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Diastereomeric Salt Resolution Based Synthesis of LY503430, an AMPA (α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid) Potentiator

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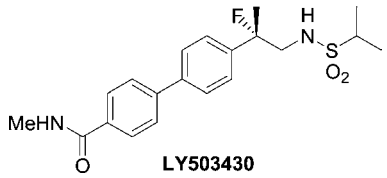
Abstract:

This article describes the development and optimization of chemical reactions and subsequent preparation of the API LY503430 under cGMPs to fund first human dose (FHD) clinical evaluation as a potential therapeutic agent for Parkinson's disease. Reasons and rationale are presented for changes in solvents and reagents. One of the major developments presented here is the replacement of a chiral chromatography with a diastereomeric salt resolution. This article also discusses a preferred orientation issue with LY503430 which complicated the XRPD analysis.

Introduction

We were charged with preparing about a kilogram of LY503430 to permit its evaluation in the clinic as a potential



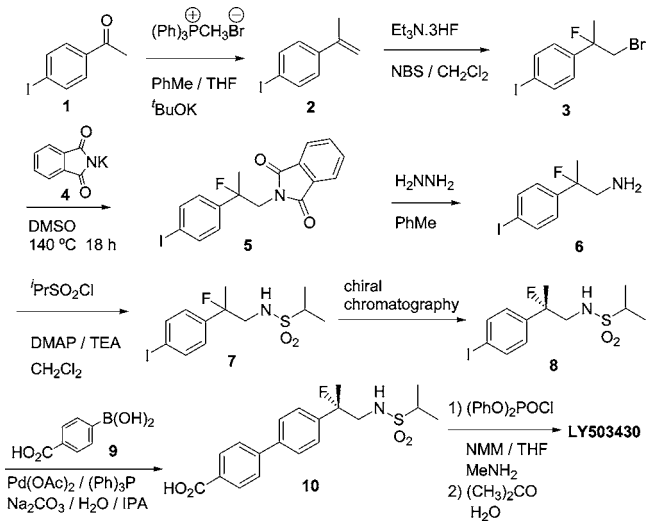
LY503430

therapeutic agent for Parkinson's disease.[1] LY503430 had been prepared at the multigram scale in our process department in laboratory glassware and had required a chiral chromatography (Scheme 1). To prepare LY503430 at the kilogram scale we needed to make the chemistry amenable to "fixed" pilot plant equipment for the first few reactions and, if possible, replace the chiral chromatography with a diastereomeric salt resolution. The poor solubility of the biphenyl acid **10** and ultimately LY503430 (and any biphenyl-related impurities as a result of the synthesis of **10** and LY503430) led us to develop an impurity control strategy that relied on having high chemical and optical purity of the Suzuki coupling partner **8** prior to assembling the biphenyl linkage.

Results and Discussion

The first step in the synthesis is a Wittig olefination to convert 4-iodoacetophenone **1** into the corresponding alkene

Scheme 1



2.[2] This reaction had been performed in a binary solvent system of toluene and THF, employing solid ^{t}BuOK. The reaction was refluxed for 24 h, worked up with water, dried with $MgSO_4$, concentrated to dryness, and slurried in hexanes to facilitate filtration of the triphenylphosphine oxide byproduct. The Wittig olefination had some development opportunities: (1) simplify the solvent system by going from a binary reaction solvent to a single solvent, (2) avoid solid ^{t}BuOK charges for safety reasons and better control of the reaction temperature, (3) remove the drying-agent operation and resulting waste, and (4) avoid concentrating to dryness to proceed with the triphenylphosphine oxide precipitation. It was found that the reaction ran cleanly to completion in THF alone, and that the solid ^{t}BuOK could be replaced with a 1 M ^{t}BuOK solution in THF. After the 1 M ^{t}BuOK in THF was added to the reaction mixture of ketone **1** and methyltriphenylphosphonium bromide in THF over 0.5 h at 25 °C and the reaction mixture held for 1.5 h, the conversion of **1** to **2** was complete. The workup was changed to adding the reaction to a mixture of heptane and water. After phase separation, the organic phase was concentrated to azeotropically remove water and THF to give a dry slurry of the phosphine oxide in heptane directly. The phosphine oxide was removed very productively by filtration, and the alkene **2** was processed forward as a heptane stock solution. These

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modifications allowed the process to run in standard pilot plant equipment with yields of alkene **2** obtained in >95%.

Step 2 in Scheme 1 involves converting alkene **2** into the fluorobromo adduct **3** by exposing **2** to the in situ generated fluorine bromine mixed halogen.[3] The original reaction procedure was run by dissolving alkene **2** in dichloromethane and adding triethylamine trihydrofluoride (TREAT) to that mixture at 25 °C. At this point, the reaction mixture was analyzed, and no reaction had taken place. The mixture was cooled to 0−5 °C, and *N*-bromosuccinimide was introduced to the reaction mixture to generate the mixed halogen and effect fluorobromination of the alkene **2**, presumably via Markovnikov attack of a bromonium ion by fluoride. This reaction mixture was quenched into aqueous ammonium hydroxide, the organic phase was separated and dried with $MgSO_4$, and the adduct **3** was isolated as a crude oil after concentration. Minor changes were made for pilot plant scale-up. The heptane stock solution of **2** was diluted with dichloromethane, and the reaction was conducted as described above with similar results. The reaction was worked up as before, but instead of concentrating the resulting mixture to a crude oil, the heptane and dichloromethane reaction solvents were replaced by DMF via azeotropic distillation. The fluorobromo adduct **3** was isolated as a DMF stock solution, due to **3** being an oil and handling more easily as a stock solution and DMF being the preferred solvent for the subsequent Gabriel reaction.[4] On the basis of laboratory use tests, the solution yields of **3** were estimated to be 90%.

