Organic Process Research & Development **2008,** *12,* 178–182

# An Improved Synthesis of a Selective Serotonin Reuptake Inhibitor

Robert Anthes, Serge Benoit, Chien-Kuang Chen,* Elisabeth A. Corbett, Richard M. Corbett, Albert J. DelMonte, Stephane Gingras, Robert C. Livingston, Yadagiri Pendri, Justin Sausker, and Maxime Soumeillant

*Process Research and Development, Bristol-Myers Squibb Company, One Squibb Drive, P.O. Box 191, New Brunswick, New Jersey 08903-0191, U.S.A.*

**Abstract:**

**A practical synthesis of 3-((1*S*, 2*S*)-2-dimethylaminomethylcyclopropyl)-1*H*-indole-5-carbonitrile hydrochloride (1), a selective serotonin reuptake inhibitor (SSRI), is described. The process to prepare 1 was demonstrated on laboratory scale and highlights an enantioselective Simmons−Smith cyclopropanation of allylic alcohol 3 using Charette's chiral dioxaborolane ligand. The improved synthesis enabled production of 1 in 8 chemical steps (5 isolations) in an overall yield of 38%.**

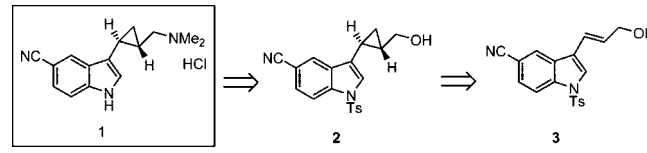
## Introduction

In the preceding paper, we described the development of a 13-step synthesis of SSRI candidate **1**,[1] which provided the first kilogram quantities of **1** in an overall yield of 34%. The process hinged upon the efficient Nishiyama[2] catalyst-mediated asymmetric cyclopropanation of a vinyl indole with ethyl diazoacetate, to generate a *trans*-disubstituted cyclopropane in 85–88% enantiomeric excess (ee) and a 10:1 diastereomeric ratio. We proposed intersection of the existing route at cyclopropylmethanol **2** by enantioselective Simmons−Smith cyclopropanation of the corresponding allylic alcohol **3** (Scheme 1).[3] This paper describes our effort in this area as well as expansion of our knowledge of the conversion of **2** to **1**.

## Results and Discussion

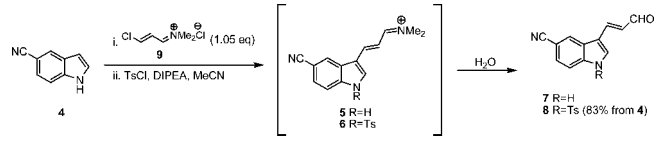
**Preparation of Allylic Alcohol 3.** We reasoned that substrate **3** could be prepared through reduction of the corresponding aldehyde **8** (Scheme 2). The synthesis of **8** began with

***Scheme 1.*** **Retrosynthetic analysis of 1 featuring an asymmetric Simmons−Smith cyclopropanation**



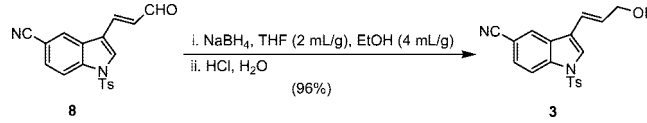

reaction of 5-cyanoindole **4** with *N*-(3-chloroallylidene)-*N*-methylmethanaminium chloride (**9**), generated by exposure of 3-(*N*,*N*-dimethylamino)acrolein to $POCl_3$,[4] to produce the corresponding iminium salt **5**. Hydrolysis under basic conditions provided the desired aldehyde **7**, but the process was complicated by a tedious quench procedure to consume unreacted $POCl_3$. As such, alternatives to $POCl_3$ were evaluated. Triflic anhydride was effective,[5] but this process was accompanied by competing side reactions. (Chloromethylene)dimethyliminium chloride (Vilsmeier reagent), however, was a suitable alternative to $POCl_3$, as addition to 3-(*N*,*N*-dimethylamino)acrolein in acetonitrile led to in situ formation of **9**. Subsequent addition of **4** cleanly generated **5**, which underwent hydrolysis to aldehyde **7** at pH 8.5. Tosylation of **7** provided aldehyde **8**. Later, it was shown that **5** could be converted to tosylate **6** by direct addition of tosyl chloride (TsCl) and diisopropylethylamine to the reaction mixture. Subsequent hydrolysis of **6** afforded **8**. This one-vessel process afforded indole-protected aldehyde **8** in 83% yield from **4** (99 HPLC area % purity) (Scheme 2).

