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The Synthesis of a $5HT_{2C}$ Receptor Agonist

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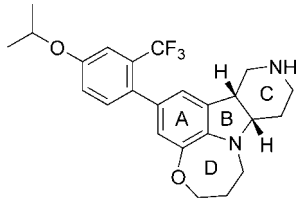
Abstract:

This report describes the large-scale synthesis of 1 that features a Fischer indole strategy to form an advanced intermediate followed by reduction to the indoline to construct the tetracyclic core of the molecule. Resolution using dibenzoyl-D-tartaric acid affords access to a single enantiomer, from which a Suzuki coupling builds in the biaryl functionality. Deprotection followed by salt formation furnishes the desired target molecule.

Introduction

The $5HT_{2C}$ receptor is believed to be one of two receptors,[1] along with $5HT_{1B}$, responsible for the major satiety enhancing effect of 5HT on the central nervous system. Target molecule **1** was selected as a promising drug candidate for the treatment of obesity.[2] To this end, the production of kilogram quantities of **1** was required to support drug development (i.e., toxicology, formulation development, and pharmacologic assessment). To meet these requirements the identification and execution of a scalable synthetic sequence was essential and is outlined below.



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Results and Discussion

The synthetic approach to **1** utilizes as the key step a Fisher indole cyclization to assemble the tetracyclic core (rings A, B, C, and D). The Drug Discovery chemistry team had used this approach for their preparation of analogues in this series, thereby having the ability to vary the aryl group. With this approach the aryl portion could be introduced by a Suzuki coupling reaction of the required boronic acid and a halogenated tetracycle. Scheme 1 outlines the retrosynthetic analysis of **1**, which shows the initial disconnection of the aryl linker to give the tetracyclic core **2** and the required boronic acid **3**. The tetracyclic indoline **2** can in turn be obtained from reduction of the corresponding indole **4**, which can be obtained from a Fischer indolization of 4-piperidone monohydrate hydrochloride with hydrazine **5**. Hydrazine **5** can be obtained from bicyclic amine **6** via formation of the *N*-nitroso compound followed by reduction.

The known bicyclic amine **6**[3] can be obtained in two ways, as shown in Scheme 2, either by a Beckmann rearrangement of the chromanone oxime **7** or by alkylation/ring opening/cyclization of 2-benzoxazolinone **8**.

The key difference between the Drug Discovery chemistry route and the process route was the method used to introduce the chirality. The Discovery Chemistry route utilized a chiral chromatographic separation of the racemic BOC-protected indoline, **19**, prior to the Suzuki coupling reaction. During the development of the process route the possibility of a resolution process was investigated, which would provide a more cost-efficient process.

Within the Chemical Process R & D group both routes to **6** were investigated. The route that had been utilized by the Discovery chemists employed the alkylation of 2-benzoxazolinone with 1-bromo-3-chloropropane using sodium hydride as base in a mixture of THF and DMPU.[4] This resulted in a 68% yield of the alkylated benzoxazolinone **9**, Scheme 3. The major impurity in the reaction was shown to be the alkylated dimer **10**. A small amount of the bromoalkylated product, **11**, forms, which should also be converted to the desired product **6**. Treatment of **9** with potassium hydroxide in 2-methoxyethanol

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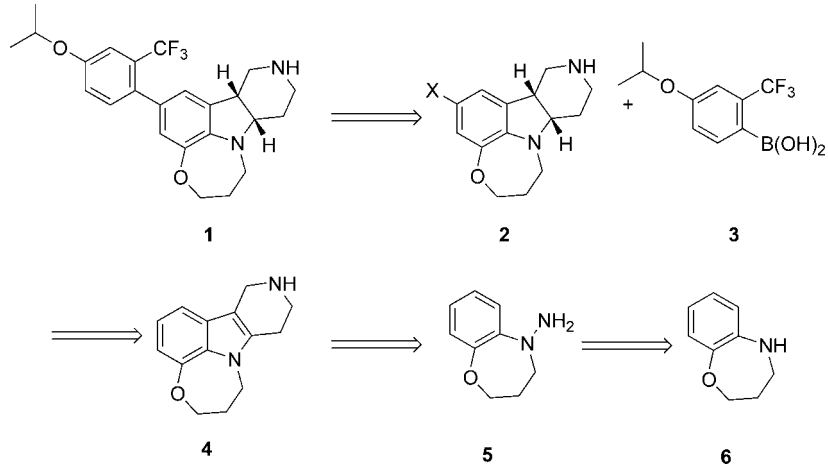
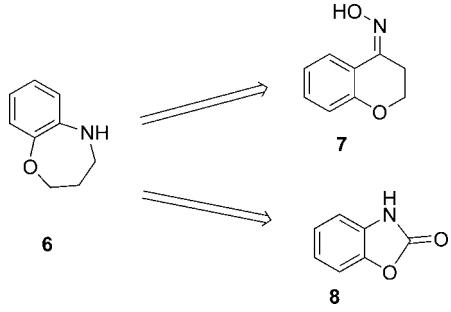
Scheme 1. **Retrosynthetic analysis**



Scheme 2. **Retrosynthetic analysis of the 1,5-benzodiazepine**



at reflux effected the ring opening of the oxazolinone followed by displacement of the chloride and decarboxylation to generate **6** in 70% yield.

Due to the low yields obtained, the hazards associated with the use of sodium hydride on scale, and the toxicity of 2-methoxyethanol, a study was performed to investigate alternate bases, solvents, and temperatures in conjunction with a reduction of reagent stoichiometry. The objective was to optimize an alternate base/solvent combination that would minimize the formation of the dimer impurity and improve the yield, while resulting in a more scalable synthesis. Table 1 summarizes the different reaction conditions investigated to optimize the reaction along with the results.

The course of the reaction is significantly impacted by solvent, reagent choice, and stoichiometry. The choice of base had a dramatic effect on the formation of dimer. Changing the base from sodium hydride to potassium *tert*-butoxide dropped the amount of dimer from 12.8 area % to <0.03 area % (HPLC) and also increased the yield to 92%. Investigating additional potassium bases showed that potassium hydroxide led to increased formation of the dimer, whereas potassium carbonate was comparable to potassium *tert*-butoxide in minimizing the dimer formation. The choice of solvent and temperature were also factors that affected the amount of dimer. Although there were many acceptable alternatives, the conditions chosen for scale-up were potassium carbonate in dimethylacetamide (DMAC) at 15 to 25 °C, with 2 equiv of the alkylating reagent.

The subsequent step involved opening of the oxazolinone ring in the presence of base with closure on the alkyl chain to give the 1,5-benzodiazepine **6**. The literature indicates that this transformation can be carried out using potassium hydroxide in 2-methoxyethanol over a period of 48 h in 55% yield.[5] In order to optimize the yield of this reaction, an investigation using both potassium hydroxide and potassium *tert*-butoxide in a number of solvents was undertaken. This revealed that the combination of THF and potassium *tert*-butoxide gave better reaction impurity profiles compared to potassium hydroxide. Upon addition of potassium *tert*-butoxide to a solution of **9** in THF at 0 to 10 °C, HPLC analysis indicated the formation of a new compound, which was shown to be compound **12**, where potassium *tert*-butoxide had opened up the oxazolinone ring to provide a BOC-protected amine. Upon heating to 55 to 60 °C, **12** was readily converted to cyclic ether **13**. Treatment of **13** with either methanesulfonic acid or 5 M hydrochloric acid removed the BOC group and afforded either the methanesulfonic acid salt or the hydrochloride salt of **6** in 70–80% yield, Scheme 4.

