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Development of a New Practical Synthesis of a 5-HT_{2C} Receptor Agonist†

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Abstract:

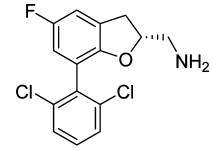
A new practical synthesis of a 5-HT_{2C} receptor agonist has been developed and implemented on multikilogram scale. The key step, the selective epoxide opening in the glycidyl tosylate with the aryl Grignard reagent, allowed the incorporation of this commercially available chiral C_3 synthon into the molecule and elaboration of the resulting intermediate into the target aminomethyldihydrobenzofuran without loss of enantiomeric purity.

Introduction

The 5-HT_{2C} receptor is one of a family of 14 G-protein coupled receptors which respond to stimulation by the endogenous ligand 5-hydroxytryptamine or serotonin.[1] Our interest in 5-HT_{2C} agonism stems from the fact that, in some brain regions such as the mesolimbic system, dopamine is under the control of 5-HT_{2C} receptors. 5-HT_{2C} agonists diminish dopamine receptor firing and dopamine release in these areas without affecting dopamine levels in other areas, such as the nigrostriatal track, in which dopamine is important for control of movement. Reducing dopamine activity in the mesolimbic system has a beneficial effect on the most florid of the symptoms of schizophrenia, the so-called positive symptoms. Stimulation of 5-HT_{2C} receptors would also produce an antidepressant effect similar to selective serotonin reuptake inhibitors which stimulate serotonin receptors indirectly by increasing synaptic levels of serotonin. However, because of negative feedback controls, they take some time to achieve their effect. Direct serotonin agonists would achieve the same effect immediately. Correspondingly, 5-HT_{2C} agonists are not only active in animal models of depression, but indicate a faster onset in models which predict onset.

Another one of the most widely appreciated functions of the 5-HT_{2C} receptor is the regulation of appetite and feeding behavior. Agonists of 5-HT_{2C} decrease appetite and feeding and thus lead to loss of weight.

WAY-255719 (**1**)[2] has been shown to be a potent 5-HT_{2C} full agonist and demonstrates greater than 100-fold selectivity over 5-HT_{2A} and 5-HT_{2B} receptors in binding and functional assays. It has been effective in several animal models predictive of anti-psychotic activity, with an atypical anti-psychotic profile and has been selected from a series of analogue compounds and advanced as a development candidate for treatment of schizophrenia in Wyeth's 5-HT_{2C} agonist program.



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On a small scale, the lead compound was first prepared as a racemate (*rac*-**1**) via an eight-step synthetic sequence (Scheme 1).[2] Most of the SAR analogues of **1** were synthesized in a similar manner, one variation being the point at which Suzuki coupling was done: for many analogues it followed the dihydrobenzofuran ring formation and utilized a reverse nucleophile−electrophile position of functionalities. In the case of **1**, the alternative approach did not work due to the instability of *o*,*o*-dichlorophenylboronic acid under the conditions of Suzuki coupling.

To resolve the enantiomers, *rac*-**1** was converted to its Cbz derivative and subjected to chiral HPLC separation. Subsequent removal of the Cbz protection gave the enantiomerically pure **1**.[3]

Although the synthesis described above is adequately efficient for the preparation of the racemic product and, with minor modifications, could be scaled up to produce a few

† Wyeth was acquired by Pfizer on 16 October 2009.

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(1) For a review of therapeautic aspects of the 5-HT_{2C} receptor, see: Rosenzweig-Lipson, S.; Dunlop, J.; Marquis, K. L. *Drug News Perspect.* **2007**, *20*, 565.

(2) (a) Gross, J. L.; Williams, M. J.; Stack, G. P.; Gao, H.; Zhou, D. Dihydrobenzofuranyl alkanamine derivatives as brain serotonin 2C receptor agonist and partial agonists and their preparation, pharmaceutical compositions and use in the treatment of CNS disorders. *Chem. Abstr.* **2008**, *149*, 471316. U.S. Patent 7,435,837, 2008. (b) Gross, J. L.; Dunlop, J.; Gao, H.; Grauer, S.; Harrison, B. L.; Huselton, C.; Kalgaonkar, S.; Lai, M.; Logue, S.; Marquis, K.; Mazandarani, H.; Stack, G. P.; Sung, A.; Williams, M. J.; Zhang, J.; Zhou, D.; Rosenzweig-Lipson, S. 2-[Aminomethyl]dihydrobenzofurans as 5-HT_{2C} receptor agonists. *Abstracts of Papers of the 238th ACS National Meeting*; American Chemical Society: Washington, DC, August 2009, MEDI-334.

(3) It was found later that the enantiomers of the unprotected amine could also be separated by a normal phase preparative HPLC. The separation was performed on a 100-g scale and took about 1 week to complete using a 25 cm × 3 cm column.

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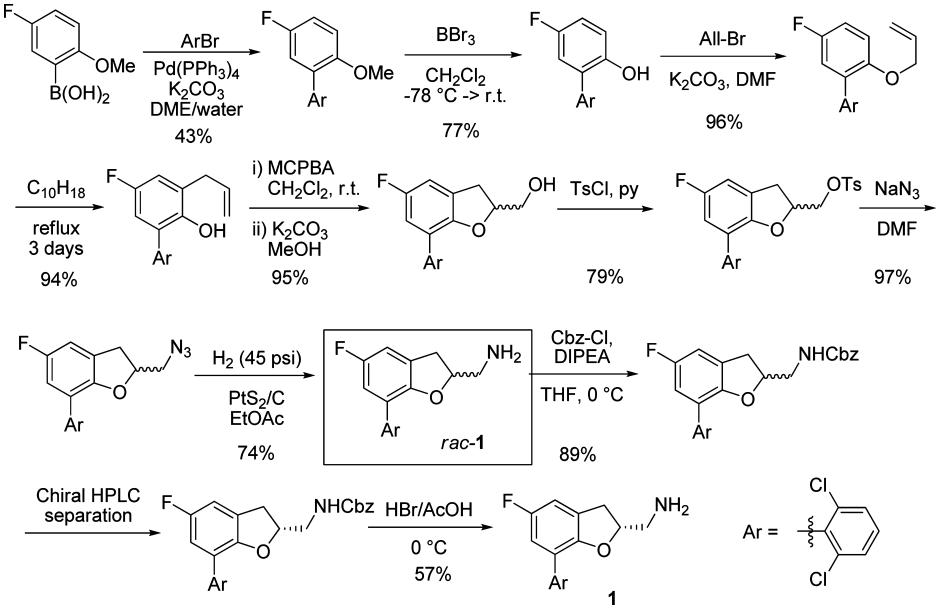
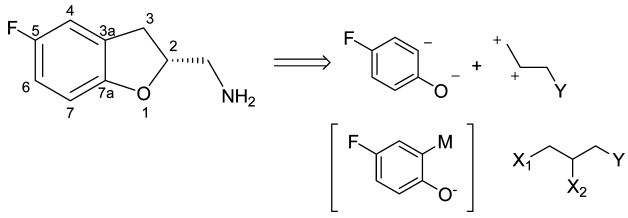
Scheme 1. **Medicinal Chemistry approach to preparation of 1**



Scheme 2. **Retrosynthetic considerations for new multikilogram route to 1**



hundred grams of material,[4] the need for chiral separation at the end, via either chemical resolution or chromatography, undoes all of its advantages. This contribution describes development of a new practical synthesis of **1** and its implementation for preparation of kilogram quantities of the active pharmaceutical ingredient (API).

