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Kilogram Synthesis of a Selective Serotonin Reuptake Inhibitor

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Abstract:

Process development of a selective serotonin reuptake inhibitor (1) is described. The synthesis features Nishiyama catalyst-mediated asymmetric cyclopropanation of vinyl indole 2 with ethyldiazoacetate to install the *trans*-disubstituted cyclopropane. The active pharmaceutical ingredient (1) was prepared in 13 chemical steps with 9 isolations and proceeded in an overall yield of 34%.

Introduction

The neurotransmitter 5-hydroxytryptamine (serotonin) plays many key physiological roles,[1] and not surprisingly, selective serotonin reuptake inhibitors (SSRIs) are an important class of drugs that have widespread application.[2] One approach to the optimization of the activity of an SSRI is the derivatization of an indole core through incorporation of a conformationally restricted side chain.[3] Recently, a neuroscience drug candidate (**1a**, Figure 1) fitting this description entered development and required material for toxicological and first-in-human studies. This paper details the development of an expedient and efficient chemical route that showcased a catalytic asymmetric cyclopropanation reaction and the production of kilogram quantities of the maleate salt **1a**, as well as the corresponding HCl salt **1b**.

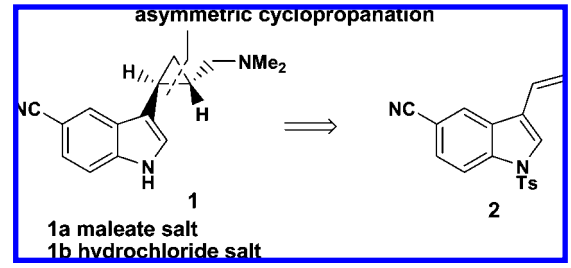
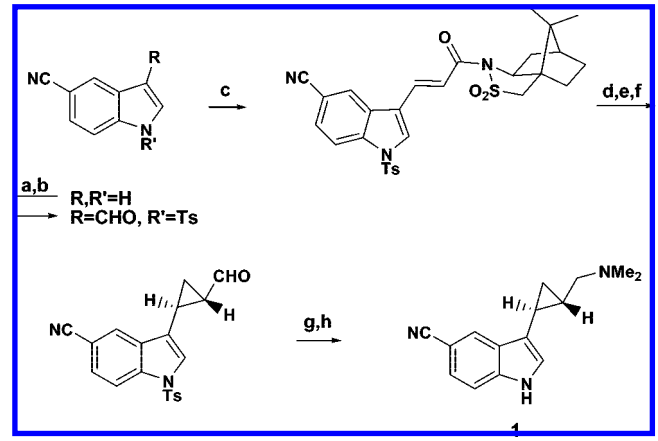


Figure 1. **Asymmetric cyclopropanation approach to 1a and 1b.**

Results and Discussions

The original synthesis[3h,4] of **1** (Scheme 1) by our Discovery colleagues provided the first 40 g required for early toxicology studies. This route involved cyclopropanation of a chiral enamide through the use of an expensive chiral auxiliary, employed hazardous reagents including diazomethane, sodium hydride, and lithium aluminum hydride, whose use at scale is preferred to be limited, and required chromatographic purification of several intermediates.

Scheme 1. **Discovery synthesis of 1**[a]



[a] Reagents and conditions: (a) $POCl_3$, DMF (75%); (b) TsCl, Et_3N (65%); (c) NaH, diethyl 2-(*N*-(1*R*)-(+)-2,10-camphorsultam)-2-oxoethylphosphonate (58%); (d) CH_2N_2 (62%); (e) LAH, THF (81%); (f) $(COCl)_2$, DMSO; (g) $HNMe_2$, $NaBH(OAc)_3$; (h) NaOH, EtOH (77%, 3 steps).

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(1) (a) Nagatomo, T.; Rashid, M.; Muntasir, H. A.; Komiyama, T. *Pharmacol. Ther.* **2004**, *104*, 59. (b) Middlemiss, D. N.; Price, G. W.; Watson, J. M. *Curr. Opin. Pharmacol.* **2002**, *2*, 18.

(2) (a) Currently available drugs in this class include Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, and Sertraline. Malinin, A.; Oshrine, B.; Serebruany, V. *Med. Hypothesis* **2004**, *63*, 103. (b) Chen, J.; Mabjeesh, H.; Greenstein, A. *Urology* **2003**, *61*, 197. (c) Dimmock, P. W.; Wyatt, K. M.; Jones, P. W.; Shaughn O'Brien, P. M. *Lancet* **2000**, *356*, 1131. (d) Moore, K. *Int. J. Gynecol. Obstet.* **2004**, *86* (1), S53. (e) Pogarell, O.; Poepperl, G.; Mulert, C.; Hamann, C.; Sadowsky, N.; Riedel, M.; Moeller, H.-J.; Hegerl, U.; Tatsch, K *Eur. Neuropsychopharmacol.* **2005**, *15*, 521–524.

(3) (a) King, H.; DMeng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Dedong, W.; Gao, Q.; Macor, J. E *Org. Lett.* **2005**, *7*, 3437. (b) Taylor, E. W.; Nikam, S.; Weck, B.; Martin, A.; Nelson, D. *Life Sci.* **1987**, *41*, 1961. (c) Vangveravong, S.; Kanthasamy, A.; Lucaites, V. L.; Nelson, D. L.; Nichols, D. E. *J. Med. Chem.* **1998**, *41*, 4995. (d) Ezquerra, J.; Pedregal, C.; Lamas, C.; Pastor, A.; Alvarez, P.; Vaquero, J. J. *Tetrahedron Lett.* **1996**, *37*, 683. (e) Macor, J. E.; Blank, D. H.; Post, R. J. *Tetrahedron Lett.* **1994**, *35*, 45. (f) Macor, J. E.; Blank, D. H.; Ryan, K.; Post, R. J. *Synthesis* **1997**, 443. (g) Schmitz, W. D.; Denhart, D. J.; Brenner, A. B.; Ditta, J. L.; Mattson, R. J.; Mattson, G. K.; Molski, T. F.; Macor, J. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1619. (h) Mattson, R. J.; Catt, J. D.; Denhart, D. J.; Deskus, J. A.; Ditta, J. L.; Higgins, M. A.; Marcin, L. R.; Sloan, C. P.; Beno, B. R.; Gao, Q.; Cunningham, M. A.; Mattson, G. K.; Molski, T. F.; Taber, M. T.; Lodge, N. J. *J. Med. Chem.* **2005**, *48*, 6023.

(4) (a) 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. (Bristol-Myers Squibb) Cyclopropylindole derivatives as selective serotonin reuptake inhibitors, U.S. patent US6777437 B2, Aug 17, **2004**. (b) Mattson, R. J. (Bristol-Myers Squibb) Cyclopropylindole derivatives as selective serotonin reuptake inhibitors, U.S. patent US6822100 B2, Nov 23, **2004**. (c) 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. (Bristol-Myers Squibb) Cyclopropylindole derivatives as selective serotonin reuptake inhibitors, PCT Int. Appl. WO 0279152, 2002.

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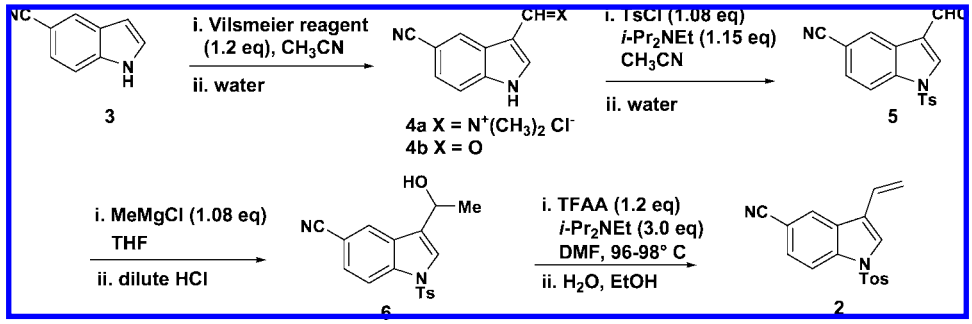
Scheme 2. **Synthesis of vinyl indole 2**



Drawing on prior Process group experience,[5] an alternative route to **1a** involving catalytic asymmetric cyclopropanation of vinyl indole **2** with ethyl diazoacetate was considered (Figure 1). The feasibility of this approach was demonstrated by our Discovery colleagues.[6] In this paper we present details of the development and plant-scale implementation of this route, which enabled production of kilogram quantities of **1a**.