It is possible that the two steps from 2-benzoxazolinone to compound **6** could be conducted sequentially without isolation of intermediate **9**; however this was not explored. An alternative approach to **6** was examined in parallel to this work. This involved the treatment of 4-chromanone with hydroxylamine to form the known oxime **14**.[3b,6] Treatment of oxime **14** with a hydride source such as di-isobutylaluminium hydride would effect the Beckmann rearrangement to give the required 1,5-benzodiazepine **6**, Scheme 5.[3d,7,8]

4-Chromanone was treated with a slight excess of both hydroxylamine hydrochloride and triethylamine in methanol at 70 °C for 3 h. The process was investigated with and without triethylamine. It was found that the yields for the two processes were similar (92–95%); however the reaction time was slower when triethylamine was not present, 5 h versus 2 h. Upon completion of the reaction, water was added and the oxime directly crystallized from the reaction solution. The product was dried at 60 °C/25 mmHg in order to produce material with a

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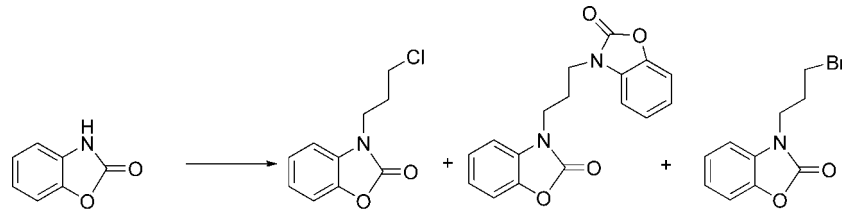
Scheme 3. **Alkylation of 2-benzoxazolinone**

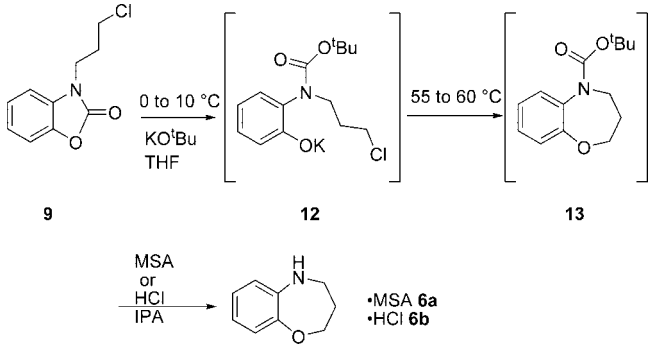


8 **9** **10** **11**

Table 1. **Effects of solvent/base/temperature/stoichiometry**

solvent	temp, °C	time, h	base (equiv)	$Br(CH_2)_3Cl$ equiv	area % **9**	area % **10**	area % **11**	yield %
THF/ DMPU	65	7	NaH (1.15)	1.1	65	12.8	22	51
THF/ DMPU	80	4	^{t}BuOK (1.05)	3	92	ND	ND	92
THF/ NMP	62	1.5	^{t}BuOK (1.05)	3	95.6	ND	ND	77
NMP	20	5	K_2CO_3 (2)	2	95	ND	5	85
NMP	25	19	K_2CO_3 (1.5)	1.5	92.8	3.7	3.5	94
IPA	82	5	KOH (1.0)	3.1	87.3	6.7	2.5	75
IPA	82	3.5	KOH (1.0)	4	92	7.7	ND	75
NMP	0–10	1.15	KO^{t}Bu (1.15)	2	98.5	1.46	ND	89
DMAC	0–10	3	KO^{t}Bu (1.15)	2	96.2	2.8	1	86
DMAC	15–25	6	K_2CO_3 (1.5)	2	95	3.1	2.2	92

Scheme 4. **Formation of 1,5-benzodiazepine 6 from benzoxazolinone 9**



9 **12** **13**

water content of less than 0.5%. This level of water was shown to be acceptable for use in the next reaction using di-isobutylaluminum hydride. The isolated yield of oxime **14** was high, 94% (25 kg scale), with a purity of 98.7 wt %. However, it was found that the crystalline product showed instability under typical storage conditions (closed polyethylene bag, inside a fiber drum at room temperature). The product reverted back to 4-chromanone, as identified by HPLC. This occurred after storage for ~6 h, with the HPLC purity of oxime **14** changing from 100 area % to 83 area %. The cause of the autoreversion has not been clearly established, but laboratory stability studies showed that the presence of residual acid induced reversion. Additional studies showed that the compound was stable at 22 °C overnight, 100 °C under vacuum, and as a slurry in water (process water from the plant) at 100 °C for 3 h. Prior to the next step, the 4-chromanone was removed from the product by slurrying the material in methanol/water followed by filtration to isolate the product, which was then stored under vacuum in a tray drier to ensure that no further degradation took place. Further studies demonstrated that reagents such as nitric acid, hydrogen peroxide, and bleach also converted the product back to starting material.

Oxime **14** was then treated with 3 equiv of di-isobutylaluminium hydride in toluene at low temperature (−5 to −15 °C). Following the addition, the reaction was allowed to warm to 15 °C, and after a 1 h hold time the reaction was found to be complete by HPLC analysis. The reaction was quenched by the addition of a solution of Rochelle's salt. The quench was addition controlled to limit the release rate of the hydrogen and isobutane gases generated.[9] Following the workup of the reaction mixture, the product was treated with HCl in IPA to form the hydrochloride salt, which was isolated in 90% yield with a purity of 98.5%.

The preferred method to prepare **6b** was determined to be from 4-chromanone due to the higher yield over the two steps.

With 1,5-benzodiazepine **6b** in hand, the next step required N-nitrosation[3d,10] to give the N-nitroso compound **15**, which, following reduction, would produce hydrazine **5** (Scheme 6) in readiness for the Fischer indolization step.

Treatment of a solution of **6b** in hydrochloric acid with a solution of sodium nitrite in water generated the N-nitroso compound **15**, which was taken directly into the reduction without isolation. Reduction of **15** to the hydrazine **5** was achieved by heating with sodium dithionite in a mixture of ethanol and sodium hydroxide for 2 h.[11] A small amount of the N–N cleavage product, **6**, was observed, but this was minimized by shortened reaction times. Hydrazine **5** was not isolated but taken directly into the Fischer indole reaction.

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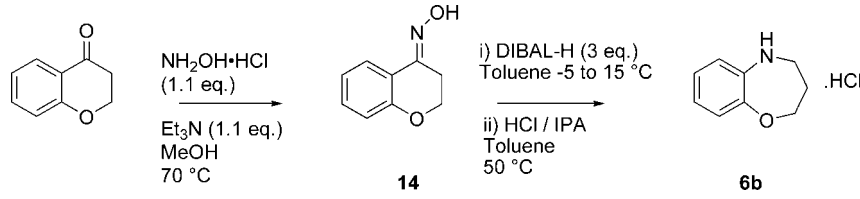
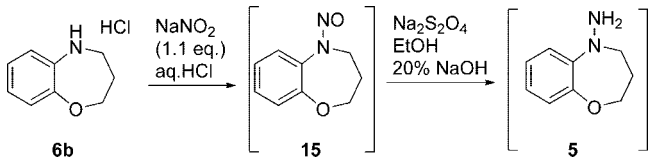
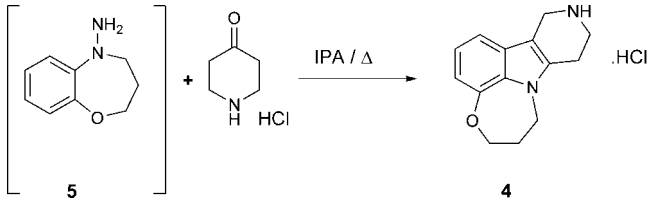
Scheme 5. **Formation of 1,5-benzodiazepine 6 from 4-chromanone**



Scheme 6. **Formation of hydrazine 5 from 1,5-benzodiazepine 6**



Scheme 7. **Formation of indole 4 from hydrazine 5**

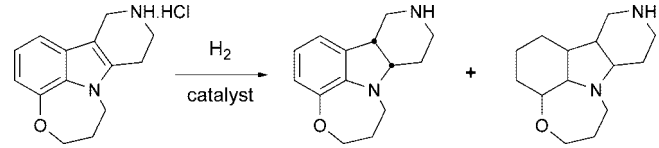


Treatment of **5** with 4-piperidone monohydrate hydrochloride in IPA furnished indole **4**, Scheme 7.[7]

Due to the product's low solubility in IPA, isolation was achieved via a precipitative crystallization, which also entrained ammonium chloride in the product. To remove the ammonium chloride, a slurry of the material in water was performed and produced a fine particulate solid that was comprised of agglomerated needles with a particle size distribution in the 5–30 μm range and thus filtered very poorly. To improve the physical properties of the isolated material and the performance of the filtration, a controlled crystallization using 2-propanol/water (1:9) was developed, which resulted in material of larger particle size (50–100 μm plates) and thus faster filtration. The indole was isolated following the improved recrystallization conditions in an overall yield of 73% with a typical purity of >99.7 wt %.

