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An efficient and convergent synthesis of the potent and selective H_3 antagonist ABT-239

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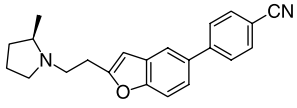
Abstract—An efficient and convergent process for the preparation of a potent and selective H_3 receptor antagonist, ABT-239, **1A** was accomplished with an overall yield of 64%. The key step in the synthesis is a Sonogashira coupling/cyclization reaction of 1-but-3-ynyl-2-(*R*)-methylpyrrolidine (**9**) with 4′-hydroxy-3′-iodo-biphenyl-4-carbonitrile (**3**). Additionally, the key amine component 2-(*R*)-methylpyrrolidine (**7**) was effectively synthesized from the readily available Boc-L-prolinol with a simple catalytical hydrogenolysis as the key step. This column chromatography-free process is highlighted by several simple work-up and purification procedures and is amendable to the large-scale preparation of **1A**.

1. Introduction

Histamine H_3 receptor antagonists have been demonstrated to modulate the release of a variety of neurotransmitters,[1] and antagonists of this receptor have been shown effective in animal models of ADHD (attention-deficit hyperactivity disorder).[2] In addition, H_3 antagonists, unlike stimulants, do not increase locomotive activity in animals and are thus expected to have low abuse potential. Because H_3 receptors function as both auto- and heteroreceptors to modulate the release of several neurotransmitters, H_3 antagonists have the potential to provide greater efficacy, or at least have a different pharmacological profile than drugs that target a single neurotransmitter. Based on studies in animal models, H_3 receptor antagonists have also been proposed to have potential benefits in treating disorders of cognition, attention, pain, allergic rhinitis and obesity. In spite of their projected medical utility, no H_3 antagonists have achieved clinical approval as a drug for human use. Due in part to suggestions that some of imidazole-based H_3 antagonists have potential to inhibit cytochrome-P450 enzymes leading to drug–drug interactions,[3] non-imidazole H_3 antagonists have received increasing attention as potential drug candidates.[1] One example of this class, ABT-239, **1A**[4a] is a potent and highly selective H_3 antagonist, that has been shown to be very efficacious in a variety of animal models of CNS disease. This, coupled with the favorable CNS safety profile, PK, and drug-likeness has led to the need for more advanced studies. In order to further evaluate its effectiveness and profile in extended studies, a highly efficient and convergent three-step chromatography-free process was developed for the preparation of **1A** in high purity.



ABT-239
1 = Free base
1A =Tartrate salt

2. Results and discussion

Preparation of **1A**, was initially accomplished by a four-step process in 36% overall yield (Scheme 1)[5] starting with commercially available 4′-hydroxy-biphenyl-4-carbonitrile **2**. The chiral 2-(*R*)-methylpyrrolidine **7C** was obtained via classical resolution with L-tartaric acid.

Although the process was used to provide a sufficient amount of **1** for the initial toxicology evaluations, there were several drawbacks to the synthesis. For example, a side product was produced by an E2 elimination occurring during the final displacement reaction, producing an olefinic

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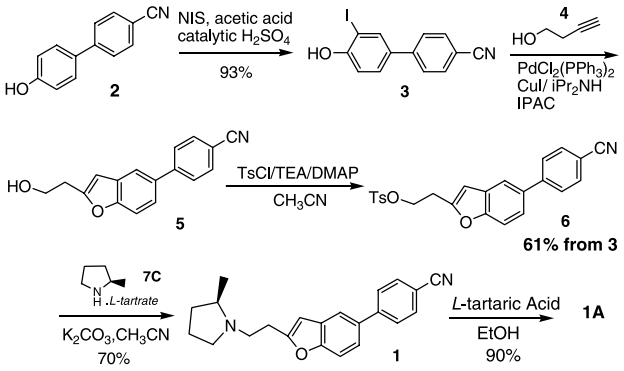
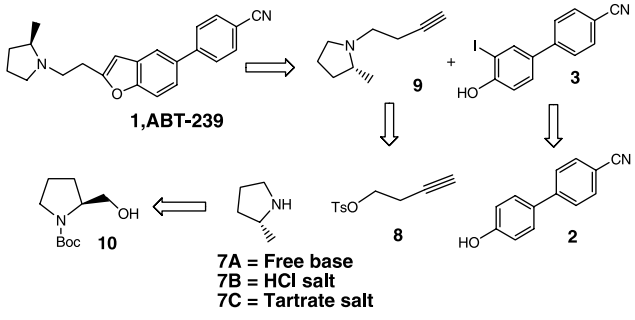