Preparation of the Vinyl Indole Cyclopropanation Substrate. In developing a scalable route to **1a**, the Discovery synthesis of vinyl indole **2**[6] was modified to four direct-drop processes (Scheme 2).[7] Initial development efforts toward a scalable preparation of 3-formyl-5-cyanoindole (**4b**) showed that acetonitrile was the most favorable solvent from the standpoint of operability (facile stirring) and acceptable product quality. Addition of **3** to a mixture of commercially prepared Vilsmeier reagent and acetonitrile (7 mL/g)[8] was exothermic (65.27 kJ/kg solution), but the heat evolution could be controlled by adjusting the addition rate. Upon reaction completion, water (16–17 mL/g) was added, and warming to 70 °C for 1 h facilitated hydrolysis of the iminium salt **4a**. During cooling, aldehyde **4b** crystallized spontaneously and was isolated in high yield with only minimal loss (4%) to the mother liquor. Upon scale-up, this procedure gave excellent yield, reproducibility, and purity (5.0 kg, 95% yield, 99.2–99.7 HPLC area % purity).

After a thorough solvent screen, acetonitrile was chosen for tosylation of indole **4b**. Addition of diisopropylethylamine (*i*-Pr_2NEt) to an acetonitrile slurry of **4b** and *p*-TsCl led to a mild, exothermic reaction (temperature increase from 23 to 30 °C) and dissolution of solids. As the reaction proceeded, **5** precipitated as a crystalline solid. Addition of water (5 mL/g, final concentration 17 mL/g) led to increased recovery to 97–98% yield (>99 HPLC area % purity) on laboratory scale. This procedure successfully produced *N*-tosyl indole **5** on approximately 3.5 kg scale in 96–99% yield (99.3–99.5 HPLC area % purity).

Commercially available methyl Grignard reagents were evaluated for their ability to effect the transformation of aldehyde **5** to indolyl alcohol **6**. High conversions were observed with both 1 M methylmagnesium bromide and chloride in THF. Methylmagnesium iodide gave low conversion and resulted in poor product quality. Reactions in dimethoxyethane gave less than 5% conversion. Optimized conditions for the production of alcohol **6** entailed the addition of methylmagnesium chloride in THF (1.1 equiv) to a solution of **5** at 15–30 °C. No extractive workup was needed as addition of dilute hydrochloric acid to the reaction medium (total volume 25 mL/g) gave rise to a coarse solid that converted into fine crystalline material in 1 h with stirring. More extensive aging of the slurry was of further benefit, as this led to lower levels of residual magnesium in isolated product **6**. On kilogram scale (6.4–6.5 kg) the yield ranged between 91% and 95% (95.5–97.6 HPLC area % purity).

Indolyl alcohol **6** underwent dehydration to vinyl indole **2** in the presence of catalytic *p*-toluenesulfonic acid upon warming in toluene.[9] A competing side reaction, however, led to significant levels of a dimeric impurity. ^{1}H NMR analysis suggested the impurity to be **7** (Figure 2), the product of reaction between vinyl indole and a putative intermediate carbocation. In looking for an alternate dehydration process, we found that heating the trifluoroacetyl derivative of **6** with excess *i*-Pr_2NEt also gave facile conversion to vinyl indole **2**. Although this reaction proceeded well in a variety of solvents, a new dimeric impurity was observed. ^{1}H NMR evidence suggested the new dimer to be one or more stereoisomeric Diels–Alder adducts (**8**, Figure 2). Selection of suitable workup conditions (vide infra) minimized formation of these side products.

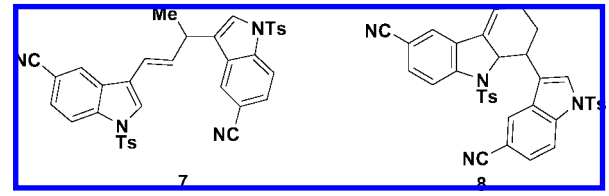


Figure 2. **Impurities from the dehydration of vinyl alcohol 6.**

As would be expected, the rate of dimer formation increased with increasing product concentration. Timely analytical assessment and the ability to effect rapid temperature changes on scale became important. To minimize dimer formation, kilogram-scale preparation of vinyl indole **2** entailed controlled addition of trifluoroacetic anhydride (TFAA) to a solution of **6** and *i*-Pr_2NEt in DMF (5 L/kg) while maintaining the batch temperature below 25 °C. React-IR monitoring experiments

(5) Similar disconnection was employed during multi-kilogram scale preparation of a melatonin antagonist. Simpson, J. H.; Godfrey, J.; Fox, R.; Kotnis, A.; Kacsur, D. J.; Hamm, J.; Totleben, M.; Rosso, V.; Mueller, R.; Delaney, E.; Deshpande, R. P. *Tetrahedron Asymmetry* **2003**, *14*, 3569.

(6) Marcin, L. R.; Denhart, D. J.; Mattson, R. J. *Org. Lett.* **2005**, *7*, 2651.

(7) The Drug Discovery conversion of aldehyde **5** to vinyl indole **2** involved Wittig olefination. Although the Wittig chemistry was effective, two-step methyl Grignard addition followed by dehydration was found to be operationally simpler.

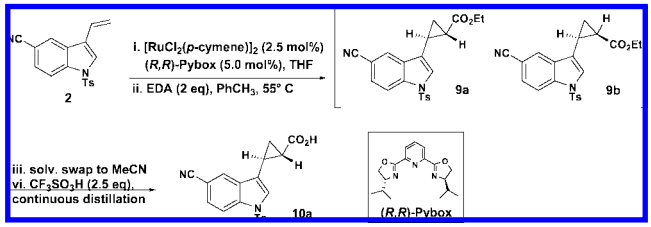
(8) mL/g refers to milliliters of solvent per grams of substrate.

(9) Sundberg, R. J.; Amat, M.; Fernando, A. M. *J. Org. Chem.* **1987**, *52* (14), 3151.

performed prior to scale-up demonstrated reaction of TFAA with alcohol **6** was nearly instantaneous. The solution subsequently was heated to 96–99 °C to effect elimination. Upon completion,[10] water was added to quickly lower the batch temperature and thus suppressed the competing dimerization process. Incorporation of ethanol during cooling enabled a controlled crystallization. Further cooling to 0 °C allowed for isolation of vinyl indole **2** in good yield containing less than 2% of **8**. Glass plant implementation of this process was demonstrated on approximately 7.7 kg scale (85% yield; 97.8 HPLC area % purity).

Cyclopropanation and Hydrolysis. Prior successful large-scale cyclopropanation of a styrene derivative[5] using Nishiyama's catalyst[11] and ethyldiazoacetate (EDA) suggested this system also would be suitable for cyclopropanation of **2** (Scheme 3).[12] Good enantio- and diasteroselectivities for

Scheme 3. **Asymmetric cyclopropanation and chemoselective ester hydrolysis**



cyclopropanation of **2** with the Nishiyama catalyst (enantiomeric ratio (er) = 93:7, diastereomeric ratio (dr) = 9.2:1)[6] and our group's prior experience in preparing and using commercially available (*R*)-pybox ligand on kilogram scale,[5] coupled with the need to advance the active pharmaceutical ingredient (API) quickly to enable toxicity studies, encouraged us to focus development work on this catalytic system in lieu of initiating a catalyst screen.While initial development work was performed with isolated Nishiyama catalyst, we also investigated in situ catalyst generation. This approach allowed us to circumvent the use of ethylene gas required for isolation of the stable catalyst and also improved cycle times. In addition, the in situ method avoided loss of catalyst to mother liquors. As such, combination of (*R*)-Pybox and dichloro(*p*-cymene)ruthenium(II) dimer in THF followed by addition of **2** and heating to 55 °C gave a rich purple solution similar to that seen when using isolated Nishiyama catalyst. Addition of a 2 M solution of freshly prepared EDA in toluene[13] to the catalyst/substrate solution at 55–65 °C gave predominantly *trans*-cyclopropane **9a** (dr = 10:1, er = 93:7). Although the reaction could be performed in a variety of solvents, with the notable exception of acetonitrile,[14] THF was selected because of favorable azeotropic properties. Although higher temperatures led to faster reaction rates with minimal effect on the enantioselectivity, concerns over the high-temperature stability of EDA[15] prompted us to set the operating temperature at 55–65 °C.

