Organic Process Research & Development **2008,** *12,* 76–80

First Scale-Up: Problems and Resolutions on the Synthesis of WAY-253752, a Novel, Dual-Acting SSRI/5HT$_{1A}$ Antagonist

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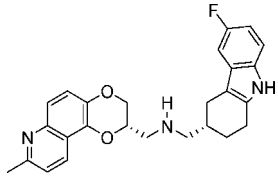
Abstract:

An alternative synthesis of WAY-253752, 1, a novel, dual-acting SSRI/5HT$_{1A}$ antagonist, was developed and used for the first scale-up. Initially, the target compound was synthesized as part of a diasteromeric mixture separated by chiral preparative HPLC. The new route was designed around intermediates suitable for chiral resolution, and its conditions were successfully determined.

Introduction

SSRI/5-HT$_{1A}$ antagonists potentially provide a significant improvement over SSRIs in the treatment of depression by addressing a major unmet therapeutic need for a faster-acting antidepressant agent. SSRI/5-HT$_{1A}$ antagonists act by a dual mechanism to (1) selectively inhibit the 5-HT transporter and (2) antagonize 5-HT$_{1A}$ autoreceptors to prevent feedback inhibition of neuronal firing. There has been a substantial amount of work reported by our group,[1] as well as by others,[2–5] aimed at creating a single molecular entity that possesses both 5-HT$_{1A}$ antagonism and 5-HT reuptake inhibition. The in vitro data for the compound described below, WAY-253752, suggest that it has potential as a dual-acting SSRI/5-HT$_{1A}$ antagonist. For further investigations, a practical scale-up synthesis was needed.



1, WAY-253752

Previously, we devised a novel method to synthesize this class of molecules by the reductive amination of aminomethylquinolinodioxane **7** with the racemic aldehyde **6**.[6] The aldehyde, in turn, was synthesized in three steps from commercially available ethyl 4-cyclohexanonecarboxylate **2** and 4-fluorophenylhydrazine hydrochloride **3** (Scheme 1). Amine **7** was synthesized in two steps from chiral quinolinodioxane derivative **9** (Scheme 2), which had been used as a common intermediate for several earlier projects.[7–11]

Analysis of this synthetic route from a scale-up viewpoint indicated several problems. First, the yields of two of the four synthetic steps, oxidation and reductive amination, were reported as inconsistent and, on average, low. Second, the synthesis produced a diastereomeric mixture requiring separation by chiral preparative HPLC. This technique, invaluable for medicinal chemists in lead optimization, posed a problem in scale-up; in this particular case, the largest run produced only milligram quantities of the target compound.

Thus, we had to introduce the second chiral center selectively, by either chiral synthesis or chiral resolution. This approach presented its own set of problems. First, we had to develop a new synthetic route, as the existing method did not provide for the possibility of a chiral synthesis, and none of the racemic intermediates **4–6** were suitable for crystallization with a chiral acid or base (chiral resolution). Furthermore, the absolute configuration of the second chiral center was initially unknown. Until we had it determined, the way to evaluate experiments on resolution would be conversion of intermediates into the final compound and comparison with the standard.

Results and Discussion

An Alternative Synthesis. Because the initial scheme did not provide racemic intermediates suitable for chiral resolution, we examined a new route that would involve both acidic and