***Scheme 2.*** **Preparation of protected indole-aldehyde 8**




Reduction of the aldehyde **8** to the desired allylic alcohol **3** (Scheme 3) with sodium borohydride ($NaBH_4$) proved to be sensitive to the nature of the solvent system. In pure alcohol solvents, poor conversion accompanied by competing product degradation was observed. Mixed solvent systems, however, consisting of THF in methanol (MeOH) or ethanol (EtOH), gave cleaner and more rapid reaction upon treatment with 0.5 equiv

***Scheme 3.*** **Preparation of allylic alcohol 3**




* To whom correspondence should be addressed. Telephone: 732-227-6863. Fax: 732-227-3932. E-mail:chien.chen@bms.com.

(1) (a) Anthes, R.; Bello, O.; Benoit, S.; Chen, C.-K.; Corbett, E.; Corbett, R. M.; DelMonte, A. J.; Gingras, S.; Livingston, R.; Sausker, J.; Soumeillant, M. *Org. Process Res. Dev.* **2008**, *12*, 168. (b) Cyclopropylindole derivatives as selective serotonin reuptake inhibitors: Mattson, R. J.; Denhart, D. J.; Deskus, J. A.; Ditta, J. L.; Marcin, L. R.; Epperson, J. R.; Catt, J. D.; King, D.; Higgins, M. A. U.S. Patent US6777437 B2, Aug 17, 2004. (c) Cyclopropylindole derivatives as selective serotonin reuptake inhibitors: Mattson, R. J. U.S. Patent US6822100 B2, Nov 23, 2004.

(2) (a) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B. *J. Am. Chem. Soc.* **1994**, *116*, 2223. (b) Park, S.-B.; Murata, K.; Matsumoto, H.; Nishiyama, H. *Tetrahedron Asymmetry* **1995**, *6*, 2487. (c) Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh., K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247. (d) Totleben, M. J.; Prasad, J. S.; Simpson, J. H.; Chan, S. H.; Vanyo, D. J.; Kuehner, D. E.; Deshpande, R.; Kodersha, G. A. *J. Org. Chem.* **2001**, *66*, 1057.

(3) (a) For reviews of enantioselective Simmons−Smith reactions, see: Singh, V. K.; DattaGupta, A.; Sekar, G. Synthesis 1997, 137. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

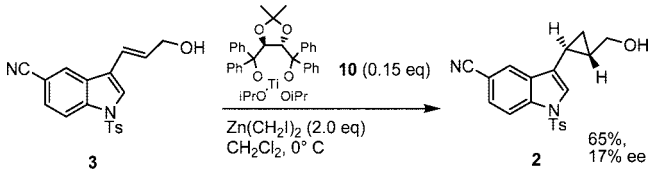
(4) Ullrich, F.-W.; Breitmaier, E. *Synthesis* **1983**, 641.

(5) Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **1998**, *54* (1–2), 119.


Published on Web 01/17/2008

10.1021/op700126w CCC: $40.75 

***Scheme 4.*** **Cyclopropanation of allylic alcohol 3 using catalytic chiral titanium-TADDOLate 10**

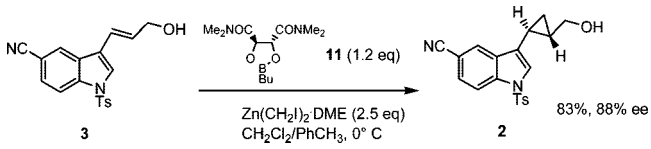



of $NaBH_4$. By contrast, a mixed solvent system of THF/2-propanol led to lower reaction rates with competing detosylation. Ultimately, a solvent system of THF (2 mL/g[6]) and EtOH (4 mL/g) was selected as the rate of $NaBH_4$ degradation was slower than what was observed in other systems. Workup was simplified to the addition of dilute aqueous HCl, which led to direct crystallization of alcohol **3** (98.8 HPLC area % purity).

