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Development of a Scalable Synthetic Process for DG-051B, A First-in-Class Inhibitior of LTA4H

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Abstract:

DG-051B is a first-in-class small molecule inhibitor of leukotriene A4 hydrolase (LTA4H), currently in Phase II clinical development for the prevention of heart attack. Process optimization led from a linear seven-step synthetic procedure to a convergent four-step manufacturing sequence that has been used to manufacture at 100-kg scale. The entire process can be telescoped due to high conversion reactions, low impurity levels, efficient separations, and a very effective final purification. Two key aspects of the process are: (a) bypassing the isolation of a reactive electrophile by using its aqueous-washed reaction mixture directly into a coupling reaction with a phenoxide nucleophile and (b) modulating the properties of the final product solutions for optimal extraction, purification, and crystallization.

Introduction

Myocardial infarction (MI) is the leading cause of death in the industrialized world. Despite widespread use of drugs to treat dyslipidemia, hypertension, and diabetes as risk factors for MI and stroke, morbidity and mortality from cardiovascular (CV) disease remain unacceptably high. Our recent studies using human population genetics pinpointed the leukotriene (LT) pathway[1,2] as a major risk factor for MI and stroke.[3] We further narrowed our focus on leukotriene A4 hydrolase (LTA4H) as a key pathway enzyme responsible for the increased production of leukotriene B4 (LTB4) in atherosclerotic plaque.[4,5] The central role of LTA4H in other diseases[6] including inflammatory bowel disease (IBD),[7] rheumatoid arthritis,[8] and inflammatory lung conditions including asthma[9] has been confirmed by numerous research groups.

In our structure-based approach to the identification of nonpeptidic LTA4H inhibitors, we iteratively used fragment-based crystallography and medicinal chemistry to arrive at the optimized clinical candidate designated as DG-051.[10,11] This compound featured good potency against the enzyme combined with good aqueous solubility, high oral bioavailability and efficacy featuring significant reduction of LTB4 as a biomarker. Our agent DG-051 is currently undergoing a phase II clinical evaluation for the treatment of myocardial infarction and stroke. In this contribution, we summarize our efforts to both develop and demonstrate a process-scale chemical synthesis of DG-051 suitable for the human clinical trials. Our starting point was the medicinal chemistry procedure.[11] Scaling up this protocol presented a number of drawbacks including the formation of several byproducts (up to ~30% of the total conversion, for certain steps), several chromatographic purifications, and low overall yield (~10%) of the targeted molecule. Our development goals were to simplify and streamline the process, increase overall yield, reduce materials and processing costs, and meet regulatory guidelines.

Results and Discussion

tert-Butyl (2*S*)-2-{[4-(4-chlorophenoxy)phenoxy]methyl}-pyrrolidine-1-carboxylate, **6** (Scheme 1), was identified as a key intermediate in all our approaches to DG-051. The presence of the electron-withdrawing group (EWG) (Boc) on the pyrrolidine nitrogen of **6** was beneficial in yielding the targeted bis-ether core in high yields and purity. Attempts to use respective *N*-(4-butyryl) derivatives as direct precursors to DG-051 for the coupling reaction with phenoxide consistently led to the

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(1) Helgadottir, A.; Manolescu, A.; Thorleifsson, G.; Jonsdottir, H.; Thorsteinsdottir, U.; Samani, N. J.; Gretarsdottir, S.; Johannsson, H.; Gudmundsson, G.; Grant, S. F. A.; Sveinbjornsdottir, S.; Valdimarsson, E. M.; Matthiasson, S. E.; Gudmundsdottir, O.; Gurney, M.; Sainz, J.; Thorhallsdottir, M.; Andresdottir, M.; Frigge, M. L.; Gudnason, V.; Kong, A.; Topol, E. J.; Thorgeirsson, G.; Gulcher, J. R.; Hakonarson, H.; Stefansson, K. *Nat. Genet.* **2004**, *36*, 233.

(2) Helgadottir, A.; Manolescu, A.; Helgason, A.; Thorleifsson, G.; Thorsteinsdottir, U.; Gudbjartsson, D. F.; Gretarsdottir, S.; Magnusson, K. P.; Gudmundsson, G.; Hicks, A.; Jonsson, T.; Grant, S. F. A.; Sainz, J.; O'Brien, S. J.; Sveinbjornsdottir, S.; Valdimarsson, E. M.; Matthiasson, S. E.; Levey, A. I.; Abramson, J. L.; Reilly, M.; Vaccarino, V.; Wolfe, M.; Gudnason, V.; Quyyumi, A. A.; Topol, E. J.; Rader, D. J.; Thorgeirsson, G.; Gulcher, J. R.; Hakonarson, H.; Kong, A.; Stefansson, K. *Nat. Genet.* **2006**, *38*, 68.

(3) Meng, C. Q. *Curr. Top. Med. Chem.* **2006**, *6*, 93.

(4) Cipollone, F.; Mezzetti, A.; Fazia, M. L.; Cuccurullo, C.; Iezzi, A.; Ucchino, S.; Spigonardo, F.; Bucci, M.; Cuccurullo, F.; Prescott, S. M.; Stafforini, D. M. *Arterioscler. Thromb. Vasc. Biol.* **2005**, *25*, 1665.

(5) Qiu, H.; Gabrielsen, A.; Agardh, H. E.; Wan, M.; Wetterholm, A.; Wong, C. H.; Hedin, U.; Swedenborg, J.; Hansson, G. K.; Samuelsson, B.; Paulsson-Berne, G.; Haeggström, J. Z. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8161.

(6) Werz, O.; Steinhilber, D. *Pharmacol. Ther.* **2006**, *112*, 701.

(7) Sharon, P.; Stenson, W. F. *Gastroenterology* **1984**, *86*, 453.

(8) Tsuji, F.; Oki, K.; Fujisawa, K.; Okahara, A.; Horiuchi, M.; Mita, S. *Life Sci.* **1999**, *64*, PL 51.

(9) Holloway, J. W.; Barton, S. J.; Holgate, S. T.; Rose-Zerilli, M. J.; Sayers, I. *Allergy* **2008**, *63*, 1046.

(10) Davies, D. R.; Mamat, B.; Magnusson, O. T.; Christensen, J.; Haraldsson, M. H.; Mishra, R.; Pease, B.; Hansen, E.; Singh, J.; Zembower, D.; Kim, H.; Kiselyov, A. S.; Burgin, A. B.; Gurney, M. E.; Stewart, L. J. *J. Med. Chem.* **2009**, *52*, 4694.