Scheme 1.

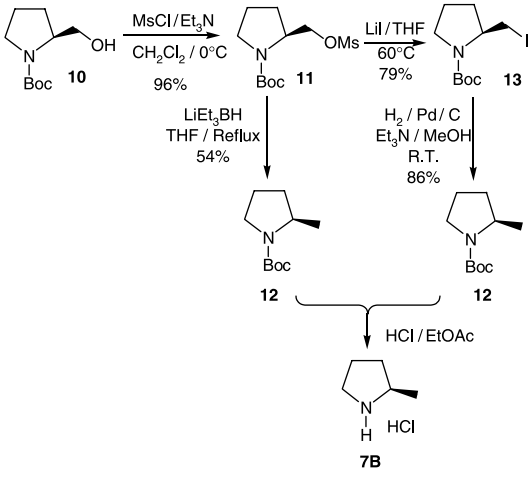
by-product in about 25% yield; even more significant was that the undesired elimination was even more severe on scales larger than a few grams.

Another drawback to the original synthetic route was that the resolution process that led to 2-(*R*)-methylpyrrolidine **7C** was tedious, requiring a minimum of four rounds of diastereoselective crystallization of an L-tartrate salt to increase the enantiomeric excess to an acceptable (>98% ee) level. These drawbacks motivated us to develop a more efficient process for **1**, as well as a more practical alternative synthesis for 2-(*R*)-methylpyrrolidine **7A**. A short, more practical process was envisioned, as outlined in Scheme 2. The retrosynthetic analysis to ABT-239, **1** suggests that it could be prepared by the Pd-catalyzed Sonogashira–Stevens coupling of **9** and **3** followed by a subsequent in situ cyclization to the benzofuran. The 1-but-3-ynyl-2-(*R*)-methylpyrrolidine **9** would arise from the displacement reaction of the commercially available tosylate **8** with 2-(*R*)-methylpyrrolidine **7A**, while the iodophenol derivative **3** can be easily obtained from 4′-hydroxy-biphenyl-4-carbonitrile **2** by selective ortho-iodination.[5]



Scheme 2.