Reduction to the indoline from indole **4** was now required. The literature describes many methods for the reduction of indoles to indolines, most of which include the use of reagents such as borohydrides/cyanoborohydrides with a strong acid,[12] borane,[13] or catalytic hydrogenations.[14] One example potentially applicable to this substrate was an asymmetric hydrogenation of an indole using Rh(acac)(cod) with a chiral ligand to produce monosubstituted indolines in high ee's.[15] The catalytic hydrogenation of compound **4** proved challenging, since the indole double bond is both tetrasubstituted and stabilized by the heteroaromaticity of the indole ring. Conditions that were sufficiently vigorous to overcome these factors also promoted competitive hydrogenation of the phenyl ring to afford **17**, Scheme 8. To minimize this problem, we focused on reductions performed under acidic conditions. Protonation of the indole to form an indolinium ion was expected to suppress the aromaticity of the indole nucleus and thus activate the double bond toward hydrogenation.

Scheme 8. **Reduction of indole 4**



Adams catalyst (platinum oxide) gave higher conversion and selectivity for **16** as compared with 5% ruthenium on carbon or 5% platinum on carbon under a variety of conditions. Formic acid has been advocated as a solvent for the hydrogenation of indoles.[16] However, the use of formic or acetic acid alone or in combination with methanesulfonic acid for the hydrogenation of **4** resulted in low conversions. Higher conversions (50–100%) were achieved using 1:1 ethanol/aqueous HBF_4 as solvent,[17] but selectivity was limited and in one case resulted in complete conversion to **17** (as a mixture of diastereomers). The transfer hydrogenation of indoles to indolines is known.[18] However, attempted transfer hydrogenations of **4** under the reported conditions afforded only recovered starting material.

Our best results for catalytic hydrogenation were obtained using platinum oxide catalyst in 90:10 dichloromethane/methanesulfonic acid (10% catalyst, 30 psi H_2, 25 °C, 24 h). These conditions afforded 100% conversion of **4**, but selectivity was only 7/3 in favor of **16**. In parallel, achiral reductions were also being investigated. Due to delivery requirements and the lack of success with chiral reductions, we turned our attention

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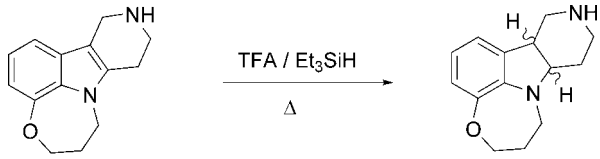
Scheme 9. **Formation of indoline 16**



4 **16**

to the stoichiometric reduction of **4** using triethylsilane in trifluoroacetic acid, Scheme 9.[19]

Treatment of indole **4** with 3.5 equiv of triethylsilane in 5 volumes of trifluoroacetic acid at 45 °C for 24 h provided indoline **16**. Upon completion of the reduction (95% conversion), water was added and the organic phase that contained side products was discarded. The aqueous layer was then washed with *n*-heptane to further remove the siloxane byproducts before the acidic phase was basified. The aqueous phase was cooled to 5 °C, treated with sodium hydroxide until the pH had been adjusted to 12 or higher, and then extracted with isopropyl acetate followed by a solvent exchange to methanol to provide a crude solution of indoline **16**.

During a crystallization screen of indoline **16** with chiral acids it was found that dibenzoyl-D-tartaric acid gave the desired enantiomer in high ee in 20% yield. During the course of the development work it was found that a higher yield could be obtained if indoline **16** was initially treated with dibenzoyl-L-tartaric acid. This removed the undesired enantiomer from the mixture, thus enriching the mother liquors in the desired enantiomer to a ratio of 67:33, Scheme 10. After treating the mother liquors with sodium hydroxide and dissolving the free base in dichloromethane, a solvent exchange to methanol was carried out. The methanol solution containing the enriched desired enantiomer of the indoline was then treated with dibenzoyl-D-tartaric acid to afford the product, **18**. The resolution was demonstrated on pilot plant scale to produce 25 kg of **18** in 25–30% yield (99.1 wt %, >97% enantiomeric excess).[20]

With the desired enantiomer of the indoline in hand the next step required protection of the piperidine nitrogen followed by bromination of the aromatic ring to provide the precursor for the Suzuki coupling reaction. To this end a solution of indoline **18** in dichloromethane was treated with an excess of aqueous sodium hydroxide, followed by di-*tert*-butyldicarbonate to directly afford the BOC-protected indoline **19**, Scheme 11.

During the development of the bromination reaction it was found that molecular bromine was preferred over *N*-bromosuccinimide, affording **20** as its hydrobromide salt, which could be crystallized directly from the reaction mixture. In contrast, *N*-bromosuccinimide gave a difficult-to-crystallize gum, even after an aqueous workup. However, in using molecular bromine for this reaction, the temperature needed to be maintained below 0 °C to minimize competitive BOC cleavage to compound **21**.[21] The organic phase from the BOC-protection containing **19** was cooled to −5 to −10 °C and treated with a solution of bromine in dichloromethane. The reaction was complete 30 min after the addition, at which point *n*-heptane was added to crystallize the product as the hydrobromide salt. On a >9.5 kg scale product **20** was obtained in >88% yield over two steps with a purity of >97 wt %.

With aryl bromide **20** in hand, the Suzuki coupling reaction[22] was investigated. The literature describes a number of potential conditions that can be used for Suzuki couplings. The initial conditions evaluated were those implemented in the Discovery Chemistry route to the compound which utilized barium hydroxide as the base and tetrakis(triphenylphosphine) palladium as the catalyst in aqueous dimethoxyethane. The required boronic acid could be synthesized from 4-bromo-3-trifluoromethylphenol in two steps as shown in Scheme 12: protection of the phenol group with 2-bromopropane followed by formation of the boronic acid with *n*-butyllithium and triisopropylborate followed by acidification. The boronic acid used in the scale-up work was purchased from a vendor.

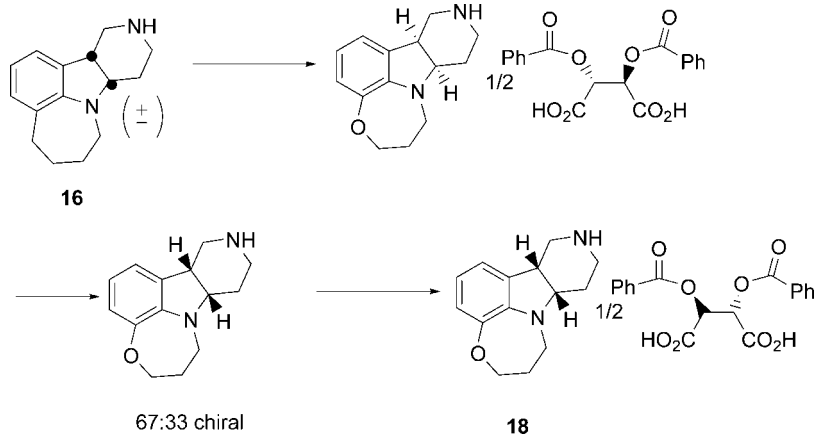
The reaction of **20** with boronic acid **22** was complete in 3 h when using a 2.5 mol % catalyst loading as shown in Scheme 13. Workup of the reaction to isolate compound **23** proved capricious. Compound **23** could not be isolated as a solid and also contained high levels of palladium (2500−3500 ppm). It was found that treatment of a solution of **23** with Picachem carbon[23] directly after the Suzuki coupling did not sufficiently remove the residual palladium to an acceptable level. Washing the organic phase with a solution of tris(hydroxymethyl)aminomethane[24] was likewise inefficient in removing the residual palladium. Ultimately, the residual palladium was removed by treatment of the organic phase with a 20% sodium carbonate solution of trithiocyanuric acid.[25]

Upon treatment of the organic phase with trithiocyanuric acid/sodium carbonate and cooling to <5 °C a solid palladium-containing precipitate formed, which was easily removed via filtration. The aqueous phase was then discarded and the organic phase was treated with Picachem carbon 80PN to further reduce palladium levels to less than 100 ppm. The organic phase was then solvent exchanged to isopropyl acetate. The isopropyl acetate solution of **23** was heated to 87 to 89 °C, and methanesulfonic acid was added over a period of 30 min to effect the BOC group cleavage. After holding for an additional 1 h at 87 to 89 °C, the reaction was complete and the solution was cooled to <30 °C. Following aqueous workup, the organic phase was treated with diphenylacetic acid to generate the diphenylacetic acid salt of **1**. On a 1 kg scale the yield was 65–70% with 30 ppm of palladium in the diphenylacetic acid salt and with a purity of 99.4 wt %.

