An Improved Synthesis of Enantiomerically Pure RWJ 69442, A Development Candidate for The Treatment of Benign Prostatic Hyperplasia

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This report describes an improved synthesis of enantiomerically pure (*S*)-2-[4-(Dimethylamino)phenyl]-2,3-dihydro-*N*-[2-hydroxy-3-[4-[2-(1-methylethoxy)-phenyl]-1-piperazinyl]propyl]-1,3-dioxo-1*H*-isoindole-5-carboxamide **(**RWJ 69442), a potent and selective α_{1a}-adrenergic receptor antagonist for the treatment of benign prostatic hyperplasia. The synthesis highlights less hazardous reagents, easier purification and higher enantiomeric purity. The *N*-benzyl-*N*-*t*-butoxycarbonyl amine **6** could serve as an enantiomerically pure chiral building block for asymmetric synthesis.

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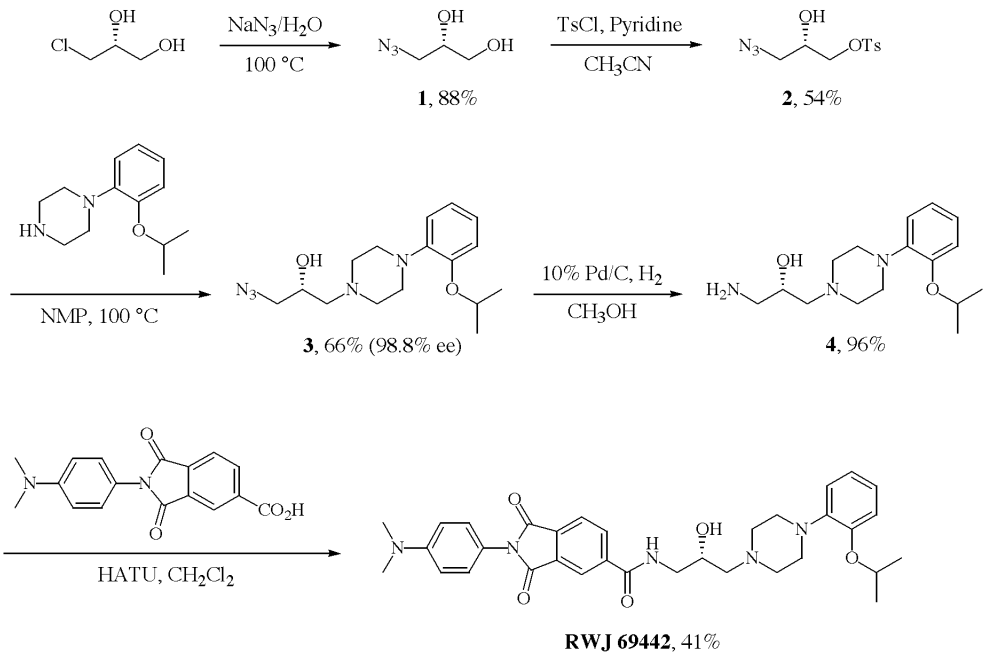
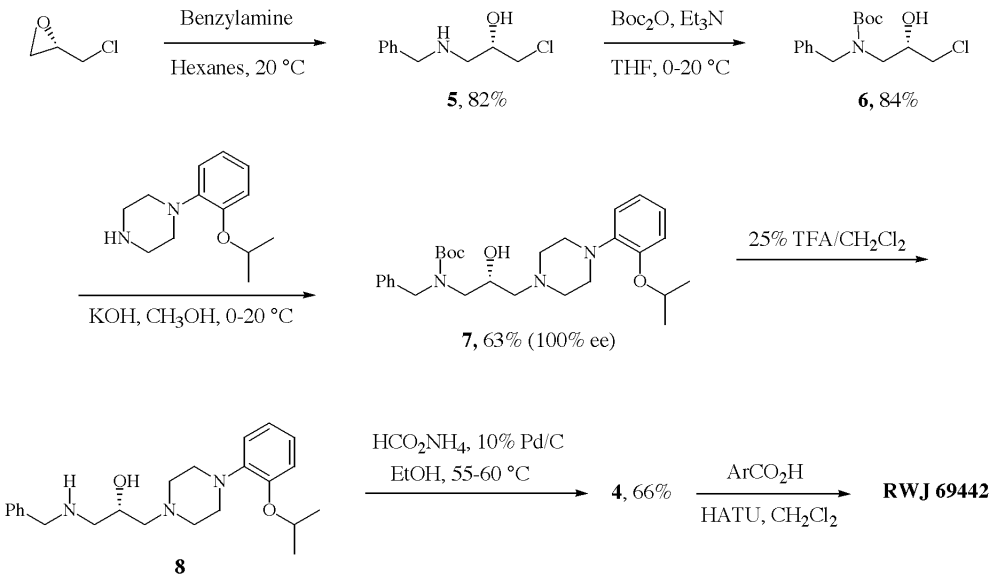
In a program to develop a potent and selective α_{1a}-adrenergic receptor antagonist for the treatment of benign prostatic hyperplasia (BPH), (*S*)-2-[4-(Dimethylamino)phenyl]-2,3-dihydro-*N*-[2-hydroxy-3-[4-[2-(1-methylethoxy)-phenyl]-1-piperazinyl]propyl]-1,3-dioxo-1*H*-isoindole-5-carboxamide **(**RWJ 69442) was identified as a development candidate [1]. A sample of 25 g of RWJ 69442 was prepared based upon the approach shown in Scheme I [1]. However, there were some drawbacks associated with this approach that were not ideal for larger scale synthesis. First, the preparation of azido-diol **1** [2] involved the use of the highly toxic and potentially explosive sodium azide reagent. Second, the chromatographic purification of azido-tosylate **2** [2] was not trivial even on multi-gram scale. Third, in order to obtain greater than 99% ee of RWJ 69442, column chromatography followed by repeated recrystallizations of the intermediates were required.

