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# Process Research and Scale-Up for a β-3 Adrenergic Receptor Agonist

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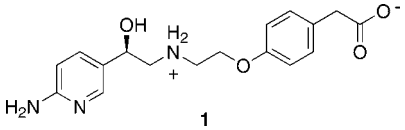
**Abstract:**

**A scaleable synthesis of the β-3 adrenergic receptor agonist, (4-{2-[2-(6-aminopyridin-3-yl)-(2*R*)-hydroxy-ethylamino]ethoxy}-phenyl)acetic acid is presented. The key coupling step utilizes a silyl-protected β-hydroxy tosylate to alkylate a primary amine, thus avoiding water-soluble intermediates and reducing unwanted side products. Deprotection strategies and isolation of a zwitterionic species are described.**

(4-{2-[2-(6-Amino-pyridin-3-yl)-(2R)-hydroxy-ethylamino]-ethoxy}phenyl)acetic acid **1** is a β-3 adrenergic receptor agonist discovered at Pfizer Global Research and Development by Robert Dow.[2] In this contribution, the efforts to provide kilogram quantities of **1** are described. The key issues were selection of protecting groups, the high water solubility of many of the intermediates, purification of complex reaction mixtures, and racemization of the single asymmetric center. The final compound was isolated as the zwitterion.



**1**

The original synthesis of **1** was sufficient for the preparation of multihundred-gram lots of material (Scheme 1). 2-Amino-5-bromopyridine was acetylated and treated under Heck reaction conditions to provide 2-acetamido-5-vinylpyridine as described by Raggon.[3] *N*-Acyl protecting groups such as benzoyl were tried but were difficult to hydrolyze, and imide protecting groups were found to react with primary amine **7**[4,5] in the coupling step. Introduction of the single chiral center was accomplished via asymmetric dihydroxylation of olefin **3** to give diol **4**. Tosylation of **4** was done with *p*-toluenesulfonyl chloride in pyridine at 0 °C to provide the primary tosylate **5** selectively. Treatment of tosylate **5** with base provided epoxide **6**.

Initially, on laboratory scale, sodium hydroxide supported on alumina was used for this transformation to allow workup without using water. This was changed to potassium *tert*-butoxide in tetrahydrofuran (THF) for further scale-up. Either of these procedures required a filtration to remove salts from the water-soluble epoxide **6**. These filtrations turned out to be problematic. As reaction size and filtration time increased, significant racemization of epoxide **6** was seen. This was presumably due to deprotonation of the amide nitrogen, leading to equilibrium with the quinone methide **6a** (Scheme 2).

Using less than one equivalent of base and keeping the filtration cold helped to reduce this racemization, but the process was not robust. Epoxide **6** of varying chiral purity, ranging from 96% to 40% ee was isolated. A weaker base such as potassium carbonate in acetone initially performed well on small scale in the lab without racemization but gave inconsistent chemical yields on larger scale. Because of these problems, the epoxide formation step was done in multiple 22-L batches with potasium *tert*-butoxide in THF to minimize loss of the expensive diol **4**.

The carboxylic acid group in amine **7** was protected as the *N*-methylamide. When an alkyl ester protecting group was tried, the primary amino group in **7** would displace the alcohol and form an amide. This resulted in oligomeric side products. More hindered amides such as the *N*,*N*-dimethylamide of **7** were more difficult to hydrolyze at the end of the synthesis. The opening of epoxide **6** with the amino side chain **7** was initially done in 90 °C dimethyl sulfoxide (DMSO). This gave poor yields, and the epoxide was found to be unstable in DMSO at that temperature. By using a 5:1 mixture of toluene and DMSO at 95 °C, epoxide **6** itself was much more stable, and reaction of **6** with excess **7** in this solvent system was used. Treatment of the crude reaction mixture with di-*tert*-butyl dicarbonate yielded organic soluble BOC derivatives **10** and, to a lesser extent **11**, from which the water-soluble bis-alkylated products could be washed away along with DMSO and excess of amine **7**. The minor amount of the isomeric BOC derivative **11** detected suggested that epoxide opening at the α-carbon to yield alcohol **9** might not be an issue. However, a mass balance analysis of the reaction mixture before the protection sequence showed it to consist of desired **8** (48%), α-opened product **9** (20%), bis-alkylated **7** (9%), and unreacted **6** (7%). The remaining components were not identified. At this point, it was realized that the low levels of **11** observed were due to the slower rate of reaction of **9** with di-*tert*-butyl dicarbonate and not to the lack of formation of **9** itself.

