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A Facile and Scaleable Synthesis of ABT-239, A Benzofuranoid H_3 Antagonist

Yu-Ming Pu,* Timothy Grieme, Ashok Gupta, Daniel Plata, Ashok V. Bhatia, Marlon Cowart,† and Yi-Yin Ku

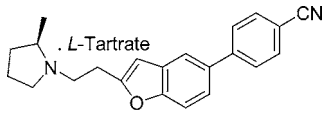
Process Research and Development, Global Pharmaceutical Research and Development, Abbott Laboratories, North Chicago, Illinois 60064-4000, U.S.A.

Abstract:

A facile and scaleable synthesis of a potent and selective histamine H_3 receptor antagonist, ABT-239 (1), was developed starting from commercially available 4′-hydroxy-biphenyl-4-carbonitrile (2). The synthesis comprised four chemical steps and a salt formation step with an overall yield of 40%. A highly selective monoiodination of a phenol was developed and used to prepare iodophenol (3b) in near quantitative yield using NIS in AcOH in the presence of a small amount of H_2SO_4. A Pd-catalyzed cross coupling reaction of the iodophenols (3b) with butyn-3-ol (4a) provided benzofuran (5) in one step in >80% yield, en route to 1. The new process required no chromatographic purification throughout the synthesis and was successfully demonstrated on scale-up to prepare 1.7 kg of the target ABT-239 (1).

Introduction

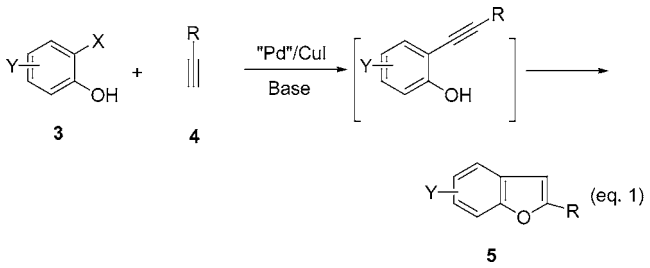
The histamine H_3 receptor (H_3R) is a presynaptic G protein-coupled receptor that regulates the release of a variety of neurotransmitters.[1] Antagonists of this receptor are thought to offer an attractive therapeutic target for cognitive disorders. Despite intense interest in the field,[2] as yet, no H_3R antagonist has advanced through clinical trials and been approved for human use. Syntheses and biological evaluation of imidazole-based H_3R antagonists have been described in recent years.[3] However, these compounds can give rise to drug−drug interactions by inhibiting hepatic CYP enzymes and also exhibit relatively poor CNS penetration. For this reason, clinical acceptability will likely be greater for nonimidazole H_3R antagonists. More recently, a new class of nonimidazole H_3R antagonists has been discovered at Abbott laboratories.[4] In vitro and in vivo studies indicate that ABT-239 (**1**) is a potent and highly selective H_3R antagonist with a potent procognitive activity in several animal models suggestive of clinical utility for treatment of attention-deficit hyperactivity disorder (ADHD) or other cognitive disorders. To enable



ABT-239 (1)

advanced toxicological and safety profiling of this compound, a large quantity of this drug substance was needed for both preclinical and clinical studies. Therefore, a facile and scaleable synthetic route capable of preparing kilogram quantities of ABT-239 (**1**) was required.

This compound belongs to a recently described class of structurally novel benzo[*b*]furan derivatives that are of great interest due to their remarkable biological and pharmacological properties, including modulation of androgen biosynthesis,[5] inhibition of 5-lipoxygenase, and the blood coagulation factor Xa.[6] Of the several general and versatile methodologies considered for the synthesis of 2-substituted benzo[*b*]furans,[7] the palladium-catalyzed Sonogashira reaction of *o*-halophenol (**3**) with substituted 1-alkynes (**4**) represents a very efficient procedure and was deemed best suited for our purposes (eq 1).[8]



With adaption of this strategy, the synthesis of ABT-239 (**1**) could be envisioned as proceeding through a palladium-catalyzed cross-coupling reaction of halo-phenol (**3**) with 3-butyn-1-ol (**4a**) as the key step (Scheme 1). This strategy was initially used to prepare small quantities of **1** from

* To whom correspondence should be addressed. Phone: (847) 935-2984. Fax: (847) 938-2258. E-mail: yuming.pu@abbott.com.

