4.8, 18.1, 26.0, 28.5, 29.5, 32.6, 37.1, 40.9, 43.2, 51.4, 72.5, 120.0, 139.9, 148.5, 153.0, 154.9.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{31}N_5OSi$ + Na: 396.2196; found: 396.2194.

N^6-{*endo*-2′-[*endo*-5′-*O*-(*tert*-Butyldimethylsilyl)]norbornyl}-8-iodo-9-methyladenine (19)

To a stirred solution of diisopropylamine (1.25 mL, 8.84 mmol) in THF (10 mL) at –78 °C under N_2 was added BuLi (1.6 M in hexanes, 5.03 mL, 8.04 mmol). The yellow solution was stirred at –78 °C for 15 min and then at 0 °C for another 15 min. After cooling to –78 °C, a solution of **18** (1.00 g, 2.68 mmol) in THF (15 mL) was slowly added over 10 min. The resultant dark solution was stirred at –78 °C for 2 h and then a solution of I_2 (2.38 g, 9.38 mmol) in THF (19 mL) was added at once. After stirring at –78 °C for 30 min, the mixture was poured into a stirred 5% AcOH solution (70 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 extracts were washed with $NaHCO_3$ (30 mL), $Na_2S_2O_3$ (30 mL), brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography (40 g Isco silica gel column) using 0 → 1% MeOH–CH_2Cl_2 afforded **19** (0.87 g, 65%) as a white solid; mp 135–137 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 3 H), 0.09 (s, 3 H), 0.94 (s, 9 H), 1.30–1.40 (m, 1 H), 1.45–1.55 (m, 1 H), 1.56–1.62 (m, 1 H), 1.65–1.80 (m, 2 H), 1.82–2.00 (m, 1 H), 2.23 (br t, 1 H), 2.56 (br t, 1 H), 3.72 (s, 3 H), 4.22–4.30 (m, 1 H), 4.54 (br s, 1 H), 5.99 (br s, 1 H), 8.39 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.6, 18.4, 26.2, 28.8, 32.3, 32.9, 37.4, 41.1, 43.4, 51.7, 72.7, 99.3, 122.5, 151.0, 153.3, 153.8.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{30}IN_5OSi$ + Na: 522.1162; found: 522.1159.

N^6-{*endo*-2′-[*endo*-5′-*O*-(*tert*-Butyldimethylsilyl)]norbornyl}-8-(*N*-methylisopropylamino)-9-methyladenine (20)

A mixture of **19** (0.87 g, 1.74 mmol) and *N*-methylisopropylamine (4.6 mL) in toluene (4.6 mL) was heated at 155 °C in a steel bomb for 3 days. After cooling to r.t., the mixture was concentrated in vacuo. Chromatography (40 g Isco silica gel column) using 0 → 2% MeOH–CH_2Cl_2 afforded **20** (0.31 g, 40%) as an oil. The recovered starting material **19** (0.38 g) was then recycled to provide additional 0.20 g of **20** (total 0.51 g, 66% after two cycles).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 3 H), 0.09 (s, 3 H), 0.95 (s, 9 H), 1.23 (d, *J* = 6.0 Hz, 3 H), 1.25 (d, *J* = 6.0 Hz, 3 H), 1.35–1.51 (m, 2 H), 1.53–1.75 (m, 2 H), 1.78–2.00 (m, 2 H), 2.23 (br t, 1 H), 2.57 (br t, 1 H), 2.81 (s, 3 H), 3.59 (s, 3 H), 3.70–3.82 (m, 1 H), 4.20–4.30 (m, 1 H), 4.60 (br s, 1 H), 5.60 (d, *J* = 6.0 Hz, 1 H), 8.59 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.7, –4.6, 18.2, 19.2, 19.3, 26.2, 29.4, 29.8, 31.5, 33.3, 37.6, 41.3, 43.4, 51.1, 52.1, 72.4, 117.6, 150.0, 151.0, 152.9, 155.7.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd $C_{23}H_{40}N_6OSi$ + Na: 467.2931; found: 467.2923.

N^6-[*endo*-2′-(*endo*-5′-Hydroxy)norbornyl]-8-(*N*-methylisopropylamino)-9-methyladenine (1)

To a stirred solution of **20** (0.28 g, 0.63 mmol) in THF (5 mL) at r.t. under N_2 was added Bu_4NF (1 M solution in THF, 1.26 mL, 1.26 mmol). After stirring at r.t. for 1 h, the mixture was diluted with CH_2Cl_2 (100 mL), the CH_2Cl_2 layer was washed with brine (3 × 30 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography (40 g Isco silica gel column) using 0 → 2% MeOH–CH_2Cl_2 afforded **1** (0.20 g, 95%) as a white solid; mp 191–193 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.0 Hz, 6 H), 1.48–1.55 (m, 1 H), 1.57–1.70 (m, 2 H), 1.75–1.90 (m, 1 H), 1.91–2.01 (m, 2 H), 2.25 (br s, 1 H), 2.55 (br t, 1 H), 2.83 (s, 3 H), 3.59 (s, 3 H), 3.62–3.78 (m, 1 H), 4.35–4.46 (m, 1 H), 4.51–4.65 (m, 1 H), 5.03 (br s, 1 H), 6.56 (d, *J* = 6.0 Hz, 1 H), 8.35 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 19.3, 26.9, 29.8, 30.4, 31.2, 36.9, 41.4, 43.4, 52.5, 52.9, 72.8, 116.9, 150.3, 151.4, 153.0, 155.3.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{26}N_6O$ + H: 331.2246; found: 331.2239.

