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

Chunyang Jin, Jason P. Burgess, Kenneth S. Rehder, George A. Brine
Organic and Medicinal Chemistry, Science and Engineering Group, Research Triangle Institute, PO Box 12194, Research Triangle Park, NC 27709, USA
Fax +1(919)5416499; E-mail: cjin@rti.org
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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 A1 receptor, is presented. The overall yield is 14%. The key step involved the stereoselective reduction of endo-2’-(diphenylmethylamino)norboman-5-one to generate the endo-5-hydroxy substituent using the Luche reagent (NaBH4–CeCl3) at \(-40^\circ\) 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. 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 (A1, A2a, A2b and A3) 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.

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 A1 receptor both in vitro and in vivo. WRC-0571 inhibited \([H]N^6\)-cyclohexyladenosine (CHA) binding to guinea pig A1 receptor with a \( K_I \) value of 1.1 nM and was 200-fold less potent at inhibiting \([H]N^6\)-N-ethylcarbamidoadenosine binding to bovine A2a receptor. In human adenosine receptors, WRC-0571 is 62-fold selective for the A1 vs. A2a and 4670-fold selective for the A1 vs. A2 receptors. The synthesis of WRC-0571, a nine-step linear synthetic sequence, was first reported in a patent by Peck et al. However, their synthesis had several steps with low yields, especially the key NaBH4 reduction of \( N^6\)-(endo-2’-(5’-oxo)norborno)-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.

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procedure. 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-\textit{amine} 9 in 93% yield. Deketalization of 9 with HCl then led to \textit{endo}-2-(diphenylmethylamino)norbornan-5-one (10) quantitatively. Reduction of ketone 10 to generate the \textit{endo}-5-hydroxy substituent was first carried out using NaBH₄ in MeOH at 0 °C, yielding alcohol 11 as an 84:16 diastereoisomeric mixture as determined by ¹H NMR spectroscopy. Use of LiAlH₄ or the bulkier reducing agent 9-BBN did not give better results. After extensive optimization, Luche reduction⁸ using NaBH₄ and CeCl₃·7H₂O did not give better results. 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. Unfortunately, treatment of 4 with N-methylisopropylamine (5) using Buchwald’s conditions for aryl iodides⁴ using lithium-diisopropylamide, phosgene, and triethylamine in refluxing MeOH also did not produce 3. Instead 14, a substitution product on the 6-position, was isolated in 36% yield⁶ (Scheme 3). We believe that the formation of 14 was through a nucleophilic aromatic substitution reaction and the Pd catalyst was simply a spectator.

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) in 68% yield. Treatment of 13 with N-iodosuccinimide (11) 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. However, the facile palladium-catalyzed amination of aryl and heteroaryl halides has been shown to be a general method for the formation of aromatic carbon–nitrogen bonds. Unfortunately, treatment of 4 with N-methylisopropylamine (5) using Buchwald’s conditions for aryl iodides using sodium hydride and CeCl₃·7H₂O 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 \textit{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  \textit{Reagents and conditions:} (a) 2-chloroacrylonitrile, MeCN, reflux, 66%; (b) KOH, DMSO, 55 °C, 67%; (c) aminodiphenylmethane, PO₂⁺, H₂, 45 psi, 93%; (d) 3 N HCl, MeOH, reflux, ~100%; (e) NaBH₄, CeCl₃·7H₂O, MeOH, –40 °C, 99%; (f) H₂, Pd(OH)₂, 45 psi, 98%.

Nucleophilic substitutions of 6,8-dichloropurines are well-documented in the literature. 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 \textit{N}-[(\textit{endo}-2’-(\textit{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...