During scale-up, a reaction sample was analyzed soon after the EDA addition had begun to ensure the in situ generated catalyst was active. This procedure was followed to help prevent a build-up of EDA in the reactor in the event the catalyst preparation failed. With the assurance that EDA was being consumed, the remaining portion was then added over 8 h. Cyclopropyl ester **9a** was produced as a 10:1 mixture of *trans*/*cis*-cyclopropane isomers, in agreement with development runs. Chiral HPLC analysis of the crude mixture indicated an enantiomeric excess (ee) of 86% for the major *trans*-isomer **9a**.

While the cyclopropanation proceeded well and with good selectivity, the resulting cyclopropylester **9a** proved difficult to crystallize without chromatographic removal of the catalyst. All attempts to isolate **9a** from the reaction mixture gave poor yields and highly colored material. Owing to the difficulty in procuring clean ester **9a** and on the basis of our prior experience with related chemistry,[5,11d,13f] we sought to develop a process wherein cyclopropanation followed by ester hydrolysis would give acid **10a** directly. A consequence of this work was the discovery that hydrolysis of the desired *trans*-ester under basic conditions was faster than hydrolysis of the undesired minor *cis*-ester. However, this process was complicated by competing hydration of the cyano group, as well as detosylation. Phase transfer

(10) A 4 min HPLC method was developed to minimize exposure of the product to the reaction conditions.

(11) (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.

(12) (a) Subsequent to the work described here, significant advances in the field of cyclopropanation chemistry were reported by many research groups. For representative examples, see: Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B *Chem. Rev.* **2003**, *103*, 977. (b) Liao, W.-W.; Li, K.; Tang, Y *J. Am. Chem. Soc.* **2003**, *125*, 13030. (c) Long, J.; Yuan, Y.; Shi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13632. (d) Aggarwal, V. K.; Fang, G. Y.; Meek, G. *Org. Lett.* **2003**, *5*, 4417. (e) Risatti, C. A.; Taylor, R. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6671. (f) Moreau, B.; Charette, A. *J. Am. Chem. Soc.* **2005**, *127*, 18014. (g) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (h) Bykowski, B.; Wu, K.-H.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 16038. (i) Thompson, J. L.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 6090. (j) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886.

(13) (a) Kotnis, A. S.; Simpson, J. H.; Deshpande, R. P.; Kacsur, D. J.; Hamm, J.; Kodersha, G.; Merkl,W.; Domina, D.; Wang, S. S. Y. Manuscript in preparation. (b) Clark, J. D.; Shah, A. S.; Peterson, J. C.; Patelis, L.; Kersten, R. J.; Heemskerk, A. H. *Thermochim. Acta* **2002**, *386*, 73. (c) Clark, J. D.; Shah, A. S.; Peterson, J. C.; Patelis, L.; Kersten, R. J.; Heemskerk, A. H.; Grogan, M.; Camden, S. *Thermochim. Acta* **2002**, *386*, 65. (d) Armstrong, R. K. *J. Org. Chem.* **1996**, *31*, 618. (e) Searle, N. E. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 424. (f) DelMonte, A. J.; Dowdy, E. D.; Watson, D. J. Development of Transition Metal-Mediated Cyclopropanation Reactions. In *Topics in Organometallic Chemistry*; Larsen, R. D., Ed.; Springer: Berlin, New York, 2004; Vol. 6, Organometallics in Process Chemistry; pp 97−122.

(14) Results from the solvent screen at 30 mL/g with the slow addition (16 h) of 2.2 M EDA intoluene are as follows: in THF (50–60 °C), 86–89% ee with 9.7–10.8:1 *trans*:*cis* ratio with 91–99% conversion; in ethyl acetate (50 °C), 87.1% ee with 9.7:1 *trans*:*cis* ratio with 98.6% conversion; in toluene (50 °C), 88.2% ee with 11.4:1 *trans*:*cis* ratio and 95.9% conversion; in acetone (reflux), 82.6% ee with 10.7:1 *trans*:*cis* ratio and 87.8% conversion; in CH_2Cl_2 (reflux), 92.4% ee with 13.1:1 *trans*:*cis* ratio and 56.5% conversion; in MTBE (50 °C), 87.6% ee with 12.9:1 *trans*:*cis* ratio and >99% conversion; in methylisobutylketone (50 °C), 86.3% ee with 14.7:1 *trans*:*cis* ratio and 82.7% conversion; in butylacetate (50 °C), 85.6% ee with 11.6:1 *trans*:*cis* ratio and 98.7% conversion; in triflurotouluene (50 °C), 86.3% ee (*trans*:*cis* ratio ND) and 67.9% conversion; in acetonitrile no conversion was achieved, most likely due to complexation of acetonitrile with ruthenium (See: Cadierno, V.; Gamasa, M. P.; Gimeno, J.; Inglesias, L.; Garcia-Granda, S. *Inorg. Chem.* **1999**, *38*, 2874.

(15) Clark, J. D.; Shah, A. S.; Peterson, J. C. *Thermochim. Acta* **2002**, *177*, 392–393.

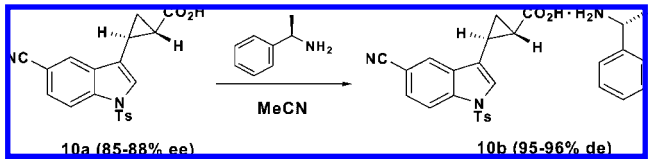
catalysis only accentuated the rates of these side reactions. Typical yields of **10a** using these protocols ranged from 30% to 50%.

Alternatively, hydrolysis under acidic conditions at high temperature gave a much cleaner reaction profile with no detosylation and minimal hydration of the cyano group. Significantly, the *trans*-isomer still hydrolyzed 3–4 times faster than the *cis*-ester. This selectivity, as well as the difference in solubility between the *cis*-ester and *trans*-acid ultimately led to an efficient process for separating the undesired *cis*-ester from the product. After screening various acids, triflic acid was identified as the most efficient for catalyzing the hydrolysis. Crystallization development work led to the identification of aqueous acetonitrile for isolation of **10a**. Additionally, toluene was found to inhibit the hydrolysis and lower the recovery of acid **10a**. Thus, upon completion of the cyclopropanation, water (3 mL/g) was added, and most of the toluene and THF were removed by azeotropic distillation. The displaced volume was replaced with acetonitrile. Upon completion of the partial solvent exchange, hydrolysis was then conducted with triflic acid (2.5 equiv) in acetonitrile/water (3–5:1 v/v). In order to drive the hydrolysis to completion, the byproduct ethyl alcohol was removed continuously by distillation. Acetonitrile and water were added throughout the distillation to maintain a constant volume. This protocol successfully drove the hydrolysis reaction to 97–98% completion. Acid **10a** was crystallized by the introduction of additional water and was isolated by simple filtration.

Scale-up of the cyclopropanation/hydrolysis was conducted in two separate batches (7.6 and 7.8 kg), providing acid **10a** in crude yields of 93% and 100% (91.0 and 83.8 HPLC area % purity, 85.4% and 87.6% ee, respectively). The ratio of *trans*-acid **10a** to *cis*-ester **9b** increased from 10:1 in the reaction mass to 40–150:1 in isolated acid **10a**.