Selection of Synthetic Route. Among a variety of plausible approaches to the chiral benzodihydrofuran, we selected one which retrosynthetically puts the molecule together from the phenolic part and a C_3-fragment (Scheme 2). The advantage of this approach would be the possibility to introduce the chirality into the target molecule with the chiral C_3 fragment, and there is a considerable selection of compounds of this type commercially available in enantiomerically pure form.[5] As the two furan cycle-forming reactions would be done sequentially, a proper choice of X_1, X_2, and Y functionalities as well as the utilization of protecting groups would be required to ensure the selectivity of the transformations. An epoxide was considered a proper choice for the X_1, X_2 functionalities as it would provide the necessary regioselectivity (nucleophilic opening usually occurs at the terminal carbon for steric reasons).[6] It may also provide good chemoselectivity with respect to other nucleophilic substitutions (if needed), and a number of compounds containing C_3-fragments with epoxides are commercially available in enantiomerically pure form, particularly glycidol derivatives **3**.

The synthetic plan shown in Scheme 3 illustrates the general strategy for constructing the chiral dihydrobenzofuran moiety. Epoxide opening with an aryllithium, organocopper, or a Grignard reagent would create the carbon−carbon bond of the heterocycle, and such openings are well documented in the literature.[7] The hydroxyl formed as a result of the epoxide opening would be converted to a leaving group and used to close the five-membered cycle by a nucleophilic substitution. The pendant functional group, Y, would need to be a properly protected amine or a functional group which could be converted into the amine later so as not to interfere with the ring formation. Details such as the choice of the protecting groups and reagents, as well as how and at which point to incorporate the dichlorophenyl substituent, were to be filled in along the way.

Proof of Concept. The key step of the new strategy was likely to be the opening of the epoxide with the aryl nucleophile. There are multiple examples of epoxide openings by aryllithium and Grignard reagents, but the implementation of this chemistry on scale has been scarce. Reactions between organometallic reagents and epoxides are catalyzed by the copper(I) salts[8] or Lewis acids (e.g., BF_3 etherate).[9] Without any catalysts, these reactions have been reported to be sluggish and are accompanied by a variety of side products.[7a]

In a model reaction, *o*-methoxyphenylmagnesium bromide **2a** taken in an excess as a commercial THF solution was treated with benzyl glycidol **3a** in the presence of CuI as a catalyst at −40 °C (Scheme 4). Reaction was complete in 1 h, and no

(4) The process in Scheme 1 has been successfully scaled up to 70 g for preparation of **1** and its des-fluoro analogue (unpublished results).

(5) Sheldon, R. A. *Chirotechnology: Industrial Synthesis of Optically Active Compounds*; Marcel Dekker: New York, NY, 1993; Chapter 5.

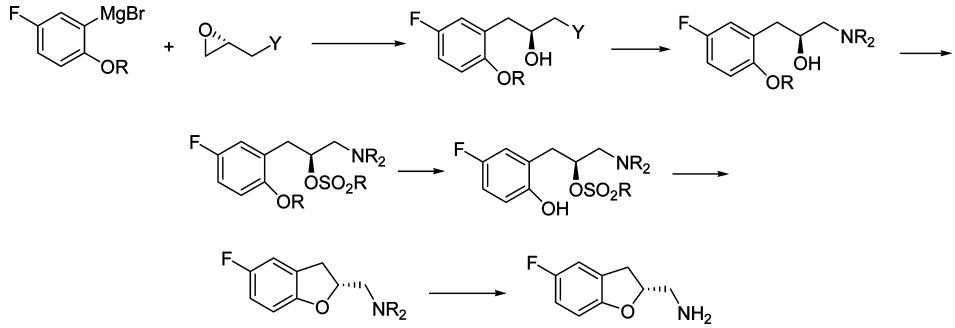
(6) For general reference, see: Lewars, E. G. Oxiranes and Oxirenes. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 7, pp 95−129.

(7) (a) Silverman, G. S. In *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Chemical Industries Series, Vol. 64; Marcel Dekker: New York, NY, 1996; pp 322−325. (b) Gaylord, N. G.; Becker, E. I. *Chem. Rev.* **1951**, *49*, 413. (c) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928. (d) Kurth, M. J.; Abreo, M. A. *Tetrahedron* **1990**, *46*, 5085.

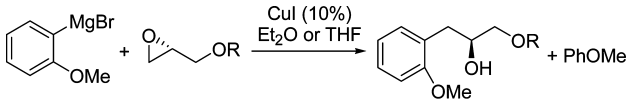
(8) (a) Schuda, A. D. C.; Mazzocchi, P. H.; Fritz, G.; Morgan, T. *Synthesis* **1986**, 309. (b) Review: Erdik, E. *Tetrahedron* **1984**, *40*, 641.

(9) (a) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693. (b) Alexakis, A.; Vrancken, E.; Mangeney, P. *Synlett* **1998**, 1165.

Scheme 3. **General strategy for construction of the chiral dihydrobenzofuran core**



Scheme 4. **Addition of *o*-methoxyphenyl Grignard reagent to glycidol derivatives**



2a **3a**: R = Bn; **3b**: R = Ts **4a**: R = Bn; **4b**: R = Ts

starting epoxide remained in the mixture. Alcohol **4a** and the quenched Grignard reagent (anisole) together with some minor impurities were present in the isolated product mixture.

To allow for more efficient functional group manipulation in the subsequent synthetic steps, glycidyl tosylate **3b**[10] was also subjected to the reaction conditions with *o*-methoxyphenylmagnesium bromide (1 equiv). The reaction was complete in 3 h at −40 °C, resulting in the epoxide opening. No tosylate displacement in the product was observed.

Demethylation of the methoxyaryl in **4a** and **4b** with BBr_3 solution was attempted at this point to study the possibility of direct cyclization of the resulting hydroxyphenol, but it led to a complex mixture of products in both cases.

To facilitate deprotection of the phenol in the later intermediates, methyl protection in the starting arene was changed to benzyl protection. Corresponding 2-benzyloxy-5-fluorophenylmagnesium bromide **2c** (prepared in two steps from 2-bromo-4-fluorophenol) was reacted with glycidol tosylate (Scheme 5). The markedly lower reactivity of the new Grignard reagent toward epoxide opening was apparent from the first experiment, which could be attributed to both electronic contribution of the fluoride substituent and the steric influence of the benzyl group; whereas the reaction with methoxyphenyl Grignard **2a** was complete in 1−3 h, barely a trace of the product **4c** formed with benzyloxyphenyl Grignard **2c** under similar conditions. Raising the reaction temperature to −25 °C and extending the reaction time to 20 h did drive the epoxide opening to completion but also caused in situ cyclization of product **4c** to form the terminal epoxide **5c**.[11] Fortunately, we did not observe detectable opening of **5c** with the starting Grignard reagent **2c**. Increasing the amount of the catalyst or switching from CuI to CuCN did not have any effect on the reaction.

The glycidol tosylate opening was successfully scaled up to 10 g of the starting aryl bromide. The mixture of products in THF was treated with aq NaOH to convert the remaining **4c** to epoxide **5c** (Scheme 6). The resulting mixture of **5c** and side product **6c** (80:20 area % ratio at 215 nm) was treated with a mixture of phthalimide and its potassium salt in DMF[12] which cleanly gave the epoxide opening product **7c**. The latter was an amorphous solid, and we were able to separate it from **6c** that we carried along thus far by simple trituration. The yield of **7c** was estimated at 52% based on the amount of the aryl bromide taken for Grignard formation. Treatment of **7c** with methanesulfonyl chloride in the presence of triethylamine gave mesylate **8c** cleanly as a solid in 95% yield.