**Development of the Enantioselective Simmons−Smith Reaction.** Enantioselective cyclopropanation of allylic alcohols is well documented.[3,7] Application of Charette's[7] conditions through exposure of alcohol **3** to catalytic titanium-TADDOL complex **10** (0.15 equiv) and $Zn(CH_2I)_2$ (2 equiv) provided cyclopropane **2** in 65% yield but in low enantiomeric excess (17% ee) (Scheme 4).[7a]

As the first set of conditions afforded unsatisfactory ee, employment of a different Charette procedure[7b–d] involving use of stoichiometric (*R*,*R*)-dioxaborolane **11** was investigated next. Ligand **11** was prepared in a modification of the previously reported procedure,[7c] by heating commercially available butylboronic acid in the presence of a slight excess of *N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide in toluene under Dean–Stark conditions. Cooling, filtration of excess diamide, and concentration of the filtrate provided pure dioxaborolane **11**. Subjection of **3** to the conditions specified in Charette's procedure[7d] gave cyclopropylmethanol **2** in 83% yield and significantly improved enantioselectivity (88% ee) (Scheme 5).

***Scheme 5.*** **Cyclopropanation of the allylic alcohol 3 using (*R*,*R*)-dioxaborolane 11**




Because of the pyrophoric nature of neat diethylzinc ($Et_2Zn$), which is employed in the Charette procedure to generate the di(iodomethyl)zinc carbenoid, we turned our attention to use of less air-sensitive toluene solutions of this reagent for the preparation of the di(iodomethyl)zinc carbenoid, $Zn(CH_2I)_2$. The use of commercially available 30 wt % $Et_2Zn$ toluene solution permitted decreasing the overall reaction volume, although the enantioselectivity was poor (47% ee), with a low solubility of the starting material and product complicating the process. Incorporation of methylene chloride as cosolvent (3:1 volume ratio of $CH_2Cl_2$/toluene) improved the solubility, and acceptable enantiomeric ratios (85–90% ee) were obtained. Excess carbenoid ($Zn(CH_2I)_2$·DME) (3.5 equiv) and >12 h reaction time were required to drive the reaction to completion at 23 °C, whereas at reflux (47–49 °C) lower carbenoid charges (2.5 equiv) were sufficient and improved volume efficiency (30 mL/g) was also realized. Unfortunately, the full 1.2 equiv of dioxaborolane was still required to effect conversion, even at the elevated temperatures. Under these modified reaction conditions, the enantioselectivity was consistently in the range 85–90% ee.

Quench of the cyclopropanation reaction with either saturated, aqueous ammonium chloride or dilute HCl led to precipitation of zinc byproduct, thereby complicating the ensuing phase separation. To circumvent this issue, we successfully developed a novel quenching strategy that employed anhydrous conditions to produce a zinc species that was easily removed by a simple filtration. Thus, upon completion of the reaction, addition of 2-propanol and acetic acid at 35 °C followed by cooling to 0–5 °C resulted in precipitation of zinc acetate. After filtration, two subsequent 3 M NaOH washes of the filtrate separated butylboronic acid and *N*,*N*,*N*′,*N*′-tetramethyltartaric amide byproduct from the product stream. This modified workup procedure eliminated the oxidative conversion of butylboronic acid to boric acid which is traditionally employed.[7b–d] Charcoal treatment (powder or cartridge) of process streams, however, was essential for reproducible crystallization of cyclopropylmethanol **2**. In all, the modified workup procedure offered several practical improvements to published procedures.

Simple crystallization systems did not lead to any significant enhancement of the enantiomeric purity of **2**, and some systems actually led to erosion of the ee due to cocrystallization of the racemate. Fortunately, mixed solvent systems consisting of $CH_2Cl_2$/toluene/heptane led to high-yielding crystallizations with no deterioration of enantiopurity. In practice, concentration of worked-up process streams to 8 mL/g, followed by addition of heptane, led to crystallization of **2**, which was isolated in >80% yield and good ee and purity (86–89% ee, 98 HPLC area % purity).

**Conversion of Cyclopropylmethanol 2 to API 1.** A key consideration in the demonstration of any new synthetic route is the assessment of final product quality through comparison to material prepared with existing chemistry. In our original chemical development studies,[1a] we demonstrated that cyclopropylmethanol **2** having 95% ee could be converted to **1** with >98% ee. We hoped that **2** prepared through the Charette protocol (86–89% ee) would undergo a significant boost in enantiopurity during conversion to **1** and meet or exceed the targeted quality of 98% ee.