Partial Resolution of Acid 10a. The intermediacy of acid **10a** provided an opportunity to enhance the enantiopurity through selective crystallization of a diastereomeric salt (Scheme 4). Using the bottom-up strategy and parallel crystallization

Scheme 4. **Augmentation of chiral purity via resolution of 10a**



techniques,[16] (*R*)-(+)-α-methylbenzylamine was identified as the preferred base, as it gave salt **10b** in high analytical purity (>98 HPLC area % purity) and diastereomeric purity (95–96% de). Various solvent systems were evaluated, with acetonitrile offering the best combination of operability (efficient stirring), yield (82–84%), analytical purity (>98 HPLC area % purity), and de (95–96%). Isopropyl alcohol yielded **10b** having good de (96%) but poor operability, whereas ethyl and *n*-butyl acetates produced **10b** of lower de (94%), and THF/heptane gave good de (97%) but lower overall purity (96 HPLC area % purity). Filtration of an acetonitrile solution of **10a** through a 10 μm filter prior to addition of (*R*)-(+)-α-methylbenzylamine proved beneficial by lowering residual ruthenium from the cyclopropanation to <310 ppm (initial value >3100 ppm). The resolution was performed in two batches (6.4 and 9.4 kg), providing salt **10b** in 56–64% yield, 97.8–98.6 HPLC area % purity, and 95–96% de.

Reduction of Acid 10 to Alcohol 11. Direct reduction of the α-methylbenzylamine salt **10b** with borane−THF complex (BH_3·THF) led to unacceptable levels of nitrile reduction products. Reduction of the free acid **10a**, on the other hand, was highly selective when carried out at sufficiently low temperature (below 10 °C). Solutions of free acid **10a** could be produced by suspending salt **10b** in *tert*-butyl methyl ether and THF, washing with sulfuric acid, and azeotropic drying. The liberated acid solution was then filtered through a 5 μm filter to remove insoluble ruthenium residues prior to reduction. Reaction of solutions of **10a** with BH_3·THF (1.15 equiv, 3.45 hydride equiv versus 3.00 theoretical requirement) typically gave high conversion with less than 2% competing nitrile reduction. The amine byproduct stemming from nitrile reduction was purged to a great extent through precipitation of the alcohol **11** from solvent systems containing dilute hydrochloric acid. Ultimately the alcohol was obtained in 96% yield with greater than 98 HPLC area % purity.

Calorimetry studies showed two distinct exothermic events during the reaction sequence (Figure 3).[17] The first, associated with acid deprotonation, was easily controlled by modulation of the addition rate of the reagent. Nearly all of the hydrogen offgassing was observed during this initial phase. The second exotherm, associated with reduction of the carboxylate, showed an induction period and peak heat flow extending beyond the completion of the reagent addition. This had significant safety ramifications and required careful consideration before initiating large scale processing.

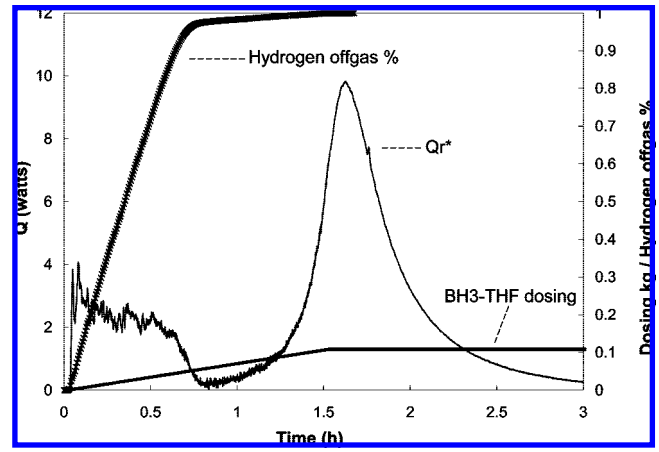


Figure 3. **Strong secondary exotherm attributable to carboxylate reduction. * Qr = Heat of reaction.**

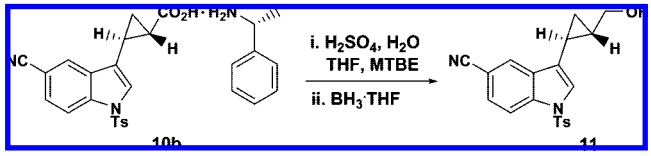
Efforts to conduct the reaction at elevated temperature and push the reduction kinetics into an addition-controlled regime were unsuccessful as a result of decreased selectivity for carboxylate versus nitrile reduction. The low-temperature

(16) Chen, C.-K.; Singh, A. A. *Org. Process Res. Dev.* **2001**, *5*, 508.

(17) For a detailed analysis of a similar system see: *Org. Process Res. Dev.* **2004**, *6*, 1072–1075.

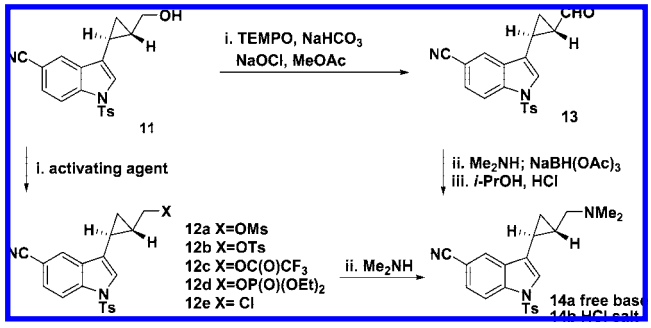
procedure adopted on scale involved a combination of modulation of the borane addition rate and active cooling to maintain the batch temperature below 10 °C throughout the reduction sequence. The modulated borane addition permitted careful reaction temperature monitoring and the opportunity to immediately halt the dosing in the event an unexpected temperature increase occurred. Additional safety measures implemented in the glass plant included the low-temperature transport and storage of BH_3·THF solution,[18] as well as oxygen monitoring in the reactor headspace. The procedure was conducted on two batches (5.4 and 6.4 kg) and provided alcohol **11** (Scheme 5) in 90–96% yield, 98.3 HPLC area % purity, and 96% ee. The ruthenium levels for both batches were below 85 ppm.

Scheme 5. **Borane reduction of carboxylic acid 10**



Transformation of Alcohol 11 to Amine 14. Early work dedicated to conversion of alcohol **11** to final intermediate **14** entailed transformation of the hydroxyl group in **11** to a leaving group, followed by substitution by dimethylamine (Scheme 6). Analogs possessing a variety of leaving groups including mesylate, tosylate, trifluoroacetate, and phosphate (**12a–12d**) were screened. Of these, only the mesylate could be prepared reproducibly, although it was prone to decomposition. In contrast, the chloride **12e** could be prepared cleanly using Vilsmeier reagent in DMF. Chloride displacement by dimethylamine, however, was slow. Exposure to >12 equiv of dimethylamine at 60 °C for 40 h gave incomplete conversion. Addition of sodium iodide led to complete conversion in 20–24 h at 60 °C; however, amine **14** proved difficult to isolate under these reaction conditions. As a result, alternatives to the displacement chemistry were investigated.

Scheme 6. **Conversion of alcohol 11 to amine 14**



Free base **14a** had been prepared previously by our Discovery colleagues[3h,4] via Swern oxidation of **11** followed by reductive amination. As an alternative to Swern conditions, oxidation with TEMPO[19a] was explored. Optimal conditions consisted of combining **11** with sodium bicarbonate (1.1 equiv), TEMPO (0.025 equiv), and NaOCl (1.2 equiv) in water/THF, water/CH_2Cl_2, or water/methyl acetate. Subsequent addition of dimethylamine rapidly afforded the corresponding iminium species, and reduction (1.3 equiv of sodium triacetoxyborohydride) typically was complete within 30 min.

Sodium hypochlorite lots examined during laboratory development varied widely in potency. Due to this variability, the titre of the material to be used during the campaign was determined immediately prior to use.[20]

The primary impurity formed in the oxidation/reductive amination sequence was carboxylic acid **10a**, which could be minimized by operating under oxygen-free conditions.[19b] If precautions to eliminate oxygen were not taken, the amount of acid **10a** formed was as high as 10%. Upon scale-up, the amount of **10a** formed was less than 1%. A slow addition rate of the bleach also was crucial, as more rapid addition led to the competing formation of unidentifed side-products.