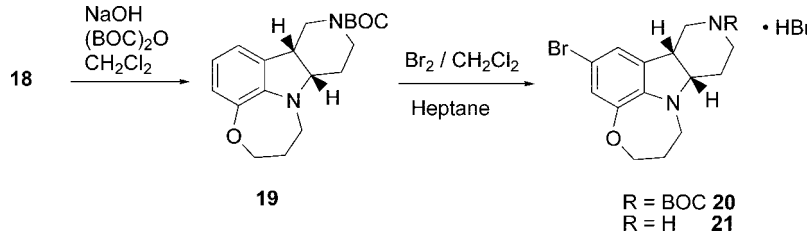
The Suzuki reaction proceeded well on scale; however the filtration of the large amount of solid palladium-containing precipitate from the trithiocyanuric acid treatment proved slow

(19) Ketcha, D. M.; Lieurance, B. A. *Tetrahedron Lett.* **1989**, *30*, 6833.
(20) The absolute stereochemistry of the free base of compound **18** had previously been determined by single-crystal X-ray in the Discovery Chemistry group, and **18** was compared to authentic samples using HPLC retention times.
(21) Compound **21** was not isolated and could be carried through to the Suzuki reaction without impacting the step.
(22) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. Suzuki, A. *J. Organmet. Chem.* **1999**, 147, and references therein.
(23) Picachem carbon was identified from adsorbent screening studies and was found to be the best in terms of loading and removal. For further information on Picachem carbon see www.picacarbon.com/en/.
(24) Private communication with J. Sherbine.
(25) Rosso, V. W.; Lust, D. A.; Bernot, P. J.; Grosso, J. A.; Modi, S. P.; Rusowicz, A.; Sedergran, T. C.; Simpson, J. H.; Srivastava, S. K.; Anderson, N. G. *Org. Process Res. Dev.* **1997**, *1*, 311.

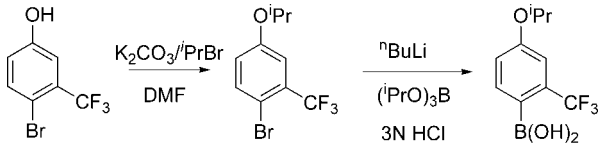
Scheme 10. **Resolution of indoline 16**



Scheme 11. **Formation of bromoindoline 20**



Scheme 12. **Formation of boronic acid 22**



and troublesome due to the large amount of solid generated and the need to filter through Celite. To avoid this type of filtration in the future, the reaction was further optimized to reduce the amount of palladium used. During the development work on the Suzuki reaction it was found that a solvent mixture of isopropyl acetate and water worked as well as aqueous DME. Implementing this change eliminated a solvent exchange. Alternate bases were also investigated, and potassium carbonate and cesium carbonate were found to be comparable to barium hydroxide in terms of reaction rate and impurity profile. The catalyst loading could be lowered to 1 mol % without impacting the reaction conversion, but the reaction rate was slower, as would be expected. Modifying the Suzuki reaction conditions to potassium carbonate as the base and isopropyl acetate as the solvent and 2 mol % of catalyst allowed a streamlined procedure for the deprotection reaction followed by salt formation. Employment of alumina or triphenylphosphine to remove residual palladium showed no significant improvements from the trithiocyanuric acid/carbon treatments. One promising alternative was to treat both the organic phase following the Suzuki reaction and also the organic phase after the deprotection with carbon. Further investigation showed that one treatment of the organic phase after the deprotection reaction with Picachem carbon 80PN (10% wt/wt) at 50 °C for 2 h provided an efficient removal. Following formation of the diphenylacetic acid salt residual levels of palladium were <50 ppm. The levels were slightly higher (<50 ppm vs <30 ppm) than those from the two-treatment protocol, but the simplified process was more amenable to scale-up. The palladium level could be reduced further during the final step, which involved the conversion to the selected final pharmaceutical salt form. This improved procedure was run on a 10 kg scale to give the diphenylacetic acid salt **1a** in 55% yield, 98.1 area % with <50 ppm of palladium with 1 to 2% of the product being left in the liquors during the crystallization.

The final step in the preparation was a salt exchange from the diphenylacetic acid salt, **1a**, to a pharmaceutically acceptable salt form for delivery of the drug. The citrate salt was chosen as the initial form for development of the API. Aqueous sodium hydroxide was used to extract the free base into isopropyl acetate. The solvent was then exchanged to an ethanol/n-heptane (70:30) mixture, and citric acid was added to form the citrate salt, **1b**, Scheme 14.

The citrate salt was isolated in 92% yield, 100.7 wt % on a 900 g scale, and was shown to have 100% chiral purity by SFC and <14 ppm of residual palladium.

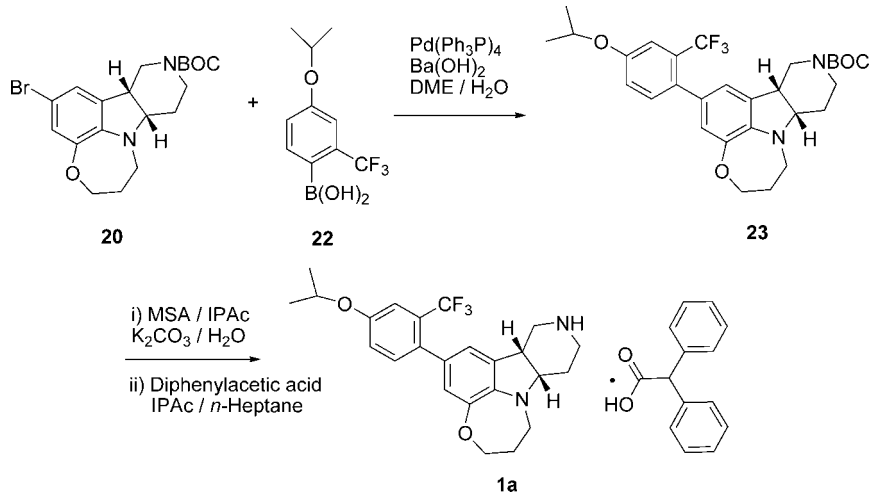
Conclusion

An efficient route has been developed and demonstrated on multikilogram scale for the synthesis of **1**, a potential drug candidate for the treatment of obesity. A chemical resolution was utilized on scale to provide the desired enantiomer of the indoline, which could be efficiently progressed via a Suzuki coupling to provide the API.

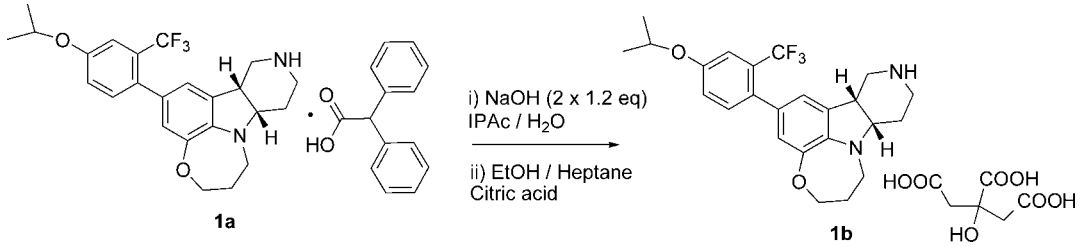
Experimental Section

NMR spectra were obtained at 25 °C in $CDCl_3$ except as indicated, and field strengths for the various nuclei were as follows: ^{1}H (400.1 MHz), ^{13}C (100.6 MHz), ^{19}F (376.5 MHz). Coupling constants (*J*) are given in hertz.