Scheme 3  \textit{Reagents and conditions:} (a) NaH, MeI, DMF, r.t., 68%; (b) NIS, THF, reflux, 63%; (c) Pd(0), N-methylisopropylamine (5).
In order to investigate the amination reaction of the 8-bromo or 8-chloro analogue of 15, direct bromination or chlorination of 17 using Br₂ in CHCl₃, Br₂ in Na₂HPO₄ and H₂O (pH 7), or N-chlorosuccinimide (NCS) 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 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\(^{5}\)-[endo-2'-(endo-5'-hydroxy)norborny1]-8-(N-methylisopropylamino)-9-methyldenine (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)norborean-5-one (10) to generate the endo-
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 H2O (7.5 mL). The mixture was heated at 55 °C for 4 h. The resultant orange solution was poured into H2O (300 mL) and extracted with CH2Cl2 (3 × 100 mL). The combined organic extracts were washed with brine (3 × 50 mL) and dried (Na2SO4) and concentrated in vacuo. Chromatography (40 g Isco silica gel column) using 10% MeOH–CH2Cl2 afforded 8 (7.90 g, 67%) as an oil.

1H NMR (300 MHz, CDCl3): 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).

13C NMR (75 MHz, CDCl3): 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 Ac2O (3.97 mL, 69.0 mmol) in MeOH (50 mL) containing PtO2 (281 mg) 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 Et3O 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.

1H NMR (300 MHz, CD3OD): δ = 2.95 (d, J = 13.9 Hz, 1 H), 1.59–2.02 (m, 10 H), 2.55 (br t, 1 H), 2.63 (br s, 2 H), 2.73 (br t, 1 H), 2.97 (br s, 1 H), 7.68 (s, 1 H), 8.36 (s, 1 H).

13C NMR (75 MHz, CD3OD): δ = 13.5, 30.4, 37.5, 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-5 Ethylene Ketal (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. NaHCO3 solution (50 mL) and extracted with CH2Cl2 (3 × 100 mL). The combined organic extracts were washed with brine (3 × 50 mL) and dried (Na2SO4). 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.

1H NMR (500 MHz, CDCl3): δ = 1.10 (dd, 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), 7.18–7.40 (m, 10 H).

13C NMR (125 MHz, CDCl3): δ = 33.8, 37.0, 38.3, 38.6, 50.6, 55.8, 65.7, 127.4, 127.6, 127.7, 128.7, 143.8, 144.3, 217.8.


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 Et3O 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.

1H NMR (300 MHz, CD3OD): 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).

13C NMR (75 MHz, CD3OD): δ = 26.4, 31.2, 38.1, 41.6, 44.2, 53.3, 72.1.


N6-endose-2-(endo-5'-Hydroxy)nornorbornyl)-9-methyladenine (17)

1H NMR (300 MHz, CD3OD): 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).

13C NMR (75 MHz, CD3OD): 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.


N6-endose-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 N2, 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 CH2Cl2 (3 × 50 mL). The combined CH2Cl2 extracts were washed with brine (3 × 50 mL), dried (Na2SO4) and concentrated in vacuo. Chromatography (40 g Isco silica gel column) using 0 → 3% MeOH–CH2Cl2 afforded 18 (1.85 g, 99%) as an oil.
1C NMR (75 MHz, CDCl3): 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.


N°-[endo-2-endo-5′-O-(tert-Butyldimethylsilyl)]norbornyl]-8-iodo-9-methyladenine (19)

To a stirred solution of disopropylamine (1.25 mL, 8.84 mmol) in THF (10 mL) at –78 °C under N2 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 I2 (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 the mixture was washed with brine (3 × 50 mL), dried (Na2SO4) and concentrated in vacuo. Chromatography (40 g Isco silica gel column) using 0 → 1% MeO–CH2Cl afforded 19 (0.87 g, 67% as a white solid; mp 135–137 °C.

1H NMR (300 MHz, CDCl3): 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, t H), 2.56 (br t, t H), 3.72 (s, 3 H), 4.22–4.30 (m, 1 H), 4.54 (br s, 1 H). 5.09 (s, 1 H), 1.59 (s, 3 H), 3.30 (br s, 3 H).