In our efforts to improve the synthesis without involving azide functionality, we examined a variety of amine equivalents including methoxyamine, phthalimide, aminodiphenylmethane, benzylamine, tritylamine, benzophenone imine, di-*t*-butyl iminodicarboxylate and ammonia. We found that the use of benzylamine followed by *t*-butyloxycarbonyl (Boc) protection best fulfilled our overall requirements (Scheme II).

Scheme I



Scheme II



Reaction of (*S*)-(+)-epichlorohydrin (97% ee) and benzylamine [3] in hexane gave a white solid at 20 °C. Simple filtration and recrystallization gave pure crystalline product **5** in 82% yield. Protection of benzylamine **5** with 2,2-dimethylpropanoic anhydride (Boc_2O) gave the *N*-benzyl-*N*-*t*-butoxycarbonyl amine **6** in 84% yield as a white crystalline solid. Protection of **5** with *t*-butoxycarbonyl group was necessary to avoid the loss of enantiomeric purity in the following step due to the symmetrical attack at the azetidine intermediate [3] by either the chloride anion or the piperazine used. In comparison to the oily azido-tosylate **2**, the *N*-benzyl-*N*-*t*-butoxycarbonyl amine **6** had the advantage of easier synthesis, higher yield, higher chemical purity and higher enantiomeric purity that was reflected in the next step.

Attempted alkylations of 2-isopropoxyphenylpiperazine with **6** under a variety of reaction conditions only resulted in poor yields. On the other hand, alkylation with the assumed epoxide intermediate generated *in situ* by treatment of **6** with a base gave the desired product **7** in 63% yield as a single enantiomer analyzed by Chiralpak OD HPLC. Removal of the Boc-protecting group with trifluoroacetic acid (TFA) gave the deprotected amino alcohol **8** that was used directly without further purification. Hydrogenolysis of **8** under standard conditions (1 atm H_2, 20% $Pd(OH)_2/C$) gave only 50% conversion after seven days of reaction. We found that de-benzylation of **8** was best achieved with catalytic transfer hydrogenolysis [4]. Reaction of **8** with an excess of ammonium formate in the presence of catalytic amounts of 10% palladium on carbon gave amino-alcohol **4** in 66% yield that was identical to the compound prepared previously [1]. Coupling of **4** with [2-(4-dimethylamino)phenyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid [1] using HATU, indeed, gave the enantiomerically pure RWJ 69442 as determined by Chiralpak AD HPLC.