Refluxing crude isolated BOC-alcohol **10** with 6 N HCl removed all the protecting groups. Chiral zwitterion **1** was isolated in 10−15% yield (from epoxide **6**) with good chiral purity following adjustment of the solution to pH 7. While the throughput was low, the synthesis did allow the preparation of multihundred-gram quantities of **1** for early studies.

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(2) Dow, R. L. U.S. Patent 6,001,856 1998; *Chem. Abstr*. **1999**, *130*, 81419.

(3) Raggon, J. W.; Snyder, M. W. *Org. Process Res. Dev*. **2002**, *6*, 67−69.

(4) DeVries, K. M.; Dow, R. L.; Wright, S. W. WO98/21184.

(5) DeVries, K. M.; Raggon, J. W.; Shanker, R. M.; Urban, F. J.; Vanderplas, B. C. U.S. Patent 6,124,457, 2000.

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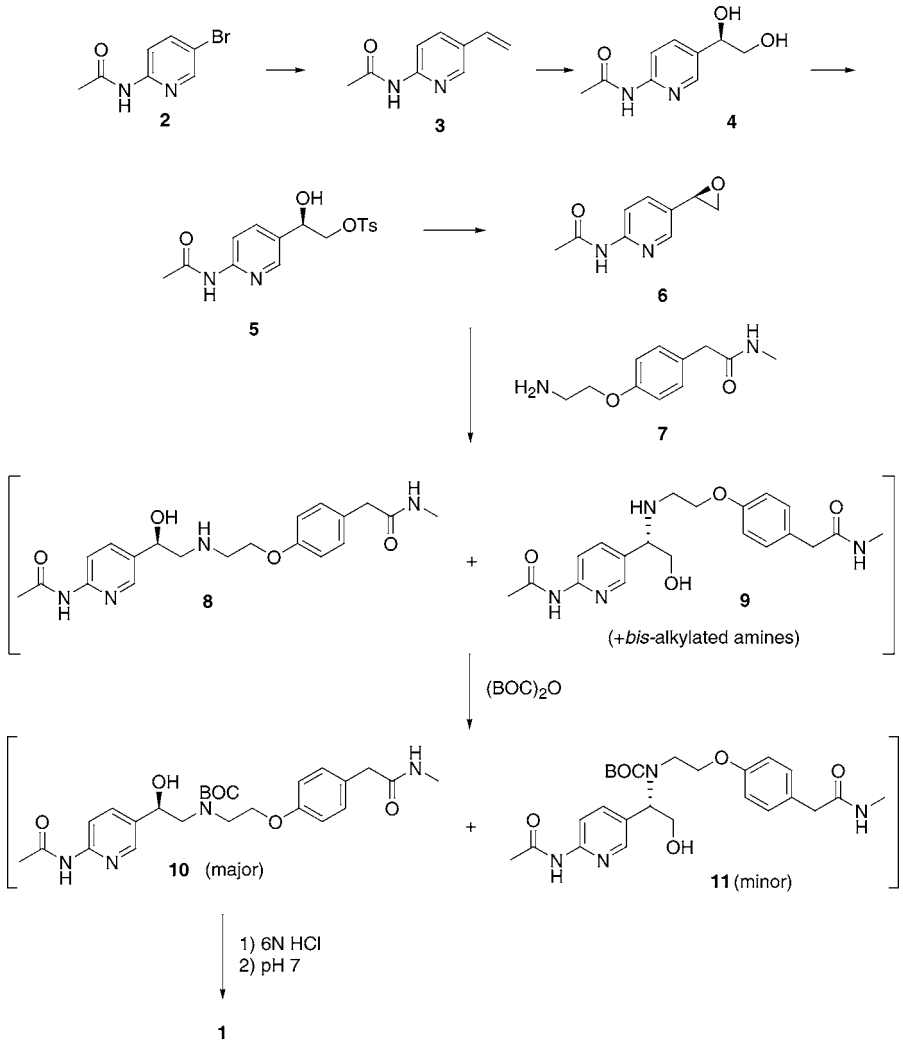
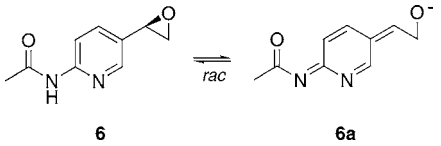
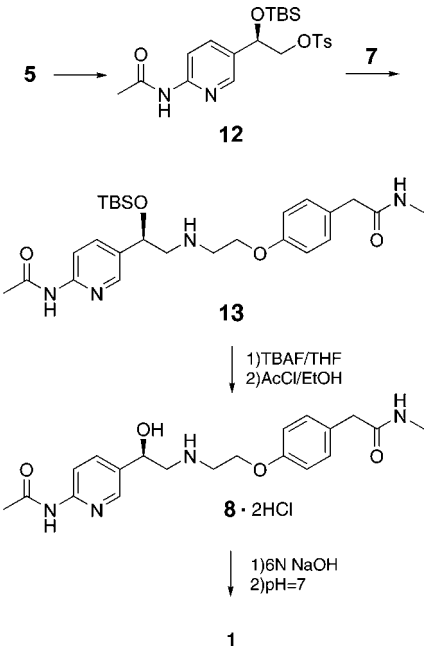
***Scheme 1***