Intermediate **2** was converted to the final intermediate hydrochloride salt hemihydrate **13** via TEMPO oxidation[1,8] followed by reductive amination (Scheme 6). Although the chemical purity of **13** was excellent (99.8 area % purity), no enhancement in enantiopurity occurred during crystallization. We were pleased to find, however, that detosylation of **13** and crystallization of **1** using existing protocols[1] led to a substantial

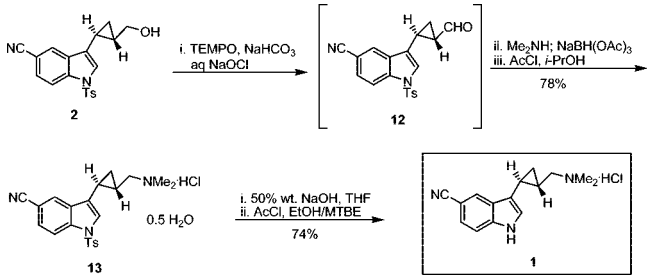
(6) mL/g refers to milliliters of solvent per gram of substrate.

(7) (a) Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168. (b) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651. (c) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081. (d) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943.

(8) Anelli, L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.

enhancement of enantiopurity and produced SSRI candidate **1** in good yield, with purity and enantiopurity equivalent to the values for material prepared from the previous route (74% yield, 99.8 HPLC area % purity, and >98% ee).

***Scheme 6.*** **Preparation of final intermediate 13 and API 1**




## Conclusions

In summary, an improved synthesis of SSRI candidate **1** was developed. The new synthetic route was demonstrated on 130 mmol scale and featured an effective method for preparing the vinylogous Vilsmeier reagent used for installation of the three-carbon unit in cyclopropanation substrate **3**. In addition, a practical enantioselective Simmons−Smith reaction to convert allylic alcohol **3** to late-stage intermediate **2** with good enantioselctivity (88% ee) has been developed. Finally, we demonstrated that the enantiopurity of **1** may be enhanced from 86% to 89% ee to >98% ee through crystallization.

## Experimental Section

**General Methods.** Acetonitrile, THF, $CH_2Cl_2$, toluene, 2-propanol, heptane, and MTBE were purchased from EM Science and were used without further purification. EtOH was purchased from Les Alcools de Commerce and was used without further purification. Methyl acetate and all other reagents were purchased from Aldrich and were used without any further purification. Melting points were measured on a MEL-TEMP 3.0 melting point apparatus and were uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on Bruker AVANCE 400 or Bruker AVANCE 500 instruments. Chemical shifts are given on a $\delta$ (ppm) scale. HPLC purities of samples were determined on a YMC Pro C18, 3 $\mu$m, 4.6 mm × 50 mm column. The method conditions were mobile phase A, 0.05% TFA in $CH_3CN$/water (10:90); B, 0.05% TFA in $CH_3CN$/water (90:10), gradient from 5% B to 100% B over 5 min, flow rate 3 mL/min, wavelength 230 nm. Enantiomeric purity of compounds was determined by chiral HPLC. For compound **6**, a Daicel Chiralcel OD-R 4.6 mm × 250 mm, 10 $\mu$m column was used. The mobile phase was $CH_3CN$/water (50:50). The chiral method conditions were isocratic run for 60 min, column temperature 35 °C, flow rate 0.3 mL/min, wavelength 230 nm. For compound **1** a Daicel Chiralpak AD 4.6 mm × 250 mm, 5 $\mu$m column was used. The mobile phase was hexanes/ethanol/diethylamine (90:10:0.1). The chiral method conditions were isocratic run for 30 min, column temperature 30 °C, flow rate 1 mL/min, wavelength 230 nm.