In the reductive amination, development work indicated that dichloromethane or methyl acetate performed well. Methyl acetate ultimately was selected as dichloromethane led to alkylation of the amine. Methanol initially was selected as a suitable solvent for crystallization of the free-base **14a**; however, the crystalline solid obtained was a solvate, which melted readily upon drying under vacuum, even at 20–25 °C. To overcome this problem, a study to identify a suitable salt of **14a** was conducted. This work revealed that HCl salt **14b** could be crystallized from 2-propanol in high recovery. Following this lead, solvent exchange to 2-propanol after workup of the reductive amination, followed by addition of a solution of HCl in 2-propanol (formed by adding acetyl chloride to 2-propanol) produced crystalline **14b** in high yield (88%) and purity (99.8 HPLC area % purity). This process also was effective in further reducing the ruthenium content of the batch from 80 ppm in **11** to 30–40 ppm in **14b**. Such ruthenium levels, however, were not acceptable for the final intermediate. To address this issue, we tested various ZetaCarbon pads[21] and Smopex resins.[22] ZetaR53SP was found to be the most effective for lowering residual ruthenium levels (80 to 7 ppm), while also minimizing product adsorption to the filter media (3%).

The process for converting alcohol **11** to hydrochloride salt **14b** was demonstrated on 3.5 and 4.5 kg scale (75 and 88% yield; 99.7–99.8 HPLC area % purity). The Zeta filtration method also scaled up effectively, as the final ruthenium content was <10 ppm (initial values 30 and 83 ppm).

Detosylation/Maleate Salt Formation. The procedure used by the Discovery team[3h,4] for conversion of final intermediate **14a** to **1a** involved detosylation with sodium hydroxide, an extractive workup and wash sequence, and maleate salt formation. Development team goals for this process included reducing the number of operations and enhancing the enantiomeric excess (95.6% ee in the final intermediate **14**).

Work on detosylation of final intermediate **14b** and conversion to the maleate salt **1a** began with investigation of nucleophile/solvent combinations. Using parallel screening

(18) *Chem. Eng. News* **2002**, *80*, 7.
(19) (a) Anelli, P. L.; Biffi, F. M.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559. (b) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Tetrahedron* **1995**, *51*, 8023.
(20) Jeffery, G. H.; Bassett, J.; Mendham, J.; Denney, R. C. *Vogel's Textbook of Quantitative Chemical Analysis*, 5th ed.; Prentice Hall: Singapore, 1989; pp 396–397..
(21) http://www.cuno.com/labstore/dfs_zetacarbon.shtml.
(22) http://www.jmcatalysts.com/pct/marketshome.asp?marketid=69&id=250.

techniques, compound **14b** was subjected to a wide range of nucleophiles (metal alkoxides, silanolates, carbonates, tetrabutylammonium fluoride, and others), in an array of protic, ethereal, and polar aprotic solvents. Notably, conditions utilizing THF as solvent or cosolvent often led to clean detosylation. The screen identified metal alkoxides and silanolates as effective reagents for rapid detosylation (1–2 h, 40–60 °C) in several solvents including alcohols, THF, and combinations thereof. Investigations later focused on alcohol-free systems, in order to eliminate the possibility of forming the toxic alkyl tosylate byproduct.

This work revealed that treatment of **14b** with 10 N NaOH in THF in various volume ratios led to complete detosylation in 4 h at 65 °C. Final conditions called for use of 50 wt % NaOH (2.5 mL/g **14b**) in THF (3.0 mL/g **14b**) at 65–68 °C for 3–4 h. Detosylated free base **1** could be separated efficiently from the byproduct sodium tosylate via phase split, after dilution of the reaction mass with water, THF, and MTBE (volume ratio 7.5:1:3.3). Typical product loss to the aqueous portion was <6%, and residual sodium tosylate in the organic phase was <2%.

Higher yields of **1a** were obtained through crystallization from a dry organic phase having Karl Fischer (KF) values of <0.35% (w/w). KF values taken of the organic phase immediately after phase separation ranged from 3.3% to 3.7% (w/w). To achieve the desired KF value, azeotropic removal of water was effected by using dry 1:1 THF/MTBE mixtures and concentrating to approximately 2.5 mL/g of input (**14b**) until the KF was <0.8% (w/w). Upon meeting the KF criterion, the concentrated batch was charged with THF (KF after charge <0.35%) to a volume corresponding to 7 mL/g of input (**14b**). Conveniently, as the drying process progressed, any remaining sodium tosylate precipitated from the mixture and could be removed efficiently by filtration. Addition of a solution of maleic acid (1.1 equiv) in THF afforded a slurry of **1a** which filtered well. Two THF/MTBE (1:1 v/v) rinses provided maleate salt **1a** in >99.5 HPLC area % purity and >98% ee.

Two kilogram-scale reactions (1.8 and 1.7 kg **14b**) were conducted in a 40 L Hastelloy vessel, compatible with hot 50 wt % NaOH. Upon reaction completion, the thick reaction mass was diluted with water (9 L/kg), THF (1.1 L/kg), and MTBE (2.9 L/kg) and transferred to a borosilicate 50 L vessel. Phase separation, distillative drying, filtration through 10 and 0.5 μm polish filters in series, and maleic acid addition/crystallization proceeded similarly in the first kilogram batch as it did in the laboratory with four significant exceptions. First, the final MTBE concentration during crystallization was higher than in typical laboratory runs (12% versus 6% by GC analysis). Additionally, aspects relating to product quality including particle size and enantiopurity were different from those of development runs. The particle size in the first batch was larger than observed in laboratory runs (D_{90} = 264 μm, as opposed to 31 μm), and the ee was lower than expected (97% versus >98% in laboratory runs). Finally, during the first batch, rapid, uncontrolled crystallization occurred 2 h subsequent to completion of the maleic acid addition, whereas in laboratory runs crystallization consistently occurred during the maleic acid addition. This run generated 1.24 kg of **1b** (83.3% yield) with 99.1 HPLC area % purity.

The deviations in the first kilogram batch from the laboratory runs were addressed during a second batch through modification of the crystallization protocol. To better control the final MTBE content, the distillation end points were modified to depend on internal batch volume instead of distillate volume. Additionally, a seeding protocol was incorporated to control the onset of crystallization and to improve particle size and ee. After implementing these modifications, the final MTBE content of the slurry was 5.7% and the isolated product had a D_{90} value of 41 μm. This second batch produced 1.1 kg of **1b** (77% yield) with 99.5 HPLC area % purity and 98% ee.

HCl Salt (1b) Development. Subsequent to the delivery described above, an alternate form of API **1** possessing different pharmacokinetic properties was desired. After extensive screening, the HCl salt (**1b**) was identified. Paramount to the efficient crystallization of the HCl salt was the method of its preparation. HCl introduced as an aqueous solution produced a hygroscopic foam. Alternatively, addition of anhydrous HCl in MTBE (prepared by reaction of oxalyl chloride with 1 equiv of water or acetyl chloride and 1 equiv of methanol) to an MTBE solution of free base generated a fluffy white solid. Upon prolonged stirring this amorphous suspension transformed into crystalline material. As crystalline material had now been isolated, all future experiments could be seeded, avoiding the slow transition from amorphous to crystalline material. HCl prepared from acetyl chloride and ethanol performed well under these conditions and was used for all subsequent experiments.

We anticipated performing the detosylation of **14b** as it was previously conducted and modifying the workup and crystallization to prepare the HCl salt. Crystallization development indicated MTBE was a suitable solvent, providing good product recovery and augmentation of the enantiomeric excess. Further examination indicated higher ee values could be obtained by incorporation of ethanol in the crystallization system. Use of 3–8 mL ethanol per gram of **14b** was critical, as smaller charges resulted in gummy material and larger charges resulted in unacceptable product losses to the mother liquor. To provide additional control over the crystallization, seeds were added to the batch prior to adding the HCl.

Two batches (1.8 kg each) of **14b** were converted successfully to HCl salt **1b** using this protocol. The phase split was conducted as before, but the distillation procedure was changed in that only MTBE (as opposed to 1:1 THF/MTBE) was used to replenish the volume distilled. Polish filtration to remove residual sodium tosylate provided a clear MTBE solution. To this was added a slurry of seeds (**1b**, 6–8 g) in MTBE, followed by a solution of HCl in ethanol, prepared by the addition of acetyl chloride to ethanol at <10 °C. To ensure a controlled addition of HCl to the free base, a metering pump calibrated at <50 mL/min was used for the addition of approximately 8 L of HCl solution. Crystallization occurred gradually after about 20% of the HCl was charged. After overnight stirring, salt **1b** was collected by filtration under nitrogen. The two batches provided **1b** in 88–89% yield, with 99.9 HPLC area % purity and 98.5–98.6% ee.