***Scheme 2***




***Scheme 3***




Efforts to improve this chemistry focused on avoiding the complex reaction mixture formed in the epoxide-opening step while looking to improve the organic solubility of the intermediates (Scheme 3). Crystalline tosylate **5** was protected as a *tert*-butyldimethylsilyl ether **12** by treatment with *tert*-butyldimethylsilyl chloride and imidazole in *N*,*N*-dimethylformamide.[6] The reaction of tosylate **12** with two equivalents of amine **7** and one equivalent of diisopropylethylamine was carried out in very concentrated DMSO solution (0.6 vols with respect to **12**) at 80 °C. The reaction mixture was initially a very thick slurry, which collapsed into a stirable oil at ca. 50 °C. More dilute reaction conditions, use of less than two equivalents of **7**, or omission of the additional tertiary amine led to incomplete consumption of **12**. Higher reaction temperatures induced acetyl

(6) The protection of chlorohydrins as triethylsilyl ethers followed by conversion to the iodo compound and reaction with a primary amine has been described: Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442−447. Brodfuehrer, P. R.; Smith, P.; Dillon, J. L.; Vemishetti, P. *Org. Process Res. Dev.* **1997**, *2*, 176−178.

transfer from the acetamide group of the pyridine to primary amine **7**. Use of other tertiary amines such as pyridine, DABCO or *N*-methylmorpholine resulted in incomplete reaction, and pyridine itself was quaternized by **12**. After heating overnight, the reaction mixture was cooled and diluted with ethyl acetate. Excess amines were washed away with water, and the organic layer was concentrated to an oil that consisted mainly of desired **13** with <2% of bis-alkylated product.

In analogy to the previous route using BOC-derivative **10**, a complete deprotection of **13** was carried out by heating in 6 N HCl. Chiral HPLC analysis of the reaction mixture showed nearly racemic **1**. A variety of desilylation procedures such as TBAF/THF, TFA/$CH_2Cl_2$, HF·pyridine, and HOAc/THF/$H_2O$ were used to remove the TBDMS group first. Hydrolysis of the resulting amino alcohol **8** by 6 N HCl gave racemic **1**. In comparison, the methyl ester of **1** (prepared by treatment of **1** with thionyl chloride in methanol) could be hydrolyzed by heating in 6 N HCl to afford a high yield of **1** without measurable racemization. Furthermore, zwitterionic **1** could be heated in aqueous HCl and recovered after pH adjustment without racemization. These observations suggested that it was the presence of an *N*-acetamide moiety in **8** that led to racemization of the benzyl alcohol group. On the other hand, in the unprotected 2-aminopyridines **1** and its methyl ester, the 2-amino group would be protonated in 6 N HCl, and this would deactivate the benzylic position to ionization and racemization. It was also found that only the excess of desired enantiomer **1** precipitated as the zwitterion **1** at pH 7, while the material left in aqueous solution was racemic. This helped explain the low recoveries seen with the epoxide process.

