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The Synthesis of (*S*)-5-Fluoro-1-(2-fluorophenyl)-3-(piperidin-3-ylmethoxy)-1*H*-indazole, a Norepinephrine/Serotonin Reuptake Inhibitor for the Treatment of Fibromyalgia

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Abstract:

Compound 1, a norepinephrine/serotonin reuptake inhibitor (NSRI) for the treatment of fibromyalgia, has been synthesized in optically pure form in six linear steps and 48% overall yield with no chromatography. This route features a novel and efficient intramolecular cyclization to generate the indazolone core *via* a diazotization reaction and the preparation of a stable polymorph of the tartaric acid salt as the desired final form. The original synthetic route has been modified to avoid the use of toxic and expensive reagents, thus enabling the preparation of multigram quantities of API for toxicology studies.

Introduction

Fibromyalgia (FM) is a chronic disease characterized by widespread musculoskeletal pain, sleep disturbance, fatigue, and anxiety. FM is not well understood by the medical community, and as a consequence, it is difficult to diagnose since many of the symptoms are very nonspecific or vague. It is estimated to have an incidence of approximately 3.4% in women and 0.5% in men.[1] In the past, this condition has been treated with anti-inflammatories, analgesics, and sedatives, but these types of drugs can cause severe side effects, such as gastrointestinal bleeding, or create addiction. More recently, pregabalin (Lyrica) has become available for the treatment of pain caused by FM. Other medications such as duloxetine hydrochloride (Cymbalta), typically used as an antidepressant, and pramipexole dihydrochloride (Mirapex), administered to Parkinson patients, have also shown promising results to treat the condition (Figure 1).

Recently, tartrate salt **1** has been identified in our laboratories as a norepinephrine/serotonin reuptake inhibitor (NSRI) for the treatment of FM.[2] This contribution describes the development of a scalable route for the preparation of this compound that showcases a novel approach for the synthesis of the indazolone core.

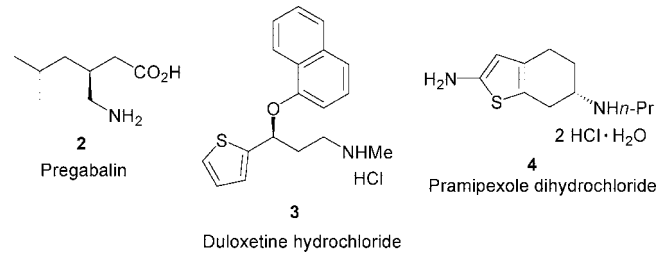

Figure 1. **Structures of fibromyalgia drugs.**

Results and Discussion

During the early stages of development, the HCl form **14** had been identified as a potential clinical candidate, and our synthetic efforts were directed toward its preparation (Figure 2).

Medicinal Chemistry Route. The original synthesis of the indazolone core from our Discovery group is shown in Scheme 1.

2-Amino-5-fluorobenzoic acid (**5**) was treated with phosgene in a biphasic mixture of water and toluene to give cyclic intermediate **6** in excellent yield.[3] The reaction between **6** and 2-fluorophenylhydrazine (**7**) in THF at reflux provided hydrazide **8**, which set the stage for the cyclization to provide the indazolone core. The preparation of indazolones from hydrazides has been previously reported *via* halide displacement,[4] nitro displacement,[5] azide decomposition,[6] through the use of strong basic conditions,[7] or through the cleavage of sydnones.[8]

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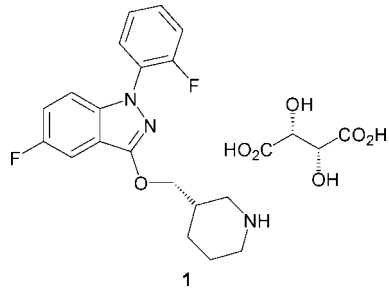

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Figure 2. **Structure of NSRI inhibitor 1.**

Our group employed an alternative approach that involved the diazotization of hydrazide **8** to give diazonium salt **9** as a sticky solid which, without isolation, was cyclized to give indazolone **10** in 44% overall yield from **5**. To the best of our knowledge, this is a novel approach for the preparation of this type of compound.

With the indazolone core in hand, the synthesis of **14** was completed as shown in Scheme 2. Commercially available chiral alcohol **11** was converted into the corresponding mesylate **12** under standard conditions.[9] Crude **12** was then coupled with indazolone **10** in the presence of Cs_2CO_3 to afford *N*-Boc-protected piperazine **13**[10] which, after chromatographic purification, was treated with 4 M HCl in a dioxane/ethyl acetate mixture to provide HCl salt **14**.[11] The longest linear sequence for this approach was five steps, and the overall yield was 22%.