(11) Sandanayaka, V.; Mamat, B.; Mishra, R. K.; Winger, J.; Krohn, M.; Zhao, L.-M.; Keyvan, M.; Enache, L.; Sullins, D.; Onua, E.; Zhang, J.; Halldorsdottir, G.; Sigthorsdottir, H.; Thorlaksdottir, A.; Sigthorsson, G.; Thorsteinnsdottir, M.; Davies, D. R.; Stewart, L.; Zembower, D. E.; Andresson, T.; Kiselyov, A. S.; Singh, J.; Gurney, M. E. *J. Med. Chem.* **2009**. Manuscript submitted.

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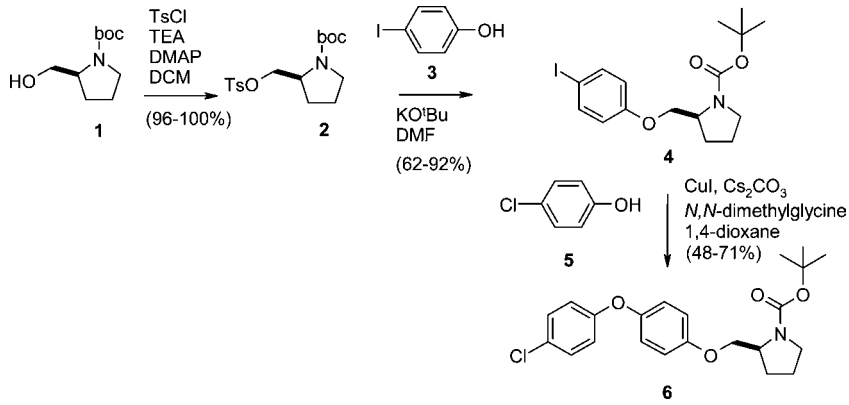
Scheme 1. **Sequential synthetic route to intermediate 6**



increased formation of side products (mainly *N*-alkylated piperidine analogues), potentially via intramolecular nucleophilic attack of the nitrogen at the carbon bearing the OTs leaving group, followed by rearrangement. A formal study of all the side products and their mechanism of formation has not been conducted.

First-Generation Approach to Compound 6. We initially focused on the synthesis of compound **6** following the three-step sequence illustrated in Scheme 1. According to this approach, prolinol **1** was tosylated using *p*-toluenesulfonyl chloride (TsCl) in the presence of triethylamine (TEA) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in dichloromethane (DCM). The reaction in DCM was notably faster (4−8 h at ambient) than in other solvents.[12] The yields were consistently high and reproducible (96−99%). Intermediate **2**,[10] when stored refrigerated and used within 1−2 weeks of preparation, required no further purification. In later applications, DMAP could be easily replaced by trimethylamine hydrochloride (TMA·HCl), thus reducing materials costs.

Displacement of the tosylate group in **2** by the phenoxide generated from 4-iodophenol (**3**) with potassium *tert*-butoxide (KOtBu) in DMF yielded ether intermediate **4.** Other solvents, such as THF or 1,4-dioxane, were respectively ruled out due to increased reaction time or stirrability issues. NaOH or KOH as the base also resulted in increased reaction time, as well as more impurities. We used an Ullmann-type protocol to couple **4** with 4-chlorophenol (**5**) in the presence of CuI and Cs_2CO_3. Unfortunately, this step afforded **6** only in moderate yields (48−71%). In following this route, we also noticed significant formation of impurities as exemplified by structures **7** and **8** in Figure 1. Attempts to purify **6** by chromatography failed, but trituration techniques did afford analytically pure material; however, the recovery was <50%. Overall, this route was cumbersome and poorly utilized the expensive building block, **1**.

Second-Generation Approach to Compound 6. In order to address the observed issues associated with the harsh conditions of the Ullmann reaction, we selected a convergent scheme featuring the reaction of the preformed diaryl ether building block **12**[13] with tosylate **2** (Scheme 2). This development work resulted in substantial modifications to the preparative techniques.

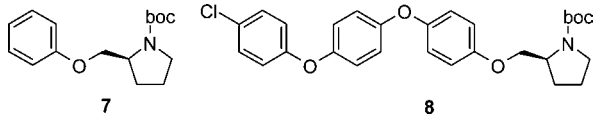


Figure 1. **The two major impurities from the Ullmann reaction in Scheme 1.**

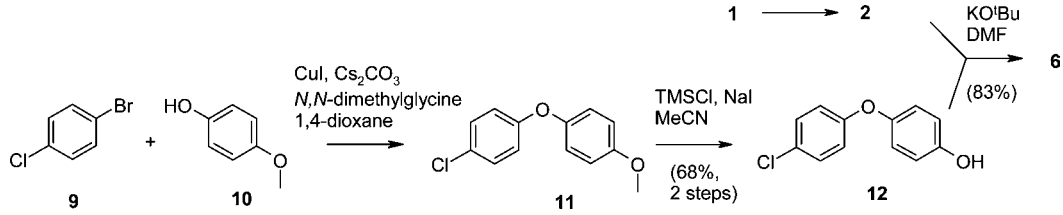
In following this path, our preferred approach to 4-(4-chlorophenoxy)phenol **12** was the Ullmann-type coupling of 4-bromochlorobenzene (**9**) and 4-methoxyphenol (**10**) in 1,4-dioxane mediated by Cs_2CO_3 and catalytic CuI. Yields of the intermediate diaryl ether **11**[14] were typically around 90%. Addition of a Cu-complexing cocatalyst such as *N,N*-dimethylglycine[15] resulted in both a better conversion rate and more manageable temperature control (100 °C) of this step. Deprotection of **11** to **12** was accomplished with TMSI formed *in situ* from the cheaper NaI and TMSCl. Phenol **12** was isolated in 65−85% yields (over two steps) and 98−99% purity[16] after recrystallization from heptane. This two-step synthesis was successfully validated on a 100-kg scale as we designated **12** to be a key starting material in manufacturing DG-051. Our attempts to access **12** in a one-pot procedure *via* either coupling of 4-chlorophenol and 4-iodophenol or diazotization of 4-(4-chlorophenoxy)aniline were unsuccessful. These one-pot approaches, while achieving reasonable chemical conversion (~70%) for the synthetic method screening stage, did not lend themselves to easy isolation of **12** with high enough recovery and purity.

For the *O*-alkylation of phenol **12** with tosylate **2**, conditions similar to those developed for the reaction of **2** with **3** (DMF as the solvent and KOtBu as the phenol deprotonating base) still provided the best yields (consistently above 80%) and shortest reaction times at a reasonable temperature (6−16 h at 45−60 °C). The reaction proceeded cleanly in the presence of a relatively small excess of **12** (1.05−1.15 equiv) and corresponding KOtBu. Tosylate **2** was completely consumed, and the excess of **12** was easily removed during the aqueous workup by alkaline washes.