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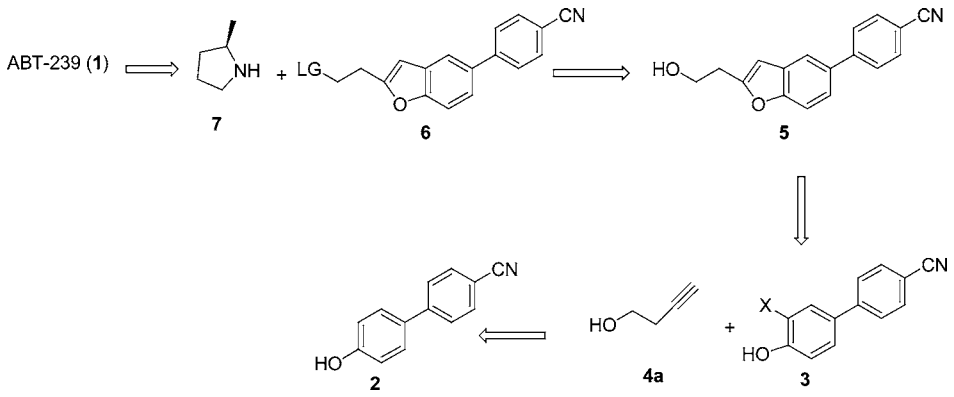
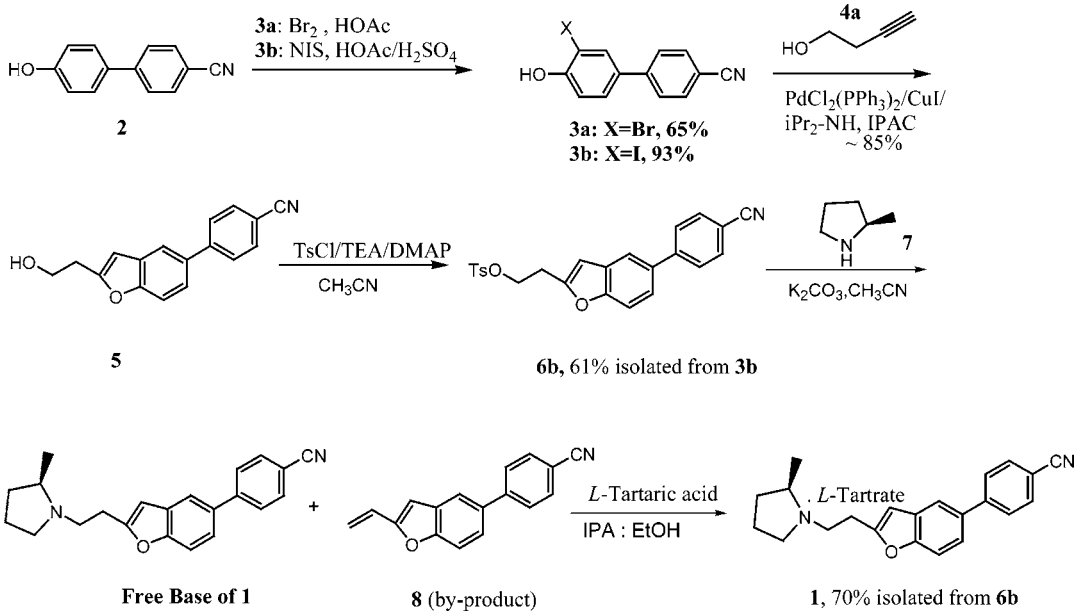
Scheme 1. **Retrosynthetic analysis**



Scheme 2. **Scaleable process for the synthesis of 1**



commercially available 4-cyano-4′-hydroxy-biphenyl (**2**).[4] Although the initial synthesis provided a sufficient amount of **1** for the in vitro and in vivo biological tests, the synthesis was not amenable for scale-up, as it involved several chromatographic purifications and the use of toxic solvents and reagents in large quantities. Additionally, the preparation of (*R*)-2-methylpyrrolidine (**7**) itself was tedious, as it involved a four-step process.[9] In this paper, we describe the successful development of a practical and scaleable process for the synthesis of **1**.