A problem was encountered when we attempted the cleavage of the benzyl protection by catalytic hydrogenation. A variety of conditions was screened, none of which presented anything appropriate for optimization on a larger scale.[13]

In parallel with our debenzylation work, we considered changing the protection on the phenol to a MOM group which should withstand Grignard reactions and be removable under mild acidic conditions.[14] MOM-protected 2-bromo-4-fluorophenol was prepared using the procedure developed previously at Wyeth by heating a mixture of the phenol, dimethoxymethane, DMF, and $POCl_3$ in heptane.[15] The Grignard reagent was prepared by reaction with Mg in THF. Addition to the epoxide, however, occurred much slower than in previous cases. The reaction was not complete after 24 h at −23 °C, and the product mixture was overwhelmed by impurities (over 60% by total HPLC peak area). After treatment with aq NaOH, it was reacted with phthalimide−phthalimide K salt mixture. The desired product failed to crystallize or solidify, giving us no means of isolation and purification besides flash chromatography. This route was not pursued any further.

(10) (a) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295. (b) Maruyama, T.; Asada, M.; Shirraishi, T.; Yoshida, H.; Maruyama, T.; Ohuchida, S.; Nakai, H.; Kondo, K.; Toda, M. *Bioorg. Med. Chem.* **2002**, *10*, 1743.

(11) Theoretically, the enantiomer of epoxide **5c** can form by a direct displacement of the tosylate in **3b** without epoxide opening. It has been reported, however (ref 10), that this does not happen in practice and **5c** forms via the epoxide opening and subsequent closure on the other side. This was confirmed as we established that no loss of enantiomeric purity occurred, whereas direct tosylate displacement would lead to the terminal epoxide of opposite stereo configuration.

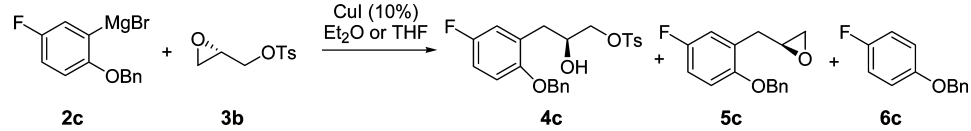
(12) This phthalimide buffer is necessary for the epoxide opening as phthalimide alone is not nucleophilic enough to open the epoxide, whereas its presence is crucial in providing acidic catalysis of the reaction: (a) Lawrence, N. J.; Bushell, S. M. *Tetrahedron Lett.* **2001**, *42*, 7671. (b) Williams, T. M.; Crumbie, R.; Mosher, H. S. *J. Org. Chem.* **1985**, *50*, 91.

(13) The list of hydrogenation conditions screened includes Pd/C (50 psi hydrogen or transfer hydrogenation, no reaction observed), Pd black (stalled after 10% conversion), $Pd(OH)_2$ on carbon (80% conversion after high multiple catalyst charges, phthalimide reduction observed).

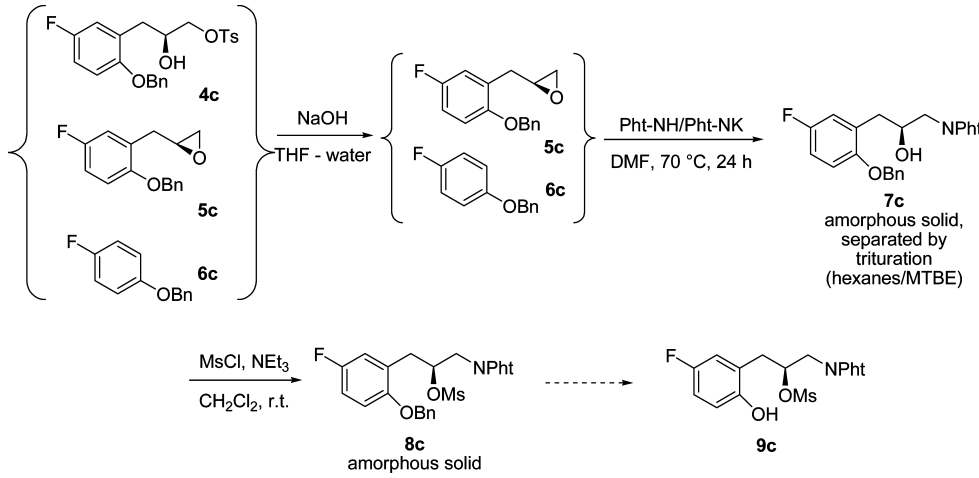
(14) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley & Sons: New York, 1999; pp 257−258.

(15) Schouten, H. G. Preparation of Alkoxy Methyl Ethers. U.S. Patent 4,500,738, Feb. 19, 1985.

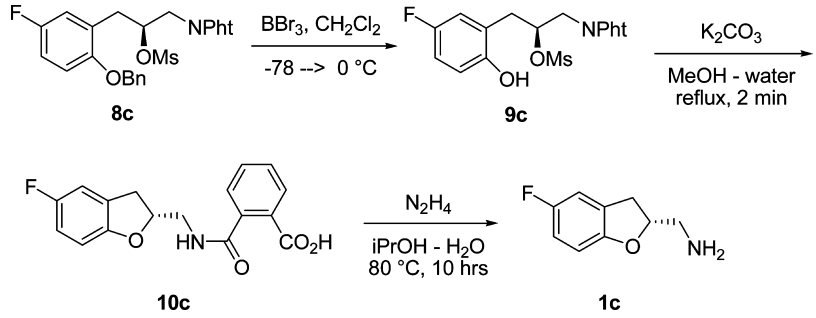
Scheme 5. **Addition of *o*-benzyloxyphenyl Grignard reagent to glycidyl tosylate**



Scheme 6. **Introduction of the phthalimide fragment and setting up for the dihydrobenzofuran cyclization**



Scheme 7. **Formation of dihydrobenzofuran ring and removal of phthalimide protection**



Returning to benzyl-protected phenol derivatives, nonreductive ether cleavage was attempted and gave encouraging results. On treatment of **8c** with BBr_3 in methylene chloride at −78 to 0 °C,[16] the benzyl group was cleanly removed, resulting after aqueous workup, in a mixture of deprotected phenol **9c** and benzyl bromide (Scheme 7). This result suggested that methyl-protected phenol might work in the reaction sequence as well as benzyl, additionally easing up steric hindrance around the aryl-magnesium group during epoxide opening.

Treatment of a methanolic solution of **9c** with aq NaOH led immediately to two new products, one of which was identified as **10c**, the other had the same $(M + H)^+$ in LC/MS as that of **10c** but a different fragmentation pattern. The structure of the latter side product has not been determined. Screening of the reagents and conditions for the cyclization allowed identification of the set in which the reaction occurred cleanly and no side products formed (Scheme 7) (no conditions were found in which cyclization occurred without phthalimide ring opening). Removal of the phthalic amide group was achieved by heating **10c** with hydrazine hydrate in IPA.