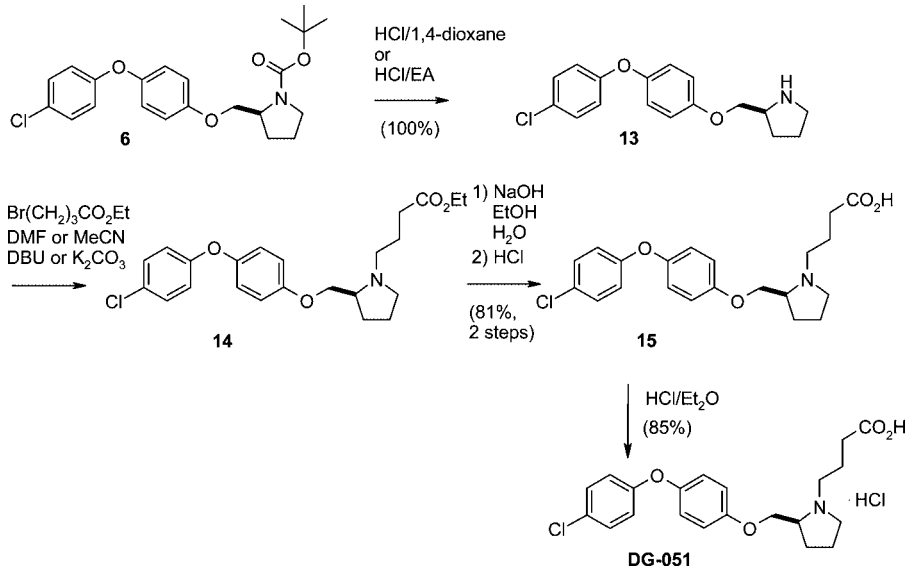
One of the most important achievements of our process development was telescoping the two-step synthesis of intermediate **6** from **1**. The tosylate formation and isolation from

(12) Other solvents examined included: EtOAc, tetrahydrofuran (THF), 1,4-dioxane, *tert*-butyl methyl ether (MTBE), and 1-methyl-2-pyrrolidinone (NMP).
(13) Yeager, G. W.; Schissel, D. N. *Synthesis* **1991**, 63.
(14) Tulp, M. T. M.; Hutzinger, O. *Biomed. Mass Spectrom.* **1978**, 224.
(15) Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799.
(16) All chemical purity values are provided as area % by HPLC.

Scheme 2. **Concerted synthetic route to intermediate 6**



Scheme 3. **Original route to DG-051 from intermediate 6**



DCM was a high-yielding procedure, but intermediate **2** needed to be stored under refrigeration and only for a limited time (1−2 weeks). The purity of **2** ranged from 99% (on 100-g scale) to slightly over 92% (on 5-kg scale) due to some instability during concentration, which would have posed a problem on a manufacturing scale (100 kg and above).

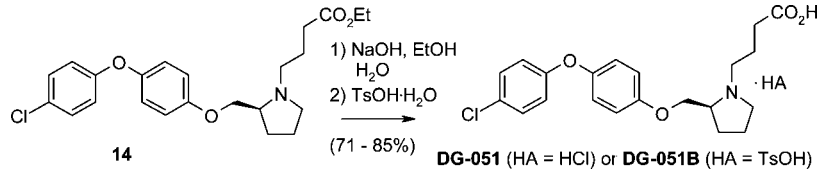
A desirable modification was to combine both tosylation and coupling in a single manufacturing step, thus bypassing any concerns regarding isolation and storage of tosylate **2**. To that effect, intermediate **2** needed to be prepared in a solution that could be directly mixed with the phenoxide generated from **12**. We ruled out solvents such as DCM, DMF, THF, 1,4-dioxane, MTBE, NMP, or EtOAc due either to compatibility concerns in any of the combined steps or to stirrability issues and increased reaction time. We eventually solved the problem by developing a new, multisolvent system. Specifically, we carried out the tosylation in a 1:1 (v/v) mixture of toluene and acetonitrile, which after 3 h was worked up (neither toluene nor acetonitrile alone had been completely satisfactory in the combined procedure). The resulting solution of **2** reproducibly carried less than 1% water and could be reacted directly with the phenoxide of **12** that had been preformed in DMF. Intermediate **6** was readily isolated after aqueous quench and heptane extraction. Isolated crude yields of **6** were typically in the 85−90% range over the two-stage reaction step, at ∼97% purity. The purity of intermediate **6** could be improved to 99.8% by trituration with heptane, but crude **6** could be used in the next step without any further manipulation. By eliminating the issues connected with the potential for tosylate decomposition, we significantly increased the feasibility and scalability of the synthetic protocol. In addition, both manufacturing time and overall processing costs were greatly reduced.

Synthesis of DG-051 from Intermediate 6. From intermediate **6**, the completion of the synthesis appeared to be straightforward: deprotection of the pyrrolidine nitrogen, *N*-alkylation, saponification, salt formation, and isolation (Scheme 3).

We have used two procedures to deprotect intermediate **6** to yield the free pyrrolidine nucleophile **13**. A 4 M HCl/1,4-dioxane solution proved to be the reagent of choice for the removal of Boc-protecting group on gram to ∼6 kg scale; however, on the manufacturing scale (∼90 kg), it was more feasible to perform the reaction in ethyl acetate saturated with gaseous HCl. In both cases, the reaction proceeded cleanly, and intermediate **13** was consistently isolated after a simple aqueous workup in close to quantitative yields while purity routinely exceeded 98%.

The introduction of the four-carbon side-chain was performed *via* the nucleophilic attack of commercially available alkyl 4-bromobutyrates. Application of 4-bromobutyric acid resulted in slow reaction and, after overnight reaction at 50 °C, a 22% conversion to DG-051 and 36% of an unidentified byproduct. Whereas methyl 4-bromobutyrate had been used in our medicinal chemistry preparations of the targeted molecule,[11] we chose the cheaper ethyl 4-bromobutyrate as an electrophile for development. For our small-scale needs, we ran the reaction with very good yield in DMF, utilizing 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) as the base. At later stages of manufacturing protocol development, we resorted to a more scalable procedure, utilizing K_2CO_3 in acetonitrile. Under these conditions, the

Scheme 4. **Preparation of DG-051 salts from the corresponding ethyl ester without isolation of the intermediate zwitterion**



reaction was completed in 8−16 h with 1.1−1.2 equiv ethyl 4-bromobutyrate and 2.0−2.5 equiv of K_2CO_3. Following workup, the resulting crude ester **14** could be used in the next step without further purification.