It is very interesting to note that the 2-hydroxy-1,3-diaminopropane chiral moiety present in RWJ 69442 is also embedded in many biologically interesting molecules such as the antibacterial drugs – Linezolid [5], Eperezolid [5] and DUP-721 [6] and also monoamine oxidase inactivators [7]. The synthesis of these molecules almost all involved the usage of the sodium azide reagent. It is conceivable that the use of compound **6** may provide a practical and efficient alternative synthesis of these important drugs.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were measured on a Bruker AC-300 spectrometer using tetramethylsilane as an internal standard. Elemental analyses were obtained by Quantitative Technologies Inc. (Whitehouse, New Jersey), and the results were within 0.4% of the calculated values unless otherwise mentioned. Melting points were determined in open capillary tubes with a Thomas-Hoover apparatus and were uncorrected. The optical rotations were measured at 25 °C with an Autopol III polarimeter. Electrospray mass spectra (MS-ES) were recorded on a Hewlett Packard 59987A spectrometer. High resolution mass spectra (HRMS) were obtained on a Micromass Autospec. E. spectrometer. The acronym "DMAP" refers to dimethylaminopyridine, "TFA" refers to trifluoroacetic acid, "HATU" refers to O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, and "NMP" refers to 1-methyl-2-pyrrolidinone.

(2*S*)-1-Chloro-3-[(phenylmethyl)amino]-2-propanol (**5**).

A mixture of (*S*)-(+)-epichlorohydrin (10 g, 108.1 mmol, Aldrich, 97% ee) and benzylamine (11.57 g, 108.1 mmol) in hexane (40 mL) were stirred at 20 °C for 62 hours. A white solid precipitated. More hexane (~ 350 mL) was added, the mixture was stirred for 20 minutes, and then sonicated to break up the big chunks of the white solid. The white solid was collected by filtration, washed with hexane, and dried under vacuum to give 19.8 g (92%) white solid. The white solid was recrystallized from EtOAc/hexane to give 17.76 g (82%) of **5** as a white crystalline solid; mp 88.5-90.5 °C; $[\alpha]_D^{25}$ = -14.5° (c = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 5 H), 3.88 (m, 1 H), 3.79 (m, 2 H), 3.53 (d, J = 5.3 Hz, 2 H), 2.89 (m, 2 H), 2.81 (dd, J = 12.4, 4.1 Hz, 1 H), 2.69 (dd, J = 12.2, 7.9 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 141.1, 128.5, 128.2, 126.9, 70.0, 53.3, 52.2, 48.5; MS (ES) m/z: 200 ($M+H^+$).

Anal. Calcd. for $C_{10}H_{14}NOCl$: C, 60.15; H, 7.07; N, 7.01. Found: C, 60.10; H, 7.02; N, 6.92.

((2*S*)-3-Chloro-2-hydroxypropyl)(phenylmethyl)carbamic Acid, 1,1-Dimethylethyl ester (**6**).

2,2-Dimethylpropanoic anhydride (Boc_2O) (11 g, 50.1 mmol) and triethylamine (10.12 g, 100 mmol) were dissolved in THF (25 mL) and cooled to 0 °C. The amine **5** (10 g, 50.1 mmol) was added in portions and the reaction mixture was stirred for 20 hours while allowing to warm to 20 °C overnight. The solvent was removed under reduced pressure and water was added to the residue. The mixture was extracted with ether (3x), dried (Na_2SO_4) and concentrated. The crude residue was recrystallized from EtOAc/hexane to give 9.9 g (66%) of **6** as a white crystalline solid. The filtrate was concentrated (3.1 g of oil) and more product was obtained by column chromatography (short column, 8 cm height of SiO_2, EtOAc/hexane as eluent). The oil was recrystallized from EtOAc/hexane to give another 2.78 g (18%) of **6** as a white crystalline solid; mp 64.5-65.5 °C; $[\alpha]_D^{25}$ = -10.2° (c = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.22-7.36 (m, 5 H), 4.52 (m, 2 H), 4.30 (brs, 0.5 H), 3.96 (m, 1 H), 3.36-3.97 (m, 4 H), 1.47 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2, 138.2, 129.0, 127.8, 127.7, 81.5, 71.9, 53.0, 51.1, 46.8, 28.7; MS (ES) m/z: 322 (M+Na).

Anal. Calcd. for $C_{15}H_{22}NO_3Cl$: C, 60.10; H, 7.40; N, 4.67. Found: C, 60.26; H, 7.42; N, 4.63.

[(2*R*)-2-Hydroxy-3-[4-[2-(1-methylethoxy)phenyl]-1-piperazinyl]propyl]-(phenylmethyl)-carbamic acid, 1,1-dimethylethyl Ester (**7**).