**Preparation of 3-(3-Oxopropenyl)-1-(toluene-4-sulfonyl)-1*H*-indole-5-carbonitrile (8).** To a cooled (0–5 °C) suspension of (chloromethylene)dimethylammonium chloride (20.7 g, 162 mmol, 1.15 equiv) and $CH_3CN$ (200 mL) under argon was added 3-(dimethylamino)acrolein (15.4 mL, 148 mmol, 1.05 equiv) over 15 min. The resulting suspension was stirred at 0–5 °C for an additional 10 min. A solution of 5-cyanoindole **4** (20.0 g, 141 mmol) in $CH_3CN$ (45 mL) was added, and the resulting solution was warmed to 20–25 °C over 30 min. The solution was heated to 70–75 °C, and the reaction mixture was stirred for 5 h. The reaction mixture was cooled to 20–25 °C and *N*,*N*-diisopropylethylamine (61.3 mL, 352 mmol, 2.50 equiv) was added over 20 min, followed by a solution of *p*-toluenesulfonyl chloride (32.2 g, 169 mmol, 1.20 equiv) in $CH_3CN$ (40 mL). The resulting slurry was stirred for 15 min. Water (100 mL) was added, and the solution was heated to 75 °C and held for 2 h. The product slurry was cooled to 20–25 °C and stirred for 2 h, and the solid was collected by filtration. The cake was rinsed with 1:1 $CH_3CN/H_2O$ (2 × 60 mL). The solid was dried in vacuo (5–6 mmHg) at 45–50 °C to constant weight to afford 40.8 g (82.7%) of **8** as an off-white solid. Mp: 220.0–221.0 °C. $^1$H NMR ($d_6$-DMSO, 400.13 MHz) $\delta$ 9.63 (d, $J$ = 7.9 Hz, 1H), 8.76 (s, 1H), 8.64 (d, $J$ = 1.2 Hz, 1H), 8.14 (d, $J$ = 8.5 Hz, 1 H), 7.99 (d, $J$ = 8.3 Hz, 2H), 7.92 (d, $J$ = 16.2 Hz, 1H), 7.83 (dd, $J$ = 8.5, 1.2 Hz, 1H), 7.44 (d, $J$ = 8.3 Hz, 2H), 7.05 (dd, $J$ = 16.2, 7.9 Hz, 1H), 2.33 (s, 3H); $^{13}$C NMR ($d_6$-DMSO, 125.77 MHz) $\delta$ 194.11, 146.59, 142.46, 136.30, 133.18, 131.49, 130.59, 129.36, 128.71, 127.69, 127.09, 126.01, 118.77, 117.47, 114.41, 107.05, 21.03. Anal. Calcd for $C_{19}H_{14}N_2O_3S$: C, 65.12; H, 4.02; N, 7.99; S, 9.15. Found: C, 64.85; H, 3.78; N, 7.93; S, 9.21.

**Preparation of 3-(3-Hydroxypropenyl)-1-(toluene-4-sulfonyl)-1*H*-indole-5-carbonitrile (3).** A suspension of 3-(3-oxopropenyl)-1-(toluene-4-sulfonyl)-1*H*-indole-5-carbonitrile **8** (40.0 g, 114 mmol), THF (80 mL), and EtOH (160 mL) under argon was cooled to 5–8 °C. Sodium borohydride (2.16 g, 57.1 mmol, 0.501 equiv) was added all at once. The reaction mixture was warmed to 20–25 °C and stirred for 3 h. A solution of 0.18 N HCl (485 mL, 87.3 mmol, 0.766 equiv) was added over 20 min. The resulting slurry was stirred at 20–25 °C for 1 h, and the solids were collected by filtration. The cake was rinsed with $H_2O$ (2 × 80 mL), and the solid was dried in vacuo (5–6 mmHg) at 45–50 °C to constant weight, affording 38.6 g (96.0%) of **3** as an off-white solid. Mp: 142.5–143.5 °C. $^1$H NMR ($d_6$-DMSO, 400.13 MHz) $\delta$ 8.40 (d, $J$ = 1.3 Hz, 1H), 8.16 (s, 1H), 8.10 (d, $J$ = 8.6 Hz, 1H), 7.91 (d, $J$ = 8.2 Hz, 2H), 7.76 (dd, $J$ = 8.6, 1.3 Hz, 1H), 7.40 (d, $J$ = 8.2 Hz, 2H), 6.69 (d, $J$ = 16.4 Hz, 1H), 6.58 (dt, $J$ = 16.4, 4.7 Hz, 1H), 4.91 (t, $J$ = 5.4 Hz, 1H), 4.15–4.11 (m, 2H), 2.31 (s, 3H); $^{13}$C NMR ($d_6$-DMSO, 125.77 MHz) $\delta$ 146.04, 136.34, 133.56, 133.41, 130.38, 128.62, 128.04, 126.78, 125.69, 125.60, 119.86, 119.00, 117.70, 114.31, 106.35, 61.52, 20.98. Anal. Calcd for $C_{19}H_{16}N_2O_3S$: C, 64.75; H, 4.57; N, 7.94; S, 9.09. Found: C,64.46; H, 4.48; N, 7.88; S, 8.97.