Alternative Conditions. Other conditions were tried to both replace phosgene and shorten the synthesis by avoiding the preparation of intermediate **6**. Thus, the synthesis of **6** could also be accomplished by treating 2-amino-5-fluorobenzoic acid (**5**) with more easily handled triphosgene, but the lower reactivity of this reagent resulted in a considerably decreased yield.[12]

A second option to prepare hydrazide **8** without going through **6** is described in Scheme 3, where acid **5** and hydrazine hydrochloride **15** were combined under peptide coupling conditions.[13] Unfortunately, the purification of **8** turned out to be cumbersome due to the presence of residual HOBt[14] that could only be removed by chromatography, which also resulted in a lower yield.

This synthetic approach proved adequate for the preparation of small amounts of material to satisfy the immediate needs for preliminary studies. However, when it was decided to advance this candidate and the need to manufacture larger quantities of API arose, our options were either looking for an alternative route or optimizing the current synthesis to make it more amenable for scale-up. In order to quickly advance the program, we decided to focus on the second approach since we believed that, with some modifications, the original process could meet the larger API demand. At the same time, and due to the hygroscopicity of the HCl salt **14**, a search for other salt candidates was initiated, which resulted in the identification of tartrate **1** as the preferred salt and the need to develop a protocol to reproducibly manufacture a stable polymorph.

Optimized Route. Several improvements had to be implemented before large quantities of **1** could be produced in a safe and economical way. Optimized coupling conditions between acid **5** and hydrazine **15** had to be found to avoid going through or isolating intermediate **6**, which would simplify the synthesis and, at the same time, avoid the use of either phosgene or triphosgene. Also, a more atom-economical procedure would be desirable. The diazotization reaction conditions had to be worked out as well to prevent the formation of the gummy diazonium salt that made efficient stirring difficult even on small scale. The cost ($400/g) and availability of alcohol **11**, only in gram quantities, were major concerns, and identifying a much more affordable source that could provide large quantities of this valuable material was mandatory. We were also interested in replacing toxic dioxane in the deprotection step by a more user-friendly solvent. Finally, we sought to replace Cs_2CO_3 with a less costly base in the reaction between indazolone **10** and mesylate **12**.

After addressing all these issues, an optimized preparation of **1** was implemented that begins with the synthesis of indazolone **10** as shown in Scheme 4.

Acid **5** was treated with 1,1′-carbonyldiimidazole (CDI)[15] to give intermediate **6**, which could be detected by mass spectrometry. Without isolation, to **6** was added hydrazine hydrochloride **15**, which provided hydrazide **8** in excellent yield and purity, suitable for use in the next step without further purification.

In the original synthesis, the subsequent diazotization step was carried out by suspending **8** in 1 N HCl and adding a solution of $NaNO_2$ in water, which gave rise to the intermediate diazonium salt **9** as a sticky solid. Then, ethanol and more water were added, and the mixture was brought to reflux, which caused the formation and precipitation of indazolone **10**. In this protocol, all of **8** was first fully transformed into **9** and then cyclized to **10** by applying heat. Due to the well-known instability of diazonium salts, this step posed an evident risk on scale unless it could be redesigned to avoid the buildup of **9**. Under the optimized conditions, hydrazide **8** was suspended in a mixture of 1 N HCl and ethanol. The resulting slurry was heated to reflux, which fully brought the hydrazide into solution, and an aqueous solution of $NaNO_2$ was slowly added. The newly generated diazonium salt immediately cyclized to indazolone **10** and precipitated from the solution.[16] This protocol has been successfully implemented on several hundred gram scale with no safety issues.