Results and Discussion

The key intermediate, iodophenol (**3b**), was originally prepared by employing sodium iodide and sodium hypochlorite for the oxidative iodination of 4′-hydroxy-biphenyl-4-carbonitrile (**2**) (Scheme 2). While the yield for this transformation on a small scale routinely exceeded 50% after column chromatographic purification, the reaction was plagued with problems on the multigram scale. For example, the reaction resulted in reduced regioselectivity and lower conversion, and consequently the isolation of the desired product **3b** proved to be difficult. An alternative procedure suitable for scale-up was deemed necessary. The main challenge was to control the regioselectivity of mono- versus di-iodination while still achieving good conversion. Our initial attempts to improve this iodination reaction included varying the reaction conditions with respect to the iodination agents (NIS, I_2), solvents (methanol, chloroform, and acetonitrile), and reaction temperature (0 to 50 °C). All reactions initially tried gave either higher levels of regioisomeric di- and tri-iodinated products or poor conversion. Recently, an improved iodination procedure (NIS−TFA in acetonitrile) has been reported to be highly regioselective for electron-rich aromatics.[10] However, when **2** was subjected to the same reaction conditions, over-iodination remained a serious problem. On the other hand, the reaction of **2** with bromine in acetic acid was found to afford the desired product (**3a**) in 69% isolated yield after crystallization.[11] This finding of a possible advantage of acetic acid as halogenation solvent prompted us to investigate the iodination of **2** with NIS in acetic acid. The iodination reaction initially gave only ~65%

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of the desired product (**3b**) with 25% of the di-iodinated byproduct. However, the yield was increased to 93% by addition of a small amount of concentrated sulfuric acid (0.5 equiv). The high yield of our procedure was rationalized as proceeding through the in situ formation of proton-solvated iodinating species. [10]

The iodinated product (**3b**) could be conveniently precipitated by the addition of water to the reaction mixture and isolated by filtration. This intermediate was of acceptable purity (93% peak area by HPLC, ~2% di-iodoproduct) and was used directly in the next step without further purification. The practicality of this robust procedure was demonstrated by the preparation of >3 kg of iodophenol (**3b**). Coupling of the halo-phenol **3** with but-3-yn-1-ol (**4a**) was achieved by a standard Sonogashira−Stevens protocol, and the hydroxybutynyl-phenol intermediate subsequently cyclized under the reaction conditions to give the benzofuran alcohol (**5**) in a one-pot reaction. The reaction was originally carried out by employing $PdCl_2$ $(PPh_3)_2$ as the catalyst, with copper(I) iodide as the cocatalyst and with dichloromethane as the solvent in the presence of excess of an organic base. Cross coupling of the less reactive bromophenol (**3a**) with the but-3-yn-1-ol (**4a**) proved to be sluggish, with the reaction often requiring at least 3 equiv of **4a** and a high palladium loading (5 mol %) at elevated temperature (80−100 °C) to push the reaction to completion. When the iodophenol (**3b**) was used as the coupling partner, the Sonogashira reaction proceeded smoothly under milder reaction conditions. For example, the reaction required less but-3-yn-1-ol (**4a**) (1.3 equiv) and could be run at the lower temperature (20 °C). The catalyst loading could also be reduced to 1 mol % for palladium acetate and 2% for copper(I) iodide. Isopropyl acetate was selected as a much more environmentally benign replacement for the hazardous dichloromethane. After simple filtration and aqueous washing of the reaction mixture of the alcohol intermediate (**5**), the organic phase could be carried out directly to the next step without further purification. This simplification did much to streamline the synthesis but did not compromise the final product's specifications in terms of purity and heavy metal levels.

The crude alcohol (**5**) was found to be quite difficult to isolate without incurring a significant loss of product to the mother liquors, due to the high solubilities of **5** in many organic solvents. In contrast, and much to the benefit of the synthetic efficiency, the tosylate (**6b**) was found to be a highly crystalline solid with limited solubility in many solvents. Therefore, the crude alcohol was not isolated but rather was converted to tosylate (**6b**) by reaction with TsCl and TEA in acetonitrile containing a catalytic amount of DMAP. The tosylate (**6b**) was thereby obtained in excellent purity (99% by HPLC) and good yield (~60%) from **3** by a simple purification and isolation procedure, which involved direct addition of 2-propanol to the reaction mixture with vigorous stirring to crystallize **6b**. This procedure rejected all impurities including the Et_3N and DMAP tosylate salts present in the reaction mixture, thereby eliminating the need for any extractive workup.