Another major focus of the development work addressed both saponification and acidification steps. During the course of our studies, we discovered that both zwitterion **15** and the corresponding salts are easily soluble in water, leading to considerable losses of the final product. Multiple extractions of aqueous solutions of **15** with organic solvents did not address this issue adequately. The saponification itself could be easily carried out in ∼ 2:1 (v/v) ethanol/water in the presence of 2−2.5 equiv NaOH (other alkalis were also effective) in 4−6 h. Initially, this apparently simple chemistry approach had two distinct operational steps, namely: (a) saponification reaction with the isolation of the zwitterion **15** and (b) formation, isolation, and purification of the respective salt (in that case, the hydrochloride form) (Scheme 3). At the end of the saponification reaction, the alkaline reaction mixture was concentrated and worked up (including a wash with MTBE or MTBE/heptanes of pH 9.5 aqueous solution); eventually the pH of the aqueous layer was adjusted to 6.0−6.3, corresponding to the estimated range of the DG-051 isoelectric point (confirmed experimentally to be 6.185). Water was completely removed *in vacuo* to afford the zwitterion as the solid reaction residue. Redissolution in organic solvent(s), filtration to clarify, dilution with diethyl ether, acidification with 2 M HCl in diethyl ether, filtration, rinse with diethyl ether, and drying produced crystalline DG-051. This was consistently of high purity (better than 99% on up to 100 g scale); however, the method was extremely laborious. Multiple operations, lengthy concentrations from aqueous solutions, and the use of diethyl ether would pose problems for transferring this protocol to a multikilogram scale.

In amending the described procedure to a large-scale preparation of **15**, we achieved a major breakthrough by extracting DG-051 from acidic (pH 2) aqueous solutions whose ionic strength had been increased by addition of NaCl. Namely, we were able to efficiently extract DG-051 in THF and especially 2-butanone (MEK) but to also solve problems with drying, we added the structurally related but more hydrophobic 4-methyl-2-pentanone (MIBK) (very effective at the level of 5−10% v/v in MEK). In addition, MIBK facilitated azeotropic removal of water from the organic extract prior to the final crystallization. DG-051 generation in aqueous medium, its direct extraction into an organic solvent and ability to work with aqueous HCl (vs ether solutions thereof) allowed us to scale up the process (Scheme 4).

The operation of washing at pH 9.5 was effective in removing most organic impurities into the MTBE or MTBE/heptane layer and contributed to the eventual isolation of a very pure final product. Unfortunately, it was also lengthy and cumbersome due to the frequent formation of emulsions. This problem was addressed by developing a recrystallization solvent system capable of efficiently excluding all impurities, without the need for a pH 9.5 prewash. At early stages of this particular development operation, we found that we could isolate DG-051 of higher than 99% purity by simply concentrating the crude DG-051 sodium salt at the end of the saponification step, generating and extracting the HCl salt from salified aqueous medium, and performing a final recrystallization of DG-051 from MTBE, MEK, or MEK/MTBE mixtures. MEK as a single solvent afforded low recovery of the targeted molecule, while MTBE, whether used alone or in combination with MEK, proved difficult to remove from the final product which led to increased drying time. Once we developed the adjusted MEK/MIBK mixtures for the extraction of DG-051 from aqueous media (*vide supra*), we experimented with similar modifications of MEK/MIBK ratios as crystallization solvents. We successfully isolated DG-051 in good yield (70−85%) by crystallizing the product from 7:1 to 12:1 (v/v) MIBK/MEK mixtures to furnish DG-051 in high purity (≥99%, 100% ee) on up to 1.3 kg scale.

Eventually, the hydrochloride form of DG-051 proved not to be an optimal choice for advanced development, due mainly to its hygroscopicity, multiple polymorphs, and low melting point (96−103 °C). A salt screen resulted in the selection of the *p*-toluenesulfonate (tosylate) salt, DG-051B, as a better candidate for development. DG-051B is not hygroscopic, has a higher melting point (115−116 °C), and has a single known polymorphic form.

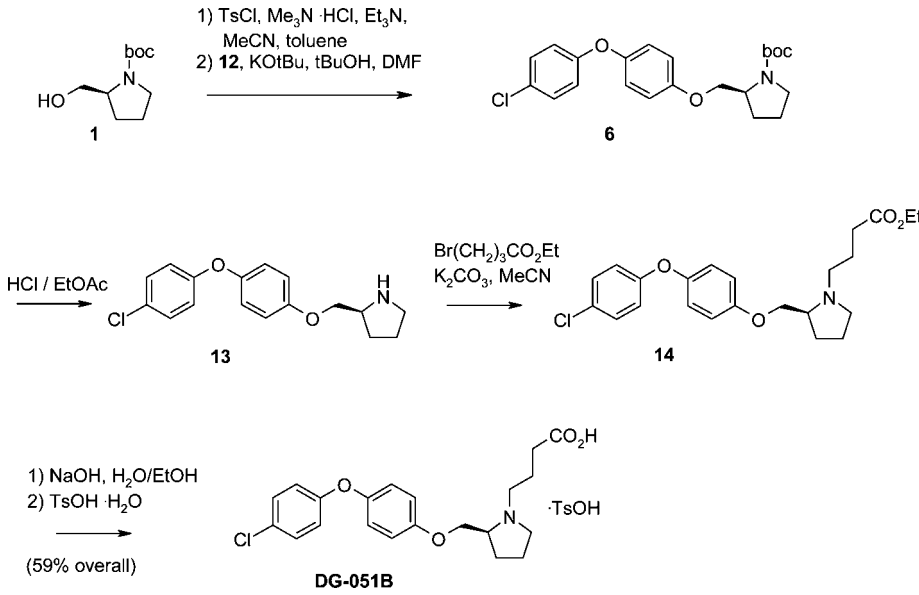
From the preparative point of view, working with the tosylate form resulted in further simplification of the isolation/purification procedure, since its extraction from aqueous solution by MEK/MIBK mixtures required only a moderate excess of *p*-toluenesulfonic acid (*p*-TsOH, 2−4 equiv) and no additional NaCl.

Finally, the purification of DG-051B by crystallization from MIBK/MEK mixtures proved to be a very effective procedure for the removal of practically all major impurities generated in the process. Also, the newly developed process was simple, high-yielding, and resulted in only small amounts of byproduct. As a result, the entire synthesis of DG-051B from prolinol **1** could be telescoped. The reaction intermediates needed neither individual purification nor isolation and were transferred to the progressive steps *via* solvent swaps. The current process (Scheme 5) has been applied to produce up to 88 kg of DG-051B, which was isolated in 52−66% overall yield, 100% ee, and >99% purity. A similar procedure was used to prepare the high-purity (>99%, 100% ee) (*R*)-enantiomer of DG-051B.