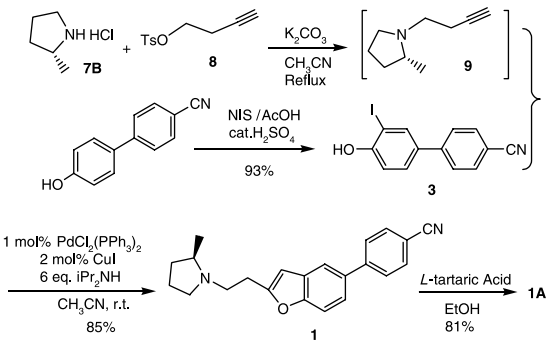
Chiral 2-(*R*)-methylpyrrolidine **7A** has been incorporated into many biologically active compounds[6] and their preparations have been the subject of a number of recent reports.[7] However, a careful literature search revealed a lack of practical and cost-effective processes for the large-scale preparation of 2-(*R*)-methylpyrrolidine **7** in high ee%. The intramolecular hydroamination of alkenes catalyzed by chiral metal complexes remains the most promising approach,[7a–c] however, the chiral purity of 2-methylpyrrolidine is normally moderate. The most recent report uses yttrium complexes of axially chiral bis(thiolate) ligands to obtain the chiral 2-methylpyrrolidine in 73% ee.[7a] Other approaches also have drawbacks. For example, in one of the syntheses, a large excess of a highly toxic tin hydride Bu_3SnH was required for the reductive de-chlorination of Boc-protected 2-chloromethylpyrrolidine.[7i] In another synthesis, 1 equiv of an expensive chiral auxiliary reagent was used for the condensation of γ-chloroketone with (*R*)-phenylglycinol.[7d] On the other hand, **7C** has been prepared by a classical resolution of racemic 2-methylpyrrolidine with L-tartaric acid in ethanol.[8] Indeed, we were able to use this process in our earlier synthetic route, but were unsatisfied with the four crystallizations required to achieve 98% ee due to considerable loss of material with a low overall yield of 31%. Several alternative approaches were considered to develop a more practical process for **7**. We were particularly interested in the strategies employing the 'chiral pool', which is one of the most attractive approaches for the synthesis of chiral compounds, provided that suitable precursors can be selected.[9] Considering the fact that Boc-L-prolinol **10** is readily available and inexpensive, its use as a chiral starting material was thought to provide a superior route to obtain chiral 2-(*R*)-methylpyrrolidine **7A** in the required high ee%. First the Boc-L-prolinol **10** was converted to the mesylate **11** in excellent yield (96%) under the standard conditions of $MsCl/Et_3N/CH_2Cl_2/0$ °C (Scheme 3). Direct conversion of the methanesulfonyloxymethyl group to the methyl group was attempted with several reduction conditions including the use of $LiAlH_4$,[10a] or $NaBH_3CN/BF_3\cdot OEt_2$[10b] and Super Hydride. Among the reagents evaluated, Super Hydride was most effective in producing the target *N*-Boc-2-(*R*)-methylpyrrolidine **12**, with a 54% yield under reflux conditions (Scheme 3). Concerns over the rigorous reaction conditions coupled with the hazardous nature of the Super Hydride, led us to consider other possibilities, particularly the use of an iodide intermediate **13**. The mesylate **11** was converted to the iodide **13** in 79% yield under conditions of LiI/THF/60 °C. Conventionally, de-iodination is accomplished via a free radical reaction;[11] however, hazardous and toxic tin reagents are often required. We were delighted to find that iodide **13** was conveniently de-iodinated by a simple hydrogenation procedure, with hydrogen gas under ambient pressure in the presence of 5% Pd on carbon, to obtain **12** in



Scheme 3.

86% yield and >99% ee. The hydrogenolytic de-iodination of simple alkyl iodides by catalytic hydrogenation has not often been reported. In our hands, the conditions are ideal with respect to cost, convenience and environmental impact, and may be applicable to other simple alkyl iodides. Deprotection of the Boc group was carried out using HCl in EtOAc in essentially quantitative yield to obtain the HCl salt of 2-(*R*)-methylpyrrolidine **7B**. With a highly practical and cost-effective route to 2-(*R*)-methylpyrrolidine in hand, efforts were next focused on developing a more efficient process for ABT-239, **1** with a particular focus on overcoming the problem of the undesired elimination reaction present in the original synthesis.