Scheme 13. **Formation of the API**



Scheme 14. **Formation of the desired API salt form**



(*E*)-Chroman-4-one oxime (14). 4-Chromanone (25 kg, 169 mol) was charged to a 100 gallon glass-lined reactor followed by hydroxylamine hydrochloride (12.9 kg, 185 mol) and methanol (37.6 kg). Agitation was set to 100 rpm and the jacket temperature to 20 °C. Triethylamine (19.1 kg, 189 mol) was charged to the reactor over 15 min, adjusting the addition rate in order to maintain the batch temperature at <30 °C. The agitation was increased to 150 rpm and the batch set to heat to 80 °C in jacket mode over a period of 30 min. The batch began to reflux at ∼70 °C and was held at reflux with a jacket temperature of 80 °C for 2 h or until HPLC indicated >99.5% conversion. The batch was then cooled to 50 °C, and water (250 kg) was added above surface over a 60 min period. The batch was then cooled to 15 °C over 90 min. The batch was held at 15 °C for 30 min with the agitator set at 60 rpm. A sample of the slurry was taken and the mother liquor submitted for analysis to ensure <0.5 wt % of compound **14** remained. The batch was then filtered on a Nutsche filter using a 1 μm Dacron cloth. The cake was washed with 98 kg of purified water in three portions. The wet cake was then dried in a tray drier at 60 °C under full vacuum for 12 h or until the KF level was <0.3 wt % to provide 25.7 kg of compound **14** in 93% yield (100 area %, 100.3 wt %, <0.1% MeOH). Metal results were Fe 1.6 ppm, Cd 1 ppm, Ba 0.8 ppm, all other metals ≤0.5 ppm.

2,3,4,5-Tetrahydrobenzo[*b*][1,4]oxazepine hydrochloride (6b). Compound **14** (25.6 kg, 157 mol) was charged to a 50 gallon glass-lined reactor followed by anhydrous tetrahydrofuran (53.8 kg), which was charged through the dip leg using nitrogen pressure. The agitation was set to 90 rpm and the batch temperature to 25 °C. A sample of the solution was taken for KF analysis to ensure that the KF was <500 ppm. To a 200 gallon glass-lined reactor venting to a flame arrestor was added DIBAl-H (50 wt % solution in toluene, 185.8 kg, 653 mol) using ∼10 psig nitrogen pressure on the DIBAl-H cylinder. On completion of the addition the cylinder block valve was closed and the DIBAl-H cylinder was slowly vented to 5 psig. Toluene (2 kg) was charged to a stainless steel pressure cylinder. The nitrogen feed port on the DIBAl-H cylinder was connected to the toluene cylinder and the toluene cylinder pressurized to 15–20 psig with nitrogen. The feed line was flushed by transferring the toluene from the pressure cylinder into the reactor followed by blowing the line with nitrogen. The reactor containing the DIBAl-H was cooled to ensure the contents were <2 °C, the reactor was vented to the flame arrestor, and the nitrogen purge was 0.5 scfm. The solution of compound **14** in THF was transferred using nitrogen pressure to the reactor containing the DIBAl-H such that the addition was above surface and that the reaction temperature was <10 °C over 2 h 40 min. On completion of the addition, the batch was warmed to 25 °C over 50 min. THF (4 kg) was used to rinse the 50 gallon reactor and then transferred using nitrogen pressure to the reaction vessel. The nitrogen purge was reduced to 0.1 scfm, and the batch was aged at 25 °C for 2 h or until HPLC indicated >99.5% conversion. A 2-propanol cylinder was connected to a nitrogen line and pressurized to ∼5 psig nitrogen pressure. 2-Propanol (10.5 kg) was then charged to the batch using nitrogen pressure over a period of 30 min. The addition rate was controlled using a needle valve in order to maintain the temperature of the batch at <30 °C and control the evolution of hydrogen. To a 300 gallon glass-lined reactor was added water (203 L) followed by potassium sodium tartrate (Rochelle's salt) (200 kg, 709 mol). Sodium hydroxide (50 wt %, 39.5 kg) was then added to the solution of Rochelle's salt using deadhead vacuum, and the charging line was rinsed with water (2 L).

The batch temperature of the quench solution was checked to be <30 °C, and the reactor was aligned to vent to the thermal oxidizer. At this point the reaction solution was transferred to the quench tank using nitrogen pressure and a needle valve to control the addition rate and to maintain the reactor temperature between 25 and 30 °C. The addition was carried out above surface and took 2 h 50 min. During the addition ~22 000 L of isobutane gas was expected to be generated. After the addition was complete, toluene (5 kg) was charged to the 100 gallon reaction tank through the dip leg using deadhead vacuum and then transferred to the quench tank using a slight nitrogen pressure. Dry nitrogen purges were then carried out through the dip leg and headspace of the quench tank at 1 scfm each. The temperature was set to 30 °C in batch mode, and the agitation was increased to 125 rpm. During the heat-up the isobutane gas dissolved in the toluene was released. The nitrogen sparge through the dip leg was continued for 75 min until the isobutane gas evolution had stopped. At this point the nitrogen purge through the dip leg was stopped and the headspace nitrogen purge was reduced to 0.1 scfm. The remaining isobutane dissolved in the toluene phase was then vacuum stripped from the reaction mass by applying ~600 mmHg vacuum and gradually increasing the vacuum to 300 mmHg in 25 mmHg steps, each time allowing for the oxidizer gas flow rate to stabilize. The batch was held at 300 mmHg for 30 min until the isobutane evolution had ceased. The reactor vents were aligned with the process scrubber, the agitation was stopped, and the phases were allowed to separate. The aqueous phase was discharged into drums. The organic phase was discharged into drums, and a toluene rinse (10 kg) was charged to the reactor and combined with the organic phase. The combined organic phase was sampled for KF (criterion <1.0 wt %). The organic layer was recharged to the 300 gallon glass-lined reactor through a 0.5 μm cartridge filter using deadhead vacuum of ~300 mmHg. The agitation was set to 75 rpm, and HCl in 2-propanol (3.5 kg, 5.5 N) was charged through the dip leg using a Teflon-coated wilden pump. The HCl was charged through the dip leg to avoid losing HCl to the vapor space during the addition. The batch was then heated to 70 °C in batch mode. When the batch reached 70 °C, a further charge of HCl in 2-propanol (32 kg) was added through the dip leg over a period of 60 min. On completion of the addition, the batch was held at 70 °C for 30 min, after which time the batch was cooled to 20 °C over 3 h and the agitation was set to 50 rpm. When the batch temperature reached <25 °C, a sample was taken to ensure that the mother liquor contained <1.0 wt % of compound **6b**. The slurry was filtered on a Nutsche filter containing a 1 μm Dacron filter cloth. Toluene (50 kg) was charged to the reactor using deadhead vacuum and agitated at 100 rpm for 5 min. The toluene was then discharged to wash the cake in two portions. The wet cake was dried in a tray drier at 50 °C and 200 mmHg vacuum until a constant weight was obtained. The product was isolated as a white solid (26.4 kg) in 91% yield with 100 area % and 79.1 wt % (based on freebase).