Conclusions

In conclusion, we have developed scalable and commercially viable processes for the preparation of a clinical phase II leukotriene A4 hydrolase (LTA4H) inhibitor DG-051 and its

Scheme 5. **Final optimized four-step route to DG-051B**



tosylate salt DG-051B. The process furnished up to 66% yield of either targeted molecule over four manufacturing steps (six chemical transformation steps) that did not require intermediate isolation or purification. The final products were isolated as analytically and chemically pure optical isomers that successfully met regulatory requirements. The key to achieving process development goals was our careful consideration of the specific chemical and physical properties of our substrates, intermediates, and products in order to evolve general synthetic procedures into product-specific ones, at maximized conversion and isolation/purification rates. Key discoveries that allowed us to streamline the scale-up include: (i) a streamlined route and specific synthetic procedures that afforded both the intermediate **6** and the target products in high yields and purity, (ii) a specific solvent mixture that allowed for the telescoped preparation of a reactive tosylate electrophile and its coupling with a phenoxide nucleophile, (iii) an optimized extraction protocol that allowed us to generate and extract DG-051 and DG-051B directly from solutions of increased ionic strength, and (iv) an efficient final crystallization procedure that, together with the high-yielding and clean individual steps, allowed us to forego intermediate purifications.

Experimental Section

General Experimental. HPLC chemical purity analysis of products and intermediates was performed using an Agilent 1100 liquid chromatograph equipped with a Zorbax SB-CN 4.6 mm × 250 mm column. Standard method: 85:15 to 15:85 over 45 min gradient of water−acetonitrile containing 2.5% H_3PO_4, flow rate 1.0 mL/min. The retention time for DG-051 is 14.5 min, while the relative retention times (RRT) for the key intermediates are respectively 1.86 for **6**, 0.96 for **13**, and 1.18 for **14**. HPLC chiral purity determination was done on a Chiralpak AD-H 4.6 mm × 250 mm column eluted isocratically with a mixture of 80:20:0.1 hexane/IPA/ethane sulfonic acid, flow rate 1.0 mL/min. DG-051 elutes at 12−13 min, while its enantiomer at 15−16 min. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Oxford 400 and 500 MHz spectrometers. APCI-MS and ESI-MS were recorded with an Agilent 1100 LC/MS system in either positive or negative ionization mode. IR spectra were recorded neat on a Nexus 470 FT-IR system and are reported in cm^{-1}. Melting points were measured on first isolated material using a TA Instruments digital scanning calorimeter. Elemental analysis data are reported in wt %.

Pilot-Plant Procedure. *4-{(2S)-2-[4-(4-Chlorophenoxy)phenoxymethyl]pyrrolidin-1-yl}butyric Acid p-Toluenesulfonate (DG-051B) from Prolinol* ***1*** *by Telescoped Procedure, with No Intermediate Isolation.* To a solution of prolinol **1** (58.0 kg, 288.2 mol) and trimethylamine hydrochloride (2.7 kg, 28.3 mol) in 166 L of 1:1 (v/v) mixture of acetonitrile and toluene was added triethylamine (62.1 kg, 613.7 mol) at 20−30 °C. The mixture was cooled to 15 °C, a solution of TsCl (65.9 kg, 345.7 mol) in 144 L of 1:1 (v/v) mixture of acetonitrile and toluene was added, and the resulting mixture was stirred 2 h at ambient temperature. The reaction was quenched by addition of water (290.9 L) at 20−25 °C. The organic layer containing intermediate **2** was washed with 25% aqueous NaCl solution (2 × 293 L). In a separate vessel, 4-(4-chlorophenoxy)phenol **12** (70.2 kg, 318.1 mol) was dissolved in DMF (423.0 L). A solution of 15% KOtBu in *tert*-butanol (299.9 kg, 400.9 mol) was added at 20−25 °C. After 30 min, to the resulting potassium 4-(4-chlorophenoxy)phenoxide solution was added the solution of **2** previously prepared, at 20−22 °C. The resulting reaction mixture was heated to 55−63 °C over 6 h, then held at that temperature for 27 h, cooled to 22 °C, quenched by addition of water (76.4 L), diluted with more water (695 L) and heptanes (772 L), and allowed to separate. The organic layer was washed sequentially with 1 M citric acid (1 × 826 L), 0.5 N sodium hydroxide (2 × 786 L), and water (771 L), after which the bulk of the solvents was removed by vacuum distillation, and the remaining solvents were exchanged to EtOAc by repeated (3×) vacuum concentration from EtOAc. The amount of dissolved crude **6** was determined by concentration of a small aliquot to be 89.4 kg, and to the EtOAc solution was added the necessary EtOAc to adjust the concentration to 21 wt %. Through this solution, kept at 15−20 °C, was bubbled gaseous HCl (40.3

kg, 1105.3 mol) over 4.4 h. Water (558 L) was added, the mixture was stirred 30 min, and the layers were allowed to separate. The aqueous layer was extracted with EtOAc (193 L). The combined organic extracts were washed with 50% aqueous K_2CO_3 (480 kg), after which the bulk of the EtOAc was removed by vacuum distillation, and the remaining EtOAc was exchanged to acetonitrile by repeated (3×) vacuum concentration from acetonitrile. The amount of dissolved crude **13** was determined by concentration of a small aliquot to be 63.7 kg, and to the acetonitrile solution was added the necessary acetonitrile to adjust the concentration to 17.4 wt %. To the resulting solution were added ethyl 4-bromobutyrate (47.5 kg, 243.5 mol) and K_2CO_3 (67.5 kg, 488.4 mol). The mixture was stirred at 50−58 °C for 10.8 h, cooled to 25 °C, stirred for 30 min with water (398 L), and the layers were allowed to separate. The organic layer was vacuum distilled to remove most of the acetonitrile, after which the remaining acetonitrile was exchanged to ethanol by repeated (3×) vacuum concentration from ethanol. The amount of dissolved crude **14** was determined by concentration of a small aliquot to be 94.7 kg, and to the ethanol solution was added the necessary ethanol to adjust the concentration to 18.7 wt %. The resulting mixture was stirred with a solution of aqueous 10.5% NaOH (198.9 kg solution, 522.1 mol) for 6 h at 21−25 °C, after which it was concentrated to 39% of the original volume to remove most of the ethanol, diluted with 214 L water, and partially concentrated again, then diluted with 183 L water. The aqueous solution was stirred with *p*-TsOH·H_2O (159.4 kg, 838.0 mol) for 30 min at 20 °C, then extracted repeatedly with MIBK/MEK mixtures (1 × (3:1, v/v), 578 L; 1 × (1:1, v/v), 288 L; 8 × (1:2, v/v), 285 L each). The combined organic extracts were washed with water (2 × 264 L), vacuum concentrated to remove the bulk of MEK, then concentrated again from MIBK (438 L) until the resulting suspension in MIBK contained 19.2 wt % DG-051B. The slurry was cooled to 25 °C, and the solid product was isolated by filtration, rinsed with MIBK (428 L; 396 L), and dried 23 h at 50 ± 5 °C to afford 71 kg (43.8%) DG-051B of 99.9% purity. More DG-051B (17 kg; 99.5% purity) could be isolated from the aqueous mother liquors that remained after the MIBK/MEK extractions (further diluted with 1 vol water) by one more extraction with 3:1 (v/v) MIBK/MEK, thus achieving a cumulated yield of 54.3%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 1.83 (m, 1 H), 1.86−1.98 (m, 2 H), 2.03 (m, 1 H), 2.24 (m, 1 H), 2.28 (s, 3H), 2.37 (t, 2 H, J = 7.0 Hz), 3.12−3.24 (m, 2 H), 3.48 (m, 1 H), 3.64 (m, 1 H), 3.94 (m, 1 H), 4.19 (m, 1 H), 4.30 (dd, 2 H, J = 11.0 Hz, 3.5 Hz), 6.94 (d, 2 H, J = 9.0 Hz), 7.05 (s, 4 H), 7.11 (d, 2 H, J = 8.0 Hz), 7.40 (d, 2 H, J = 9.0 Hz), 7.51 (d, 2 H, J = 8.0 Hz), 9.54 (br s, 1H), 12.30 (br s, 1 H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 20.61, 20.74, 22.32, 26.18, 30.44, 39.75, 54.35, 66.19, 66.79, 116.03, 118.97, 120.78, 125.46, 126.41, 128.11, 129.71, 137.84, 145.31, 149.71, 154.17, 156.81, 173.51. IR 2986, 1721, 1504, 1484, 1221, 1151, 1120, 1033, 1009, 824, 814, 681, 565. MS (APCI+) m/z 390.2 $M^+ + 1$. Mp 115.5 °C. Anal. Calcd for $C_{28}H_{32}ClNO_7S$: C, 59.83; H, 5.74; Cl, 6.31; N, 2.49; S, 5.70. Found: C, 60.03; H, 5.81; Cl, 6.07; N, 2.41; S, 5.90.