The tandem Sonogashira–Stevens coupling/cyclization reactions of *o*-halophenols with substituted 1-alkynes are the most commonly used and most efficient methodology for 2-substituted benzo[*b*]furans,[12] which are prevalent in many biologically important compounds.[13] However, the use of this methodology for the preparation of β-ethylamine-benzo[*b*]furans such as **1** has not been well documented.[14] In a series of close benzofuran analogs of **1A**, this type of process previously gave very low (<20%) and variable yields of products.[15] In our earlier synthesis of **1**, the key intermediate **5** was prepared in 85% yield using a standard protocol with $PdCl_2(PPh_3)_2$ and CuI as catalysts, and iPr_2–NH as base (Scheme 1). To increase the efficiency of the route, it was proposed that Sonogashira–Stevens coupling of 1-but-3-ynyl-2-(*R*)-methyl-pyrrolidine **9** with 4′-hydroxy-3′-iodo-biphenyl-4-carbonitrile **3** and subsequent spontaneous cyclization could provide the desired final product **1** in fewer number of linear steps. The use of the synthetic intermediate **9** in the synthesis also circumvented the main shortcoming of the earlier linear synthetic route, in which a substantial amount (~25%) of olefinic elimination by-product was formed in the final displacement reaction of the tosylate **6** with 2-(*R*)-methylpyrrolidine.[5] Thus, 1-but-3-ynyl-2-(*R*)-methylpyrrolidine **9** was prepared by a displacement reaction of the commercially available toluene-4-sulfonic acid but-3-ynyl ester **8** with 2-(*R*)-methylpyrrolidine **7A**, which was in turn conveniently generated in situ from its HCl salt **7B** in acetonitrile in the presence of K_2CO_3. The displacement of the tosylate proceeded well, with the desired product **9** obtained in high yield (98%) (Scheme 4). When the tartaric salt of 2-(*R*)-methylpyrrolidine **7C** was used, similar results were obtained. In both reactions, no elimination by-products were observed.



Scheme 4.

The 1-but-3-ynyl-2-(*R*)-methyl-pyrrolidine **9** in CH_3CN was then subjected to the Sonogashira reaction conditions with iodophenol **3**, followed by a simple filtration to remove the excess K_2CO_3 and inorganic salts produced. The coupling–cyclization went smoothly under the protocol, employing 1 mol% $PdCl_2(PPh_3)_2$, 2 mol% CuI in CH_3CN in the presence of 6 equiv of i-Pr_2NH at room temperature. The desired product **1** was obtained in 85% yield (Scheme 4).

The iodophenol **3** was prepared in high yield (93%) by the optimized conditions previously reported,[5] using 0.95 equiv of *N*-iodosuccinimide and 0.5 equiv of sulfuric acid in acetic acid at ambient temperature.

The development of an effective and practical column chromatography-free purification and isolation procedure was essential for this new convergent route to be used for large-scale preparations. To support advanced profiling, the final product **1A** had to meet or exceed the product quality specifications established in the earlier synthesis. Extrapolating from the experience gained from the initial process, upon completion of the final reaction the solvent was switched from acetonitrile to toluene. The desired product **1** was readily extracted into a mixture of water–*N*-methylpyrrolidinone–methanesulfonic acid (70/20/10 by volume), thereby leaving all the neutral by-products in the organic layers; the aqueous layers were extracted twice with isopropyl acetate to ensure removal of non-basic organic impurities. The free base **1** was then extracted back to the organic layer with isopropyl acetate, after a pH adjustment of the aqueous phase to ~14 with 50% NaOH. The free base **1** in isopropyl acetate was then suspended with silica gel (equal weight of product) and further purified by crystallization after being converted to the desired L-tartaric salt **1A**. The final product **1A** was obtained in high purity (99% p.a.) with acceptable metal residual levels (Pd and Cu <10 ppm by ICP) in 81% recovery.

3. Conclusions

In summary, we have developed an efficient and convergent process for the preparation of ABT-239, **1** (Scheme 4) in high purity (99%) with an improved overall yield of 65 versus 36% in the earlier linear route. The convergent process is highlighted by the Sonogashira coupling/cyclization reaction of 1-but-3-ynyl-2-(*R*)-methyl-pyrrolidine **9** with 4′-hydroxy-3′-iodo-biphenyl-4-carbonitrile **3** to produce the final product **1**, demonstrating the feasibility of the Sonogashira–Stevens reaction for the large-scale synthesis of β-ethylamine-benzo[*b*]furan derivatives. The new process successfully overcomes the drawbacks of a troublesome elimination side reaction that plagued the key step of an earlier large-scale process to **1**. Additionally, 2-(*R*)-methylpyrrolidine was effectively synthesized from the readily available Boc-L-prolinol **10** in good overall yield (65%) and excellent ee% (>99%). The synthesis of this intermediate featured a highly effective de-iodination procedure enabled by catalytic hydrogenation, a process, which may be applicable to other alkyl iodide compounds. This column chromatography-free process involved several simple work-up and purification procedures and is amendable to the large-scale preparation of ABT-239, **1**.