Conclusions

In summary, we have described an efficient (9 isolations), 13-step synthesis of **1**. All key intermediates were crystalline, and no special processing equipment was needed, ensuring maximum manufacturing site flexibility. In situ preparation of the Nishiyama catalyst for the cyclopropanation eliminated the use of ethylene gas, thereby greatly simplifying the process and improving safety. A simple chemical resolution with the inexpensive chiral amine (*R*)-(+)-α-methylbenzylamine was developed to enhance the enantiomeric excess of intermediates. Compound **14b** was accessible via a straightforward process from cyclopropylmethyl alcohol **11**. Finally, a simple process for detosylation of **14b** and API crystallization was found, providing **1b** in 34% overall yield from 5-cyanoindole (**3**). The overall process was demonstrated on multikilogram scale.

Experimental Section

All reactions were performed under a nitrogen atmosphere. All reagents purchased from vendors were used as received unless otherwise indicated. Chiral analysis was obtained on a Shimadzu HPLC with a Chiracel AD or AD-H column unless stated otherwise. Proton and carbon NMR data were collected on a Bruker AC-300 at 300 MHz for proton and 75 MHz for carbon or on a Bruker AVANCE 400 at 400 MHz for proton and 100 MHz for carbon. Melting points were obtained with a Mettler-Toledo FP 62 melting point instrument by measurement of the change of luminous intensity during the melting process.

Preparation of 3-Formyl-1*H*-indole-5-carbonitrile (4b). To a stirred suspension of (chloromethylene)dimethylammonium chloride (Vilsmeier reagent, 5.31 kg, 41.5 mol) in acetonitrile (CH_3CN, 19.7 L) at 15–25 °C was added a solution of 1*H*-indole-5-carbonitrile **3** (4.90 kg, 34.5 mol) in CH_3CN (14.8 L) over 25 min while maintaining the temperature <45 °C. The resulting suspension was adjusted to 25 °C. Upon completion of the reaction, water (43.5 L) was added. The reaction mixture was heated at 70 °C for 1 h and then cooled to 0–5 °C. After stirring at 0–5 °C for 1 h, the solids were collected by filtration, and the cake was washed with water (2 × 14 L). The material was dried in vacuo at 55–60 °C until constant weight to yield 5.58 kg (95.1% yield) of indole **4b**. Mp: 275.0–275.9 °C. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 12.56 (s, 1H), 9.99 (s, 1H), 8.47 (d, J = 3.0 Hz, 1H), 8.44 (s, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 8.1 and 1.5 Hz, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 185.34 (CH), 140.20 (CH), 138.78 (C), 126.36 (CH), 125.66 (CH), 123.94 (C), 119.87 (C), 117.98 (C), 113.92 (CH), 104.37 (C). Raman 2222.2, 1650.9, 1416.8 cm^{-1}. Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.35; H, 3.59; N, 16.57.

Preparation of 3-Formyl-1-(toluene-4-sulfonyl)-1*H*-indole-5-carbonitrile (5). To a stirred suspension of **4b** (3.44 kg, 20.2 mol) and *p*-toluenesulfonyl chloride (4.16 kg, 21.8 mol) in CH_3CN (52.9 L) at 20–25 °C was added *N*,*N*-diisopropylethylamine (DIPEA, 4.04 L, 3.00 kg, 23.2 mol) over 21 min while maintaining the temperature at 20–25 °C. Upon completion of the reaction, water (17.2 L) was added to the resulting slurry, and the suspension was stirred for 60 min. The product was collected by filtration. The cake was washed sequentially with a 1:1 (v/v) mixture of CH_3CN/water (18.5 L) and water (2 × 9.3 L). The material was dried in vacuo at 55–60 °C until constant weight to give 6.46 kg (98.5% yield) of tosylate **5**. Mp: 244.6–246.0 °C. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 10.08 (s, 1H), 9.06 (s, 1H), 8.48 (d, J = 1.0 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 8.6 Hz, 2H), 7.86 (dd, J = 8.6 and 1.5 Hz, 1H), 7.47 (d, J = 8.1 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 199.09 (C), 186.52 (CH), 147.03 (C), 139.86 (CH), 135.99 (C), 132.85 (C), 130.75 (CH), 129.36 (CH), 127.41 (CH), 125.86 (CH), 120.66 (CH), 118.59 (C), 114.52 (CH), 107.81 (C), 21.09 (CH_3). IR 3121.3, 2229.7, 1677.6, 1382.7, 1172.7 cm^{-1}. Anal. Calcd for $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.72; N, 8.63; S, 9.88. Found: C, 62.94; H, 3.69; N, 8.64; S, 9.69.

Preparation of 3-(1-Hydroxy-vinyl)-1-(toluene-4-sulfonyl)-1*H*-indole-5-carbonitrile (6). To a stirred suspension of aldehyde **5** (6.35 kg, 19.6 mol) in THF (22.3 L) at 0–5 °C was added 3 M methylmagnesium chloride in THF (7.05 L, 21.2 mol) over 50 min while maintaining the temperature <15 °C. After a THF rinse (3.1 L) the solution was stirred at 0–5 °C until completion of the reaction by HPLC. The reaction was quenched by addition of 0.3 N aqueous HCl (78.2 L) over 45 min while maintaining the temperature <10 °C. The resulting slurry was stirred for 60 min at 15–25 °C and the product was collected by filtration. The cake was washed with water (2 × 19.8 L) and dried in vacuo at 55–60 °C until constant weight to give 6.35 kg (95.2% yield) of alcohol **6**. Mp: 155.6 °C. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 8.23 (d, J = 1.5 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 1.0 Hz, 1H), 7.72 (dd, J = 8.6 and 1.5 Hz, 1H), 7.40 (d, J = 8.6 Hz, 2H), 5.33 (d, J = 5.1 Hz, 1H), 4.97 (qt, 1H), 2.32 (s, 3H), 1.44 (d, J = 6.6 Hz, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 172.6 (C), 158.1 (C), 146.0 (C), 136.6 (C), 133.8 (C), 130.4 (CH), 128.9 (C), 128.2 (C), 127.6 (CH), 126.8 (CH), 126.1 (CH), 124.0 (CH), 119.1 (C), 114.2 (CH), 105.6 (C), 81.5 (C), 61.5 (CH), 23.8 (CH_3), 21.0 (CH_3). Anal. Calcd for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.73; N, 8.23; S, 9.42. Found: C, 63.45; H, 4.75; N, 8.19; S, 9.27.

Preparation of 1-(Toluene-4-sulfonyl)-3-vinyl-1*H*-indole-5-carbonitrile (2). To a stirred solution of alcohol **6** (9.55 kg, 28.1 mol) and DIPEA (10.9 kg, 84.2 mol) in *N*,*N*-dimethylformamide (DMF, 46.1 L) at 0–5 °C was added trifluoroacetic anhydride (TFAA, 7.07 kg, 33.7 mol) over 30 min while maintaining the temperature <25 °C. A DMF rinse (1.6 L) was added, and the solution was heated to 96–98 °C until <1 area % (AP) of **6** remained by HPLC. Upon completion of the reaction, water (23.9 L) was added over 10 min, followed by ethyl alcohol (EtOH, 32.4 L) over 8 min, and water (23.9 L) over 4 min while maintaining the temperature >56 °C. The solution was stirred at 50–55 °C for 20 min and cooled to 0–5 °C for 1 h. The product was collected by filtration. The cake was washed with a 1:4 mixture of EtOH/water (2 × 28.7 L) and dried in vacuo at 55–60 °C until constant weight to give 7.69 kg (85.0% yield) of vinyl indole **2**. Mp: 133.2–133.6 °C. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 8.43 (d, J = 1.0 Hz, 1H), 8.22 (s, 1H), 8.11 (d, J = 8.6 Hz, 1H), 7.92 (dm, J = 8.6 Hz, 2H), 7.76 (dd, J = 8.6 and 1.5 Hz, 1H), 7.40 (dm, J = 8.6 Hz, 2H), 6.86 (dd, J = 17.2 and 11.2 Hz, 1H), 6.00 (d, J = 17.2 Hz, 1H), 5.38 (d, J = 11.6 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR

(d_6-DMSO, 100 MHz) δ 146.2 (C), 136.3 (C), 133.5 (C), 130.5 (2CH), 128.4 (C), 128.2 (CH), 126.9 (CH), 126.5 (CH), 126.2 (CH), 125.7 (CH), 120.2 (CH), 119.0 (C), 116.9 (CH_2), 114.3 (CH), 106.5 (C), 21.0 (CH_3). Raman 3069.2, 3017.8, 2920.2, 2224.4, 1640.7, 1541.3, 771.6, 123.0 cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_2O_2S$: C, 67.07; H, 4.37; N, 8.69; S, 9.94. Found: C, 66.84; H, 4.39; N, 8.63; S, 9.90.