Two different methods were then developed to convert **13** to **1** in high yield and optical purity. In the simplest procedure, basic hydrolysis of **13** with excess sodium hydroxide at reflux removed all the protecting groups. The cooled reaction mixture was a slurry. Activated charcoal was added, the mixture was filtered, and the solids were washed with water. Zwitterion **1** was precipitated by lowering the pH of the solution to pH 7. While eliminating additional isolation steps was attractive from a processing prospective, the removal of the silyl protection in this manner provided a product contaminated with residual silicon-containing impurities. The preferred deprotection method was a stepwise removal of protecting groups. Intermediate **13** was treated with tetrabutylammonium fluoride in THF to remove the *tert*-butyldimethylsilyl moiety, and ethanolic HCl was added to the reaction mixture to precipitate the dihydrochloride salt of **8**. This isolation of a crystalline solid provided a convenient purification point. Hydrolysis of the amide protecting groups in **8** was carried out with aqueous sodium hydroxide at reflux, and zwitterion **1** was isolated by adjusting the pH of the solution. Further purification, if needed, was accomplished by dissolution of the zwitterionic **1**, filtration of the solution to remove insolubles, and reprecipitation of zwitterion **1** by adjustment of the pH of the aqueous solution to pH 7.

In summary, a relatively simple process for a large-scale preparation of amino alcohol **1** was developed that successfully dealt with the issue of complex mixtures of water-soluble compounds. This process was used to provide batches as large as 30 kg of material suitable for clinical supplies.

## Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained on either a Brucker WM 300 (300 MHz) or a Varian Unity 400 (400 MHz) spectrometer in deuteriochloroform or DMSO-$d_6$. Infrared spectra were taken in KBr by diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS). Mass spectra were determined with a Finnigan 4510 mass spectrometer using fast atom bombardment (FAB). Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

**Toluene-4-sulfonic Acid 2-(6-Acetylamino-pyridin-3-yl)-(2*R*)-(hydroxy)ethyl Ester (5).** Chiral diol **4** (71.3 kg, 363.4 mol) was dissolved in pyridine (55 gal) and cooled to −10 °C. *p*-Toluenesulfonyl chloride (86.6 kg, 545.3 mol) was added in three portions over 1.5 h. The reaction mixture was stirred for 4 h at 0 °C, at which time TLC (9.5:0.5 methylene chloride/methanol) and HPLC analysis indicted the reaction was complete. Water (34 gal) was added to the reaction over 60 min. The quenched reaction was added over 20 min to a biphasic mixture of ethyl acetate (157 gal) and a solution of sodium carbonate (96.3 kg) in water (254 gal), keeping the reaction temperature between 5 and 10 °C. This was stirred for 20 min, after which time agitation was stopped, and the layers were allowed to separate. The organic layer was washed with water (4 × 63 gal) and concentrated under vacuum to an oil. Isopropyl alcohol (16.6 gal) and toluene (168 gal) were added to the oil, and the mixture stirred for 16 h at 25 °C. Additional toluene (82 gal) was charged, and the slurry was cooled and stirred at 10 °C for 3 h. The product was collected by filtration, washed with toluene (15 gal), and dried under vacuum at 50 °C to yield 73.7 kg (57.6%) of **5** as a pale yellow solid; mp 118−122 °C. $[\alpha]_D$ −48.9° ($c$ = 1.01, MeOH). $^1$HMR (400 MHz, DMSO-$d_6$) $\delta$ 10.42 (s, 1), 8.16 (s, 1), 7.93 (d, 1, 8.7 Hz), 7.7−7.59 (m, 3), 7.37 (d, 2), 4.93 (t, 1), 4.00 (s, 2), 3.28 (s, 1), 2.35 (s, 3), 2.03 (s, 3), 0.73 (s, 9), −0.04 (s, 3), −0.19 (s, 3).