One of the challenges in the development of a scaleable process for **1** was the need for a practical method for the large-scale preparation of (*R*)-2-methylpyrrolidine (**7**). Although several synthetic methods for the preparation of **7** have been published in the literature, none of these syntheses were practical for large-scale preparation. For example, in one of these syntheses, the de-chlorination of Boc-protected 2-chloromethylpyrrolidine required the use of a large excess of toxic tin hydride.[9] Another synthesis called for the condensation of γ−chloropentane-2-one with (*R*)-phenylglycinol and required the use of 1 equiv of an expensive chiral auxiliary reagent.[12] Classical resolution of racemic 2-methylpyrrolidine with L-tartaric acid in ethanol has been reported in the literature,[13] although little information was given in the report concerning experimental conditions as well as the enantiomeric excess (ee%) of the resolved product. Regardless, this resolution could not be overlooked as a viable and alternative method to chemical synthesis. The racemic amine (**7**) was commercially available and inexpensive. Given these considerations, the resolution was pursued.

To evaluate and optimize the resolution process, an analytical tool for determining the enantiomeric purity of the resolved tartrate was required. Chiral derivatizing agents (CDAs), combined with HPLC, appeared to be the most convenient and best suited for our needs. Cbz valine anhydride is a powerful acylating agent with the convenience of a UV absorbing chromophore facilitating product detection.[14] This CDA reacted rapidly with 2-methylpyrrolidine L-tartrate to form diasteromeric derivatives in high yield without racemization. The two diastereomers were easily separated by reversed-phase HPLC. Therefore, Cbz-valine anhydride was chosen as the CDA for analytical purposes.

With an LC method in hand, we initiated a methodical screening of the important parameters for salt formation such as the equivalents of L-tartaric acid, solvents, concentration, and isolation temperature. Experimental results were judged by recovery (*r*) of the desired *R*-isomer and ee% of the salt obtained. A mixture of methanol and ethanol at the ratio 30:70 by volume was found to be the optimal solvent. Design of experiment (DOE) was next applied to optimize the combination of three parameters: equivalents of tartaric acid, amount of solvent used (concentration), and isolation temperature. From these studies, the best procedure for salt formation (ee ~50%, recovery ~80%) was realized by using 0.86 equiv of L-tartaric acid and ~35 L of solvent per kg of racemate (**7**) at about 5 °C. The high ee% (>97.0%) material was obtained in 55−60% yield (theory) after successive

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recrystallizations, four times, on a kilogram scale. Attempts at resolution with other chiral acids, such as dibenzoyl L-tartaric acid, L-malic acid, etc. were investigated, but either all gave no solid product or else the product was obtained in lower ee%.

Displacement of tosylate (**6b**) with 2-(*R*)-methylpyrrolidine, generated in situ from its L-tartrate in acetonitrile with K_2CO_3, produced the desired free base of **1** in 70−80% yield. Typically, this reaction was accompanied by 15−20% of the styrene elimination product (**8**). To minimize the formation of this elimination product, other substrates with different leaving groups were prepared and subjected to similar reaction conditions. From these studies, the relative yield for these derivatives of **5** was OTf ≈ OTs > OMs ≫ I > Br > Cl. Although the triflate reacted rapidly with **7** at ambient temperature, it was also highly reactive, even toward many tertiary amines. Overall, in the terms of yield, convenience, and stability, the tosylate (**6b**) remained as the superior alkylating agent among those tested.