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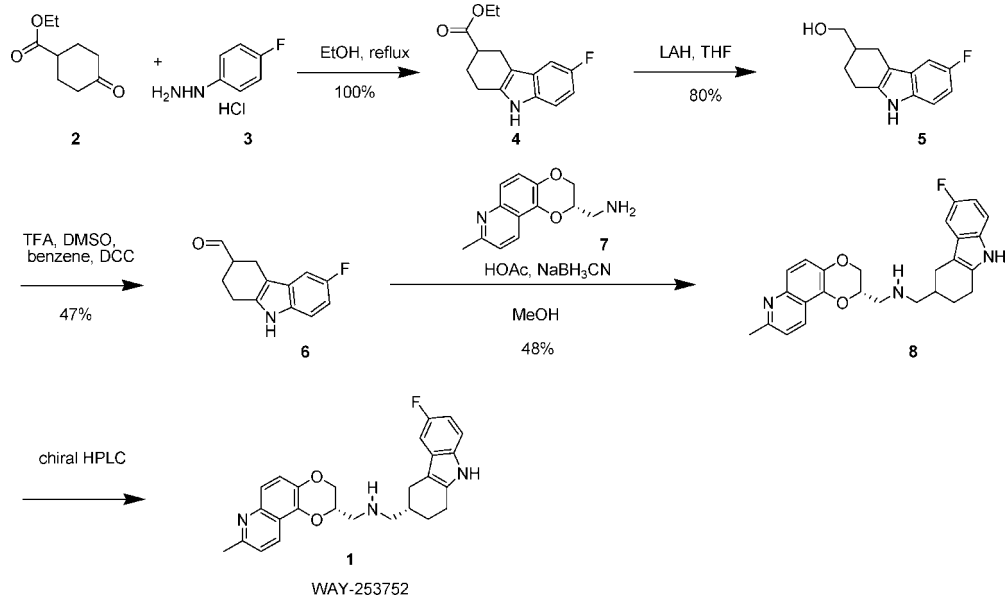
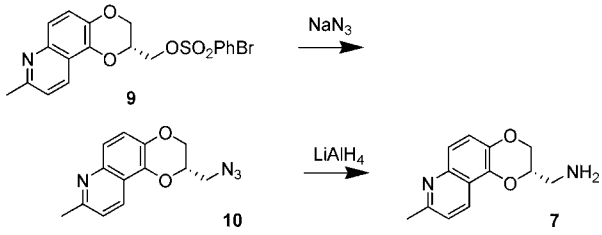
10.1021/op700181n CCC: $40.75
Published on Web 11/27/2007

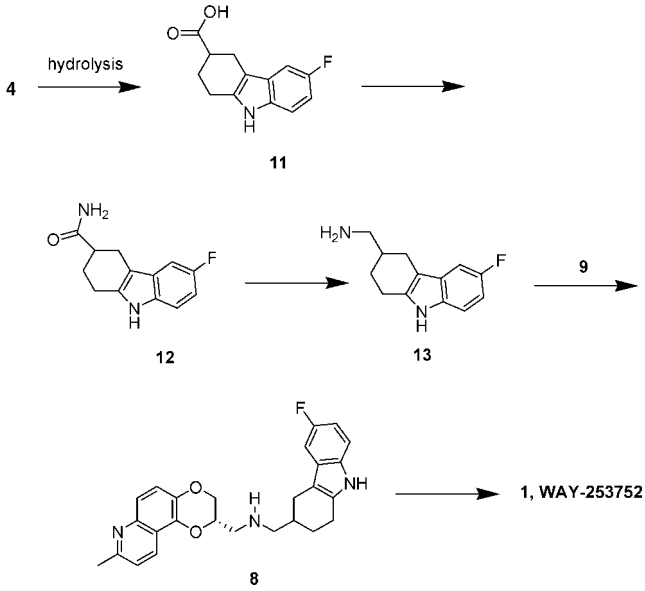
Scheme 1. **Initial synthesis of compound 1**



Scheme 2. **Synthesis of the penultimate fragment 8**



Scheme 3. **Alternative approach to WAY-253752**



basic intermediates (Scheme 3). Instead of reducing the ester, compound **4** was hydrolyzed into the acid, **11**, and then converted to the amide, **12**, and, subsequently, to the amine, **13**. The final step in this sequence was a nucleophilic substitution involving amine **13** and quinolinodioxane brosylate **9**.

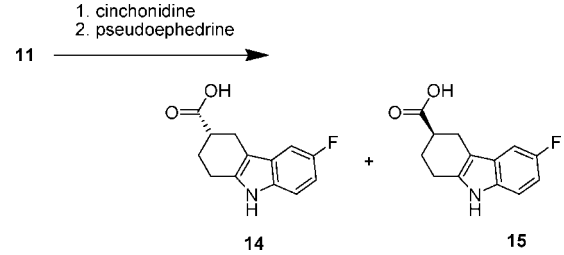
In addition to shortening the synthesis (brosylate **9** is used without conversion to the amine), this scheme provides two possibilities for chiral resolution of a racemic mixture: we could resolve the acid, **11**, with a chiral base or the amine, **13**, with a chiral acid.

A small-scale trial run provided us with conditions for each step. Hydrolysis of the ester was accomplished with sodium hydroxide, conversion of the acid to the amide proceeded through the acid chloride (treatment with oxalyl chloride followed by cold aqueous ammonia), and amide to amine reduction was achieved with lithium aluminum hydride. With reasonable amounts of racemic acid **11** and racemic amine **13**, we began work on chiral resolutions.