**Preparation of (−)-(*R*,*R*)-2-Butyl-*N*,*N*,*N*′,*N*′-tetramethyl-1,3,2-dioxaborolane-4,5-dicarboxamide (11).** A mixture of butylboronic acid (11.9 g, 116 mmol, 1.05 eq), *N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide (25.0 g, 122 mmol) and toluene (95 mL) under argon was heated at reflux in a Dean–Stark apparatus until no more water distilled (3 h, temperature rise of 90 → 118 °C). The disappearance of butylboronic acid also could be followed by $^1$H NMR in DMSO-$d_6$. The mixture was

cooled to 20–25 °C. The solids were collected by filtration and washed with toluene (10 mL). The combined filtrates were concentrated under reduced pressure to afford 31.6 g (100%) of **11** as a colorless oil. $[\alpha]_D$ −114.3 (*c* 1.71, $CHCl_3$). $^1$H NMR ($d_6$-DMSO, 500.13 MHz) $\delta$ 5.39 (s, 2H), 3.03 (s, 6H), 2.85 (s, 6H), 1.36–1.23 (m, 4H), 0.83 (t, $J$ = 7.15 Hz, 3H), 0.78 (t, $J$ = 7.51 Hz, 2H); $^{13}$C NMR ($d_6$-DMSO, 125.77 MHz) $\delta$ 167.83, 75.09, 36.33, 35.29, 25.57, 24.44, 13.65, 9.50 (broad). Anal. Calcd for $C_{12}H_{23}BN_2O_4$: C, 53.35; H, 8.58; N, 10.37. Found: C, 53.25; H, 8.29; N, 10.57.

**Preparation of 3-((1*S*,2*S*)-2-Hydroxymethylcyclopropyl)-1-(toluene-4-sulfonyl)-1*H*-indole-5-carbonitrile (2).** To a solution of $CH_2Cl_2$ (156 mL) and DME (28.8 mL, 277 mmol, 2.50 equiv) under argon at −15 °C was charged a solution of $Et_2Zn$ (28.4 mL, 277 mmol, 2.50 equiv) in toluene (92 mL) while maintaining the temperature between −10 and −15 °C. Diiodomethane (44.6 mL, 553 mmol, 4.98 equiv) was added at a rate to maintain the internal temperature below −8 °C (ca. 50 min). The resulting clear solution was stirred for an additional 10 min at <−12 °C, and a solution of the dioxaborolane ligand **11** (35.9 g, 133 mmol, 1.20 equiv) in $CH_2Cl_2$ (78 mL) was added over 5 min keeping the internal temperature <−5 °C. A solution of (*E*)-3-(3-hydroxyprop-1-enyl)-1-tosyl-1*H*-indole-5-carbonitrile **3** (39.0 g, 111 mmol) in $CH_2Cl_2$ (156 mL) was added dropwise over 15 min keeping the internal temperature <0 °C. The reaction mixture was warmed to 20–25 °C over 30 min and then heated at reflux (48 °C). The reaction mixture was stirred at 48 °C for 5 h. The reaction mixture was cooled to 35 °C, 2-propanol (117 mL) was added, and the reaction mixture stirred for 15 min while cooling to 30 °C. Acetic acid (31.7 mL, 553 mmol, 4.98 equiv) then was added while maintaining the temperature at 35 °C until precipitation was observed. The mixture was cooled to 0–5 °C and stirred for 30 min. The salts were removed by filtration, and the solid was rinsed with $CH_2Cl_2$ (156 mL). The combined filtrate was stirred with $H_2O$ (312 mL) for 15 min. The two layers were separated, and the aqueous layer was back-extracted with $CH_2Cl_2$ (117 mL). The combined organic layers then were washed (agitation for 15 min) with 3 M NaOH (2 × 195 mL) followed by $H_2O$ (195 mL). Charcoal (19.5 g) was added to the organic phase, and the mixture was stirred for 15–20 min, followed by filtration through celite. The cake was rinsed with $CH_2Cl_2$ (156 mL), and the combined organic layers were concentrated by distillation to a volume of 310 mL. The solution was cooled to 55 °C, and heptane (660 mL) was added over 1 h at 50–55 °C. The resulting slurry was cooled to 20–25 °C and stirred for 18 h. The solids were collected by filtration and washed with heptane (2 × 117 mL). The solid was dried in vacuo (5–6 mmHg) at 45–50 °C to constant weight, affording 33.5 g (82.6%, 88.5% ee) of **2** as an off-white solid. Mp: 143.5–144.5 °C. $^1$H NMR ($d_6$-DMSO, 400.13 MHz) $\delta$ 8.29–8.28 (m, 1H), 8.05 (d, $J$ = 8.59 Hz, 1H), 7.90–7.86 (d (br), $J$ = 8.45 Hz, 2H), 7.73 (dd, $J$ = 8.59, 1.76 Hz, 1H), 7.65 (d, $J$ = 1.76 Hz, 1H), 7.38 (d (br), $J$ = 8.45 Hz, 2H), 4.70 (t, $J$ = 5.81 Hz, 1H), 3.59–3.52 (m, 1H), 3.31–3.22 (m, 1H), 2.31 (s, 3H), 1.85–1.79 (m, 1H), 1.23–1.14 (m, 1H), 1.07–1.01 (m, 1H), 0.85–0.79 (m, 1H); $^{13}$C NMR ($d_6$-DMSO, 100.62 MHz) $\delta$ 145.90, 136.11, 133.77, 131.15, 130.37, 127.88, 126.80, 125.23, 125.06, 123.49, 119.24, 114.26, 105.77, 63.81, 24.61, 21.04, 10.95, 10.74. Anal. Calcd for $C_{20}H_{18}N_2O_3S$: C, 65.55; H, 4.95; N, 7.64; S, 8.75. Found: C, 65.62; H, 5.10; N, 7.71; S, 8.39.