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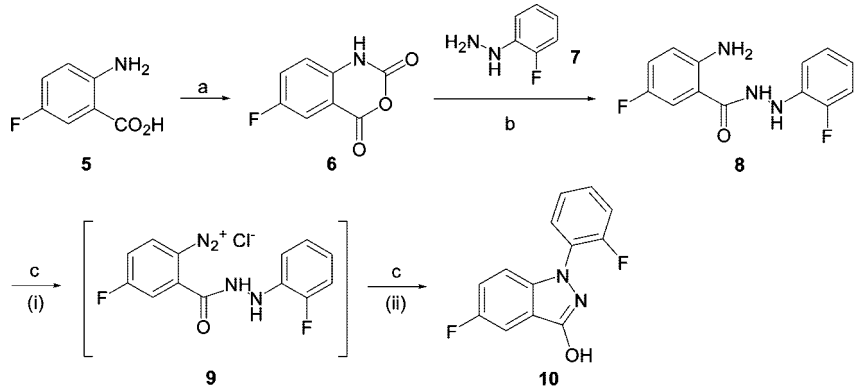
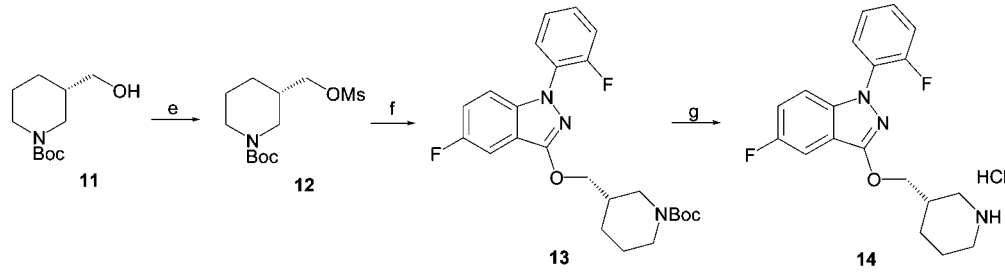
Scheme 1. **Medicinal Chemistry synthesis of the indazolone core**



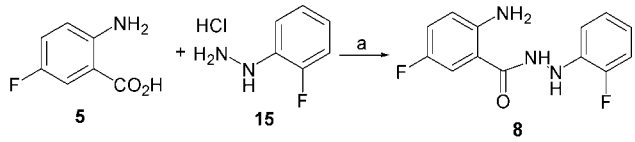
(a) Phosgene, Na_2CO_3, H_2O/PhMe, rt, 96%. (b) THF, reflux, 62%. (c) (i) $NaNO_2$, 1 M HCl, H_2O, 0 °C; (ii) EtOH/H_2O, 0 °C to reflux, 75%.

Scheme 2. **Completion of the synthesis of HCl salt 14**



(e) MsCl, TEA, CH_2Cl_2, 0 °C to rt, 92%. (f) **10**, Cs_2CO_3, DMF, 80 °C, 77%. (g) 4 M HCl, dioxane/EtOAc, rt, 67%.

Scheme 3. **Alternative coupling conditions for the preparation of hydrazide 8**



(a) EDC-HCl, HOBt-H_2O, 4-methylmorpholine, THF, -12 °C to rt, 73%

We next addressed the preparation of chiral alcohol **11** due to its scarce availability from commercial sources and its high cost. A literature search revealed that the racemic precursor **16** could be resolved *via* a classical resolution or through an enzymatic process.[17] Since the classical resolution gave the desired (*S*)-enantiomer directly, we opted for this methodology, which is summarized in Scheme 5.

(±)-3-Hydroxymethylpiperidine (**16**) was treated with one equivalent of L-(−)-dibenzoyl tartaric acid (**17**) in absolute ethanol at reflux. Upon cooling, the tartrate salt **18** crystallized and could be isolated by filtration. The salt thus obtained was recrystallized three more times from smaller volumes of absolute ethanol. The salt was then neutralized with aqueous sodium hydroxide to liberate (*S*)-3-hydroxymethylpiperazine which, in situ, was allowed to react with di-*tert*-butyl dicarbonate (Boc_2O) to give alcohol **11** as a white crystalline solid with ee > 99.5%. The overall yield for the two steps combined was 43% out of a possible 50%. In agreement with what is reported in the literature procedure, this method could be reliably scaled up to produce hundreds of grams of **11**.

The synthesis of **1** was completed as described in Scheme 6.

Alcohol **11** was transformed into the corresponding mesylate **12** following the conditions found in the original synthesis. The crude mesylate was then treated with indazolone **10** in the presence of inexpensive K_2CO_3 as base[18] to give *N*-Boc-protected piperazine **13** with no detrimental effect on the yield. Intermediate **13** is a low-melting solid that was difficult to crystallize even on small scale. Since the use of crude material was contaminated with impurities that were difficult to purge in the subsequent steps, it was decided to purify it at this stage by passing it through a plug of silica gel, which removed the highly polar and colored byproduct and gave material of excellent purity. The Boc-protecting group was removed by treating an ethyl acetate solution of **13** with 10 equiv of a freshly made HCl solution in ethanol, prepared by adding acetyl chloride to cold ethanol.[19] This procedure afforded HCl salt **14** in excellent yield and allowed for the efficient purification of this intermediate.