Resolution of Acid 11. First, extensive screening of optically active bases in an attempt to crystallize a single enantiomer gave only one positive result. The salt with cinchonidine was 98% enantiomerically pure, whereas the other bases did not yield any crystalline salts. We carried the pure isolated enantiomer through the rest of the synthesis shown in Scheme 3 and found that the resulting product was not our target compound, WAY-253752, but rather its diastereomer. Optical purity of the second enantiomer in mother liquors for this crystallization was about 60%. As cinchonidine, a natural product, exists only in one enantiomeric form, we could not isolate other enantiomer with suitable optical purity using the same protocol and another enantiomer of the base.

We worked up the mother liquor, separated the acid from cinchonidine, and subjected an 80:20 mixture of the enantiomers to a second screening of optically active bases. The results were quite different from the crystallization of the racemate: most of the salts came out crystalline. Chiral HPLC analysis,

Scheme 4. **Resolution of the racemic acid 11**



however, showed that only one of the crystallizations, with (+)-pseudoephedrine, improved the optical purity of the desired enantiomer to 98%; the rest of the salts had the same 80:20 ratio of enantiomers as the initial mixture.

NMR Confirmation of the Absolute Configuration of Enantiomerically Pure Acids 14 and 15. Having access to both enantiomers of the acid **11**, we were able to assign the absolute configuration of the chiral centers. The analyses were performed using a chiral derivatizing method, in which the carboxylic acid containing an unknown stereochemical center is condensed with (*R*)- and (*S*)-phenylglycine methyl ester (PGME) [12,13] (Schemes 5 and 6). The stereochemistry was determined by measuring the chemical shift differences ($\Delta\delta = \delta_S - \delta_R$) of the protons adjacent to the unknown stereochemical center in the (*R*)- and (*S*)-PGME amides.

Scheme 5. **(*R*)- and (*S*)-PGME derivatization of the optically pure acid 14**

Scheme 6. **(*R*)- and (*S*)-PGME derivatization of the optically pure acid 15**

Proton spectra of the derivatives are shown in Figures 1 and 2. As seen in the spectra, the most predominant chemical shift changes are the methylene protons at 2 and 4 positions adjacent to the chiral center. For compound **14** (Scheme 5, Figure 1), the observed $\Delta\delta$ values are 0.063/0.019 ppm for $H_4/H_{4'}$ and −0.067/−0.004 ppm for $H_2/H_{2'}$. These shifts indicate the (*S*)-configuration of enantiomer **14**. The chemical shift changes of H2 and H4 in (*R*)- and (*S*)-PGME derivatives of compound **15** are opposite to those observed for **14**. Therefore, this sample represents the (*R*)-enantiomer.

First Scale-Up of WAY-253752: The Modified Synthesis. The resulting optimized synthesis for WAY-253752 is shown in Scheme 7. It involves two optical resolutions of the acid **11**, first with cinchonidine and second with (+)-pseudoephedrine, with a 75% overall yield of optically active acid **14** after two crystallizations. The synthesis of amine **17** from chiral acid **14** was accomplished with complete stereointegrity (chiral HPLC). Final condensation of the amine **17** with the brosylate **9** was carried out in dimethylsulfoxide with dimethylaminopyridine as a base at 90 °C; full conversion into the target compound **1**,WAY-253752, was achieved in 3 h.

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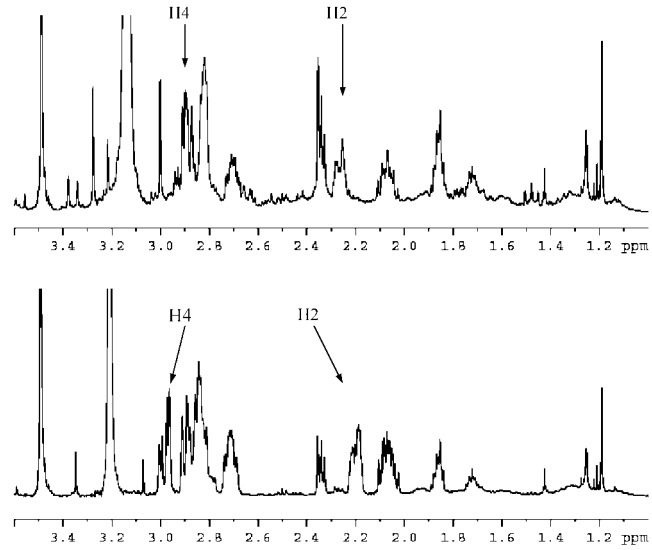