Advanced Laboratory Procedures. *tert-Butyl (2S)-2-[(p-toluenesulfonyloxy)methyl]pyrrolidine-1-carboxylate (2).* A solution of Boc-(*S*)-(−)-2-pyrrolidinemethanol (**1**) (1.43 kg, 7.10 mol) and DMAP (86.40 g, 0.71 mol) in DCM (11 L) was cooled to 5 °C. TsCl (1.49 kg, 7.81 mol) was added in portions over 20 min at 0−5 °C. The resulting mixture was allowed to warm up to ambient temperature over 18 h, after which it was quenched with 6 L water. The organic layer was separated, washed with 6 L water, 4 × 5 L 0.3 M aqueous HCl, 2 × 6 L water, and 4 L brine, after which it was dried over anhyd Na_2SO_4, filtered, and concentrated *in vacuo* to afford the desired intermediate **2** (2.42 kg, 96%). The purity (96.3%) was suitable for the material to be used in the following step without further purification. This material could be stored at 2−8 °C, under inert atmosphere, for 2 weeks; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 and 1.41 (two singlets without baseline separation, 9 H), 1.75−2.05 (m, 4 H), 2.44 (s, 3 H), 3.23−3.40 (m, 2 H), 3.85−4.20 (m, 3 H), 7.35 (m, 2 H), 7.78 (d, 2 H, J = 8.0 Hz). ^{13}C NMR (500 MHz, $CDCl_3$; 2 rotamers) δ 21.57, 22.79 and 23.77, 27.58 and 28.48, 28.30, 46.42 and 46.88, 55.50, 69.93, 79.53 and 79.86, 127.80, 129.83, 132.92, 144.66 and 144.86, 153.97 and 154.36.

4-(4-Chlorophenoxy)phenol (12). To a solution of 4-bromochlorobenzene (**9**) (4.89 kg, 25.50 mol) and 4-methoxyphenol (**10**) (4.87 kg, 39.20 mol) in 1,4-dioxane (34.8 L) under nitrogen were added Cs_2CO_3 (17.10 kg, 52.50 mol), N,N-dimethylglycine hydrochloride (1.07 kg, 7.70 mol) and CuI (0.49 kg, 2.60 mol). The resulting suspension was heated to 110 ± 5 °C. Vigorous bubbling occurred at around 104 °C for about 40 min, after which TLC (silica gel; hexane/EtOAc 3:1, v/v) indicated consumption of **9**. After 60 min more at 105 ± 5 °C the reaction mixture was allowed to cool to ambient temperature over 18 h. MTBE (30 L) followed by water (30 L) were added. The aqueous layer was extracted with MTBE (10 L). The combined organic layers were washed with water (12 L), 10% aqueous NaOH (2 × 15 L), and brine (15 L), dried over anhyd Na_2SO_4 and concentrated to crude 4-(4-chlorophenoxy)anisole **11** (5.24 kg, 88.4% crude yield) as an oil that solidified upon standing and could be used as such in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3 H), 6.86 (d, 2 H, J = 9.2 Hz), 6.88 (d, 2 H, J = 9.2 Hz), 6.96 (d, 2 H, J = 9.2 Hz), 7.24 (d, 2 H, J = 9.2 Hz).

Acetonitrile (22 L) and NaI (16.54 kg, 110.4 mol) were charged to a different vessel and chlorotrimethylsilane (11.99 kg, 110.4 mol) was added over 40 min and stirred for 30 min after which crude **11** (5.18 kg) dissolved in acetonitrile (8 L) was added in one portion. The mixture was stirred for 20 min, brought to reflux, held 16 h, and then cooled to 23 °C over 2 h. Water (20 L) was added over 40 min to the reaction mixture and stirring continued for 40 min. Isopropyl acetate (IPAC, 25 L) was added and the aqueous layer was extracted with IPAC (7 L). The combined organic layers were washed with water (10 L), 10% aqueous $Na_2S_2O_3$ (3 × 10 L) and brine (10 L), dried over anhyd Na_2SO_4, filtered, and concentrated to afford crude phenol **12** (4.80 kg). This material was recrystallized from heptane (4 L) to afford intermediate **12** of 98.3% purity (3.80 kg, 68.3% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96 (br s, 1 H), 6.83 (d, 2 H, J = 9.0 Hz), 6.88 (d, 2 H, J =

9.0 Hz), 6.92 (d, 2 H, $J = 9.0$ Hz), 7.25 (d, 2 H, $J = 9.0$ Hz). ^{13}C NMR (500 MHz, $CDCl_3$) δ 116.44, 118.80, 120.97, 127.45, 129.55, 149.95, 151.86, 157.04. IR 3440, 1501, 1481, 1450, 1208, 1188, 1097, 826. Mp 84.8 °C. A small portion of this material was further purified by a second recrystallization for elemental analysis. Anal. Calcd for $C_{12}H_9ClO_2$: C, 65.32; H, 4.11; Cl, 16.07. Found: C, 65.26; H, 4.02; Cl, 15.92.