13C NMR (75 MHz, CDCl3): δ = 15.1, 31.7, 33.3, 37.6, 41.3, 43.4, 51.1, 52.1, 72.4, 117.6, 150.0, 151.0, 152.9, 155.3.


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

To a stirred solution of 13 (1.68 g, 10.0 mmol) in THF (160 mL) at r.t. under N2, was added N-iodoacetic acid (11.3 g, 50 mmol). After refluxing for 3 d, the mixture was concentrated in vacuo. The brown residue was dissolved in CH2Cl2 (300 mL) and aq sat. NaHSO3 was added until the solution became colorless. The CH2Cl2 layer was separated, washed with brine (3 × 50 mL), dried (Na2SO4) and concentrated in vacuo. The resultant yellow solid was washed with CH2Cl2 (3 × 10 mL) to give 4 (1.85 g, 63% as a white solid; mp 250–252 °C (dec.).

1H NMR (300 MHz, DMSO-d6): δ = 3.76 (s, 3 H), 8.64 (s, 1 H).

13C NMR (75 MHz, DMSO-d6): δ = 33.1, 115.1, 133.0, 147.5, 151.7, 153.4.


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

A mixture of Pd(OAc)2 (0.011 g, 0.05 mmol) and BINAP (0.031 g, 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 Cs2CO3 (1.63 g, 5.00 mmol) in toluene (5 mL). After refluxing for 15 h, the mixture was diluted with EtOAc (100 mL), the EtOAc layer was washed with brine (3 × 30 mL), dried (Na2SO4) 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.

1H NMR (300 MHz, DMSO-d6): δ = 1.26 (d, J = 6.6 Hz, 6 H), 3.31 (br s, 3 H), 3.71 (br s, 3 H), 5.68 (br s, 1 H). 8.26 (s, 1 H).

13C NMR (75 MHz, DMSO-d6): δ = 19.7, 28.8, 32.3, 47.0, 97.4, 122.9, 151.9, 152.4, 153.2.


N°-[endo-2-endo-5′-Hydroxy)norbornyl]-8-iodo-9-methyladenine (15) and 6-Chloro-N°-[endo-2-endo-5′-hydroxy)norbornyl]-9-methylpyruvine (16)

A mixture of hydrochloride 2 (97.3% diastereomeric mixture, 0.17 g, 1.02 mmol), 4 (0.29 g, 1.00 mmol), Bu3Ni (3.70 mg, 0.01 mmol) and Et3N (0.56 mL, 4.00 mmol) in MeOH (10 mL) was refluxed under N2 for 2 d. After cooling to r.t., MeOH was removed in vacuo. The resultant residue was dissolved in CH2Cl2 (100 mL). The CH2Cl2 solution was washed with brine (3 × 30 mL), dried (Na2SO4) and concentrated in vacuo. Chromatography (40 g Isco silica gel column) using 0 → 10% MeOH–CH2Cl2 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.).

1H NMR (300 MHz, DMSO-d6): 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, t 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-$d_6$): $\delta = 25.6, 30.3, 31.8, 36.0, 40.3, 42.6, 51.7, 71.8, 103.0, 121.5, 150.2, 152.3, 152.9.$

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

Mp 283–285 °C (dec.).

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 1.20–1.31$ (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-$d_6$): $\delta = 25.3, 28.0, 30.1, 35.6, 40.0, 42.4, 54.6, 71.5, 131.1, 147.2, 153.6, 155.9.$

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

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References


(7) The endo stereochernistry at C-2 of 9 was confirmed by NMR studies of compound 11.

(8) Reduction of 10 to 11 using LiAlH$_4$ or 9-BBN did not improve the stereoselectivity significantly. In the case of LiAlH$_4$, some side reactions occurred to give a mixture of crude products as detected by $^1$H NMR spectroscopy.


(16) The coupling reaction was also tried with a similar outcome using (N-methylisopropylamino)tributyltin, generated from N-methylisopropylamine(5) and (N,N-dimethylamino)tributyltin, and Pd[(2-furyl)3P]4 in toluene at 80 °C.