Figure 1. **^{1}H NMR spectra of (*R*)- (14a, top) and (*S*)- (14b, bottom) PGME amides in $CDCl_3$.**

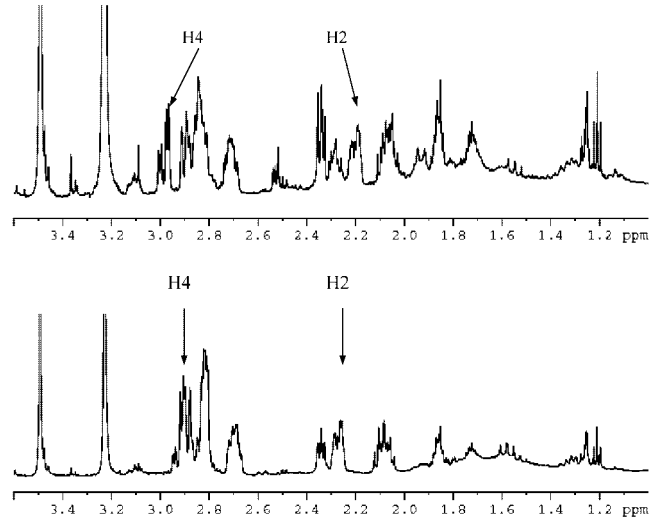


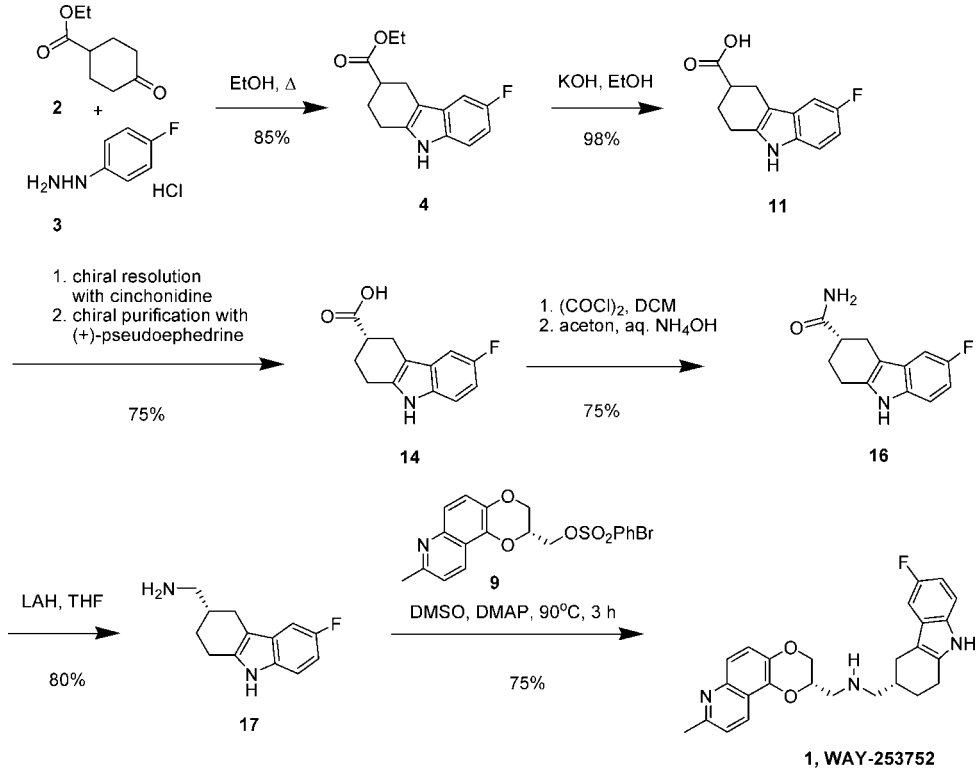
Figure 2. **^{1}H NMR spectra of (*R*)- (15a, top) and (*S*)- (15b) PGME amides in $CDCl_3$.**

Conclusion

The rapidly changing situation in the pharmaceutical industry leads to a higher degree of specialization within its structural elements, so that the goals, methods, and problems of medicinal chemistry become increasingly different from those of the process development. For example, chiral preparative HPLC, a great tool for medicinal chemists, is considered an impediment in process development, where it is rarely scalable and often necessitates the development of new chemistry.