**Preparation of 3-((1*S*,2*S*)-2-Dimethylaminomethylcyclopropyl)-1-(toluene-4-sulfonyl)-1*H*-indole-5-carbonitrile (13).** A vessel containing 3-((1*S*,2*S*)-2-hydroxymethylcyclopropyl)-1-(toluene-4-sulfonyl)-1*H*-indole-5-carbonitrile **2** (14.3 g, 39.0 mmol), TEMPO (152 mg, 1.0 mmol, 0.0256 equiv), and sodium bicarbonate (3.61 g, 42.9 mmol, 1.10 equiv) was flushed with argon for 10 min. Methyl acetate (143 mL) and water (37 mL) were added, and the resulting biphasic mixture was cooled to 0–5 °C. A solution of 5% sodium hypochlorite (81.0 g, 54.4 mmol) was charged over 90 min while maintaining the internal temperature at 0–5 °C. The reaction mixture was stirred at 0–5 °C until the HPLC area % of the alcohol **2** was <1% relative to the intermediate aldehyde **11**. The reaction then was quenched by the addition of ethanol (4.75 mL, 82.0 mmol, 2.10 equiv), and the biphasic solution was warmed to 20–25 °C over 30 min. The phases were separated, and the organic layer was passed through a 0.5 $\mu$m filter. The solution was cooled to 0–5 °C, and dimethylamine (39 mL of a 2 M solution in THF, 78.0 mmol) was charged. The reaction mixture was stirred for 10–15 min, and sodium triacetoxyborohydride (10.8 g, 50.7 mmol, 1.30 equiv) was added in one portion. Once the temperature rise had subsided, the reaction mixture was warmed to 20–25 °C. The reaction mixture was held at 20–25 °C for 15 min. The reaction was quenched by the addition of water (72 mL) and stirred for 20 min. The aqueous layer was separated and back extracted with methyl acetate (30 mL). The combined organic layers were washed sequentially with saturated sodium bicarbonate solution (72 mL) and saturated sodium chloride solution (72 mL). The organic phase was concentrated at <50 °C under vacuum to minimal volume. 2-Propanol (170 mL) was charged, and the mixture was distilled at <50 °C under vacuum to a volume of 143 mL. In a separate flask, acetyl chloride (3.05 mL, 42.9 mmol, 1.10 equiv) was charged to 2-propanol (28 mL) at 0 °C over 15 min, followed by warming to 20–25 °C. This HCl/2-propanol solution was charged over 30 min to the amine solution at 50 °C. The resulting suspension was warmed to redissolve the solids by heating to 70–75 °C. The mixture then was cooled to 62–65 °C and held for 30 min, during which time crystallization occurred. The slurry was cooled to 20 °C over >30 min and held for 1 h. The solids were collected by filtration and washed sequentially with 2-propanol (28 mL) and MTBE (28 mL). The solid was dried at 45–50 °C in vacuo to constant weight, affording 13.0 g (77.6%) of **13** as a beige solid. Mp: 211.0–212.0 °C. $^1$H NMR ($d_6$-DMSO, 400.13 MHz) $\delta$ 10.60 (s, 1H), 8.40–8.38 (m, 1H), 8.06 (d, $J$ = 8.59 Hz, 1H), 7.89 (d (br), $J$ = 8.34 Hz, 2H), 7.79 (s (br), 1H), 7.74 (dd, $J$ = 8.59, 1.51 Hz, 1H), 7.39 (d (br), $J$ = 8.34 Hz, 2H), 3.26–3.18 (m, 1H), 3.11–3.03 (m, 1H), 2.75 (s, 6H), 2.31 (s, 3H), 2.20–2.14 (m, 1H), 1.49–1.40 (m, 1H), 1.34–1.27 (m, 1H), 1.13–1.07 (m, 1H); $^{13}$C NMR ($d_6$-DMSO, 100.62 MHz) $\delta$ 145.98, 136.10, 133.71, 130.73, 130.41, 128.02, 126.83, 125.35, 124.06, 123.59, 119.20, 114.29, 105.91, 59.53, 41.45, 21.06, 16.47, 12.86, 12.02. Anal. Calcd for $C_{22}H_{24}ClN_3O_2S \cdot \frac{1}{2}H_2O$: C, 60.19; H, 5.74; N, 9.57; S, 7.30; Cl, 8.08. Found: C, 60.50; H, 5.64; N, 9.44; S, 7.47; Cl, 8.02.