Before the synthesis of the target molecule could be completed, a polymorph screen of tartaric acid salt **1** was performed to identify a stable polymorph, and subsequently, a protocol for its preparation was developed. Two-week slurries were carried out in 15 different solvents, and after PXRD analyses of the resulting solids, only one polymorph was identified. In addition, no hydrate was formed after a 2-week slurry in water or recrystallization

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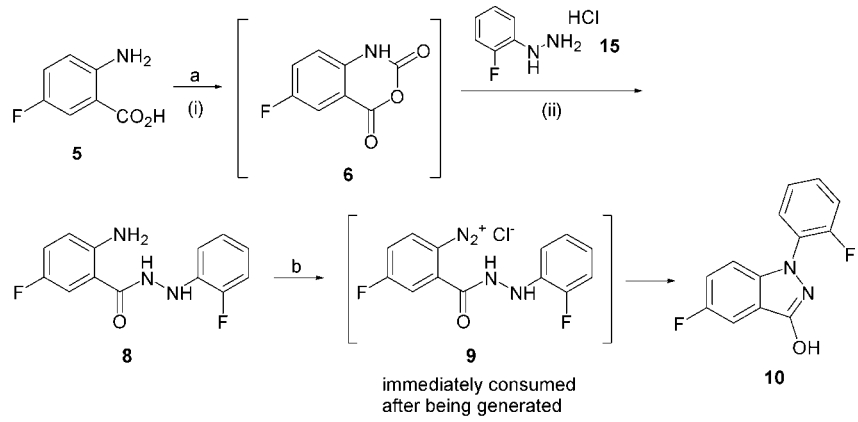
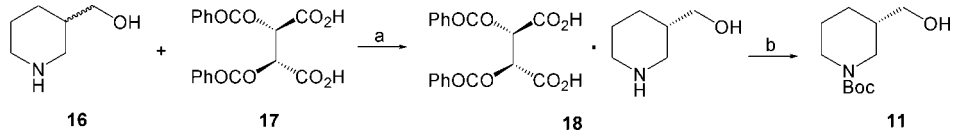
Scheme 4. **Optimized synthesis of indazolone core 10**



(a) (i) CDI, THF, rt; (ii) **15**, DIPEA, rt, 95%. (b) $NaNO_2$, 1 N HCl, H_2O/EtOH, reflux, 70%.

Scheme 5. **Classical resolution of (±)-3-hydroxymethylpiperidine (16)**



(a) (i) EtOH (absolute), reflux; (ii) cool to rt; (iii) repeat recrystallization of salt **18** from EtOH three more times. (b) (i) NaOH, pH = 10.5; (ii) Boc_2O, MTBE, 0 °C to rt, 43% (2 steps).

from this solvent. With this information on hand, the rest of the synthesis leading to **1** was implemented as follows. HCl salt **14** was neutralized in a biphasic mixture of aqueous K_2CO_3 and ethyl acetate to give free base **19**. After replacing the ethyl acetate by ethanol, one equivalent of L-tartaric acid was added, which caused the immediate precipitation of the tartrate salt. Additional ethanol was added, and the mixture was heated to reflux and then allowed to slowly cool to 20 °C. This methodology ensured the preparation of **1** in excellent chemical and optical purities and reproducibly generated the desired polymorph.

Conclusions

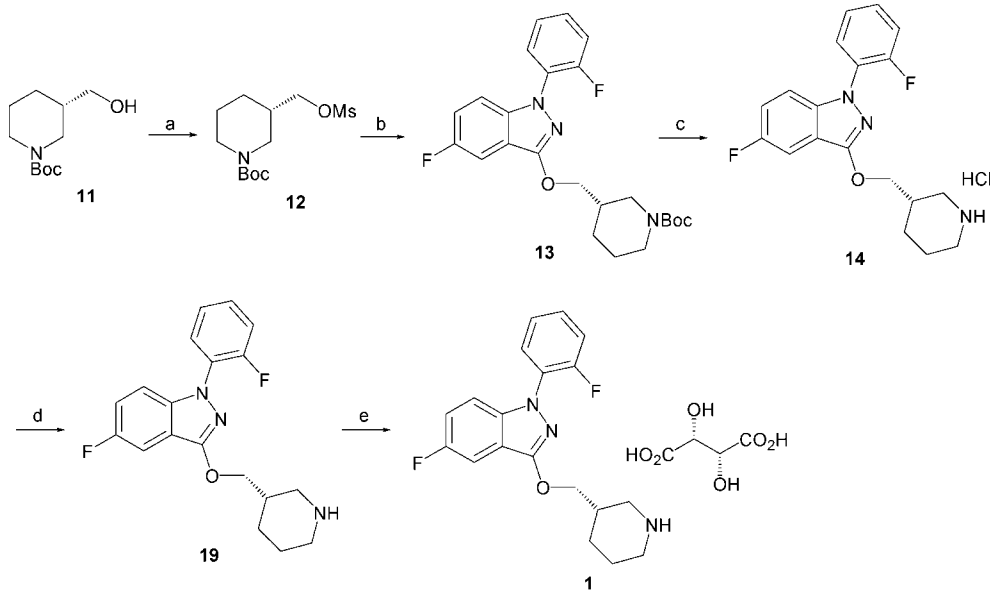
An optimized route for the preparation of NSRI candidate **1** has been described. Numerous improvements have been implemented with respect to the original synthesis, such as the use of less toxic and inexpensive reagents, as well as the development of a novel and safe approach for the preparation of an indazolone intermediate *via* a diazotization reaction that made this methodology amenable to produce large quantities of the target molecule for toxicology studies. In addition, a reproducible protocol has been developed for the preparation of the desired polymorph of **1**.