4. Experimental

4.1. General

The NMR spectra were recorded at a Varian 400 MHz instrument at 400 MHz for ^{1}H and 100 MHz for ^{13}C. The electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) mass spectra were obtained using a Hewlett Packard 1100, LC–MS, HPLC-mass spectrometer and fast atom bombardment (FAB) mass spectra were obtained using a JEOL SX102A spectrometer. All the reactions were performed under a positive pressure of nitrogen. Commercial grade anhydrous solvents and reagents were used without further purification. All reactions were monitored by HPLC (Zorbax SB-C8, 4.6 mm×25 cm column) with purities being determined by peak area % at the UV detector wavelength of 215 and 230 nm. The HPLC assay yields of the reaction mixture were determined using quantitative HPLC analysis by comparison to a know amount of analytical pure reference standards and potency refers to a wt% assay by HPLC versus a purified standard. The enantiomeric purity of the product was determined by the chiral HPLC analysis using a Chiral Pak-AD column, 10 μm, 250 mm×4.6 mm (Chiralcel Technologies) at the UV detector wavelength of 223. The enantiomeric purity of 2-(*R*)-methylpyrrolidine was determined by chiral derivatization using Cbz valine anhydride to prepare the diastereomeric derivative. The elemental analysis was performed by Quantitative Technologies Inc.

4.1.1. 2-(*S*)-Methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (11). A solution of 2-(*S*)-hydroxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (99.5 g 0.49 mol) in dichloromethane (500 mL) was cooled to 0 °C. Triethylamine (139 mL, 101 g, 1 mol) was added to the cold solution dropwise maintaining the reaction temperature below 0 °C. Methanesulfonyl chloride (58 mL, 85.8 g, 0.75 mol) was then added dropwise to the reaction mixture maintaining the reaction temperature below 0 °C. The resulting reaction mixture was stirred at room temperature for 12 h (HPLC indicated that all the starting material was consumed). The reaction mixture was quenched with 1 M H_3PO_4 (300 mL) and mixed for 15 min. The organic layer was separated and washed with 1 M aqueous H_3PO_4 (2×300 mL), followed by saturated aqueous $NaHCO_3$ (4×250 mL), dried over $MgSO_4$, filtered, and concentrated to obtain the product **11** (132 g, 95.6% yield). The spectral data was consistent with those reported.[16]

4.1.2. 2-(*S*)-Iodomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester 13. A solution of 2-(*S*)-methanesulfonyloxy-methyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (27.9 g, 0.10 mol) in anhydrous tetrahydrofuran (600 mL) was cooled to 0 °C. Lithium iodide (144 g, 1 mol) was added to the cold reaction mixture as a solid in portions maintaining the reaction temperature below 30 °C. The reaction mixture was then stirred at 62 °C for 4 h (HPLC indicated that all the starting material was consumed) and quenched with 10% aqueous sodium thiosulfate (300 mL). Ethyl acetate (600 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (2×100 mL), dried over $MgSO_4$, filtered, and concentrated to obtain the product **13** (26.3 g, 79% yield). The spectral data was consistent with those reported.[17]