In the Discovery phase of the presented project, chiral preparative HPLC of the penultimate diastereomers allowed for the separation, identification, and comparison of the biological activity of two close analogs. When the best compound was identified, however, it became clear that for a successful scale-up an alternative, scalable synthesis would have to be developed. The key to success in this case was chiral resolution of an intermediary racemic acid. Such innovations often become the foundation of further synthetic process development.

Scheme 7. **First scale-up synthesis of WAY-253752**



Experimental Section

General Methods. NMR spectra of the intermediates were recorded on a Bruker 300 NMR spectrometer. HPLC analysis of the intermediates and reaction monitoring was carried out on an Agilent 1090 liquid chromatograph equipped with a Phenomenex Prodigy ODS3 4.6 mm × 50 mm column. Standard method was 90:10 to 10:90 over 8 min gradient of water/acetonitrile containing 0.02% TFA, flow rate 1 mL/min. Chiral HPLC analysis was performed on HP 1100-6 liquid chromatograph equipped with a Whelk O1 RR 4.6 mm × 250 mm column. Mobile phase composition was 60% heptane containing 0.02% TFA and 40% isopropyl alcohol, flow rate 1 mL/min.

6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic Acid Ethyl Ester (4). 4-Cyclohexanonecarboxylic acid ethyl ester (**2**) (77 g, 0.45 moles) and 4-fluorophenyhydrazine hydrochloride (**3**) (72 g, 0.44 mol) were dissolved in ethanol (1500 mL) and heated under reflux for 16 h. After cooling, the white solid was removed by filtration, and the solvent of the filtrate was removed under reduced pressure. After partitioning of the residue between water and ethyl acetate, the organic portion was separated, dried ($MgSO_4$), and evaporated under reduced pressure to give **4** (113 g, 98%). The crude product was recrystallized from heptane, mp 116–117 °C (lit. [14] 115–117 °C); ^{1}H NMR ($CDCl_3$) 1.3 (t, 3H, J = 7.1 Hz), 1.95–2.1 (m, 1H), 2.26–2.36 (m, 1H), 2.73–2.86 (m, 4H), 2.86–3.05 (m, 1H), 4.2 (q, 2H, J = 7.1 Hz) 6.86 (dt, 1H, J_1 = 9.2 Hz, J_2 = 2.2 Hz), 7.1(dd, 1H, J_1 = 2.7 Hz, J_2 = 9.6 Hz) 7.18 (dd, 1H, J_1 = 4.2 Hz, J_2= 8.7 Hz), 7.72 (s, 1H). MS 262 (M + H). ^{1}H NMR ($CDCl_3$) 1.3 (t, 3H, J = 7 Hz), 1.9–2.1 (m, 1H), 2.3 (m, 1H), 2.7–2.9 (m, 4H), 3.0 (m, 1H), 4.2 (q, 2H, J = 7 Hz) 6.8 (ddd, 1H, J = 2, 8.5, 9.5 Hz), 7.1(dd, 1H, J = 2, 9.5 Hz) 7.2 (dd, 1H, J = 4, 8.5 Hz), 7.7 (s, 1H).

6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic Acid (11). 6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic acid ethyl ester (**4**) (80 g, 0.3 mol) was dissolved in 1 L of an ethanolic solution of KOH (28 g, 0.5 mol). The resulting mixture was stirred under nitrogen at 40–45 °C until completion of hydrolysis, as indicated by HPLC, in 3 h. To the cooled solution were added 0.5 L of 1 N aqueous HCl and 0.5 L of water; the resulting mixture was concentrated under reduced pressure. The target compound **4** crystallized out of the aqueous solution when ethanol boiled out; 71.2 g (99%) of the title compound was obtained after drying, mp 183–185 °C; MS 232.1 (M − H); ^{1}H NMR (300 MHz, $CDCl_3$) 2.03–2.13 (m, 1H), 2.29–2.38 (m, 1H), 2.81–2.96 (m, 4H), 2.98–3.09 (m, 1H), 6.87 (dt, 1H, J_1 = 8.8 Hz, J_2 = 2.5 Hz), 7.10 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.5 Hz), 7.18 (dd, 1H, J_1 = 8.8 Hz, J_2 = 4.0 Hz), 7.71 (s, 1H).