Experimental Section

All reagents were obtained from commercial sources and were used as received. *N*-Boc-(*S*)-3-hydroxymethylpiperazine (**11**) was purchased from Astatech. All reactions were performed under a nitrogen atmosphere. Reaction completion was evaluated by HPLC using the following conditions: column: YMC PackPro C18, 150 mm × 4.6 mm, 3 μm; wavelength: 215 nm; temperature: 25 °C; injection volume: 5 μL; (eluent A) water (0.2% $HClO_4$), (B) MeCN, gradient: 0 min (A) 70%, (B) 30%; 15 min (A) 5%, (B) 95%; 20 min (A) 5%, (B) 95%. The chiral purity of alcohol **11** was analyzed as described in the literature.[17] ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 or 400 MHz spectrometer in either $CDCl_3$ or DMSO-d_6 as both solvent and internal standard. Positive and negative ion atmospheric pressure chemical ionization (APCI) mass spectra were obtained on a Micromass Platform LC mass spectrometer. Melting points were measured using an open capillary tube in a Buchi melting point apparatus, model B-545, and are uncorrected.

Synthesis of Hydrazide 8. A solution of acid **5** (300 g, 1.93 mol) in dry THF (4 L) under nitrogen was cooled to 5−10 °C. 1,1′-Carbonyldiimidazole (329 g, 2.03 mol) was added in small portions over 15 min, allowing the internal temperature to rise to 27 °C. When the exotherm subsided, a very thick precipitate formed that thinned out upon stirring. The mixture was warmed and stirred at 20 °C for 1.5 h. Mass spectrometry analysis showed complete consumption of acid **5**. *N,N*′-Diisopropylethylamine (404 mL, 2.32 mol) was added as a small stream over 5 min and the remaining solid fully dissolved. Hydrazine hydrochloride **15** (346 g, 2.13 mol) was added in small portions over 15 mi, and the resulting mixture was stirred at 20 °C for 16 h. The reaction was quenched with 1 N HCl to pH = 1, and then it was neutralized to pH = 7 with 50% NaOH. Ethyl acetate (4 L) was added, and the two layers were separated. The organic layer was washed with water (2 × 1 L), saturated, aqueous $NaHCO_3$ solution (2 × 1 L), and saturated brine (1 L). The solution was concentrated under reduced pressure to give 483 g (95%) of hydrazide **8** as a light-red solid that was used without further purification in the next step. An analytical sample was recrystallized from 2-propanol. Mp: 169−170 °C. HPLC retention time: 2.66 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.35 (br s, 2 H) 6.68−6.93 (m, 3 H) 6.96−7.20 (m, 3 H)

Scheme 6. **Completion of the synthesis to produce tartaric acid salt 1**



(a) MsCl, TEA, CH_2Cl_2, 0 °C to rt, 100%. (b) **10**, K_2CO_3, DMF, 80 °C, 92%. (c) AcCl, EtOH, EtOAc, 0 °C to rt, 94%. (d) K_2CO_3, H_2O/EtOAc. (e) *L*-tartaric acid, EtOH, rt, 83% (2 steps).

7.55 (dd, $J = 10.22$, 2.97 Hz, 1 H) 7.76 (s, 1 H) 10.26 (br, s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 112.5, 112.6, 113.9, 114.2, 114.4, 115.4, 115.7, 118.4, 118.5, 119.4, 119.5, 120.5, 120.8, 125.3, 137.7, 137.9, 147.5, 149.4, 151.7, 152.5, 154.7, 168.5. MS (ES^+): 264.2 $(M + H)^+$. Anal. Calcd for $C_{13}H_{11}F_2N_3O$: C: 59.31; F, 14.43; H: 4.21; N: 15.96. Found: C: 59.16; F, 14.37; H: 4.20; N: 15.92.