Anal. Calcd for $C_{17}H_{26}N_6O·0.25H_2O$: C, 60.96; H, 7.97; N, 25.09. Found: C, 61.14; H, 7.82; N, 25.34.

6-Chloro-8-iodo-9-methylpurine (4)

To a stirred solution of **13** (1.68 g, 10.0 mmol) in THF (160 mL) at r.t. under N_2 was added *N*-iodosuccinimide (11.3 g, 50 mmol). After refluxing for 3 d, the mixture was concentrated in vacuo. The brown residue was dissolved in CH_2Cl_2 (300 mL) and aq sat. $NaHSO_3$ was added until the solution became colorless. The CH_2Cl_2 layer was separated, washed with brine (3 × 50 mL), dried (Na_2SO_4) and concentrated in vacuo. The resultant yellow solid was washed with CH_2Cl_2 (3 × 10 mL) to give **4** (1.85 g, 63%) as a white solid; mp 250–252 °C (dec.).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.76 (s, 3 H), 8.64 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.1, 115.1, 133.0, 147.5, 151.7, 153.4.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_6H_4ClIN_4$ + H: 294.9247; found: 294.9245.

6-(*N*-Methylisopropylamino)-8-iodo-9-methyladenine (14)

A mixture of $Pd(OAc)_2$ (0.011 g, 0.05 mmol) and BINAP (0.031g, 0.05 mmol) in toluene (5 mL) was stirred at r.t. under argon for 10 min. The resultant catalyst solution was transferred into a stirred solution of **4** (0.29 g, 1.00 mmol), *N*-methylisopropylamine (0.11 mL, 1.10 mmol) and Cs_2CO_3 (1.63 g, 5.00 mmol) in toluene (5 mL). After refluxing for 16 h, the mixture was diluted with EtOAc (100 mL), the EtOAc layer was washed with brine (3 × 30 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography (40 g Isco silica gel column) using 0 → 100% EtOAc–hexanes afforded **14** (0.12 g, 36%) as a pale yellow solid; mp 126–128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.6 Hz, 6 H), 3.31 (br s, 3 H), 3.71 (s, 3 H), 5.68 (br s, 1 H), 8.26 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 28.8, 32.3, 47.0, 97.4, 122.9, 151.9, 152.4, 153.2.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{14}IN_5$ + H: 332.0372; found: 332.0364.

N^6-[*endo*-2′-(*endo*-5′-Hydroxy)norbornyl]-8-iodo-9-methyladenine (15) and 6-Chloro-*N*^{8}-[*endo*-2′-(*endo*-5′-hydroxy)norbornyl]-9-methylpurine (16)

A mixture of hydrochloride **2** (97:3 diastereoisomeric mixture, 0.17 g, 1.02 mmol), **4** (0.29 g, 1.00 mmol), Bu_4NI (3.70 mg, 0.01 mmol) and Et_3N (0.56 mL, 4.00 mmol) in MeOH (10 mL) was refluxed under N_2 for 2 d. After cooling to r.t., MeOH was removed in vacuo. The resultant residue was dissolved in CH_2Cl_2 (100 mL), the CH_2Cl_2 solution was washed with brine (3 × 30 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography (40 g Isco silica gel column) using 0 → 10% MeOH–CH_2Cl_2 afforded **15** (single isomer, 0.28 g, 73%) as a white solid and **16** (single isomer, 0.02 g, 7%) as a white solid.

15

Mp 242–244 °C (dec.).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.18–1.30 (m, 1 H), 1.40–1.55 (m, 2 H), 1.60–1.88 (m, 3 H), 2.09 (br s, 1 H), 2.38 (br t, 1 H), 2.63 (s, 3 H), 3.95–4.06 (m, 1 H), 4.40–4.51 (m, 1 H), 4.65 (d, *J* = 8.4 Hz, 1 H), 7.60 (d, *J* = 6.3 Hz, 1 H), 8.15 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 25.6, 30.3, 31.8, 36.0, 40.3, 42.6, 51.7, 71.8, 103.0, 121.5, 150.2, 152.3, 152.9.

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{13}H_{16}IN_5O$ + H: 386.0478; found: 386.0475.

16

Mp 283–285 °C (dec.).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.20–1.31 (m, 1 H), 1.38–1.54 (m, 2 H), 1.56–1.70 (m, 1 H), 1.71–1.82 (m, 2 H), 2.11 (br s, 1 H), 3.60 (s, 3 H), 4.01–4.11 (m, 1 H), 4.12–4.23 (m, 1 H), 4.59 (d, *J* = 6.0 Hz, 1 H), 7.30 (d, *J* = 5.4 Hz, 1 H), 8.33 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 25.3, 28.0, 30.1, 35.6, 40.0, 42.4, 54.6, 71.5, 131.1, 139.6, 147.2, 153.6, 155.9.

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{13}H_{16}ClN_5O$ + H: 294.1122; found: 294.1117.

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