6,7,9,10,11,12-Hexahydro-5*H*-[1,4]oxazepino[2,3,4-*hi*]pyrido[4,3-*b*]indole hydrochloride (4). To a 30 gallon glass-lined reactor was charged sodium nitrite (9.8 kg, 142 mol) followed by water (21 L). The mixture was agitated at 80 rpm and 20 °C to form a homogeneous solution. To a 100 gallon glass-lined reactor was charged compound **6b** (24 kg, 129 mol) followed by water (108 L). The solution was cooled to 10 °C, and hydrochloric acid (37 wt %, 14.8 kg) was then charged to the reactor while maintaining the temperature at <20 °C. The solution of sodium nitrite was charged to the 100 gallon reactor containing compound **6b** using nitrogen pressure and controlling the addition such that the temperature was maintained between 10 and 20 °C. Water (2 kg) was used to rinse the 30 gallon reactor and transferred to the reaction vessel. The batch was warmed to 22 °C and held at 22–25 °C for 60 min or until HPLC showed >99.0% conversion to compound **15**. The batch was cooled to 0–10 °C, and ethanol (80.3 kg) was charged using deadhead vacuum. Sodium hydroxide (50 wt %, 76.1 kg) was then charged over a 30 min period using deadhead vacuum (500 mmHg to ensure minimal loss of HCl) while keeping the temperature <20 °C. The pH was checked to be >7, and the batch was cooled to 0–8 °C with 40 rpm agitation. Sodium hydrosulfite (61.9 kg, 355 mol) was charged to the reactor through the manway followed by inertion of the reactor. The agitation rate was increased to 100 rpm, and the batch was heated to reflux for 2 h or until the reaction completion was >99.0 % conversion by HPLC to compound **5**. The reaction was cooled to 20 °C, and the resultant slurry was filtered on a Nutsche filter. The product-rich filtrate was recirculated through the reactor until solids were no longer present in the reactor. The cake was washed with ethanol (37.9 kg), and the wash was discharged to the reactor containing the filtrate. The combined filtrate and wash were then distilled under vacuum (50–150 mmHg) while keeping the batch temperature <40 °C until the liquid volume remaining in the reactor was ~200 L. A second cake wash with ethanol (37.9 kg) was then transferred and the distillation continued until ~200 L remained and the amount of ethanol remaining was <5 vol %. The batch was cooled to 20–25 °C, and MTBE (59.7 kg) was charged using deadhead vacuum (~600 mmHg). The biphasic mixture was agitated for 20 min and the phases were separated (30 min). The lower aqueous phase was extracted a second time with MTBE (48 kg). The combined organic phase was then recharged to a 100 gallon reactor and distilled under vacuum (~50 mmHg) at 35–40 °C until ~60 L remained in the reactor. 2-Propanol (95.7 kg) was charged using deadhead vacuum, and the distillation continued until ~150 L remained in the reactor, when a further 95.7 kg of 2-propanol was charged. A sample was taken to ensure that MTBE was <5 vol % and water was <5 wt %. Additional 2-propanol (25.2 kg) was added in order to obtain a 12 wt % IPA solution, and the batch was then cooled to 5–8 °C. 4-Piperidone monohydrate hydrochloride (21.2 kg, 138 mol) was charged to the reactor, and the batch was heated to 40 °C. When the batch temperature was >35 °C, a solution of HCl in 2-propanol (5.5 N, 27.8 kg) was added through the dip leg using deadhead vacuum. The batch was then heated at reflux for 2 h or until HPLC conversion indicated >98.5%. The batch was then cooled to <20 °C and filtered on a Nutsche filter using a 1 μm Dacron filter cloth. 2-Propanol (67.9 kg) was added to the reactor and discharged to wash the cake in three portions. The wet cake was deliquored using a nitrogen purge and by applying vacuum (~100 mmHg) for 13 h. Water

(175 L) was charged to a 100 gallon glass-lined reactor followed by the wet cake (97.5 kg). The slurry was heated to 105 °C over a 90 min period. A clear solution was visible at 83 °C, and the batch was held at 90 °C for 20 min. The solution was cooled in batch mode from 90 to 80 °C over 30 min, 80 to 60 °C over 40 min, and then 60 to 5 °C over 60 min. Following a 60 min hold at 5 °C, the slurry was filtered on a Nutsche filter containing a 1 μm Dacron filter cloth and washed with precooled water (3–5 °C) (60 L) in three portions. The wet cake was dried at 70 °C and 50 mmHg vacuum until constant weight to provide compound **4** (24.6 kg) in 72% yield (100 wt %) over the three steps.

4: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.29 (m, 2H), 3.05 (t, J = 6.1 Hz, 2H), 3.47 (t, J = 6.4 Hz, 2H), 4.03 (t, J = 5.6 Hz, 2H), 4.26 (m, 4H), 6.69 (d, J = 7.9 Hz, 1H), 6.93 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H) and 9.71 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.44, 30.39, 40.65, 46.29, 71.14, 103.33, 110.30, 110.68, 119.90, 126.58, 128.33, 132.46, 144.75. HRMS: calcd for $C_{14}H_{16}N_2O$ 229.1341 [M + 1]; found 229.1340 [M + 1].

(8a*S*,12a*R*)-6,7,9,10,12,12a-Hexahydro-5*H*-[1,4]oxazepino[2,3,4-*hi*]pyrido[4,3-*b*]indole hemidibenzoyl-D-tartrate (18). Compound **4** (15 kg, 56.7 mol) was charged to a 100 gallon glass-lined reactor. Trifluoroacetic acid (111 kg, 974 mol) was added to the reactor using deadhead vacuum followed by triethylsilane (23.1 kg, 199 mol). The agitation was set to 150 rpm to ensure adequate mixing. The resultant solution was heated to 45 °C and held for at least 24 h until the reaction reached >94% conversion. The reaction was cooled to <5 °C, and water (56 L) was added. The batch temperature was adjusted to 20 °C, and the phases were agitated for 15 min and then allowed to settle. The product-rich aqueous phase was separated, then recharged to the reactor. *n*-Heptane (38 kg) was added to the reactor, and the biphasic mixture was agitated for 15 min and then allowed to settle. The aqueous phase was separated and washed a second time with *n*-heptane (38 kg) to remove the siloxane byproducts. The aqueous phase was separated, recharged to the reactor, and cooled to 5 °C. A solution of NaOH was prepared in a separate 30 gallon glass-lined reactor using water (80 L) and adding 50 wt % NaOH (86 kg) while keeping the temperature <30 °C. The prepared solution of NaOH was then charged to the product-rich aqueous phase such that the temperature did not exceed 30 °C (~45 min). Water (53 L) was used to rinse the NaOH vessel and transferred to the product-containing vessel. The batch temperature was adjusted to 20 °C, and a sample was taken for pH (pH > 12). Isopropyl acetate (65 kg) was added to the aqueous phase and the mixture agitated for at least 15 min. The phases were separated, and the aqueous phase was extracted with IPAc (2 × 65 kg). The combined organic phase was recharged to the 100 gallon glass-lined reactor and washed with a 20% brine solution (45.5 kg). The organic phase was then distilled under vacuum (100 mmHg), gradually increasing the jacket temperature to 50–55 °C. The distillation was continued until 30–40 L remained in the reactor. Methanol (108 kg) was added to the reactor, and the distillation was continued at 200 mmHg and a jacket temperature of 50–60 °C. The distillation was continued until ~40 L remained in the reactor. A second charge of methanol (107 kg) was added and the distillation continued until the level was ~60 L. Methanol (100 kg) was charged to the reactor, a sample was taken for residual isopropyl acetate (criterion ≤5%), and the batch was cooled to 20 °C. The solution was transferred through a 0.5 μm cartridge filter to remove any salts into a 100 gallon glass-lined reactor, and methanol (39.9 kg) was added to make a total solution weight of 178.3 kg. The batch was then heated to 50–55 °C, and water (52 L) was added while maintaining the batch temperature at 50–55 °C. To a separate 30 gallon glass-lined reactor was charged dibenzoyl-L-tartaric acid (3.95 kg, 11 mol) followed by methanol (16.5 kg) and water (5 L). The mixture was agitated until a solution formed. The dibenzoyl-L-tartaric acid solution was then charged to the solution of indoline. The solution was seeded with 65 g of the dibenzoyl-L-tartaric acid salt of the indoline and the slurry held at 50 ± 3 °C for 1 h. The batch was then cooled to 35 °C over 2 h. When the batch reached 40 °C, a sample of the slurry was filtered and the cake was submitted for analysis (criterion: ≥98% undesired enantiomer). The batch was further cooled to 25 °C over 1 h. The batch was filtered on a Nutsche filter and the cake washed with methanol (17 kg). The combined mother liquor and cake wash were recharged to a 100 gallon glass-lined reactor and distilled under vacuum (150 mmHg), heating to 50–55 °C until 30–40 L remained in the vessel. Methylene chloride (120 kg) was charged to the reactor followed by a solution of sodium hydroxide (4.7 kg of 50% NaOH in 61 L of water), maintaining the temperature at <30 °C. The pH of the reaction mixture was checked to be >10, and after agitating the biphasic mixture for 15 min the phases were allowed to separate. The organic layer was separated and washed with a 10% brine solution (66 kg). After agitating for 15 min the phases were allowed to separate. The organic phase was then distilled at atmospheric pressure until there was 30–40 L remaining, at which point methanol (124 kg) was charged and the distillation continued at 300 mmHg and a jacket temperature of 50 °C. The distillation was continued until ~60 L remained. Methanol (92 kg) was then charged to the reactor, and a sample was taken for residual DCM (criterion ≤5%). The batch was then heated to 50 ± 3 °C. Water (42 L) was charged to the reactor while maintaining the batch temperature at 50 ± 3 °C. In a separate 30 gallon glass-lined reactor a solution of dibenzoyl-D-tartaric acid (3.95 kg, 11 mol) in methanol (13 kg) and water (4 L) was prepared and then discharged to a drum. The solution of dibenzoyl-L-tartaric acid (14 kg) was added to the reactor containing the product-rich solution and then seeded with compound **18** (64.5 g, 0.15 mol). The remaining dibenzoyl-L-tartaric acid solution was then charged to the slurry, and the slurry was held at 50 ± 3 °C for 1 h. The batch was then cooled to 25 °C over 3 h. On reaching 25 °C a sample was taken, the slurry was filtered, and the cake and mother liquor were submitted for analysis (criterion: cake ≥98% desired enantiomer; filtrate 30–35% desired enantiomer present). The slurry was filtered on a Nutsche filter and washed with methanol (17 kg). The wet cake was dried in a tray drier at 70 °C under vacuum to provide the product as a white solid (5.8 kg) in 27% yield. The solid had a wt % of 99.3%, 100 area %, and the enantiomeric ratio was 98.9:1.1 desired/undesired. **18**: DSC 196.89 °C; ^{1}H NMR (400