Synthesis of Indazolone 10. A suspension of hydrazide **8** (300 g, 1.14 mol) in a mixture of 1 N HCl (4 L) and ethanol (4 L) was heated until the internal temperature reached 76 °C. The solid fully dissolved to give a light-red solution. A solution of $NaNO_2$ (236 g, 3.42 mol) in water (600 mL) was added dropwise over 1 h. After about half of the $NaNO_2$ solution had been added, a light-brown solid began precipitating from the solution. The mixture was stirred at 76 °C for an additional hour, and then it was cooled to 20 °C. The solid was filtered, washed with water (3 × 500 mL), and dried under vacuum (17 Torr) at 50 °C for 18 h to give 196 g (70%) of indazolone **10** as a light-brown solid. An analytical sample was recrystallized from ethyl acetate. Mp: 215−216 °C. HPLC retention time: 5.01 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.24−7.41 (m, 3 H) 7.42−7.57 (m, 3 H) 7.62 (dt, $J = 7.75$, 1.65 Hz, 1 H) 11.41 (s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 105.1, 105.4, 112.4, 112.6, 112.7, 114.5, 114.7, 117.5, 117.7, 117.8, 118.0, 126.0, 127.7, 127.8, 127.9, 129.2, 129.3, 138.6, 154.1, 155.8, 157.2, 157.3, 157.4, 158.9. MS (ES^+): 247.0 $(M + H)^+$. Anal. Calcd for $C_{13}H_8F_2N_2O$: C: 63.42; F, 15.43; H: 3.28; N: 11.38. Found: C: 63.16; F, 15.32; H: 3.16; N: 11.33.

Synthesis of Dibenzoyl Tartaric Acid Salt 18. To a solution of racemic 3-piperidinemethanol (**16**) (509 g, 4.42 mol) in absolute ethanol (9 L) under nitrogen at 20 °C was added dibenzoyl L-tartaric acid (**17**) (1.58 kg, 4.42 mol) in portions over 10 min. The internal temperature rose to 29 °C. The resulting pale-brown, cloudy mixture was heated to 79 °C (internal temperature). When the solid had fully dissolved, the heating was stopped, and the mixture was allowed to cool to 20 °C and stirred for 18 h. The resulting suspension was filtered, and the solid was washed with absolute ethanol (600 mL) and dried under suction on the filter for 2 h to give tartaric acid salt **18** as a white solid. Salt **18** was recrystallized three more times by using 5.1, 4.4, and 3.5 L of absolute ethanol to give 1.15 kg of **18** as a white solid. A small sample of this salt was converted into *N*-Boc-protected alcohol **11** as described in the next paragraph, and the ee was determined to be >99.5%. This salt was used in the next step without further purification.

Synthesis of Alcohol 11. The tartaric acid salt **18** obtained in the previous step was suspended in 3.6 L of water, and the flask was cooled in an ice−water bath. The pH of the solution was 3.14. Aqueous, 50% NaOH solution was slowly added until the pH was in the 10−10.5 range while the internal temperature was held below 20 °C. A solution of di-*tert*-butyldicarbonate (556 g, 2.55 mol) in MTBE (2.3 L) was added as a small stream over 15 min. The mixture was then allowed to warm to 18 °C, and aqueous, 50% NaOH solution was periodically added to keep the pH in the 10−10.5 range. Once the pH had stabilized, the mixture was stirred at 20 °C for 16 h. The two layers were separated, and the aqueous layer was extracted with MTBE (2 × 1 L). The combined organic extracts were washed with aqueous, 0.5 N NaOH solution (2 × 500 mL), water (2 × 500 mL) and saturated brine (1 L), and were dried over $MgSO_4$. The solution was concentrated under reduced pressure to give an oil that partially solidified. Heptane (2 L) was added, and the suspension was stirred for 2 h at 20 °C. The resulting solid was filtered, washed with heptane (3 × 500 mL), and dried under vacuum (17 Torr) at 22 °C for 24 h to give 227 g (43%, 2 steps) of alcohol **11** as a white solid. Mp: 96−98 °C. HPLC retention time: 2.53 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.97−1.12 (m, 1 H) 1.19−1.32 (m, 1 H) 1.33−1.49 (m, 10 H) 1.50−1.59 (m, 1 H) 1.60 −1.68 (m, 1 H) 2.43−2.52 (m, 1 H) 2.59−2.76 (m, 1 H) 3.11 −3.20 (m, 1 H) 3.21−3.31 (m, 1 H)

3.72−3.81 (m, 1 H) 3.94 (br s, 1 H) 4.50 (t, $J = 5.31$ Hz, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.4, 28.7, 39.2, 64.2, 78.9, 154.5. MS (ES^+): 115.9 (M + H − 100 (Boc group))$^+$. Chiral HPLC: >99.5% ee. Anal. Calcd for $C_{11}H_{21}NO_3$: C: 61.37; H: 9.83; N: 6.51. Found: C: 61.41; H: 9.93; N: 6.53.