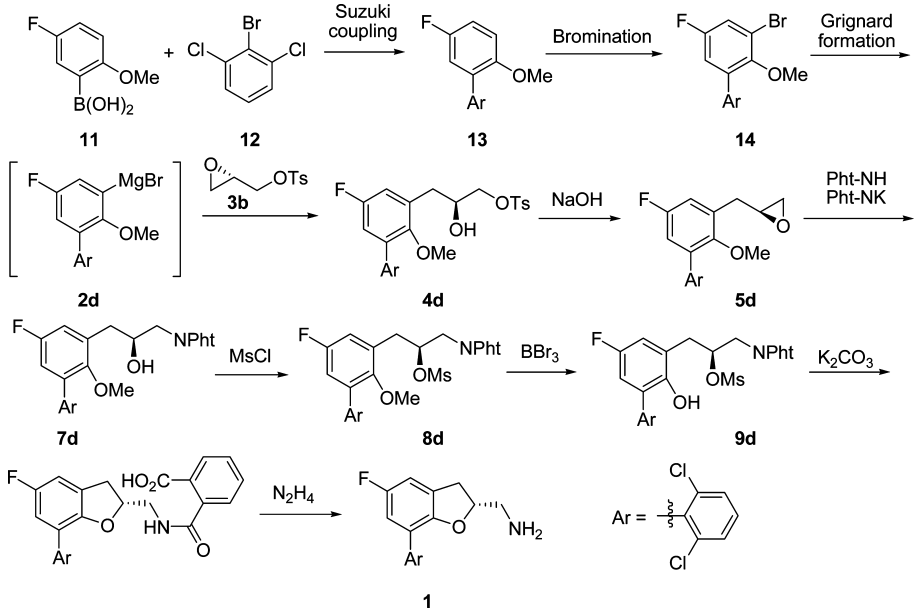
The enantiomeric purity of **1c** was confirmed by converting the product into a pair of the diastereomeric Mosher amides which were then analyzed by ^{1}H NMR and HPLC. Both experiments showed that two samples contained individual distinct diastereomers of the amides, confirming the enantiomeric purity of the amine **1c**. HPLC analysis of the diastereomer mixture established the enantiomeric purity of **1c** to be >99% ee.

This result provided the necessary proof of concept that the selected synthetic strategy would allow construction of the chiral dihydrobenzofuran core without loss of the enantiomeric purity of the starting glycidyl fragment. From here we could proceed to filling in the missing parts of the synthesis and mapping the overall synthetic strategy.

One of the remaining pieces to be fitted was incorporation of the dichloroaryl substituent. It could be added into the dihydrobenzofuran core **1c** by ortho-lithiating at the C-7 position, making the boronic ester and coupling it by Suzuki chemistry with dichlorobromobenzene. Protection and deprotection of the amino group was likely to be required as well, adding four steps to the linear synthesis. Carrying out the Suzuki coupling in the beginning of the synthesis and taking into account available starting materials would add only two steps to the synthesis and would not require cryogenic lithiation. Thus, the latter alternative was chosen.

(16) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley & Sons: New York, 1967; p 67.

Scheme 8. **Synthetic plan for preparation of 1**



Scheme 8 illustrates the synthetic plan using methyl protection of the phenol in place of benzyl this time. The starting biaryl fragment for construction of the fused bicyclic system would begin with a Suzuki coupling of commercially available 2-methoxy-5-fluorophenyl boronic acid (**11**) and *o,o*-dichlorobromobenzene (**12**), similar to the first step of the Medicinal Chemistry route. Resulting biaryl **13** was to be selectively brominated ortho to the methoxy group. Grignard reagent was to be generated from aryl bromide **14** (methodology would need to be developed to ensure the aryl chlorides remain intact). Finally, the chiral dihydrofuran ring would be constructed following the developed methodology to result in enantiomerically pure **1**.

Optimization of Reaction Conditions and the Scale-Up Campaign. The procedure for Suzuki coupling was first developed by the medicinal chemists and used 5 mol % of $Pd(PPh_3)_4$ as the catalyst, K_2CO_3 as a base, and dimethoxyethane as a solvent and afforded the coupled product in 43% yield after chromatographic purification. A rapid screen of the catalysts, bases, and reaction conditions allowed the achievement of complete conversion and 90% isolated yield using the same catalyst but switching the base to NaOH. Higher reaction temperature facilitated the conversion and also allowed lowering the catalyst loading to 2 mol %. For product isolation, dimethoxyethane was exchanged to heptane, and the insoluble catalyst residue and byproducts were removed by filtration.

The best reagent for selective bromination of **13** found in the reagent screen was NBS.[17] Bromination with Br_2 under a variety of conditions lacked the selectivity (various amounts of polybrominated side products formed) and suffered from demethylation of the methoxy group as a persistent side reaction. The reaction with NBS required the presence of an acid to effect good conversion, but the conditions needed optimization to avoid acid-induced demethylation. Sulfuric acid in dioxane at 50 °C afforded 95% conversion in 18 h without noticeable demethylation. Crystallization of the product after extractive workup allowed isolation of the product in 80% yield and 98% purity, leaving most of the unreacted starting material in the mother liquors. This method was used to prepare first batches of the product on the laboratory scale.

Further optimization of the reaction conditions in preparation for the kilolab campaign allowed replacement of toxic dioxane with acetic acid as the reaction solvent and the use of a catalytic amount of pTSA as the acid catalyst and achieved a virtually quantitative conversion. The change also allowed the simplification of the isolation: the product was precipitated by addition of water and isolated by filtration.

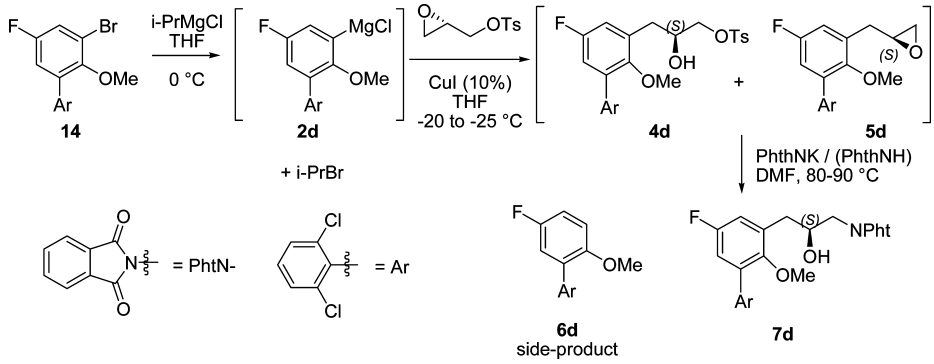
In the kilolab campaign, it was possible to run the Suzuki and bromination steps without isolation of the intermediate solid material by conducting a solvent exchange from heptane to acetic acid by vacuum distillation. The total isolated yield of the brominated biaryl intermediate was 75−80%.

In the next steps of the synthetic sequence, generation of the Grignard reagent and its reaction with glycidyl tosylate, two major problems were encountered upon subjecting the biaryl substrate **2d** to the reaction conditions developed for the monoaryl substrate **2c**. First, the Grignard formation with magnesium metal was not selective, and substantial amounts of des-chloro- and des-dichloro derivatives were found upon quenching the Grignard solution with water. The second problem was the substantially lower reactivity of the Grignard reagent toward the epoxide than what we observed for **2a** or **2c**. In fact, only about half of the epoxide reacted with the Grignard reagent, while the rest was opened by the bromide anion (when excess of the Grignard reagent was introduced into the reaction).

To circumvent the first problem, an alternative method for Grignard generation was employed: the aryl bromide was treated with *i*-PrMgCl solution[18] at 0 °C to room temperature (Scheme 9). The metal−halogen exchange was complete in 4 h and gave the desired aryl Grignard solutions with no detectable side

(17) (a) Lambert, F. L.; Ellis, W. D.; Parry, R. J. *J. Org. Chem.* **1965**, *30*, 304. (b) Leazer, J. L.; Cvetovich, R.; Tsay, F.-R.; Dolling, U.; Vickery, T.; Bachert, D. *J. Org. Chem.* **2003**, *68*, 3695.

Scheme 9. **Preparation of Grignard reagent, epoxide opening, and introduction of the phthalimide group**



products. The new approach also solved the problem of the epoxide opening by the bromide anion as it generated aryl magnesium chloride instead of bromide which was obtained in the reaction with magnesium metal.