KOH (11.23 g, 200.5 mmol) was dissolved in methanol (280 mL), and the fumarate salt of 1-(2-isopropoxyphenyl)-piperazine (10.9 g, 33.4 mmol) was added. The reaction mixture was stirred at 20 °C for 20 minutes and then cooled to 0 °C. The Boc-protected amine **6** (10 g, 33.4 mmol) was added to the methanol solution at 0 °C and stirred for another 20 hours while allowing the temperature to warmed to 20 °C. The solvent was removed under reduced pressure, and water was added. The product was extracted with ether (3x), dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (short column, 8 cm height SiO_2, EtOAc/hexane as eluent) to give 10.22 g (63%) of **7** (100% ee, Chiralpak OD 4.6 x 250 mm. 1 mL/minute, 254 nm, mobile phase: 90/10/0.1 of hexane/IPA/diethylamine) as a yellowish oil; $[\alpha]_D^{25}$ = +8.2° (c = 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.26-7.35 (m, 5 H), 6.91 (m, 4 H), 4.68 (d, J = 15.6 Hz, 1 H), 4.59 (m, 3 H), 3.95 (m, 1 H), 3.35 (m, 2 H), 3.11 (m, 4 H), 2.75 (m, 2 H), 2.54 (m, 2 H), 2.38 (m, 2 H), 1.45 (m, 9 H), 1.34 (d, J = 6.1 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 150.7, 143.2, 139.1, 128.9, 127.7, 127.5, 122.9, 122.0, 118.8, 116.8, 80.3, 70.6, 67.4, 62.2, 54.1, 52.7., 51.5, 50.9, 28.8, 22.8; MS (ES) m/z: 484 ($M+H^+$).

Anal. Calcd. for $C_{28}H_{41}N_3O_4$: C, 69.54; H, 8.54; N, 8.69. Found: C, 69.27; H, 8.60; N, 8.45.

(α*S*)-α-(Aminomethyl)-4-[2-(1-methylethoxy)phenyl]-1-piperazineethanol (**4**).

A mixture of compound **7** (10.1 g, 21.91 mmol) and 25% TFA/methylene chloride (100 mL) was stirred at 20 °C for 22 hours. The solvent was removed under reduced pressure, the residue was basified with 20% $NaOH_{(aq)}$ and extracted with methylene chloride (3x). The combined extracts were dried (Na_2SO_4) and concentrated to give 7.61 g of de-Boc product **8** as an oil which was used directly without further purification; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 5 H), 6.91 (m, 4 H), 4.59 (m, 1 H), 3.90 (m, 3 H), 3.10 (m 7 H), 2.80 (m, 2 H), 2.70-2.38 (m, 5 H), 1.34 (d, J = 6.2 Hz, 6 H); MS (ES) m/z: 384 ($M+H^+$).

A mixture of **8** (7.3 g, 19.06 mmol) in CH_3OH (100 mL) under nitrogen was stirred and treated with 10% Pd/C (1.46 g, 20% by wt.) followed by a solution of ammonium formate (6 g, 95.3 mmol) in water (20 mL). The resulting mixture was stirred at 55-60 °C for 23 hours. The cooled reaction mixture was filtered through celite and the celite was further washed with methanol. The filtrate was concentrated to remove CH_3OH. The residue was diluted with water, extracted with CH_2Cl_2 (3x), dried (Na_2SO_4) and concentrated. The product was purified by a short column (5 cm height of SiO_2) to give 3.85 g (66%) of **4** as an oil that was identical to an authentic sample [1] in all respects.

(*S*)-2-[4-(Dimethylamino)phenyl]-2,3-dihydro-*N*-[2-hydroxy-3-[4-[2-(1-methylethoxy)-phenyl]-1-piperazinyl]propyl]-1,3-dioxo-1*H*-isoindole-5-carboxamide (**RWJ 69442**).

The amine **4** (176 mg, 0.6 mmol) was dissolved in a mixture of *N*,*N*-diisopropylethylamine (310 mg, 2.4 mmol) and methylene chloride (5 mL). To this solution was added [2-(4-dimethylamino)phenyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid [1] (205 mg, 0.66 mmol) and HATU (251 mg, 0.66 mmol) and the mixture was stirred at 20 °C for 22 hours under N_2. The reaction mixture was diluted with more methylene chloride, washed with 3% $K_2CO_{3(aq)}$, dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (SiO_2) to give 193 mg (55%) of RWJ 69442 as a yellow solid (100% ee, Chiralpak AD 4.6 x 250 mm. 0.75 mL/min, 220 nm, mobile phase: 100% ethanol, retention time 43.9 min); $[\alpha]_D^{25}$ = +10.5° (c = 0.2 , $CHCl_3$). All other spectra data were identical to that of the compound prepared previously [1].

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