Other reaction parameters, such as solvent and base, were also screened. From these studies, acetonitrile was the best solvent for the reaction. Nonpolar solvents such as toluene slowed the reaction and resulted in a lower yield. Either polar solvents such as DMF and NMP or a protic solvent, such as ethanol, facilitated the elimination reaction and yielded the styrene (**8**) as the major product. The most optimal base proved to be K_2CO_3, producing an ∼80% assayed yield, higher than those for weak and organic bases, Et_3N and $^iPr_2NEt$. It should be noted that the reaction still resulted in some elimination product (∼15%) even without addition of any base. Only a trace amount of this byproduct was formed in the absence of chiral amine (**7**). This result suggested that the E_2 elimination pathway of tosylate (**6b**) was caused mainly by the reactant (*R*)-2-methylpyrrolidine itself and not by any added weak base. Since all of the undesired byproducts in the reaction mixture are neutral, the free base of **1** in toluene was extracted readily into a mixture of water/*N*-methylpyrrolidinone/methanesulfonic acid (70:20:10 by volume). The free base of **1** was then isolated in excellent recovery (>95%) and purity (99%) after basification of the aqueous solution to pH 12 and extraction with isopropyl acetate. It is significant that much of the remaining residual palladium and copper were also removed during this acid−base extractive workup. Because of this high purity, the free base of **1** could be taken onto the final salt formation step without further purification, and **1** was obtained in over 95% yield with excellent purity and acceptable residual Pd and Cu levels (<10 ppm by inductively coupled plasma−atomic emission spectrometry, ICP-AES).

In summary, we have developed a practical and scaleable process for the synthesis of ABT-239 (**1**) from commercially available 4′-hydroxy-biphenyl-4-carbonitrile (**2**). A highly selective and robust mono-iodination procedure was developed and then used to prepare kilogram quantities of iodophenol (**3b**) in excellent yield. A Sonogashira−Stevens coupling reaction was successfully scaled up on a kilogram scale with good yield and purity. A simple isolation and purification procedure was used in the large-scale preparation of tosylate (**6b**), by use of a selective precipitation of product from the reaction mixture. A subsequent displacement reaction generated the free base of **1** after which a simple acid−base extractive workup was employed to effectively remove the byproducts as well as heavy metals (Pd, Cu) at the penultimate step. The new process provided improvements to the small-scale procedure predescribed and streamlined isolation and purification procedures, resulting in a chromatography-free process. The efficiency and practicality of the process were demonstrated by the synthesis of more than 1 kg of analytically pure **1** with an overall ∼40% yield.

Experimental Section

General Remarks. The NMR spectra were recorded on a Varian 400 MHz instrument at 400 MHz for ^1H and 100 MHz for ^{13}C. The electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) mass spectra were obtained using an LC−MS spectrometer. All the reactions were performed under a positive pressure of nitrogen. All chemicals and reagents were purchased and used without further purification unless otherwise mentioned. All melting points were measured on a Thomas−Hoover capillary melting point apparatus and uncorrected. All reaction progresses were monitored by HPLC with purities being determined by peak area% at 230 nm. All assayed yields were obtained by HPLC, using the pure and characterized standards.

4′-Hydroxy-3′-bromo-biphenyl-4-carbonitrile (3a). To a 3 L three-necked flask provided with a mechanical stirrer and dropping funnel were charged 4′-hydroxy-biphenyl-4-carbonitrile (**2**) (100.0 g, 0.512 mol) and glacial acetic acid (1.75 L). Bromine (90.1 g, 0.563 mol) in glacial acetic acid (0.25 L) was added slowly over 2 h at the internal temperature ∼20 °C. The suspension was agitated overnight (20 h). The reaction mixture was diluted with water (3.0 L), mixed at 20 °C for 1 h, and cooled to 0 °C. The crude product was collected by filtration, washed with water (2.0 L × 2) and heptane (2.0 L), and dried at 55 °C under vacuum with a nitrogen bleed for 24 h. The crude product was recrystallized from hot acetonitrile (1.5 L) to afford 98.0 g (69%) of **3a** as a near white solid. Mp: 202−203 °C (lit.[11] 202−202 °C). ^1H NMR [DMSO-d_6): δ 7.04 (d, J = 8.4 Hz, 1H), 7.58 (dd, J = 8.4, 2.3 Hz, 1H), 7.7−7.5 (m, 4H), 7.86 (d, J = 2.3 Hz, 1H), 10.62 (s, br, 1H). ^{13}CNMR [DMSO-d_6]: δ 109.0, 109.8, 116.4, 118.5, 126.4, 127.0, 130.0, 130.8, 132.2, 142.6, 154.2. CI-MS (NH_3): 291, 293 ($M + NH_4^+$).