Preparation of Ethyldiazoacetate (EDA) in Toluene. To a stirred solution of sodium tetraborate decahydrate (1.07 kg, 2.81 mol) in water (21.5 L) at 25 °C was added sodium nitrite (5.58 kg, 80.9 mol) followed by glycine ethyl ester hydrochloride salt (10.8 kg, 77.0 mol). Upon complete dissolution, toluene (24.9 L) was added, and the resulting biphasic mixture was cooled to 0 °C. A 2% (w/w) phosphoric acid solution in water was added over 30 min while maintaining the temperature <20 °C until the pH was between 3.7 and 4.5 (addition of 60.3 kg resulted in a pH of 3.9). The organic layer was washed successively with water (10.8 L) and 8% (w/w) of aqueous sodium bicarbonate (2 × 21.9 L). The combined aqueous washes were neutralized with a 20 wt % solution of phosphoric acid in water. The organic layer was assayed for EDA content by HPLC, NMR and GC and was held overnight at 10 °C before being transferred to a pressure bomb. The reactor was rinsed with toluene (17.3 L), which was transferred to the pressure bomb as well. Residual EDA in the 200-L reactor was neutralized by addition of a 50 wt % solution of acetic acid in water (86 kg).

Preparation of (1*S*,2*S*)-2-[5-Cyano-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-cyclo-propanecarboxylicAcid,(*R*)-(+)-α-Methylbenzylamine Salt (10b). To a stirred solution of dichloro(*p*-cymene)ruthenium(II) dimer (0.37 kg, 0.61 mol) and Pybox (4R) ligand (0.382 kg, 1.27 mol) in THF (37.6 L) at 20–25 °C was added a solution of vinyl indole **2**(7.79 kg, 24.2 mol) in THF (36.1 L). The resulting mixture was heated to 55–56 °C, and 2 M solution of EDA in toluene (25 kg) was added at 3 L/h. Upon completion of the addition, HPLC indicated the amount of unreacted **2** was <1 AP. The reaction mixture was cooled to 20–25 °C, and water (23.4 L) was charged. The batch was concentrated to 30–35 L and cooled to 50 °C, and CH_3CN (58.5 L) was added. The resulting solution was cooled to 10 °C, and CF_3SO_3H (triflic acid, 9.25 kg, 61.6 mol) was added over 10 min while maintaining the temperature ≤25 °C during the addition. The mixture was concentrated until the batch temperature reached 82 °C. A volume of CH_3CN/water (ratio greater than 4:1) equivalent to the distillate was added, and three additional distillation/addition cycles were conducted. The reaction mixture was cooled to 72 °C, and 17.4 L of water was added while maintaining the temperature >65 °C. The mixture was cooled to 20–25 °C, and water (20 L) was added to the resulting slurry. The mixture was stirred for 1 h at 20–25 °C, and the solid was collected by filtration. The cake was washed twice with water (19.8 L,15.2 L), and the solid was dried at 50 °C in vacuo to yield 9.37 kg of acid **10a** (100% crude yield, 83.8% HPLC AP purity, 87.2% ee, Ru = 3100 ppm).

A slurry of crude **10a** (9.29 kg, 24.4 mol) in anhydrous CH_3CN (115 L) was heated at 75 °C until dissolution occurred. The solution was cooled to 35 °C and was passed through a 5 μm cartridge filter. The filter was rinsed with CH_3CN (7.2 L). The filtrate was heated to 65 °C and (*R*)-(+)-α-methylbenzylamine (3.21 kg, 26.5 mmol, 1.09 equiv) was added over 18 min. The reaction mixture was cooled to 20 °C over 3 h and was then held at 0–5 °C for 1 h. The resulting solid collected by filtration and washed with CH_3CN (2 × 18.6 L). After drying at 45 °C in vacuo, 6.84 kg of salt **10b** was obtained (64.0% yield, 97.8 HPLC AP purity, 95.5% ee, Ru = 310 ppm). Mp: 176.4–177.2 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 (dm, J = 8.4 Hz, 1H), 7.85 (s, 1H), 7.74 (dm, J = 8.4 Hz, 2H), 7.56 (dd, J = 7.7, 1.5 Hz, 1H), 7.29 (m, 9H), 5.28 (s (br), 3H), 4.23 (q, J = 6.8 Hz, 1H), 2.35 (s, 3H), 2.34–2.26 (m, 1H), 1.75–1.69 (m, 1H), 1.52 (d, J = 6.8 Hz, 3H), 1.48–1.43 (m, 1H), 1.17–1.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.80, 146.11, 140.75, 137.09, 135.12, 131.44, 130.56, 129.23, 128.65, 128.16, 127.22, 126.49, 125.08, 124.19, 123.66, 119.72, 114.79, 106.96, 51.31, 24.77, 22.61, 22.02, 15.45. Anal. Calcd for $C_{28}H_{27}N_3O_4S$: C, 67.04; H, 5.43; N, 8.38; S, 6.39. Found: C, 67.32; H, 5.58; N, 8.09; S, 6.51.