Synthesis of Mesylate 12. To a solution of alcohol **11** (408 g, 1.89 mol) in dry CH_2Cl_2 (3 L) under nitrogen at 5 °C was added triethylamine (396 mL, 2.84 mol) as a small stream over 5 min. The mixture was stirred for 10 min, and methanesulfonyl chloride (177 mL, 2.27 mol) was slowly added while the internal temperature was held below 12 °C. The mixture was warmed to 20 °C and stirred for 16 h. The suspension was filtered, and the solid (triethylamine hydrochloride) was washed with CH_2Cl_2 (500 mL) and discarded. The combined filtrates were washed with water (3 × 500 mL), and the solution was concentrated at reduced pressure to give 567 g (100%) of mesylate **12** as an oil that slowly crystallized into a white solid. Crude **12** was used in the next step without further purification. An analytical sample was purified by flash chromatography (CH_2Cl_2/EtOAc, 9:1). Mp: 72−74 °C. HPLC retention time: 4.93 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.35 (m, 1 H) 1.36−1.53 (m, 10 H) 1.58−1.69 (m, 1 H) 1.74−1.85 (m, 1 H) 1.85−1.99 (m, 1 H) 2.73 (br s, 1 H) 2.84−2.94 (m, 1 H) 3.00 (s, 3 H) 3.71−3.83 (m, 1 H) 3.92 (br s, 1 H) 4.00−4.13 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.10, 26.8, 28.6, 35.5, 37.5, 71.3, 79.9, 154.9. MS (ES^+): 294.2 (M + H)$^+$. Anal. Calcd for $C_{12}H_{23}NO_5S$: C: 49.13; H: 7.90; N: 4.77; S, 10.93. Found: C: 49.23; H: 8.14; N: 4.99; S, 10.96.

Synthesis of *N*-Boc-piperidine 13. To a solution of indazolone **10** (475 g, 1.93 mol) in dry DMF (5.8 L) was added K_2CO_3 (powder, 400 g, 2.89 mol) in one portion, and the mixture was stirred at 20 °C for 10 min. A solution of mesylate **12** (566 g, 1.93 mol) in dry DMF (1 L) was added to the flask as a small stream over 5 min, and the resulting mixture was heated to 85 °C and stirred for 18 h. The reaction was cooled to 10 °C, and water (6 L) and MTBE (2 L) were added. The layers were separated, and the aqueous layer was extracted with MTBE (2 × 3 L). The combined organic extracts were washed with water (3 × 1 L), and the solvent was removed under reduced pressure to give a pale-brown solid that was passed through a plug of silica (hexanes/ethyl acetate, 3:1 as mobile phase) to give 816 g (92%) of *N*-Boc-piperidine **13** as a yellow oil that partially solidified upon standing. HPLC retention time: 13.30 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.62 (m, 13 H) 1.66−1.77 (m, 2 H) 1.88 −1.99 (m, 1 H) 2.06−2.20 (m, 1 H) 2.52−3.06 (m, 2 H) 3.83−4.18 (m, 3 H) 4.21−4.39 (m, 2 H) 7.12−7.22 (m, 2 H) 7.22−7.30 (m, 2 H) 7.30 −7.39 (m, 2 H) 7.51 −7.60 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 28.6, 36.0, 79.6, 114.2, 117.0, 117.2, 117.5, 117.8, 125.1, 125.2, 127.7, 128.4, 128.5, 138.9, 154.7, 155.1, 156.5, 157.2, 158.9. Anal. Calcd for $C_{25}H_{31}F_2N_3O_3$: C: 65.34; F, 8.27; H: 6.80; N: 9.14. Found: C: 64.98; F, 8.57; H: 6.15; N: 9.45.

Synthesis of HCl Salt 14. Preparation of HCl solution in ethanol: Absolute ethanol (4.7 L) under nitrogen was cooled to 5 °C, and acetyl chloride (1.18 L, 16.6 mol) was slowly added while the internal temperature was held below 15 °C. The resulting HCl solution in ethanol was stirred at 0−5 °C for 1 h.