MHz, DMSO-d_6) δ 1.85–2.03 (m, 4H), 2.18 (t, J = 12 Hz, 1H), 2.29 (m, 1H), 2.75 (td, J = 12 and 4 Hz, 1H), 2.98–3.08 (m, 3H), 3.25–3.31 (m, 2H), 3.61 (t, J = 12 Hz, 1H), 4.30–4.34 (m, 1H), 5.60 (s, 1H), 6.60–6.73 (m, 3H), 7.47 (t, J = 8 Hz, 2H), 7.60 (t, J = 8 Hz, 1H) and 7.97 (2H, d, J = 8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.57, 30.72, 37.74, 38.82, 44.88, 49.97, 62.75, 71.94, 75.39, 118.12, 119.91, 120.67, 128.46, 128.86, 129.49, 129.55, 130.94, 133.29, 133.75, 142.49, 146.42, 165.53, and 170.19; HRMS calcd for $C_{14}H_{19}N_2O$ 231.1497 [M + 1]; found 231.1488 [M + 1].

(8a*S*,12a*R*)-*tert*-Butyl-2-bromo-6,7,9,10,12,12a-hexahydro-5*H*-[1,4]oxazepino[2,3,4-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (20). To a 100 gallon glass-lined reactor was charged compound **18** (9 kg, 21.97 mol) followed by methylene chloride (77.7 kg) and water (61 L). Sodium hydroxide (5.3 kg, 132.5 mol, 50 wt %) was charged to the reactor via pump while maintaining the temperature below 30 °C. The pH of the aqueous phase was checked to be pH > 7. Di-*tert*-butyldicarbonate (5.2 kg, 23.82 mol) was added followed by a rinse of the charging line with methylene chloride (1.5 kg). The biphasic mixture was stirred for 60 min at 25 °C. HPLC analysis of the reaction mixture showed the absence of starting material. The two phases were separated, and the organic phase was recharged to a second vessel (50 gallon glass-lined reactor). A sample of the organic phase was taken for KF (criterion <0.5 wt %). The organic phase was cooled to −5 °C in batch mode. A bromine solution (3.68 kg, 23.02 mol) in methylene chloride (1.7 kg) was charged to a Teflon-lined stainless steel charging cylinder. The bromine solution was transferred to the reactor containing the organic phase using ~5 psig of nitrogen pressure, subsurface over a period of ~30 min, keeping the temperature at −5 ± 3 °C. Following the charge the charging line was rinsed with methylene chloride (1 kg) and transferred to the reactor. On completion of the addition, HPLC analysis indicated the absence of starting material. *n*-Heptane (58.4 kg) was charged to the reactor using a pump over a 45 min period, keeping the batch temperature between −5 and 0 °C. During the addition the product began to crystallize. The reaction mass was held between −5 and 0 °C for 15 min. The product was collected by filtration on a 30 in. jacketed Nutsche filter using a 1 μm Dacron filter cloth. *n*-Heptane (17.5 kg) was charged to the reactor and cooled to 0 °C and used to wash the cake. The cake was dried in a tray drier at 50 °C/50 mmHg for 18.5 h to give the product, **20**, as a light brown solid, 9.8 kg (88% corrected yield, 97 wt %, 95.2 area %), with 4.8 area % of compound **21** (4.1 wt %).

20: DSC 117.85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.88–1.90 (m, 2H), 2.02–2.03 (m, 2H), 2.52–2.62 (m, 1H), 3.21–3.40 (m, 4H), 3.42–3.82 (m, 4H), 4.35–4.45 (m, 1H), 6.89 (d, J = 1.8 Hz, 1H), and 6.92 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.49, 28.41, 30.84, 39.13, 41.22, 44.77, 49.97, 64.36, 72.15, 79.62, 110.99, 121.02, 122.56, 135.60, 142.18, 146.78, and 154.76; HRMS calcd for $C_{19}H_{26}N_2O_3Br$ 409.1127 [M + 1]; found 409.1146 [M + 1].

21: DSC 104.21 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76–1.82 (m, 1H), 1.90–1.96 (dq, J = 16 and 4 Hz, 1H), 2.06 (m, 2H), 2.45–2.55 (m, 2H), 2.85 (m, 2H), 2.99 (dd, J = 12 and 8 Hz, 1H), 3.08–3.14 (dt, J = 12 and 4 Hz, 1H), 3.31–3.38 (m, 2H), 3.77 (m, 1H), 4.37 (dt, J = 12 and 4 Hz, 1H), 6.85 (1H, s) and. 6.92 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.76, 30.69, 41.55, 41.67, 49.26, 49.67, 64.76, 72.08, 111.00, 120.48, 122.14, 137.10, 142.04 and 147.02; HRMS calcd for $C_{14}H_{18}N_2OBr$ 309.0602 [M + 1]; found 309.0602 [M + 1].