Preparation of 3-((1*S*,2*S*)-2-Hydroxymethyl-cyclopropyl)-1-(toluene-4-sulfonyl)-1*H*-indole-5-carbonitrile (11). A mixture of salt **10b** (6.42 kg, 12.8 mol), THF (26.7 kg), methyl *tert*-butyl ether (53.4 kg), and 10% aqueous sulfuric acid solution (27.9 kg) was agitated until dissolution. The phases were separated, and the organic phase washed sequentially with 10% aqueous sulfuric acid (27.9 kg), 15% brine (29.8 kg), and 26% brine (32.6 kg). The organic phase was passed through a 5 μm polish filter, and 36.3 kg of solvent was distilled at atmospheric pressure. THF (20.4 kg) was charged, and an additional 24.3 kg of solvent was distilled (final batch temperature 66 °C, KF 0.20%). After holding for 16 h at 20–25 °C, the solution was cooled to 0 °C and 1 M BH_3·THF in THF (12.9 kg, 14.7 mol, 1.15 equiv) was charged over 90 min, modulating the addition rate as necessary to maintain the batch temperature below 10 °C. The O_2 content of the headspace was continuously monitored and maintained below 0.4% throughout the reduction sequence. After heat evolution had ceased, the mixture was warmed to 22 °C over 30 min, and additional 1 M BH_3·THF (1.2 kg, 1.4 mol, 0.11 eq) was added over 10 min. HPLC analysis indicated <1.5% starting material remaining, and water (2.6 kg) and CH_3CN (6.0 kg) were added. Dilute HCl (prepared from 88.3 kg water and 3.2 kg conc HCl) was charged over 45 min, and the resultant slurry was agitated for 90 min. The product **11** was collected by filtration, washed with water (2 × 7.5 kg), and dried in vacuo until LOD <1.0% to yield 4.5 kg of alcohol **11** as an off-white powder (12.3 mol, 96% yield, 98.3 HPLC AP purity). Mp: 139.0–140.5 °C. ^{1}H NMR (d_6-DMSO, 400.13 MHz) δ 8.29–8.28 (m, 1H), 8.05 (d, J = 8.59 Hz, 1H), 7.90–7.86 (dm, 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 (dm, 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) δ 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-Dimethylaminomethyl-cyclopropyl)-1-(toluene-4-sulfonyl)-1*H*-indole-5-carbonitrile, Hydrochloride, Hemihydrate (14b). A stirred mixture of alcohol **11** (3.38 kg, 9.22 mol), TEMPO (36 g, 0.23 mol), sodium bicarbonate (856 g, 10.2 mol), methyl acetate (33.7 L), and water (8.83 L) was cooled to 0–5 °C. The reactor was flushed 5 times with nitrogen, and an 11 wt % solution of sodium hypochlorite (NaOCl, 7.19 kg, 10.6 mol) was charged over 140 min while maintaining the internal temperature at 0–5 °C. HPLC analysis indicated the AP of **11** was <1% relative to the aldehyde intermediate **13**. The reaction was quenched by addition of ethyl alcohol (0.99 kg, 21 mol), and was warmed to 20–25 °C over 30 min. The organic layer was passed through a 0.5 μm cartridge filter, and the filtrate was cooled to 0–5 °C. A 2 M solution of dimethylamine in THF (7.85 kg, 18.5 mol) was charged to the batch, followed by a rinse of methyl acetate (0.4 L). The reaction mixture was stirred for 10–15 min, and the vessel was purged 5 times with nitrogen. Sodium triacetoxyborohydride (2.53 kg, 11.9 mol) was added over 30 min, leading to a 7–10 °C temperature increase. After the addition, the reaction mixture was warmed to 20–25 °C for 15 min. Water (17 L) was added, followed by stirring for 15 min. The aqueous layer was separated and back extracted with methyl acetate (6.75 L). The combined organic layers were washed sequentially with sodium bicarbonate solution (1.55 kg sodium bicarbonate in 17.0 L of water) and sodium chloride solution (4.43 kg sodium chloride in 14.5 L of water). The organic phase was passed sequentially through a Zeta R53SP filter (six 8″ diameter pads) at a rate of 2 L/min, and a 0.45 um polish filter. The organic phase was then concentrated to 17 L. 2-Propanol (IPA, 41 L) was charged, and the solution was concentrated to 27.2 L. The resulting mixture was warmed to 72 °C and additional IPA (3.4 L) was added. Concurrently, a solution of HCl/IPA was prepared by the addition of 1.16 kg (14.8 mol) of acetyl chloride over 50 min to IPA (6.8 L) while maintaining the temperature <18 °C. The resulting HCl/IPA solution was charged over 10 min to the batch while maintaining the temperature above 65–70 °C. The mixture was cooled to 62–65 °C over 25 min, during which time crystallization started. The thickening slurry was held for 30 min at 62 °C with vigorous agitation, cooled to 20 °C over 30 min, and held at 20 °C for 1 h. The crystals were collected by filtration and washed with IPA (6.8 L) followed by MTBE (6.8 L). The solid was dried at 50 °C in vacuo until LOD was <1%, affording 3.50 kg (88.1%, 99.8 HPLC AP purity, Ru = 8 ppm) of salt **14b** as an off-white solid. Mp: 212.0–213.3 °C. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 10.60 (s, 1H), 8.40–8.38 (m, 1H), 8.06 (d, J = 8.59 Hz, 1H), 7.89 (dm, J = 8.34 Hz, 2H), 7.79 (s (br), 1H), 7.74 (dd, J = 8.59, 1.51 Hz, 1H), 7.39 (dm, 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 MHz) δ 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 $C_{22}H_{24}ClN_3O_2S.1/2\ H_2O$: C, 60.19; H, 5.74; Cl, 8.08; N, 9.57; S, 7.30. Found: C, 59.77; H, 5.52; Cl, 8.56; N, 9.70; S, 7.26.

Preparation of 3-((1*S*,2*S*)-2-Dimethylaminomethyl-cyclopropyl)-1*H*-indole-5-carbonitrile, Maleic Acid Salt (1a). A mixture of salt **14b** (1.7 kg, 4.0 mol), THF (4.6 kg), and 50 wt % aqueous NaOH (6.6 kg) was heated at 68 °C in a 40 L Hastelloy vessel for 4 h with vigorous stirring. The batch was cooled to 30–35 °C, and water (5.0 L) was added while maintaining the temperature <35 °C, followed by addition of THF (2.0 L) and MTBE (3.4 L). The mixture was transferred to a 50 L borosilicate reactor. Additional water (10.3 L) and MTBE (3.4 L) were added, and the mixture was stirred at 20 °C for 15 min. The phases were separated, and the organic phase was concentrated to 4.2 L. The reactor was charged with a 1:1 (v/v) mixture of THF/MTBE (7.7 L). The mixture was concentrated again, and the KF of the batch was measured to be 0.32 wt %. To the batch was added THF (7.6 L), and the mixture was held at 25 °C. The solution was then passed sequentially through 10 μm and 0.45 μm polish filters. The filter train was rinsed with THF (1.5 L), and seeds (**1a**, 10 g in THF (0.11 L)) were added to the resulting batch. A solution of maleic acid (0.51 kg, 4.39 mol) in 1.93 L of THF was added through a 10 μm Cuno filter. The resulting slurry was stirred at 20–25 °C for 15 h, and the solid was collected by filtration. The cake was washed sequentially with THF (2.48 L) and a 1:1 (v/v) mixture of THF/MTBE (2.4 L). The product was dried at 35–40 °C in vacuo until the LOD was <1% to yield 1.08 kg of API **1a** (76.6% yield, 99.5 HPLC AP purity and 98.3% ee). Mp: 167 °C. ^{1}H NMR (d_6-DMSO, 300 MHz) δ 1.01 (ddd, J = 8.8, 4.8, 4.8 Hz, 1H), 1.14 (ddd, J = 8.1, 5.3, 5.3 Hz, 1H), 1.30 (m, 1H), 2.09 (ddd, J = 8.3, 5.3, 5.3 Hz, 1H), 2.83 (s, 6H), 3.13 (d, J = 13.1, 7.5 Hz), 3.27 (d, J = 13.1, 7.1 Hz, 1H), 6.04 (s, 2H), 7.32 (d, J = 2.3 Hz, 1H), 7.41 (dd, J = 8.5, 1.5 Hz, 1H), 7.50 (d, 8.4 Hz, 1H), 8.18 (s, 1H), 9.50 (s broad, 1 H), 11.49 (s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 171.29, 140.29, 137.11, 129.18, 125.81, 125.65, 125.16, 122.34, 117.92, 114.04, 102.87, 63.12, 43.65, 17.10, 14.92, 14.05. Anal. Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.82. Found: C, 63.86; H, 5.69; N, 11.45.

Preparation of 3-((1*S*,2*S*)-2-Dimethylaminomethyl-cyclopropyl)-1*H*-indole-5-carbonitrile, HCl Salt (1b). The detosylation described above was applied to 1.7 kg (4.0 mol) of **14b** with no modification of the protocol through the reaction and phase separation phases. After phase separation, the batch was concentrated under atmospheric pressure until the internal volume was 4.0 L. MTBE (7.55 kg) was added, and distillation was resumed until the internal volume was 4.0 L. The KF of the concentrated batch was measured to be 0.47%. THF (0.84 kg) and MTBE (3.13 kg) were added to the batch, and the mixture was cooled to 20–25 °C (KF 0.26%). The batch was passed through 10 μm and 0.5 μm filters in series. The filter train was rinsed with MTBE (0.95 kg). To the stirred batch were added seeds (7 g, **1b**) as a slurry in MTBE (1.68 kg), followed by EtOH (1.88 kg). A solution of HCl in EtOH (prepared by addition of acetyl chloride (0.31 kg, 3.95 mol) to EtOH (2.71 kg)) was added over 1 h to the batch. The resulting slurry was held for 18 h at 20–25 °C, and the solids were collected by filtration. The cake was washed with 95:5 (v/v) MTBE/EtOH (2.5 L) and MTBE (2 × 2.4 L). After drying at 50 °C in vacuo (LOD <1%), 0.964 kg of API **1b** was isolated (88.7% yield, 99.8 HPLC AP purity, 98.7% ee). Mp: 176.5–177.5

°C. ^{1}H NMR (d_6-DMSO, 400.13 MHz) δ 11.61 (s, 1H), 10.87 (s broad, 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) δ 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.

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