4′-Hydroxy-3′-iodo-biphenyl-4-carbonitrile (3b). To a reaction vessel provided with a mechanical stirrer and dropping funnel were charged 4′-hydroxy-bipehnyl-4-carbonitrile (**2**) (2.15 kg, 10.90 mol), glacial acetic acid (17.89 kg, ∼17.2 L), and concentrated sulfuric acid (533 g, 5.4 mol). *N*-Iodosuccinimide (2.40 kg, 97%, 10.36 mol) was added portionwise at the internal temperature ∼20 °C. The suspension was agitated overnight (20 h) or until **2** was less than 4% by HPLC. The reaction mixture was diluted with water (34.4 kg, 34.4 L) and mixed at 20 °C for 1 h. The product was collected by filtration, washed with water (32.2 kg) and heptane (15.0 kg), and dried at 55 °C under vacuum with a nitrogen bleed for 48 h to give 3.27 kg (93% yield) of **3b** as

an off-white solid. The product could be used directly in the next step without further purification. An analytical sample was obtained by crystallizing from methanol. Mp: 166−167 °C. ^{1}HNMR [DMSO-d_6]: δ 6.99 (d, J = 8.4 Hz, 1H), 7.62 (dd, J = 8.4, 2.3 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 2.3 Hz, 1H), 10.70 (s, br, 1H). ^{13}C NMR [DMSO-d_6]: δ 85.3, 108.8, 114.9, 118.5, 126.3, 127.9, 130.5, 132.2, 136.6, 142.5, 156.8. CI-MS (NH_3): m/z 339 (M + NH_4^+).

4-[2-(2-Hydroxy-ethyl)-benzofuran-5-yl]-benzonitrile (5). To a reaction vessel provided with a mechanical stirrer and a thermometer was added isopropyl acetate (49.2 kg, 56.4 L). The solvent was evacuated and purged with nitrogen. To this solvent were charged 4′-hydroxy-3′-iodo-biphenyl-4-carbonitrile (**3b**) (3.27 kg, 10.18 mol), palladium acetate (23.0 g, 0.10 mol, 1 mol %), copper(I) iodide (39.0 g, 0.20 mol, 2 mol %), triphenylphosphine (53.0 g, 0.20 mol, 2 mol %), and butyn-3-ol (**4a**) (0.92 kg, 13.14 mol), while maintaining a stream of N_2. Diisopropylamine (2.05 kg, 20.3 mol) was added slowly over 10 min at <30 °C. The reaction mixture was heated to ∼45 °C and mixed for ∼40 h or until the uncyclized intermediate was less than 2% by HPLC. The mixture was cooled to 25 °C and filtered through a pad of Celite. The filter was rinsed with isopropyl acetate (12.0 kg), and the combined mixture was assayed by HPLC to contain 2.30 kg (85% assayed yield) of the desired product (**5**). The mixture was washed with a 5% $NaHCO_3$ aqueous solution (17 kg × 3) and distilled water (16.0 kg). The upper organic layer was distilled down to one-fourth of the original volume, chased with isopropyl acetate (18.0 kg, 20.6 L) to near dryness. The crude product was redissolved in acetonitrile (28.6 kg, 35.6 L), and it was used in the next step without further purification. However, an analytical sample was obtained by crystallization from 2-propanol. Mp: 101−102 °C. ^{1}H NMR [$CDCl_3$]: δ 1.80 (1H, s), 3.08 (t, J = 6.2 Hz, 2H), 4.01 (t, J = 6.2 Hz, 2H), 6.56 (s, 1H), 7.42 (dd, J = 8.4, 2.1, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.60−7.75 (m, 5H). ^{13}CNMR [$CDCl_3$]: δ 32.3, 60.6, 103.6, 110.1, 111.2, 118.8, 119.0, 122.7, 127.6, 129.2, 132.2, 133.8, 145.8, 154.6, 157.0. CI-MS (NH_3): m/z 281 (M + NH_4^+).