To the above HCl solution in ethanol was added a solution of *N*-Boc-piperidine **13** (737 g, 1.66 mol) in ethyl acetate (1.5 L) as a small stream over 15 min. The mixture was warmed to 15 °C over 1 h. The solvent was removed under reduced pressure, and to the oily residue was added ethyl acetate (2 L). The solvent was removed under reduced pressure, and this same procedure was repeated once more to remove any residual ethanol. To the resulting foamy solid was added MTBE (14 L), and the mixture was stirred at 20 °C for 18 h. The suspension was filtered, and the solid was washed with MTBE (1 L) and dried under vacuum (17 Torr) at 50 °C for 24 h to give 593 g (94%) of HCl salt **14** as a white solid. Mp: 94−103 °C. HPLC retention time: 4.94 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30−1.47 (m, 1 H) 1.66−1.93 (m, 3 H) 2.34−2.46 (m, 1 H) 2.68−2.89 (m, 2 H) 3.20 (d, $J =$ 12.09 Hz, 1 H) 3.33−3.45 (m, 1 H) 4.19 −4.39 (m, 2 H) 7.24−7.43 (m, 3 H) 7.43−7.53 (m, 2 H) 7.56 (dd, $J =$ 8.33, 2.29 Hz, 1 H) 7.62 (t, $J = 7.87$ Hz, 1 H) 9.36 (br s, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.8, 25.2, 33.6, 43.8, 45.7, 71.2, 104.7, 105.0, 113.6, 113.7, 117.6, 117.7, 118.4, 118.6, 126.0, 126.1, 127.3, 127.4, 128.3, 129.8, 129.9, 138.9, 154.6, 156.5, 157.1, 157.6, 157.7, 158.8. MS (ES^+): 344.1 (M + H, free base)$^+$. Anal. Calcd for $C_{13}H_8F_2N_2O \cdot 0.35H_2O$: C: 59.10; Cl, 9.18; F, 9.84; H: 5.40; N: 10.88. Found: C: 58.78; Cl, 9.10; F, 9.72; H: 5.43; N: 10.70.

Synthesis of Tartaric Acid Salt 1. (i) HCl salt **14** (22.79 g, 60 mmol) was suspended in ethyl acetate (200 mL). A 1 M solution of K_2CO_3 in water (200 mL, 200 mmol) was added, and the biphasic mixture was vigorously stirred. After 1 h, all the solids had dissolved, and the two layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 100 mL), and the combined organic extracts were washed with saturated brine (50 mL) and dried over $MgSO_4$. The solution was concentrated under reduced pressure to give free base **19** as a beige oil that was used in the next step without further purification.

(ii) The free base from the previous step was dissolved in absolute ethanol (200 mL) to give a hazy mixture. Solid L-tartaric acid (9.00 g, 60 mmol) was added in one portion, and the mixture was stirred at 22 °C for 1 h. A white solid crystallized, and additional ethanol (600 mL) was added. The slurry was heated to reflux, which resulted in the partial dissolution of the solid. The suspension was cooled to 20 °C over 4 h and stirred for 14 h. The solid was filtered, washed with ethanol (50 mL), and dried under vacuum (17 Torr) at 50 °C for 24 h to give 18.91 g (83%) of tartaric acid salt **1** as a white solid. Mp: 181−182 °C. HPLC chemical purity: 98.7% a/a. HPLC optical purity: 100% a/a. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28−1.46 (m, 1 H) 1.59−1.74 (m, 1 H) 1.75−1.93 (m, 2 H) 2.25−2.43 (m, 1 H) 2.69−2.87 (m, 2 H) 3.23 (d, $J = 12.09$ Hz, 1 H) 3.35−3.48 (m, 1 H) 3.95 (s, 2 H) 4.19−4.38 (m, 2 H) 7.24−7.42 (m, 3 H) 7.43 −7.57 (m, 3 H) 7.62 (t, $J = 7.78$ Hz, 1 H) 8.44 (br s, 3 H). ^{13}C NMR (100

MHz, DMSO-d_6) δ 22.1, 25.4, 33.8, 71.3, 72.5, 117.8, 126.0, 126.1, 128.2, 138.9, 156.5, 157.1, 157.6, 175.3. MS (ES^+): 344.1 (M + H, free base)$^+$. Anal. Calcd for $C_{23}H_{25}F_2N_3O_7$: C: 55.98; F, 7.70; H: 5.11; N: 8.52. Found: C: 56.09; F, 7.70; H: 5.06; N: 8.47.

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Note Added after ASAP: Due to a production error, the footnotes for Schemes 1 and 2 were missing in the version published on the Internet August 9, 2008. This has been corrected in the version published ASAP August 27, 2008, and in the print version.

Supporting Information Available

Copies of ^{1}H and ^{13}C NMR spectra for compounds **1**, **8**, **10**, **11**, **12**, **13**, and **14**; PXRD data for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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