(3*S*)-6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic Acid (14). The racemic 6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic acid (**11**) (68 g, 292 mmol) was dissolved in 500 mL of acetonitrile, and the warm solution was mixed with a warm solution of (−)-cinchonidine (43 g, 146 mmol) in 500 mL of methanol. The resulting mixture was left to cool down slowly in a dark glass. The formed salt of the (*R*)-acid (**15**) was filtered and washed with acetonitrile; a second crop of crystals was also filtered, washed with acetonitrile, and combined with the first crop. The mother liquor was concentrated and partitioned between methyl *tert*-butyl ether (MTBE) and 1 N HCl. The organic layer was dried over $MgSO_4$, filtered

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through magnesol, and evaporated,and the free acid was crystallized from cyclohexane to give 42 g of **14**, 60% ee.

The (*S*)-enriched acid (**14**) (42 g, 178.5 mmol) was dissolved in 700 mL of acetonitrile, and the warm solution was mixed with a warm solution of (1*S*,2*S*)-(+)-pseudoephedrine (29.75 g, 178.5 mmol) in 550 mL of acetonitrile. The resulting mixture was left to crystallize while cooling down slowly. The salt was filtered and washed with cold acetonitrile; the free acid was isolated as before. The target compound **14** was obtained as white crystals, 98% ee; yield 28 g (83% from 42 g of the enriched mixture), mp 200–203 °C; $[\alpha]_D$ –32.8 (1% solution in methanol, 25 °C); MS 232.1 (M − H); ^{1}H NMR (300 MHz, DMSO-d_6) 1.85 (ddd, 1H, J_1 = 13.8 Hz, J_2 = 8.7 Hz, J_3 = 4.4 Hz), 2.12–2.21 (m, 1H), 2.70 (ddd, 2H, J_1 = 19.2 Hz, J_2 = 9.8 Hz, J_3 = 2.3 Hz), 2.77 (dd, 2H, J_1 = 7.1 Hz, J_2 = 2.3 Hz), 2.88 (dd, 1H, J_1 = 19.2 Hz, J_2 = 9.8 Hz), 6.87 (ddd, 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz, J_3 = 0.7 Hz), 7.11 (dd, 1H, J_1 = 9.9 Hz, J_2 = 2.6 Hz), 7.21 (dd, 1H, J_1 = 8.8 Hz, J_2 = 4.5 Hz), 10.78 (s, 1H), 12.26 (s, 1H).

(3*S*)-6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxamide (16). (3*S*)-6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic acid (**14**) (18 g, 77 mmol) was suspended in 200 mL of methylene chloride together with 50 mL of 2 N oxalyl chloride; several drops of DMF were added, and the resulting mixture was stirred at room temperature until it became a clear solution (about 2 h). The solvent was evaporated at reduced pressure at room temperature and then dissolved in 500 mL of dry acetone. The solution was cooled to −5 °C, and to the cold solution was quickly added 300 mL of 7 N aqueous ammonia, with vigorous stirring and cooling. The temperature rose to 5 °C. An additional 200 mL of aqueous ammonia was added, the resulting mixture was stirred for another 30 min, and acetone was evaporated under reduced pressure. The product **16** crystallized out of aqueous solution, was filtered, washed with water, and dried to give 13.7 g, (76%) of white crystals, ee 98%, mp 170–172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.74–1.85 (m, 1H), 2.01–2.09 (m, 1H), 2.63 (t, 1H, J = 14.0 Hz), 2.69–2.82 (m, 3H), 6.80 (dt, 1H, J_1 = 9.4 Hz, J_2 = 2.2 Hz), 6.83 (s, 1H), 7.09 (dd, 1H, J_1 = 9.4 Hz, J_2 = 2.2 Hz), 7.21 (dd, 1H, J_1 = 8.4 Hz, J_2 = 4.5 Hz), 7.37 (s, 1H), 10.76 (s, 1H).