It took substantial effort to optimize the conditions for the Grignard addition to the epoxide to identify factors that determine the outcome of the reaction. The major one was the reaction temperature which had to be maintained in the −25 to −20 °C window. Lower temperatures slowed down the reaction dramatically (at −40 °C it never went past 50% conversion), whereas higher temperatures led to significant side-product formation.

The type or amount of the copper catalyst did not play an important role in the epoxide opening except that without it the reaction did not proceed at all. Little difference was noticed among runs with equal loadings of CuCN, Li_2CuCl_4, and CuI. Runs with 5 or 10 mol % of CuCN gave very similar results as well. In laboratory preparation of smaller-scale batches, 7% of CuCN was used because the commercially supplied material is stable and nonhygroscopic and has fine particles; thus, it could be introduced into the Grignard solution as a THF suspension and could be dispersed easily in the reaction mixture. In the kilolab runs, CuCN was replaced with CuI to avoid issues associated with cyanide toxicity. There was no change in the reaction performance. The copper reagent was used as received from the vendor, and it was introduced into the Grignard solution as a solid. However, we had to use a high impeller speed to keep it from settling on the bottom of the reactor.

The reaction went to completion in 4−5 h at −26 to −22 °C as judged by the disappearance of glycidyl tosylate (a 5 mol % excess of the Grignard reagent was used; all excess Grignard byproducts were washed away in the workup). As expected, the reaction resulted predominantly in hydroxytosylate with a minor amount of the terminal epoxide (∼10 area % by HPLC). The mixture could be converted completely into the terminal epoxide by treatment with aqueous NaOH solution. The epoxide could be isolated after extractive workup as an oil in a manner similar to that described for the model substrate. Opening of the epoxide was done in DMF and required a mixture of phthalimide and its potassium salt. The reaction was complete in about 10 h at 75 °C. After aqueous workup, the product was crystallized by addition of heptane which also purged most of the impurities carried from the previous steps. The yield was 74% based on glycidyl tosylate.

Alternatively, in a more streamlined procedure used on scale in the kilolab, conversion to the terminal epoxide was omitted. Epoxide opening was followed by the aqueous extractive workup using toluene as an additional solvent to effect the phase splits. The mixture of the hydroxy tosylate and spontaneously formed terminal epoxide was isolated as a solution in toluene. The solvent was changed to DMF using vacuum distillation. The DMF solution was treated with potassium salt of phthalimide. Tosylate displacement in this case could proceed directly or via the intermediate formation of terminal epoxide **5d** induced by the base. Regardless of the pathway, 2 equiv of the phthalimide salt were necessary to force the reaction to completion, the terminal epoxide being the last unreacted species to disappear. For product isolation, the reaction mixture was diluted with a mixture of isopropyl acetate (iPAc) and THF and washed with a weak solution of NaOH in 8% aqueous NaCl to remove byproduct phthalimide. The composition of the mixture was carefully optimized to avoid precipitation of the product, allow the split of the phases, and minimize formation of emulsions. The temperature of the batch was lowered to 0−4 °C to prevent partial hydrolysis of the phthalimide and loss of the product into the aqueous washes. The resulting solution was azeotropically dried, which also removed most of THF (to ≤0.1% by GC) and induced the start of product crystallization. The precipitation was completed by addition of heptane to the batch. The product was isolated by filtration in 50−60% yield and 99.5% ee. Major impurities in the isolated product were des-bromobiaryl byproduct **6d** and the unreacted terminal epoxide **5d** (both below 1.5%). Lacking the incorporated amine functionality (as protected phthalimide), both would be easily purged when the final amine is converted to the HCl salt.

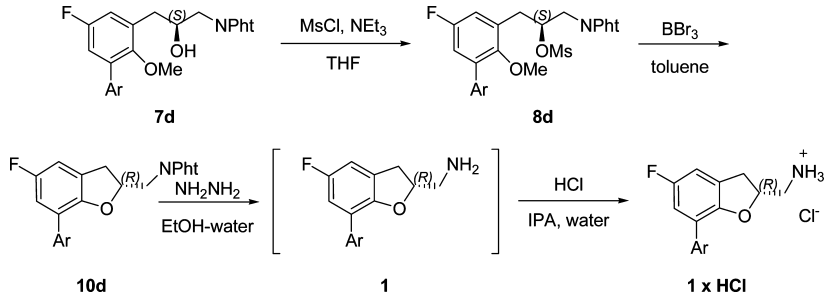
Sulfonylation of the hydroxyl in **7d** (Scheme 10) was carried out with methanesulfonyl chloride in the presence of triethylamine. On scale, the reaction was carried out in THF which allowed precipitation of the product by simple addition of water

(18) (a) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: New York, 1995; Chapter 3.2.2; (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kniesel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

(19) Kirby, A. J. *Adv. Phys. Org. Chem.* **1981**, *17*, 183. We thank a referee for this suggestion.

(20) The two signals at 7.412 and 7.406 ppm correspond to the two meta-protons of the dichlorophenyl ring. The small difference in chemical shift (0.006 ppm) is most likely due to the restricted rotation around the biaryl bond and the chirality of the molecule. This dissymmetry of the ortho- and meta-positions of the dichlorophenyl was also observed in the ^{13}C spectrum of **7d** and, to various extents, in the spectra of **8d**, **10d**, and **1** × HCl, both ^{1}H and ^{13}C, described in the following experiments.

Scheme 10. **Formation of the dihydrobenzofuran cycle, liberation of the amino group, and preparation of the HCl salt**



to the reaction mixture and isolation of the solids by filtration in 96% yield, 99.3% purity, and without any detectable loss of enantiopurity.

As expected, demethylation of **8d** occurred readily upon treatment with boron tribromide at low temperature in methylene chloride. There was, however, a substantial difference in behavior of the demethylated product under the reaction conditions relative to that observed in the model case of **8c**. In the model case, the deprotected product **9c** was isolated, and cyclization was done in a separate step by treatment with potassium carbonate. Here, the cyclization occurred immediately upon demethylation. In fact, we attempted to intercept the open-chain intermediate by quenching the reaction at the half-conversion point, but only the cyclized product **10d** and the starting methoxyaryl compound **8d** could be detected. We assume the steric repulsion between the dichlorophenyl substitutent and the phenol led to an enhanced rate of cyclization relative to the unsubstituted system.[19]

Further study of reaction conditions allowed replacement of dichloromethane with toluene. With 1.6 equiv of BBr_3, at room temperature, the reaction was complete in 20 h. For isolation, methanol was added to the reaction mixture, the volatile byproducts were removed by distillation, and the product was isolated by filtration in 79% yield. A slight loss of enantiomeric purity was observed in the kilolab run: the ee of the isolated batch was 97.4%, down from 98.6% in the starting material.

The phthalimide protecting group was removed by heating the substrate with hydrazine hydrate in an ethanol−water mixture at reflux. Presence of water in the reaction mixture increased the solubility of phthalylhydrazide and prevented it from precipitating and forming a thick suspension. The reaction went to completion in 2 h. The product was extracted into MTBE, and the solution was washed with dilute aqueous NaOH to remove phthalylhydrazide (for safety considerations, hydrazine levels were monitored in the organic phase in the plant) and to obtain an MTBE solution of the product as a free base.

Hydrochloride Salt: Polymorphs, Properties, Preparation. The hydrochloride salt has been selected as the API form on the basis of its high crystallinity, good solubility in water, good stability and low hygroscopicity.