**Preparation of 3-((1*S*,2*S*)-2-Dimethylaminomethylcyclopropyl)-1*H*-indole-5-carbonitrile hydrochloride (1).** A suspension of 3-((1*S*,2*S*)-2-dimethylaminomethylcyclopropyl)-1-(toluene-4-sulfonyl)-1*H*-indole-5-carbonitrile **13** (8.00 g, 18.6 mmol), THF (24 mL), and 50 wt % NaOH aqueous solution (30.2 g, 20.0 mL, 378 mmol, 20.3 equiv) under argon was warmed to 67–70 °C and held for 3 h. The resulting slurry was cooled to 40–45 °C, and water (72 mL) was added while maintaining the temperature <50 °C. The slurry was cooled to 35 °C, and THF (9 mL) and MTBE (32 mL) were added. The mixture then was cooled to 20–25 °C. The phases were separated, and the organic phase was concentrated to 2.5 mL/g (20 mL) by distillation under atmospheric pressure. The mixture was diluted with THF/MTBE (1:1) (80 mL) and concentrated to a volume of 5 mL/g (40 mL). Ethanol (80 mL) was added, and the mixture then was concentrated under atmospheric pressure to 4.5 mL/g (46 mL). THF (32 mL) was added to the batch. In a separate flask, acetyl chloride (1.39 mL, 19.5 mmol, 1.05 equiv) was charged to EtOH (8 mL) at 0–5 °C, and the resulting HCl/EtOH solution was stirred for 30 min. This HCl solution was added to the solution of the free base of **1** at 55–60 °C, followed by addition of MTBE (19 mL) while maintaining the temperature >50 °C. The resulting slurry was cooled to 20–25 °C over 30 min and stirred for 72 h. The solids were collected by filtration and washed with 1:1 THF/MTBE (2 × 16 mL). The cake was dried at 45–50 °C in vacuo to constant weight, affording 3.8 g (74%) of **1** as an off-white solid. Mp: 176.5–177.5 °C. $^1$H NMR ($d_6$-DMSO, 400.13 MHz) $\delta$ 11.61 (s, 1H), 10.87 (s (br), 1H), 8.25 (s, 1H), 7.49 (d, $J$ = 8.59 Hz, 1H), 7.41 (dd, $J$ = 8.59, 1.51 Hz, 1H), 7.32 (d, $J$ = 1.51 Hz, 1H), 3.24–3.07 (m, 2H), 2.82–2.68 (m, 6H), 2.20–2.13 (m, 1H), 1.37–1.27 (m, 1H), 1.17–1.10 (m, 1H), 1.06–1.00 (m, 1H); $^{13}$C NMR ($d_6$-DMSO, 125.77 MHz) $\delta$ 137.88, 127.08, 124.30, 123.84, 123.76, 120.83, 116.22, 112.70, 100.37, 59.73, 41.52, 41.34, 16.02, 12.83, 12.39. Anal. Calcd for $C_{15}H_{18}ClN_3$: C, 65.32; H, 6.57; N, 15.23; Cl, 12.85. Found: C, 65.03; H, 6.62; N, 15.23; Cl, 12.92.

## Acknowledgment

We thank the staff of Analytical R & D, Bristol-Myers Squibb, for their valuable support during the course of this work. We also thank Drs. David Kronenthal, James Sherbine, Edward Delaney, Melanie Miller, Richard Mueller, Jaan Pesti, and Robert Discordia for helpful discussions during the preparation of the manuscript.

Received for review June 5, 2007.

OP700126W