*tert-Butyl (2S)-2-{[4-(4-Chlorophenoxy)phenoxy]methyl}-pyrrolidine-1-carboxylate (**6**). Method A. From Isolated Tosylate **2** and Phenol **12**.* To a solution of phenol **12** (4.29 kg, 19.43 mol) in DMF (55 L) was added KOtBu (2.36 kg, 21.03 mol) and the resulting mixture was stirred at ambient temperature for 1 h. Tosylate **2** (6.22 kg, 17.50 mol) dissolved in 12 L DMF was added and the reaction mixture was heated to 55 ± 5 °C for 18 h. The reaction mixture was diluted with heptane (50 L) and water (31 L) at 30 ± 5 °C. The aqueous layer was extracted with heptane (50 L) at 30 ± 5 °C. The combined organic layers were washed with 5% aqueous NaOH (2 × 31 L), water (31 L) and brine (31 L) at 30 ± 5 °C. Concentration *in vacuo* afforded 6.58 kg of off-white solids that were suspended in heptane (20 L), stirred at ambient temperature 16 h, cooled to 5 ± 5 °C for 2 h, and filtered. The solids were washed with heptane (2 × 3 L) and dried *in vacuo* at 40 °C for 17 h to afford 99.7% pure intermediate **6** (5.84 kg, 82.7%).

*Method B. From Prolinol **1** and Phenol **12**, without Isolation of **2**.* To a solution of prolinol **1** (140.00 g, 0.70 mol), TEA (140.70 g, 1.39 mol) and DMAP (8.40 g, 0.07 mol) in acetonitrile (350 mL) and toluene (350 mL) was added TsCl (145.60 g, 0.76 mol) in two equal portions, 10 min apart, at 5 ± 5 °C. The resulting mixture was stirred 3 h at 25 °C and quenched with water (700 mL). The organic layer was washed with brine (2 × 700 mL). In a separate flask, KOtBu (93.80 g, 0.84 mol) was added to a solution of **12** (168.70 g, 0.76 mol) in DMF (1855 mL). The solution containing tosylate **2** was transferred into the DMF reaction mixture. The resulting mixture was stirred at 60 ± 3 °C for 20 h, cooled to ambient, quenched with water (1850 mL), and extracted with heptane (1850 mL). The organic extract was washed with 0.5 N HCl (1850 mL), 0.5 N NaOH (2 × 1850 mL) and water (1850 mL). Concentration *in vacuo* of the heptane layer afforded crude **6** (235.15 g, 83.7% crude yield, 93.5% purity) of which 227.15 g were recrystallized[17] from heptane (570 mL) to afford 166.68 g intermediate **6** (99.2% purity, 62% yield over two steps and purification).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 9 H), 1.80−2.10 (m, 4 H), 3.30−3.50 (m, 2 H), 3.73−3.95 (m, 1 H), 4.03−4.20 (m, 2 H), 6.86 (d, 2 H, $J = 9.2$ Hz), 6.88−6.97 (m, 4 H), 7.24 (d, 2 H, $J = 9.2$ Hz). ^{13}C NMR (500 MHz, $CDCl_3$; 2 rotamers) 22.69 and 23.66, 27.88 and 28.60, 28.38, 46.44 and 46.80, 55.75 and 55.86, 68.26 and 68.76, 79.12 and 79.48, 115.57, 118.56, 120.64, 127.10, 129.34, 149.53 and 149.74, 154.24 and 154.50, 155.23 and 155.31, 157.06. IR 2973, 2931, 2872, 1695, 1504, 1486, 1392, 1237, 1162, 1090, 828. MS (ES+) *m*/*z* 404.5 $M^+ + 1$, 304.0 (base peak) $M^+ + 1 -$ COOtBu. Mp 75.7 °C. Anal. Calcd for $C_{22}H_{26}ClNO_4$: C, 65.42; H, 6.49; Cl, 8.78; N, 3.47. Found: C, 65.39; H, 6.49; Cl, 8.82; N, 3.52.

(17) Crude **6** can be used in the next step without further purification.

*(2S)-2-{[4-(4-Chlorophenoxy)phenoxy]methyl}pyrrolidine (**13**).* To a solution of intermediate **6** (5.84 kg, 14.46 mol) in 1,4-dioxane (27 L) was added 4 M HCl/1,4-dioxane (18 L) over 35 min. The reaction mixture was stirred 16 h at ambient temperature, degassed by bubbling nitrogen, and concentrated *in vacuo*. The residue (4.99 kg) was dissolved in water (29 L) and washed with MTBE (3 × 22 L). K_2CO_3 (2.1 kg, 15.19 mol) was added to bring the pH to 10. The resulting mixture was stirred for 3 h and allowed to separate. The aqueous layer was extracted with IPAC (2 × 20 L). The combined organic layers were washed with brine (40 L), dried over anhyd Na_2SO_4 (6.40 kg), filtered, and concentrated *in vacuo* to afford intermediate **13** as a thick oil that solidified upon standing (4.37 kg, 99.5%; 99.1% purity). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53−1.61 (m, 1 H), 1.73−1.90 (m, 2 H), 1.90−2.00 (m, 1 H), 2.58 (br s, 1 H), 2.93−3.08 (m, 2 H), 3.53 (ddd, 1 H, $J = 14.0$, 6.8, 5.2 Hz), 3.86 (dd, 1 H, $J = 9.2$, 6.8 Hz), 3.92 (dd, 1 H, $J = 9.2$, 5.2 Hz), 6.86 (d, 2 H, $J = 8.8$ Hz), 6.89 (d, 2 H, $J = 9.2$ Hz), 6.94 (d, 2 H, $J = 9.2$ Hz), 7.24 (d, 2 H, $J = 8.8$ Hz). ^{13}C NMR (500 MHz, $CDCl_3$) δ 25.27, 27.97, 46.55, 57.31, 71.76, 115.63, 118.74, 120.75, 127.32, 129.50, 149.82, 155.53, 157.16. IR 2928, 1505, 1484, 1226, 1090, 826, 815. MS (APCI+) *m*/*z* 304.0 $M^+ + 1$. Mp 52.7 °C. Anal. Calcd for $C_{17}H_{18}ClNO_2 \cdot 0.1H_2O$: C, 66.82; H, 6.00; Cl, 11.60; N, 4.58. Found: C, 66.72; H, 5.88; Cl, 11.50; N, 4.70.