Toluene-4-sulfonic acid 2-[5-(4-cyano-phenyl)-benzofuran-2-yl]-ethyl Ester (6b). To the above solution of **5** in acetonitrile were charged *p*-(dimethylamino)pyridine (0.11 kg, 0.87 mol), triethylamine (1.87 kg, 18.4 mol), and *p*-toluenesulfonyl chloride (3.30 kg, 17.5 mol). The reaction mixture was stirred at 25 °C for ∼6 h or until **5** was consumed by HPLC (less than 2%). The mixture was concentrated to minimum volume, and 2-propanol (24.1 kg, 30.9 L) was added. The resulting slurry was stirred at 25 °C for 2 h and 5 °C for 5 h. The product was collected by filtration and washed with 2-propanol (5.2 kg, 6.7 L). The wet cake was purged with N_2 for 1 h and then dried at 45 °C under vacuum with a nitrogen bleed for 24 h to 2.59 kg (purity = 99%, 61% isolated yield from **3b**) of **6b** as a white solid. Mp: 124−125 °C. ^{1}H NMR [$CDCl_3$]: δ 2.37 (s, 3H), 3.15 (t, J = 6.5 Hz, 2H), 4.38 (t, J = 6.5 Hz, 2H), 6.50 (s, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4, Hz, 1H), 7.43 (dd, J = 8.4, 1.7 Hz, 1H), 7.65−7.75(m, 7H). ^{13}C NMR [$CDCl_3$]: δ 21.9, 28.9, 67.2, 104.3, 110.2, 111.2, 118.7, 119.1, 123.0, 127.5, 127.6, 129.0, 129.4, 132.2, 132.3, 133.9, 144.4, 145.6, 154.1, 154.4. CI-MS (NH_3): m/z 435 (M + NH_4^+).

(*R*)-2-Methylpyrrolidine L-Tartrate. To a reaction vessel provided with a mechanical stirrer and a thermometer were charged absolute ethanol 3A (96.7 kg), methanol (40.9 kg), and L-tartaric acid (7.60 kg, 50.67 mol). The mixture was agitated to dissolve all solids, and racemic 2-methylpyrrolidine (5.00 kg, 58.8 mol) was charged. The mixture was heated to 60 °C to ensure a homogeneous solution, and the solution was then cooled to 25 °C at approximately 10 °C/h. The solution was seeded with 100 g of (*R*)-2-methylpyrrolidine L-tartrate and mixed at 25 °C for 8 h (note: the white slurry was formed 3−4 h after seeding, and the nucleation was slow without it). The slurry was cooled to ∼5 °C, held for 2 h, filtered, and dried at 60 °C under vacuum with a nitrogen bleed overnight to yield 7.10 kg of the partially resolved tartrate (ee = 50.0%). The enantiomeric purity of the tartrate could be improved to >97% by repeated recrystallization from ethanol/methanol (70:30) (20 L/kg of solid) as described above. After 4× recrystallization, 3.90 kg (ee = 97.0%, 55% of theory) of the desired product was isolated. Mp: 129−130 °C. [DMSO-d_6]: δ 1.27 (d, J = 6.7 Hz, 3H), 1.48 (m, 1H), 1.88 (m, 2H), 2.02 (m, 1H), 3.18 (m, 2H), 3.56 (m, 1H), 4.04 (s, 2H).

HPLC Method for Assaying ee% of the Tartrate. Sample preparation: Add 23.5 mg of (*R*)-2-methylpyrroldine L-tartrate, 62.0 mg of CBZ-valine anhydride, 1 mL of dichloromethane, and 0.1 mL of triethylamine in a 4 mL vial. Stir for 10 min. An aliquot was assayed by HPLC.

HPLC Conditions:

Column, Zorbax Rx-C8, 4.6 × 250 mm, 5 μm.

Column temperature: 40 °C. Wavelength: 215 nm.

Injection Volume: 5 μL. Flow rate: 1.5 mL/min.

Mobile phase A: 100% H_2O with 0.1% H_3PO_4.

Mobile phase B: 100% CH_3CN with 0.1% H_3PO_4.

90% A to 50% A over 30 min, then to 10% A over 35 min, held 10% A to 45 min, back to 90% A.

Retention times: *S*-isomer, 30.1 min; *R*-Isomer, 30.7 min.