A quick and non-exhaustive polymorph screen of the hydrochloride allowed identification of two forms with very similar melting points (both had melting endotherms at 134 °C in DSC scans) but manifestly distinct XRD patterns. Form I was forming predominantly in solvents in which the hydrochloride had low solubility. e.g., MTBE, EtOAc, toluene, heptane. Form II formed in acetone, water, or IPA where solubility of the salt was substantial. Stability studies also showed that Form II was more stable in the latter set of solvents as Form I was found to convert to Form II when suspended in those solvents at 50 °C for a period of 48 h. Form II also had slightly lower solubility in water (50 vs 67 mg/mL at 20 °C). The more stable Form II has been selected as a drug substance.

Experiments designed to work out a process for preparation of Form II showed that Form I could still precipitate from the IPA solutions if supersaturation is not carefully controlled during crystallization. For that reason, we decided not to use anti-solvents in the process as mixing effects can create high local concentrations of the antisolvent and induce formation of Polymorph I. Isopropanol was found to have the most useful solubility range for the crystallization of the hydrochloride (17 mg/mL at 20 °C and 38 mg/mL at 50 °C) among several solvents screened, and this range could be greatly expanded by adding water to the system. Figure 1 shows a dramatic increase of solubility upon addition of water to the mixture. However, the solubility difference at high and low temperature in this solvent system was not large enough to afford good recovery of the product. Therefore, partial solvent removal needed to be incorporated into the process.

Under optimized conditions, the MTBE solution of the free base obtained in the previous operation underwent solvent exchange to IPA by vacuum distillation. An equimolar amount of HCl in IPA was added followed by the calculated amount of water (3 to 4% of the total IPA volume) to ensure complete dissolution of the salt at 75 °C. The resulting mixture was heated to 75 °C, cooled to 65−70 °C, and seeded with the hydrochloride Form II seeds. Once the seed bed was established, the batch was further cooled to 30−40 °C. The partial vacuum was applied to the reactor, and a portion of the solvent was distilled off. Because IPA forms an azeotrope which contains 12 wt % of water, distillation also resulted in a decrease of the relative water content in the system, decreasing the solubility of the salt. Finally, slow cooling of the batch to −10 °C and filtration of the solids at that temperature afforded 83% yield of the isolated **1** hydrochloride. The product had 99.5% chemical

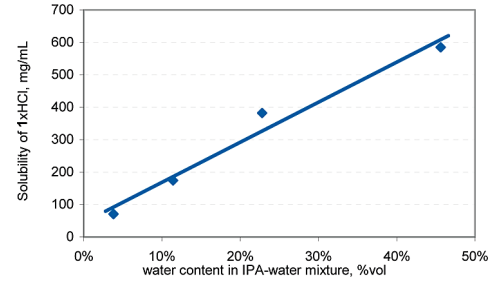


Figure 1. **Solubility of 1 HCl salt in IPA/water mixture as a function of water content at 20 °C.**

purity and 98.7% ee (a slight increase from 97.4% of the product in the previous step). The hydrazine level in the isolated solid was determined at less than 5 ppm, making the material appropriate for use in the clinical program.

Conclusions

A new process for synthesis of the 5-HT_{2C} agonist **1** in optically pure form has been developed and implemented on scale for preparation of 10 kg of the API in support of the clinical studies. The key step of the process, the opening of epoxide with aryl Grignard reagent catalyzed by a copper(I) salt allowed us to incorporate a commercially available chiral fragment into the target molecule.

Experimental Section

General. Starting materials, solvents, and reagents were obtained from commercial sources and were used as received without purification. HPLC assays were performed on Agilent 1100 chromatographs equipped with PDA detectors. Routine reaction monitoring was done using a Phenomenex Prodigy ODS3 4.6 mm × 50 mm column or an equivalent C-18 column and a standard 8-min gradient program: 10:90 to 90:10 mixture of acetonitrile−water containing 0.02% of TFA with constant flow of 1 mL/min. HPLC methods for large-scale reaction completion assays are given in the Supporting Information. HPLC determination of the API chiral purity was done using a Daicel Chiralcel OD-RH, 5 μ, 150 mm × 4.6 mm column, and an isocratic mixture of 0.05 M solution of KPF_6 in water and acetonitrile in 60:40 ratio with 1 mL/min flow rate (data collected at 220 nm). RRTs: 0.80 (distomer), 1.00 (eutomer). NMR spectra were recorded on a Bruker Avance DPX300 or a Bruker Avance DRX400 NMR spectrometer. Spectra were referenced by TMS. LC/MS data were obtained on an Agilent 1100 LC system with an Agilent 1100 LC/MS detector. HPLC conditions: Phenomenex Prodigy ODS3 4.6 mm × 50 mm column, 90:10 to 10:90 8-min gradient of water/acetonitrile containing 0.02% HCO_2H, flow rate 1 mL/min.

1-Methoxy-2-bromo-4-fluoro-2′,6′-dichlorobiphenyl (14). To a mixture of 2-bromo-1,3-dichlorobenzene (18.0 kg, 78.8 mol), 5-fluoro-2-methoxyphenylboronic acid (17.6 kg, 92.1% strength, 95.8 mol), $Pd(PPh_3)_4$ (1.85 kg, 1.60 mol), and dimethoxyethane (157 kg) maintained at 70−75 °C was added a solution of NaOH (15.9 kg, 398 mol) in water (90 kg) over 30 min. The resulting mixture was heated at reflux (80 °C) for 18 h at which point the HPLC assay of the reaction mixture showed no detectable amount of the starting aryl bromide. The batch was cooled to 20 °C, the layers were separated. The organic layer was concentrated in vacuum at 20−30 °C to a volume of 30 L. Heptane (123 kg) and water (27.0 kg) were added to the concentrate, the mixture was filtered through a bag filter to remove solids, and the phases were separated. The organic solution was washed with water (2 × 27.0 kg) and then concentrated under vacuum at 17−21 °C to a final volume of 105 L. Silica gel (Merck, grade 60 mesh 200−400, 3.6 kg) was added to the concentrated solution, and the slurry was stirred for 2 h. The silica was filtered off and washed with heptane (80 kg). The combined filtrate and wash were concentrated under reduced pressure at 16−20 °C to a 30-L volume. The residual solvent was chased by acetic acid under reduced pressure (2 × 42.6 kg, distilled down to 30−35 L at 20−36 °C after each charge). NBS (21.5 kg, 121 mol), pTSA (3.23 kg, 17.0 mol), and acetic acid (106 kg) were added to the concentrate, and the resulting mixture was heated at 55 °C for 22 h. HPLC assay of the reaction mixture showed 99.5% conversion of the biaryl Suzuki product to the bromide. A solution of sodium metabisulfite (5.7 kg) in water (20.1 kg) was added to the reaction mixture, maintaining the batch temperature between 50 and 60 °C. After ensuring the negative reaction of the mixture to the starch iodide test, the batch was cooled to 36 °C, seeded, and held at 30−35 °C for 1 h to form the crystal bed. The mixture was cooled further to 22 °C over 2 h, and then water (28.2 kg) was added over 35 min. The resulting slurry was held for 1 h at 20 °C, and then the solid was filtered and washed with water (3 × 21 kg). The cake was reslurried with 100 kg of water, filtered again, and washed with additional amounts of water (3 × 25 kg) to remove residual acetic acid. The wet product was dried in a vacuum oven at 40 °C until LOD (1.5 h at 50 °C and ≤10 mmHg) of 0.5% or lower was reached. The dry solid was tested for levels of residual acetic acid (0.054% by GC) and water (0.07% by KF titration) and was acceptable for use in the next step. Yield 24.2 kg (79.3%). For a purified sample, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42 (m, J = 8.1 Hz, 2H), 7.39 (dd, J = 3.0, 7.7 Hz, 1H), 7.30 (dd, J = 8.1 Hz, 1H), 6.86 (dd, J = 3.0, 8.0 Hz, 1H), 3.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 158.2 (d, J = 248 Hz), 151.2 (d, J = 3 Hz), 135.1, 135.0, 133.0 (d, J = 9 Hz), 130.0, 128.0, 120.8 (d, J = 25 Hz), 117.7 (d, J = 11 Hz), 117.0 (d, J = 23 Hz), 60.9.