4.1.3. 2-(*R*)-Methyl-pyrrolidine-1-carboxylic *tert*-butyl ester 12. A heterogeneous reaction mixture of 2-(*S*)-iodomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester **13** (25 g, 0.08 mol), triethylamine (11.2 mL, 8.12 g, 0.08 mol) in methanol (250 mL) and 5% palladium on carbon (2.5 g, 10 wt%, Pd/C) was allowed to react at room temperature under a blanket of hydrogen gas overnight (HPLC indicated that all the starting material was consumed). The reaction mixture was filtered and the filtrate was concentrated and the residue was dissolved in distilled water (100 mL) and ethyl acetate (100 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×50 mL). The combined organic layer was washed with 1 M aqueous H_3PO_4 (2×100 mL) followed by saturated $NaHCO_3$ (2×100 mL), dried over $MgSO_4$, filtered, and concentrated to obtain the product **12** (12.78 g, 86% yield). The spectral data was consistent with those reported.[18]

4.1.4. HCl salt of (*R*)-2-methyl-pyrrolidine 7B. 2-(*R*)-Methyl-pyrrolidine-1-carboxylic *tert*-butyl ester (12 g, 65 mmol) was dissolved in ethyl acetate (120 mL) and HCl gas was then bubbled through for 5 min until the pH of the reaction mixture was below 1. The reaction mixture was mixed at room temperature for 2 h (HPLC indicated that all the starting material was consumed). The reaction mixture was concentrated to one-fourth of the original volume, and methyl *tert*-butyl ether (200 mL) was added to the mixture, the mixture was then concentrated to ~50 mL. The solid was filtered, and dried at 40 °C overnight with nitrogen bleeding to obtain the HCl salt as a white solid (7.5 g, 96% yield). The spectral data was consistent with those reported.[19] The ee% was determined as follows: add 12.0 mg of 2-(*R*)-methylpyrrolidine hydrochloric acid, 62.0 mg of Cbz-valine anhydride, 1 mL dichloromethane, and 0.1 mL of triethylamine to a 4 mL vial. Stir for 10 min. An aliquot was assayed by normal HPLC (Zorbax SB-C8, 4.6 mm×25 cm column) with the enantiomeric purity being determined by peak area % of the two diastereomers at the UV detector wavelength of 215 nm. The ee% was determined to be >99%.

4.1.5. 1-But-3-ynyl-2*R*-methyl-pyrrolidine 9. To a 250 mL RB-flask was charged potassium carbonate powder (18.4 g, 133.2 mmol, 325 mesh), (*R*)-2-methylpyrrolidine HCl salt **7B** (10.7 g, 88.8 mmol), and CH_3CN (150 mL) and 3-butynyl *p*-toluenesulfonate **8** (15.7 mL, 88.8 mmol). The mixture was heated to reflux and stirred for 6 h or until all the tosylate was consumed as indicated by GC. The reaction mixture was cooled to room temperature, filtered, washed with CH_3CN (50 mL). The resulting filtrate (~200 mL) was assayed to contain ~12 g of the product by GC analysis using a pure and racemic standard 1-but-3-ynyl-2-methyl-pyrrolidine, which was prepared from racemic 2-methylpyrrolidine and 3-butynyl *p*-toluenesulfonate, and fractionally distilled. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, J=6.1 Hz, 3H), 1.40 (m, 1H), 1.6–1.8 (m, 2H), 1.90 (m, 1H),

1.98 (t, $J=2.7$ Hz, 1H), 2.15 (q, $J=8.8$ Hz, 1H), 2.3–2.5 (m, 4H), 3.0 (m, 1H), 3.14 (td, $J=8.6$, 2.8 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 18.7, 19.3, 21.9, 32.9, 52.9, 53.9, 59.7, 68.8, 83.0; GC–MS m/z 138 ($M^+ + 1$).