**Toluene-4-sulfonic Acid 2-(6-Acetylamino-pyridin-3-yl)-(2*R*)-(*tert*-dimethyl-silyloxy)ethyl Ester (12).** Monotosylate **5** (73.7 kg, 210.3 mol) was dissolved in *N*,*N*-dimethylformamide (20 gal) to which were added without cooling imidazole (28.6 kg, 420.1 mol) and *tert*-butyldimethylchlorosilane (34.9 kg, 231.5 mol). The reaction mixture was stirred at 25 °C for 2 h, at which time HPLC analysis indicated the reaction was incomplete. Additional *tert*-butyldimethylchlorosilane (5.50 kg, 36.5 mol) was added, and the mixture stirred for 12 h at 25 °C, when HPLC analysis indicated the reaction was complete. The reaction mixture was added to ethyl acetate (156 gal) and water (78 gal) and stirred for 15 min. Agitation was stopped, and the layers were allowed to separate. The organic layer was washed with water (78 gal) and concentrated under vacuum at 25 °C to approximately 5 gal. Hexanes (78 gal) were added, and the resulting slurry was cooled to 10 °C and

stirred for 3 h. The product was filtered, washed with hexanes (15 gal), and dried under vacuum at 50 °C, providing 92.7 kg (94.6%) of **12** as an off-white solid; mp 121−124 °C. Chiral HPLC[7] analysis showed the solid to be 99.67% desired enantiomer. $[\alpha]_D$ −52.3° ($c$ = 1.04, $CHCl_3$). $^1$HMR (300 MHz, $CDCl_3$) $\delta$ 8.64 (s, 1), 8.23 (s, 1), 8.17 (d, 1), 7.69 (d, 1), 7.14 (d, 2), 6.86 (d, 2), 5.48 (bs, 1), 4.86 (m, 1), 4.06 (t, 2), 3.50 (s, 2), 3.01 (t, 2), 2.90 (t, 1), 2.74 (m, 4), 2.20 (s, 3), 0.90 (s, 9), 0.1 (s, 3), −0.4 (s, 3). Mass spectrum: *m*/*e*: 500 ($M^+$).

**2-(4-{2-[2-(6-Acetylamino-pyridin-3-yl)-(2*R*)-hydroxyethylamino]ethoxy}phenyl)-*N*-methyl-acetamide Dihydrochloride (8).** A mixture of **12** (46.4 kg, 99.86 mol), amine **7** (41.6 kg, 199.7 mol), DMSO (8 gal), and *N*,*N*-diisopropylethylamine (4.6 gal) was heated at 75 °C for 14 h, at which time the reaction was judged complete by TLC analysis (3:1, ethyl acetate/hexanes). After cooling to 35 °C, water (39 gal) and ethyl acetate (54 gal) were added, and the mixture stirred for 15 min at 25 °C. The agitation was stopped and the mixture allowed to separate. The organic layer was washed with water (2 × 11 gal) and concentrated under vacuum to an oil. Toluene (20 gal) was added to the oil, and the resulting solution was concentrated again under vacuum to a stirrable oil. Tetrahydrofuran (86 gal) was added, followed by a 1 M solution of tetrabutylammonium fluoride in THF (34.3 gal, 130 mol), and the mixture stirred for 12 h at 25 °C. HPLC analysis indicated the reaction was complete. To this solution was added ethanolic HCl (prepared by adding acetyl chloride (5.6 gal, 299 mol) to absolute ethanol (16 gal)), keeping the temperature between 5 and 10 °C during the addition. The resulting slurry was stirred at 10 °C for 2 h, then filtered on a Rosenmund filter under $N_2$. The filter cake was washed successively with THF (15 gal), then diisopropyl ether (123 gal), and allowed to pull dry for 60 min under $N_2$. Acetonitrile (74 gal) was added to the filter cake in the Rosenmund filter. The resulting slurry was stirred at 25 °C for 12 h, filtered, and washed with acetonitrile (78 gal) followed by isopropyl ether (61 gal). The solid was dried under vacuum in the Rosenmund filter at 45 °C for 12 h, affording 38.8 kg (84.7%) of the bis-HCl salt of **8** as a nonhygroscopic pale yellow solid.

