A Facile and Scaleable Synthesis of ABT-239, A Benzofuranoid H3 Antagonist

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Abstract:
A facile and scaleable synthesis of a potent and selective histamine H3 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 H2SO4. 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 H3 receptor (H3R) 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 H3R antagonist has advanced through clinical trials and been approved for human use. Syntheses and biological evaluation of imidazole-based H3R 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 H3R antagonists. More recently, a new class of nonimidazole H3R 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 H3R 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 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 benzofuran 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

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commercially available 4-cyano-4'-hydroxy-biphenyl (2). 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. 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, I2), 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. 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. 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

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 PdCl2 (PPh3)2 as the catalyst, with copper-vigorous stirring to crystallize

direct addition of 2-propanol to the reaction mixture with simple purification and isolation procedure, which involved

(1) by a standard Sonogashira

DMAP. The tosylate (4b) 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 Et3N 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 1-tartrate to form diastereomeric 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

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 13C. 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 progressions 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.1 202–202 °C). 1H NMR (DMSO-d6): 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). 13CNMR (DMSO-d6): δ 109.0, 109.8, 116.4, 118.5, 126.4, 127.0, 130.0, 130.8, 132.2, 142.6, 145.2. CI-MS (NH₃): 291, 293 (M+1).

4′-Hydroxy-3′-iodo-biphenyl-4-carbonitrile (3b). To a reaction vessel provided with a mechanical stirrer and dropping funnel were charged 4′-hydroxy-biphenyl-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 g, 97%, 10.36 mol) was added portionwise at the internal temperature ~20 °C. The suspension was agitated overnight (20 h) 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. 1H NMR [DMSO-d6]: 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). 13C NMR [DMSO-d6]: 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 (NH3): m/z 339 (M + NH3+).

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, 356 L). The solvent was evacuated and purged with nitrogen. To this solvent were charged 3.27 kg (10.18 mol), palladium acetate (0.92 kg, 13.14 mol), while 4-carbonitrile ([3b] (3.27 kg, 10.18 mol), while 4-carbonitrile ([3b] (3.27 kg, 10.18 mol), while isopropyl acetate (49.2 kg, 356 L), and it was used in the next step without further purification. An analytical sample was obtained by crystallizing from methanol. Mp: 101–102 °C. 1H NMR [CDCl3]: 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). 13C NMR [CDCl3]: 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 (NH3): m/z: 281 (M + NH3+).

Tolwone-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 (0.87 kg, 8.5% assay yield) of the desired product (5). The mixture was cooled to 25 °C and filtered through a pad of Celite. The filter was rinsed with isopropyl acetate (20.5 kg, 2 mol %), and the combined mixture was assayed by HPLC to contain 5% NaHCO3 aqueous solution (24.0 kg all at once, and the mixture was reheated back to 60 °C and mixed for 8 h and then 10% A over 27 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 (2.82 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. 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 (5.0 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 5% NaHCO3 aqueous solution (24.0 kg all at once, and the mixture was reheated back to 60 °C and mixed for 8 h and then 10% A over 27 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.
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% NaHCO3 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. 1H NMR [CD3OD]: 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).

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