*Ethyl 4-{(2S)-2-[4-(4-chlorophenoxy)phenoxymethyl]pyrrolidin-1-yl}butyrate (**14**).* To a mixture of pyrrolidine **13** (4.36 kg, 14.38 mol) and anhyd acetonitrile (27 L) were added K_2CO_3 (4.00 kg, 28.96 mol) and ethyl 4-bromobutyrate (3.11 kg, 15.97 mol). The reaction mixture was stirred at 55 ± 5 °C for 18 h. TLC (silica gel; 6:2:1 EtOAc/heptane/TEA) indicated that about 10−15% of **13** was still present. More K_2CO_3 (1.59 kg, 11.51 mol) and ethyl-4-bromobutyrate (1.12 kg, 5.75 mol) were added, and stirring continued at 55 ± 5 °C. After a total of 68 h at 55 ± 5 °C, the reaction was complete.[18] The mixture was cooled to 29 °C, and water (27 L) was added. The organic phase was concentrated *in vacuo* to afford crude intermediate **14** of 93.0% purity (7.30 kg, 121.4%; contained unreacted ethyl 4-bromobutyrate) that could be used as such in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, 3 H, $J = 7.0$ Hz), 1.66−1.75 (m, 1 H), 1.75−1.87 (m, 4 H), 1.95−2.04 (m, 1 H), 2.22−2.47 (m, 4 H), 2.82−2.92 (m, 2 H), 3.16 (m, 1 H), 3.76 (dd, 1 H, $J = 9.0$, 6.8 Hz), 3.90 (dd, 1 H, $J = 9.0$, 5.0 Hz), 4. Eleven (q, 2 H, $J = 7.0$ Hz), 6.86 (d, 2 H, $J = 8.5$ Hz), 6.88 (d, 2 H, $J = 9.0$ Hz), 6.94 (d, 2 H, $J = 9.0$ Hz), 7.24 (d, 2 H, $J = 8.5$ Hz). ^{13}C NMR (500 MHz, $CDCl_3$) δ 14.18, 23.19, 24.17, 28.60, 32.15, 54.24, 54.83, 60.13, 62.86, 71.92, 115.53, 118.65, 120.71, 127.23, 129.44, 149.65, 155.59, 157.17, 173.54. IR 2959, 2928, 1732, 1503, 1484, 1223, 826. A small portion of this material was further purified chromatographically (silica gel; EtOAc stepwise gradient in hexane, 10% increments from 10% to 50%) for elemental analysis. Anal. Calcd for $C_{23}H_{28}ClNO_4 \cdot 0.2H_2O$:

(18) Pilot reactions of this procedure were complete in less than 16 h. In this particular scale-up, using 2.0 equiv of potassium carbonate with 1.1 equiv of ethyl 4-bromobutyrate did not result in complete reaction after 24 h reaction time. In later installments, starting the reaction with 2.3−2.5 equiv of finely powdered potassium carbonate and 1.1−1.2 equiv of ethyl 4-bromobutyrate resulted in complete conversion within 10−16 h at 52−55 °C.

C, 65.53; H, 6.79; Cl, 8.41; N, 3.32. Found: C, 65.41; H, 6.50; Cl, 8.79; N, 3.54.

4-{(2S)-2-[4-(4-Chlorophenoxy)phenoxymethyl]pyrrolidin-1-yl}butyric Acid Hydrochloride (DG-051). A mixture of crude ester **14** (1193.00 g of crude material containing some residual ethyl 4-bromobutyrate and maximum 860.96 g (2.06 mol) of **14**), EtOH (3.5 L), NaOH (165.00 g, 4.12 mol), and water (2.0 L) was stirred at ambient temperature for 21 h, after which it was concentrated *in vacuo* and dissolved in water (5.0 L). The aqueous solution was acidified (pH 1) using concd HCl (550 mL), at 15−30 °C. NaCl (500.00 g) was added, and the mixture was extracted twice with MEK (3 L, then 1 L). To the combined organic extracts was added 4-methyl-2-pentanone (MIBK, 1 L), and the resulting mixture was concentrated *in vacuo*. The solid residue was stirred with MEK (4 L) at 50 ± 3 °C for 3 h. The resulting mixture was filtered through Celite. The Celite cake was rinsed with MEK (2 × 150 mL), and the combined MEK filtrate was stirred for 20 h at ambient temperature. A suspension formed that was cooled to 5 °C, diluted with MIBK (6 L), and stirred 3 h at 5 °C. The precipitated solids were isolated by filtration, rinsed on filter with cold (5 °C) MIBK (2 × 250 mL), and dried to afford 626.00 g (71.3%) DG-051 of 99.4% purity.

^{1}H NMR (500 MHz, DMSO-d_6) δ 1.81 (m, 1 H), 1.86−2.10 (m, 4 H), 2.25 (m, 1 H), 2.40 (m, 1 H), 3.06−3.24 (m, 2 H), 3.53 (m, 1 H), 3.65 (m, 1 H), 3.89 (m, 1 H), 4.32 (dd, 1 H, J = 10.5, 3.8 Hz), 4.50 (m, 1 H), 6.96 (d, 2 H, J = 9.5 Hz), 7.05 (d, 2 H, J = 9.0 Hz), 7.07 (d, 2 H, J = 9.5 Hz), 7.40 (d, 2 H, J = 9.0 Hz), 11.26 (br s, 1H), 12.34 (br s, 1 H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 20.42, 21.87, 26.53, 30.81, 53.75, 65.82, 66.90, 116.11, 118.94, 120.78, 126.34, 129.68, 149.63, 154.22, 156.81, 173.48. IR 3436, 2950, 2599, 1729, 1503, 1484, 1404, 1220, 1086, 1056, 824. MS (APCI+) m/z 390.2 M^+ + 1. Mp 103.9 °C. Anal. Calcd for $C_{21}H_{25}Cl_2NO_4$: C, 59.16; H, 5.91; Cl, 16.63; N, 3.29. Found: C, 58.86; H, 6.08; Cl, 16.93; N, 3.47.

4-{(2S)-2-[4-(4-Chlorophenoxy)phenoxymethyl]pyrrolidin-1-yl}butyric Acid p-Toluenesulfonate (DG-051B). To a solution of crude ester **14** (7.30 kg crude containing some residual ethyl 4-bromobutyrate and maximum 6.00 kg (14.37 mol) of **14**) in EtOH (30 L) was added a solution of NaOH (1.44 kg, 36.08 mol) in water (17.2 L) and the resulting mixture was stirred at ambient temperature for 16 h (the reaction was complete after 5 h). The mixture was concentrated *in vacuo* to 11.90 kg of residue that was dissolved in water (52 L) at 30 ± 5 °C. The resulting solution was cooled to 20 °C, then *p*-TsOH·H_2O (10.97 kg, 57.67 mol) was added in two portions (6.87 and 4.10 kg) at 15−25 °C, and stirring was continued at ambient temperature for 1 h. The resulting suspension was extracted with 3:1 (v/v) MIBK/MEK (1 × 44 L, 1 × 15 L). The combined organic layers were washed with water (2 × 16 L). The organic extract was concentrated *in vacuo* to 21.50 kg suspension that was heated with MIBK (36 L) at 50 °C for 30 min. The mixture was allowed to cool to ambient temperature over 18 h. The precipitated solids were isolated by filtration, washed on filter with MIBK (3 × 8 L), suction dried, and then dried to afford 6.85 kg (84.8%) of DG-051B of 99.9% purity.

Supporting Information Available

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