(8a*S*,12a*R*)-2-[4-Isopropoxy-2-(trifluoromethyl)phenyl]-6,7,8a,9,10,11,12,12a-octahydro-5*H*-[1,4]oxazepino[2,3,4-*hi*]pyrido[4,3-*b*]indole diphenylacetate (1a). To a 50 gallon glass-lined reactor was charged water (17 L) followed by potassium carbonate (7.2 kg, 52 mol), compound **20** (8.5 kg, 17.35 mol), and 4-isopropoxy-2-trifluoromethylphenylboronic acid, **22** (5.8 kg, 23.4 mol). Isopropyl acetate (59.3 kg) was charged, and agitation was set to 180 rpm. The nitrogen purge was set to sparge through the dip tube. The reactor was degassed by pressurization to 1000 mmHg, venting to 760 mmHg and applying vacuum (300 mmHg). This was repeated three times. Tetrakis(triphenylphosphine)palladium (0) (0.44 kg, 0.38 mol) was slurried in isopropyl acetate (2 kg) and transferred to the reactor using deadhead vacuum. The contents of the batch were heated to reflux (~85 °C) and held for 3 h or until HPLC analysis indicated >99.5% conversion. The reaction mass was allowed to cool to 20 °C. A Nutsche filter was prepared with a 3–5 μm Dacron filter bag and Celite 545 (15 kg), and water was added to wet the Celite. The contents of the reactor were then filtered through the Celite, and the filtrate was collected. Isopropyl acetate (73.9 kg) was added to the reactor and then discharged to the Nutsche filter to wash the cake. The filtrate was charged back into a 50 gallon glass-lined reactor, and the phases were allowed to settle for 15 min. The bottom aqueous layer was discharged. The organic layer was then distilled under vacuum (100 mmHg), keeping the batch temperature <50 °C until ~51 L remained in the vessel and the water content was <1% by KF. The solution was then heated to reflux (~85 °C). Methanesulfonic acid (3.3 kg, 34.3 mol) was charged to a Teflon-lined charging cylinder and then added to the reactor using nitrogen pressure. The addition rate was controlled by an in-line needle valve and took ~30 min. The reaction began to off-gas CO_2 and isobutene ca. two-thirds of the way through the addition (max. 380 L of each). The reaction mixture was kept at ~85 °C for a further 1 h or until HPLC analysis indicated no starting material remaining. The reaction was cooled to 20 °C, and a solution of potassium carbonate (7.2 kg, 52 mol) in water (43 L) was added over a 30 min period; the addition rate was controlled to maintain the pressure in the reactor below 900 mmHg. The reaction mixture was stirred for 15 min, and the pH of the aqueous phase was checked to be >7. The reactor contents were filtered through water wet Celite 545 (8 kg) and washed with isopropyl acetate (73.9 kg). The filtrate was recharged to the vessel, and the phases were allowed to settle over a 15 min period. The bottom aqueous layer was then discharged. About 100 mmHg was then applied to the reactor, and the organic phase was distilled, keeping the batch temperature <50 °C until ~85 L remained in the reactor. Picachem carbon 80PN (1 kg, 10 wt %) was charged to a 100 gallon glass-lined reactor. The organic phase was transferred to the 100 gallon reactor followed by a rinse with isopropyl acetate (5 kg). The slurry was heated to 50 °C, held for 2 h, and then cooled to 20–30 °C. The slurry was filtered through Celite 545

(10 kg) and washed with isopropyl acetate (73.9 kg). A sample was removed to determine Pd content for information only. The filtrate was charged back into the 50 gallon glass-lined reactor through a 0.2 μm cartridge filter using deadhead vacuum. About 100 mmHg vacuum was applied to the reactor, and the solution was distilled, keeping the batch temperature <50 °C until ~53 L remained in the reactor. A sample was taken for wt % water and concentration of the compound (criterion: <1 wt % and 11–12 wt %, respectively). If the 11–12 wt % is not met, isopropyl acetate can be added or further distillation performed. *n*-Heptane (20.5 kg) was charged to the reactor, and the batch was heated to 60–65 °C. Diphenylacetic acid (3.7 kg, 17.4 mol) was charged to a 30 gallon glass-lined reactor followed by isopropyl acetate (13.1 kg). The batch was heated to 55–60 °C to obtain a homogeneous solution. The diphenylacetic acid solution (~4 L) was charged to the rich organic phase at 60 °C. The reaction mixture was seeded with a seed slurry (150 g in 0.7 kg of *n*-heptane). Once the batch was seeded, the remainder of the diphenylacetic acid solution was transferred to the slurry over a period of 30 min. The 30 gallon reactor was rinsed with isopropyl acetate (2 kg) and transferred to the slurry. The reaction mass was allowed to cool to 0 °C over a period of 2 h and held at 0 to 5 °C for 1 h. A sample was taken for mother liquor concentration and was found to be 2.1 wt %. The product was filtered on a 1 μm Dacron filter bag and washed with a cooled mixture (0 to 5 °C) of *n*-heptane/IPAc (14.4 kg:7.8 kg). The product was dried at 50 °C/50 mmHg for 21 h to give a white solid, 6.1 kg (55%, 98.1 area%).

1a: DSC 162.80 °C; ^{19}F NMR (376 MHz, MeOH-d_4) δ −58.83; ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.36 (d, J = 8 Hz, 6H) 2.00–2.15 (m, 3H), 2.30 (m, 1H), 2.47–2.58 (m, 2H), 3.12 (td, J = 12 and 4 Hz, 1H), 3.20–3.26 (m, 2H), 3.31–3.51 (m, 3H), 3.73–3.79 (m, 1H), 4.40–4.50 (m, 1H), 4.69 (septet, J = 8 Hz, 1H), 4.94 (s, 1H), 6.74 (s, 1H), 6.77 (s, 1H) and 7.10–7.33 (m, 13H); ^{13}C NMR (100 MHz, MeOH-d_4) 19.25, 19.74, 29.08, 36.31, 37.48, 43.38, 48.45, 59.64, 61.18, 68.62, 70.37, 111.75, 111.81, 116.44, 117.18, 119.54, 121.19, 123.91, 124.35, 126.20, 127.12, 127.46, 130.61, 131.19, 131.82, 139.92, 140.30, 144.39, 155.39, 177.42; HRMS calcd for $C_{24}H_{28}N_2O_2F_3$ 433.2103 [M + 1]; found 433.2106 [M + 1].

(8a*S*,12a*R*)-2-[4-Isopropoxy-2-(trifluoromethyl)phenyl]-6,7,8a,9,10,11,12,12a-octahydro-5*H*-[1,4]oxazepino[2,3,4-*hi*]pyrido[4,3-*b*]indole citrate (1b). The diphenylacetate salt (895.0 g, 1.4 mol) was slurried in IPAc (3.6 L). A solution of sodium hydroxide (66.6 g, 1.67 mol) in water (3.6 L) was charged to the slurry, and the biphasic mixture was stirred at 20 °C for 10 min. The two phases were separated, and the organic phase was recharged to the vessel. To this was added a second charge of sodium hydroxide (66.6 g, 1.67 mol) in water (3.6 L). The biphasic mixture was stirred for 10 min, and the two phases were separated. The organic phase was washed with water (3.6 L) and then evaporated to dryness on the rotary evaporator. The residue was dissolved in ethanol (2.7 L) and water (25 mL). Citric acid (266 g, 1.39 mol) was added, and the mixture was heated to 50 °C. *n*-Heptane (2.7 L) was charged, maintaining the temperature at ~50 °C. The solution was cooled to 35 °C and seeded with ~0.5 g of seeds. Cooling was continued to 25 °C. *n*-Heptane (3.6 L) was added over a period of 1 h. The slurry was filtered and washed with *n*-heptane/EtOH (70:30) (1 L). The product was dried on the filter under a nitrogen blanket for 24 h. The product was obtained as a white solid, 798.6 g (92%, 100 wt %, 100% chiral purity, residual Pd 14 ppm, 99.55 area % at 265 nm).

1b: ^{19}F NMR (376 MHz, MeOH-d_4) δ −58.76; ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.36 (d, J = 8 Hz, 6H), 2.00–2.40 (m, 4H), 2.50–2.64 (m, 2H), 2.80 (dd J = 12 and 16 Hz, 4H), 3.20 (m, 1H), 3.36–3.45 (m, 3H), 3.50–3.60 (m, 2H), 3.73–3.79 (m, 1H), 4.40–4.50 (m, 1H), 4.69 (septet, J = 8 Hz, 1H), 6.74 (s, 1H), 6.82 (s, 1H), 7.13 (dd, J = 4 and 8 Hz, 1H), and 7.09–7.23 (m, 2H); ^{13}C NMR (MeOH-d_4, 100 MHz) δ 22.59, 22.95, 32.43, 39.54, 40.90, 45.27, 46.68, 51.82, 64.54, 71.91, 73.73, 74.89, 115.06, 115.12, 119.73, 120.59, 122.93, 124.52, 127.24, 130.78, 133.98, 134.46, 135.19, 143.31, 147.73, 158.71, 175.54, and 180.04.

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