2S-3-[5-Fluoro-3-(2,6-dichlorophenyl)-2-methoxyphenyl]-1-N-phthalimidopropan-2-ol (7d). A 2 M solution of *i*-PrMgCl in THF (14.8 kg, 28.9 mol) was added to a solution of **14** (9.5 kg, 27.1 mol) and THF (33.8 kg), maintaining the batch temperature at −7 to −2 °C. The reaction mixture was held at 0 °C for 2 h. The completion of transmetalation was established by HPLC analysis of an aliquot of the reaction mixture quenched by water for the absence of the starting bromide. Once the level of the starting material was confirmed to be below 1%, the reactor contents were cooled to −30 to −25 °C, and CuI (0.36 kg, 1.9 mol) was added to the Grignard solution. The mixture was stirred at that temperature for 30 min, and then a solution of glycidyl tosylate (5.90 kg, 25.9 mol) in THF (5.8 kg) was added over 1.5 h, while maintaining the batch temperature in the range of −30 to −25 °C. The resulting mixture was stirred at −26 to −22 °C for 3 h and assayed by HPLC for the amount of unreacted glycidyl tosylate. Reaction was considered complete when the level fell below 2.0 area %. The batch was quenched with an aqueous solution of ammonium chloride (39.6 kg) (solution was prepared from 7.5 kg of NH_4Cl and 44.6 kg of water). The batch temperature during the addition was allowed to rise from −22 to 6 °C. The temperature was then adjusted to 5−15 °C, and the aqueous layer was separated and back extracted with toluene (26.6 kg). The combined organic layers were washed with the aqueous solution of ammonium chloride (12.5 kg) and water (4 × 14.4 kg, water washes were repeated until neutral pH of the wash) and filtered through a 2-μm cartridge filter. The solvents were

distilled off under vacuum (batch temperature 15−23 °C) to the volume of 18 L. The residual solvents were chased with toluene (15.4 kg, same conditions as above) and then DMF (35.6 kg). The final distillation went to the final volume of 43 L and was done at 40−50 °C.

Potassium salt of phthalimide (7.50 kg, 40.5 mol) was added to the batch at 20 °C, and then the mixture was heated at 86 °C for 12 h at which point the HPLC analysis of the reaction mixture showed 2.4 area % of the unreacted terminal epoxide **5c**. The mixture was cooled to 10−15 °C, and iPAc (42.0 kg), THF (10.5 kg), and water (55.0 kg) were added (exotherm was observed during water addition). The layers were split, the aqueous layer was back extracted with iPAc (38 kg), and the organic layers were combined (10.5 kg of THF was added as a reactor rinse). The resulting solution was washed at 4 °C with a solution (2 × 38 kg) prepared from NaCl (7.5 kg), NaOH (0.76 kg), and water (93 kg), then twice with a mixture of water (40 kg) and THF (10.5 kg). A small amount of brine was added to the batch during the final washes to aid phase separation. The resulting solution was distilled under vacuum at 10−20 °C to the volume of 40 L. The product partially crystallized from solution during distillation. The residual solvents were chased with iPAc (2 × 37.7 kg), distilling the batch to the same mark under similar conditions. Heptane (28.8 kg) was added to the concentrated slurry at 30 °C over 30 min; the slurry was cooled to 20 °C, and the solids were filtered. The cake was washed with a 1:1 v/v mixture of iPAc and heptane (2 × 16.2 kg), and the solid was dried on the trays in a vacuum oven at 45 °C until LOD (1 h at 70 °C and ≤10 mmHg) of 0.5% or less was obtained. Yield 6.67 kg (51% based on glycidyl tosylate as the limiting reagent), total impurities 1.13% (by HPLC), enantiomeric purity 99.0% ee. Mp 165−168 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.86 (m, 2H), 7.72 (m, 2H), 7.412 (m, J = 1.2, 8.1 Hz, 1H), 7.406 (m, J = 1.2, 8.1 Hz, 1H), 7.27 (m, J = 8.1, 8.1 Hz, 1H),[20] 7.08 (dd, J = 3.0, 8.8 Hz, 1H), 6.79 (dd, J = 3.0 Hz, 8.1 Hz, 1H), 4.23 (d[5], J = 3.3, 4.3, 5.7, 7.9, 8.5 Hz, 1H), 3.85 (dd, J = 3.3, 14.1 Hz, 1H), 3.80 (dd, J = 8.5, 14.1 Hz, 1H), 3.42 (s, 3H), 2.96 (dd, J = 4.3, 13.9 Hz, 1H), 2.92 (dd, J = 7.9, 13.9 Hz, 1H), 2.80 (d, J = 5.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 168.7, 158.4 (d, J = 244 Hz), 152.2, 135.7, 135.3 (d, J = 9.0 Hz), 134.1, 132.9 (d, J = 8.5 Hz), 132.0, 131.8 (d, J = 9.6 Hz), 129.7, 128.0, 123.4, 118.2 (d, J = 23 Hz), 116.4 (d, J = 23 Hz), 70.6, 60.9, 44.1, 36.3.

A total of four batches were run without significant differences, and the yields were in the 51−58% range (adjusted for strength).

2S-3-[5-Fluoro-3-(2,6-dichlorophenyl)-2-methoxyphenyl]-1-N-phthalimidopropan-2-yl Methanesulfonate (8d). Methanesulfonyl chloride (7.9 kg, 68.9 mol) was added over 40 min to a stirred mixture of **7d** (21.9 kg, 46.2 mol), THF (98 kg), and Et_3N (7.0 kg, 69.3 mol), keeping the batch temperature in the range of 9−17 °C (strong exotherm). The batch temperature was adjusted to 20−26 °C, and the mixture was held under these conditions for 1.5 h. A thick slurry formed in the reactor during the hold. The batch was analyzed by HPLC for conversion (0.24 area % of the unreacted starting material was detected). Water (110 kg) was added to the reactor over 30 min while the batch was maintained at 20−22 °C, and the solids were filtered and washed with a mixture of THF (18 kg) and water (20 kg), then with water (3 × 55 kg), and finally with heptane (38 kg). The solid was dried on trays in a vacuum oven at 70 °C until the LOD (1 h at 85 °C and ≤10 mmHg) of 0.5% or less was met. Yield 24.9 kg (96%), strength 97.5%, total impurities 0.71% (by HPLC), enantiomeric purity 99.0% ee. Mp > 200 °C dec. ^{1}H NMR (400 MHz, dmso-d_6) δ: 7.87 (m, 2H), 7.83 (m, 2H), 7.614 (m, J = 1.09, 8.13 Hz, 1H), 7.619 (m, J = 1.09, 8.12 Hz, 1H), 7.50 (m, J = 8.13, 8.12 Hz, 1H), 7.40 (dd, J = 3.3, 9.3 Hz, 1H), 7.06 (dd, J = 3.3, 8.6 Hz, 1H), 5.13 (m, 1H), 3.97 (dd, J = 9.2, 14.9 Hz, 1H), 3.74 (dd, J = 3.0, 14.9 Hz, 1H), 3.37 (s, 3H), 3.18−3.14 (m, 2H), 2.84 (s, 3H). ^{13}C NMR (100 MHz, dmso-d_6) δ: 167.6, 157.6 (d, J = 242 Hz), 152.4 (d, J = 2 Hz), 134.8, 134.42, 134.37, 134.26, 131.6, 131.5 (d, J = 10 Hz), 131.4 (d, J = 8 Hz), 130.8, 128.3, 123.1, 118.7 (d, J = 22 Hz), 116.7 (d, J = 24 Hz), 78.5, 60.5, 40.8, 37.6, 33.2.