**(4-{2-[2-(6-Amino-pyridin-3-yl)-(2*R*)-hydroxyethylamino]ethoxy}phenyl)acetic Acid (1).** The bis-HCl salt of **8** (74.6 kg, 162.4 mol) was dissolved in water (83 gal), and a solution of sodium hydroxide (32.5 kg, 812 mol) in water (34 gal) was added over 20 min, keeping the reaction temperature at 15−20 °C. Following the addition the thin slurry was heated to 100 °C for 12 h, then cooled to approximately 35 °C and sampled for reaction completion. HPLC analysis indicted that the reaction was complete. Darco G-60 (7.4 kg) was added to the reaction mixture, and the temperature was increased to 65 °C. After stirring slowly for 30 min, the mixture was filtered warm (55 °C) and the filter cake washed with warm water (10 gal). The filtrate was then cooled to 10 °C and adjusted to pH 7 by adding approximately 9 gal of concentrated HCl while keeping the temperature between 5 and 15 °C. The resulting slurry was then stirred at 10 °C for 2 h, filtered, washed with water (55 gal), and dried under vacuum at 50 °C for 16 h, yielding 108.5 kg crude zwitterion **1** as a water-wet solid. LOD analysis showed this product to contain 54% water; thus, the actual yield was 49.9 kg (92.8%). For analytical purposes, a small sample was dissolved in dilute HCl, the insolubles were filtered off, and **1** was precipitated at pH 7 by adding dilute aqueous NaOH. Filtering and drying under vacuum at 50 °C furnished an off-white solid, mp 210−211 °C.

To a mixture of crude zwitterion **1** (49.9 kg, 150.6 mol) in water (53 gal) was added concentrated HCl (6.57 gal) over 30 min, keeping the reaction temperature between 20 and 25 °C. The hazy mixture (pH approximately 0.8) was stirred for 10 min at 25 °C, then filtered through a pad of Celite. The pH of the filtrate was adjusted to 7.0−7.2 with 10% aqueous NaOH[8] (prepared by dissolving NaOH flakes (12.05 kg) in water (31 gal)). The resulting slurry was filtered and washed with water (26 gal) followed by THF (40 gal). The solid was added to a solution of NaOH (6.02 kg, 150 6 mol) in water (53 gal) and stirred for 60 min at 25 °C. The hazy mixture was filtered and the pH of the filtrate adjusted to 7.0−7.2 with 3 N HCl. The resulting slurry was cooled to 10 °C and stirred for 1 h. The solids were filtered and washed with water (53 gal) and THF (53 gal) and dried at 60 °C under vacuum for 4 days, providing 32.2 kg (64.5%) of zwitterion **1** as an off-white solid.

A slurry of the zwitterion **1** (32.2 kg, 97.16 mol) in USP-grade water was stirred at 50 °C for 15 h, then cooled to 25 °C, and filtered. The filter cake was washed with USP-grade water (17 gal) and speck-free THF (2 × 25 gal) and dried under vacuum at 50 °C for 2−3 days, yielding 30.3 kg (94.1%) of **1** as an ash-free white solid. The opposite enantiomer was not detected by HPLC analysis (<0.05%). $^1$HMR (300 MHz, $D_2O$ + DCl) $\delta$ 7.93 (d, 1), 7.86 (s, 1), 7.28 (d, 2), 7.05 (d, 1), 7.00 (d, 2), 5.10 (dd, 1), 4.34 (t, 2), 3.69 (s, 2), 3.60 (t, 2), 3.40 (m, 2).

Anal. Calcd for $C_{17}H_{21}N_3O_4$: C, 61.61; H, 6.40; N, 12.68. Found: C, 61.49; H, 6.29; N, 12.60.

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(7) Chiral HPLC performed on Chiralpak AD column 4.6 cm × 25 cm, mobile phase: 80:20 (hexane/isopropyl alcohol), 1.5 mL/min.

(8) The pH adjustment took up to 12 h to stabilize at pH 7−7.2. Typically, the pH was adjusted to approximately 8.5, upon which it would drift downward into the desired range then back up again until eventually stabilizing in the desired range.