4.1.6. 4′-Hydroxy-3′-iodo-biphenyl-4-carbonitrile 3. To a reaction vessel provided with a mechanical stirrer and dropping funnel were charged 4′-hydroxy-biphenyl-4-carbonitrile **2** (215 g, 1.1 mol), glacial acetic acid (1.8 kg, ~1.7 L), and concentrated sulfuric acid (53.3 g, 0.54 mol). *N*-Iodosuccinimide (240 g, 97%, 1.04 mol) was added portion-wise at the internal temperature of ~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 (3.4 kg, 3.4 L), and mixed at 20 °C for 1 h. The product was collected by filtration, washed with water (3.2 kg), and heptane (1.5 kg), dried at 55 °C under vacuum with a nitrogen bleed for 48 h to give 327 g (93% yield) of **3** as an off-white solid. The product was used directly in the next step without further purification. An analytical sample was obtained by crystallizing from methanol; mp: 166–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (3H, s), 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 (400 MHz, 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 ($M+NH_4^+$).

4.1.7. 4-{2-[2-(2-Methylpyrrolidin-1-yl)-ethyl]-benzofuran-5-yl}-benzonitrile L-tartrate 1A. A solution of 1-but-3-ynyl-2(*R*)-methyl-pyrrolidine **9** (12.0 g, 87.5 mmol) in CH_3CN (200 mL) was purged with nitrogen. To this solution were added 4′-hydroxy-3′-iodo-biphenyl-4-carbonitrile **3** (18.7 g, 58.3 mmol), CuI (220 mg, 1.16 mmol), $PdCl_2$–$(Ph_3P)_2$ (409 mg, 0.58 mmol), followed by *i*-Pr_2NH (35.0 g, 345 mmol) under N_2. The resulting mixture was stirred at room temperature overnight under nitrogen or until all the starting material 4′-hydroxy-3′-iodo-biphenyl-4-carbonitrile was consumed monitored by HPLC. The reaction mixture was concentrated to about 100 mL volume, and toluene (400 mL) and 5% $NaHCO_3$ aqueous solution were added. The mixture was stirred for ~10 min, and filtered through a layer of Celite to remove some solid impurities. The filtrate was washed with 5% $NaHCO_3$ (2×400 mL). The organic layer was extracted with mixture of solvents of CH_3SO_3H–NMP–H_2O (10/20/70 by volume) (300 and 100 mL), respectively. The combined aqueous layer was washed with isopropyl acetate (200 mL). Isopropyl acetate (400 mL) was added, and the resulting mixture was cooled to ~5 °C, and then basified to pH~13 at the internal temperature < 25 °C with 50% NaOH. The upper organic phase was separated, and the lower aqueous solution was extracted with IPAC (100 mL). The combined organic solution was washed with 5% $NaHCO_3$ (2×400 mL), then 25% brine (200 mL). The organic layer was assayed to contain 16 g of free base **1** by HPLC. Activated carbon, Darco KB-B (1.5 g), and silica gel (15.0 g) were added, and the mixture was stirred at room temperature for 1 h and filtered through a layer of Celite. The filtrate was concentrate to one-fourth of the original volume, and isopropyl acetate (200 mL) was added. The solution was filtered to remove inorganic salt, and concentrated to dryness to give the free base 4-{2-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-benzofuran-5-yl}-benzonitrile **1**. 2-Propanol (150 mL) and absolute EtOH **3A** (60 mL) were added. The resulting solution was heated to ~60 °C, and a solution of L-tartaric acid (7.5 g, 50.0 mmol) in absolute ethanol **3A** (90 mL) added slowly at 60 °C. The resulting solution was seeded with ~0.5 g of **1A**, and cooled very slowly to room temperature (approximately ~2 °C/h). The slurry was stirred at room temperature overnight, it was then cooled to 0 °C for 2 h. The solid was filtered and dried at 65 °C in a vacuum oven overnight to give 19.6 g of 4-{2-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-benzofuran-5-yl}-benzonitrile L-tartrate **1A** as a white solid (81% recovery and 70% isolated overall yield). Mp 152–154 °C; 98% pure by HPLC (PA), ee=98.2% by chiral HPLC; Pd<10 ppm, Cu<10 ppm. Mp: 166–167 °C (lit.[5] 166–167 °C). The spectral data was consistent with those reported.[5]

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