{[(3*S*)-6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazole-3-carbazol-3-yl]methyl}amine (17). (3*S*)-6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxamide (**16**) (34.7 g, 150 mmol) was dissolved in 1 L of dry THF, and to the solution was added 300 mL of 1 N lithium aluminum hydride in THF. The resulting solution, turning into a suspension, was refluxed with vigorous stirring for 1 h, with completion checked by HPLC. The resulting suspension was cooled to 0–5 °C and quenched very slowly with a saturated solution of sodium potassium tartrate (Rochelle salt). The temperature was initially kept below 15 °C and then allowed to rise to 20–25 °C; 125 mL of the salt solution were added, while the solids in the suspension became crystalline and easily filterable. The reaction mixture was filtered through paper, the filtrate dried over sodium sulfate, evaporated, crystallized from MTBE, dried in the vacuum oven at 50 °C overnight to give 26.9 g (82%) of **17** as white crystals, ee 98%, mp 121–123 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.38–1.49 (m, 2H), 1.65–1.73 (m, 1H), 1.98–2.06 (m, 1H), 2.18 (dd, 1H J_1 = 9.1 Hz, J_2 = 7.1 Hz), 2.54–2.65 (m, 2H), 2.66–2.77 (m, 3H), 6.78(dt, 1H, J_1 = 9.2 Hz, J_2 = 2.6 Hz), 7.04 (dd, 1H, J_1 = 9.4 Hz, J_2 = 2.6 Hz), 7.19 (dd, 1H, J_1 = 8.7 Hz, J_2 = 4.4 Hz), 10.71 (s, 1H).

(*S*,*S*)-(6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-3-ylmethyl)-(8-methyl-2,3-dihydro-[1,4]dioxino[2,3-*f*]quinolin-2-ylmethyl)-amine (WAY-253752, 1). A mixture of {[(3*S*)-6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazole-3-carbazol-3-yl]methyl}amine (**17**) (34.2 g, 156 mmol), [(2*R*)-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinolin-2-yl]methyl 4-bromobenzenesulfonate (**9**) (45.1 g, 100 mmol), and dimethylaminopyridine (12.2 g, 100 mmol) in 300 mL of dry DMSO was stirred under nitrogen at 90 °C for 3 h and monitored by HPLC. The resulting mixture was cooled and poured into aqueous sodium bicarbonate (1.5 L). The gum that precipitated on the bottom of the flask was dissolved in ethyl acetate, washed with brine and water, dried over sodium sulfate, and concentrated. The resulting gum was dissolved in ethanol and upon stirring crystallized to give 30 g (69.6%) of **1** as off-white crystals, mp 152–153 °C, $[\alpha]_D$ –75.0 (1% solution in DMSO, 25 °C); ^{1}H NMR (300 MHz, DMSO-d_6) 1.50 (m, 1H), 1.93 (s, 1H), 2.01–2.14 (m, 2H), 2.23 (dd, 1H, J_1 = 15.3 Hz, J_2 = 9.5 Hz), 2.60 (s, 3H), 2.68 (d, 2H, J = 7.1 Hz), 2.72 (m, 2H), 2.78 (dd, 1H, J_1 = 15.3 Hz, J_2 = 4.9 Hz), 2.93 (ddd, 2H J_1 = 23.1 Hz, J_2 = 13.1 Hz, J_3 = 6.2 Hz), 4.12 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.1 Hz), 4.42 (ddd, 1H J_1 = 13.1 Hz, J_2 = 6.1 Hz, J_3 = 2.0 Hz), 4.48 (dd, J_1 = 11.4 Hz, J_2 = 2.3 Hz), 6.79 (ddd, 1H, J_1 = 8.6 Hz, J_2 = 2.6 Hz, J_3 = 0.8 Hz), 7.03 (dd, 1H, J_1 = 10.0 Hz, J_2 = 2.7 Hz), 7.20 (dd, 1H, J_1 = 8.9 Hz, J_2 = 4.6 Hz), 7.32 (d, 2H, J = 8.9 Hz), 7.43 (dd, 1H, J_1 = 9.0 Hz, J_2 = 0.4 Hz), 8.30 (d, 1H, J = 8.6 Hz), 10.72 (s, 1H).

Note Added after ASAP: In the version published on hte Internet November 27, 2007, there was an error in Scheme 3. This has been corrected for the ASAP version and will also be correct in the print version.

Supporting Information Available

^{1}H NMR spectra for compounds **4**, **11**, **14**, **16**, **17**, and **1**. Salt screening tables for the resolution of acid **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review August 9, 2007.

OP700181N