2R-7-(2,6-Dichlorophenyl)-5-fluoro-2,3-dihydro-2-(N-phthalimidomethyl)benzofuran (10d). **8d** (24.8 kg, 44.5 mol) was suspended in toluene (217 kg), and neat BBr_3 (12.4 kg, 49.4 mol) was added to the suspension over 33 min at 17−20 °C (weak exotherm). The initial suspension turned into a red solution during the addition, and it was stirred in the range of 18−25 °C for 12 h. HPLC assay of a reaction mixture sample showed 31% of unreacted starting material. After holding further for 8 h, additional BBr_3 (2.9 kg, 11.6 mol) was added, and the reaction mixture was held longer while reaction progress was monitored by HPLC. It took 16 h after the last BBr_3 addition for the level of the starting material to drop to 1.7%. At that point anhydrous methanol (19.8 kg) was added to the batch, maintaining the temperature below 20 °C (addition was accompanied by a strong exotherm; the jacket had to be cooled to −18 °C to finish addition in 30 min and maintain the temperature in the desired range). The resulting mixture was held at 20 °C for 1 h, and then the solvents were distilled under vacuum to the volume of 105 L, maintaining the batch temperature at 20−25 °C. MeOH (39.0 kg) was added to the batch, and the resulting mixture was heated to 70 °C and then cooled to 0−5 °C over 1 h. The crystallized solid was filtered, washed with cold (2−8 °C) MeOH (2 × 20 kg), and dried on the filter at 65 °C with agitation until LOD (85 °C, ≤ 10 mmHg, 1 h) of ≤0.5% was reached. Yield 15.8 kg (79%), strength (HPLC) 99.7%, total impurities 0.36%, enantiomeric purity 97.8%. Mp 222.5−224.5 °C. ^{1}H NMR (400 MHz, dmso-d_6) δ: 7.85 (m, 4H), 7.54 (dd, J = 1.1, 8.1 Hz, 1H), 7.53 (dd, J = 1.1, 8.2 Hz, 1H), 7.41 (dd, J = 8.1, 8.2 Hz, 1H), 7.19 (dd, J = 2.7, 8.2 Hz, 1H), 6.86 (dd, J = 2.7, 9.3 Hz, 1H), 5.09 (m, 1H), 3.79 (m, 2H), 3.43 (dd, J = 9.3, 16.6 Hz, 1H), 3.15 (dd, J = 5.9, 16.6 Hz, 1H). ^{13}C NMR (100 MHz, dmso-d_6) δ: 167.8, 156.4 (d, J = 237 Hz), 152.2, 134.6, 134.5, 134.3, 133.5, 131.5, 130.6, 128.6 (d, J = 9.4 Hz), 128.1, 123.1, 118.2 (d, J = 9.5 Hz), 114.9 (d, J = 25 Hz), 112.9 (d, J = 25 Hz), 80.0, 41.1, 33.2.

2R-7-(2,6-Dichlorophenyl)-5-fluoro-2,3-dihydro-2-aminomethylbenzofuran hydrochloride (1 × HCl). Hydrazine hydrate (5.31 kg, ∼104 mol) was added to a reactor containing a mixture of **10d** (15.3 kg, 34.7 mol), ethanol (36.2 kg), and water (30.6 kg). The resulting mixture was heated at 74−84 °C for 2 h.

Once HPLC assay confirmed completion of the reaction, the batch was cooled to 45 °C, and water (45.9 kg) and MTBE (34.0 kg) were added. The mixture was further cooled to 20 °C, the layers were separated, and the aqueous layer was extracted with MTBE (2 × 17.0 kg). The combined organic phases were washed with a dilute aqueous solution of NaOH (2 × 23.1 kg, wash solution was prepared from 0.455 kg of NaOH and 45.9 kg of water) and then with water (2 × 30.6 kg). The volume of the resulting solution was reduced to 20−24 L by vacuum distillation at 10−20 °C, then the residual solvent was chased with 2 portions of IPA (53.9 kg each) distilling the solvent out after each IPA charge to the 20−24 L mark. The batch was mixed with additional IPA (13.7 kg), and the solution was filtered through a 10-μm cartridge filter followed by a 0.2-μm cartridge filter, using 3.0 kg of IPA as a rinse.

All liquid reagents added to the batch after this point were filtered through a 0.2-μm cartridge filter before the addition. A solution of HCl in IPA (prepared by dissolution of 3.24 kg of HCl gas in 18.0 kg of IPA) was added to the solution of the free base, maintaining the temperature below 25 °C, followed by 2.05 kg of water. The resulting mixture was heated to 75−78 °C and then, once the complete dissolution of all solids was visually confirmed, was cooled to 70 °C. The batch was seeded with Form II of **1** hydrochloride (10 g) at 70 °C, held for 30 min at 70 °C, cooled to 65 °C, and seeded again with the same amount of seed. The mixture was cooled to 55 °C in 1 h, held for 1 h, and sampled, and the solids were analyzed by XRPD to ensure that the correct solid form was crystallizing. The cooling continued to 30 °C in 1 h; then the vacuum was applied to the reactor, and the solvent was distilled off until the batch volume reached 36−40 L (26−36 °C batch temperature). IPA (42.2 kg) was added to the batch, and the distillation was repeated to the same mark. The resulting slurry was cooled to −10 °C over 1 h, held for 1 h, and then filtered at that temperature. The filter cake was washed with cold (2−8 °C) IPA and dried first on the filter in the nitrogen flow and then on trays in vacuum at 55 °C until LOD (65 °C, ≤10 mmHg, 1 h) of ≤0.5% was reached. Yield 9.92 kg (83% based on the amount of **10d**), strength 99.5% as hydrochloride salt, chiral purity 98.6% ee, total impurities 0.21% by HPLC. Mp 134 °C (by DSC). ^{1}H NMR (400 MHz, dmso-d_6) δ: 8.25 (broad s, 3H), 7.57 (apparent d, J = 8.2 Hz, 2H), 7.45 (dd, J = 7.8, 8.4 Hz, 1H), 7.24 (dd, J = 2.6, 8.1 Hz, 1H), 6.90 (dd, J = 2.6, 9.6 Hz, 1H), 5.05 (d[4], J = 9.2, 7.9, 7.0, 4.5 Hz, 1H), 3.45 (dd, J = 9.2, 16.6 Hz, 1H), 3.17 (dd, J = 7.0, 16.6 Hz), 3.10 (dd, J = 13.4, 4.5 Hz, 1H), 3.04 (dd, J = 13.4, 7.9 Hz, 1H). ^{13}C NMR (100 MHz, dmso-d_6) δ: 156.4 (d, J = 257 Hz), 151.9, 134.6, 134.3, 133.6, 130.6, 128.9 (d, J = 11 Hz), 128.4, 128.2, 118.4 (d, J = 9 Hz), 115.1 (d, J = 25 Hz), 113.0 (d, J = 25 Hz), 80.0, 42.1, 32.8.

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Supporting Information Available

^{1}H and ^{13}C NMR spectra of the API and the isolated intermediates, XPRD patterns of the API polymorphs, HPLC methods for reaction assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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