4-{2-[2-(2*R*-Methyl-pyrrolidin-1-yl)-ethyl]-benzofuran-5-yl}-benzonitrile, Free Base of 1. To a reaction flask provided with a mechanical stirrer and a refluxing condenser were charged with (*R*)-2-methylpyrrolidine L-tartrate (milled, 1.76 kg, 7.49 mol), potassium carbonate powder (2.28 kg, 16.52 mol), and acetonitrile (37.45 kg, ∼47.6 L). The reaction mixture was heated to 60 °C, agitated for 48 h, and cooled to 25 °C. Tosylate (**6b**) (2.10 kg, 5.00 mol) was added all at once, and the mixture was reheated back to 60 °C. The mixture was stirred at this temperature for 36 h or until no more than 1% of **6b** was present by HPLC. The reaction mixture was chilled to 25 °C and filtered. The filter was rinsed with acetonitrile (5.0 kg). The filtrate was concentrated to one-fourth of the original volume (∼14 L), and toluene (32.3 kg, ∼37 L) was charged. The mixture was washed with 5% $NaHCO_3$ aqueous solution (24.0 Kg × 2). The upper organic layer was extracted with a mixture (32.0 kg and 8.0 kg) of H_2O/*N*-methylpyrrolidinone/methanesulfonic acid (70:

20:10, v/v/v), respectively. Isopropyl acetate (32.5 kg, ~37 L) was charged into the combined aqueous extracts, and the mixture was cooled to 5 °C. Sodium hydroxide solution (~5.0 kg, 50%) was added slowly at <30 °C until the pH of the mixture was ~12. The upper organic phase was separated, and the lower aqueous phase was extracted once more with isopropyl acetate (6.0 kg). The combined organic solution was washed with 5% $NaHCO_3$ aqueous solution (33.6 kg × 3) and 25% brine (33.6 kg). The organic solution was assayed by HPLC to contain 1.20 kg (72% assayed yield) of the free base. The filtrate was concentrated to an ~10 L volume, and isopropyl acetate (20.0 kg) was added. The solution was distilled down to an ~10 L volume and filtered. The filtrate was concentrated to a 5 L volume and chased with 2-propanol (15.0 Kg × 2) to the final volume ~10 L. An analytical sample was obtained by stripping an aliquot of the above solution down to dryness. ^{1}H NMR [CD_3OD]: δ 1.03 (d, J = 6.1 Hz, 3H), 1.33 (m, 1H), 1.66 (m, 2H), 1.86 (m, 1H), 2.12 (q, J = 8.4 Hz, 1H), 2.30 (m, 2H), 2.89 (m, 2H), 3.12 (m, 2H), 6.47 (s, 1H), 7.37 (d, J = 1.3 Hz, 2H), 7.90 (m, 5H). ESI-MS: m/z 331 (M + 1).

ABT-239(1): The above free base solution (1.20 kg, 3.64 mol) in IPA was diluted with ethanol, 3A (3.20 kg, ~4.0 L), and the solution was warmed to 65 °C. An L-tartaric acid solution (600.0 g, 4.00 mol) in ethanol, 3A (4.8 kg, ~6.0 L) was added slowly at this temperature. The solution was mixed at 65 °C for 1 h and seeded with 20.0 g of **1**. The solution was cooled slowly to 25 °C and held overnight. The slurry was then cooled to 5 °C and held for 5 h. The product was collected by filtration, washed with 2-propanol (6.3 kg), and dried at 50 °C under vacuum with a nitrogen bleed for 24 h to give 1.70 kg (70% isolated yield from **6b**) of ABT-239 (**1**) as a near white solid: purity > 99.5% by HPLC; ee = 98.0% by chiral HPLC. Mp: 166−167 °C. ^{1}H NMR [DMSO-d_6]: δ 1.26 (d, J = 6.1 Hz, 3H), 1.55 (m, 1H), 1.83 (m, 2H), 2.04 (m, 1H), 2.80 (q, J = 8.4 Hz, 1H), 3.00 (m, 1H), 3.07 (m, 1H), 3.19 (t, J = 8.4 Hz, 2H), 3.44 (m, 2H), 4.13 (s, 2H), 6.78 (s, 1H), 7.60 (m, 2H), 7.90 (m, 5H). ^{13}C NMR [DMSO-d_6]: δ 16.5, 21.2, 25.5, 31.4, 49.8, 52.3, 61.5, 72.0, 103.4, 109.1, 111.0, 118.5, 118.9, 122.6, 127.2, 128.8, 132.3, 132.9, 144.6, 153.7, 156.3, 173.4. ESI-MS: m/z 331 (M + 1). Anal. Calcd for $C_{26}H_{28}N_2O_7 \cdot {}^1/_2H_2O$: C, 63.74; H, 5.76; N, 5.72. Found: C, 63.83; H, 5.60; N, 5.64. Pd = 8 ppm, Cu = 1 ppm.

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