Step 3 in Scheme 1 is a Gabriel reaction that was run by combining the fluorobromo adduct **3** with potassium phthalimide **4** in DMSO and heating the resulting mixture to 130−140 °C for about 18 h. The phthalimide adduct **5** was precipitated from the reaction as a crude amorphous solid by employing a slow water addition, and the solid was further purified by crystallization from dichloromethane with hexanes as the anti-solvent. Evaluation of this reaction in our hazard laboratory revealed a potentially dangerous exotherm with an onset at 155 °C. Since DMF is a common solvent for Gabriel reactions, we evaluated it as a substitute for DMSO, found no exothermic issues and that the reaction was virtually identical to the reaction employing DMSO as the reaction solvent. These Gabriel reactions ran as slurries with a large amount of potassium phthalimide **4** out of solution. We speculated that the 18 h reaction time was due to the poor solubility of the potassium phthalimide **4**. To remedy this problem, tetrabutylammonium bromide (TBAB) was added to the reaction as a phase transfer catalyst, and the reaction time was consequently reduced from 18 to 4 h. As before, the phthalimide adduct **5** was precipitated from the reaction by the slow addition of water. The crude precipitate of **5** filtered well and was mainly contaminated with potassium phthalimide **4**. HPLC assays of the dried crude precipitate indicated that it was about 70 wt % **5**. The 70 wt % pure adduct **5** was found to perform acceptably in the next phthalimide cleavage reaction so that no further purification was required. The yields of **5** were estimated to be about 65% over three steps starting from ketone **1** with a total of 24.3 kg of crude **5** isolated (17.2 kg of actual **5** based on weight percent purity).

Step 4, in Scheme 1 is the cleavage of the phthalimide **5** to give amine **6**, which was originally achieved with hydrazine.[5] Hydrazine was not a chemical that we wanted to handle in our pilot plant due to its toxicity. For the pilot plant campaign we chose to use 40% aqueous methylamine in ethanol to cleave the pthalimide group.[6] While the methylamine promoted phthalimide cleavage reaction worked acceptably in the laboratory, it presented problems in the pilot plant due to the reversibility of the reaction. The *N*-methyl phthalimide that was generated as a byproduct in the desired reaction was attacked by the primary amine **6** to give the bis-secondary amide **11** (Scheme 2) during the workup phase of the reaction, which led to yield fluctuation. This issue was amplified in the pilot plant due to longer residence times of the processing streams in the reactors. However, the primary amine **6** could be purified by extracting it into water as a hydrochloride salt, and the bis-secondary amide **11** and *N*-methyl phthalimide were removed by filtration and extraction with MTBE, respectively. The hydrochloride salt of **6** was treated with aqueous sodium hydroxide and the free base extracted into MTBE. The MTBE extracts containing primary amine **6** were concentrated and delivered to our kilo labs as stock solutions. The yields of amine **6** were variable (86, 61, and 56% over three runs) due to a lack of understanding of how to work up the reaction without causing reaction reversal. In total, 8.96 kg of crude amine **6** were prepared as MTBE stock solutions.

The racemic sulfonamide **7** had been separated by chiral chromatography (step 6 in Scheme 1). To avoid the costly chromatography we developed a diastereomeric salt resolution of the precursor primary amine **6** with (*S*)-(−)-(2)-pyrrolidone-5-carboxylic acid **12**. The MTBE stock solutions of **6** were concentrated to an oil and subsequently dissolved in 5% aqueous 2-propanol (v/v). The resulting mixture was heated to 65−70 °C, and a 5% aqueous 2-propanol solution of the acid **12** was slowly introduced to the mixture, inducing crystallization of the diastereomeric salt **13**. The diastereomeric salt resolution proved to be a dynamic process with the diastereomeric excess (de) of the crystals enriching over time. The de of the isolated salt **13** ranged from 92.25 to 96.77%, and averaged at 94.5% over six runs with yields in the 39−41% range.

The sulfonylation reaction (Scheme 1) was originally conducted in dichloromethane by reacting racemic amine **6** with isopropylsulfonyl chloride in the presence of triethylamine and catalytic DMAP.[7] We wanted to avoid the use of dichloromethane and DMAP in the preparation of sulfonamide **8**; therefore, alternative solvents, reagents, and condi-

(3) Dolensky, B.; Kirk, K. L. *J. Org. Chem*. **2001**, *66*, 4687−4691. Alvernhe, G.; Laurent, A.; Haufe, G. *Synthesis* **1987**, *6*, 562−564. McClinton, M. A. *Aldrichimica Acta* **1995**, *28*, *2*, 31−36.

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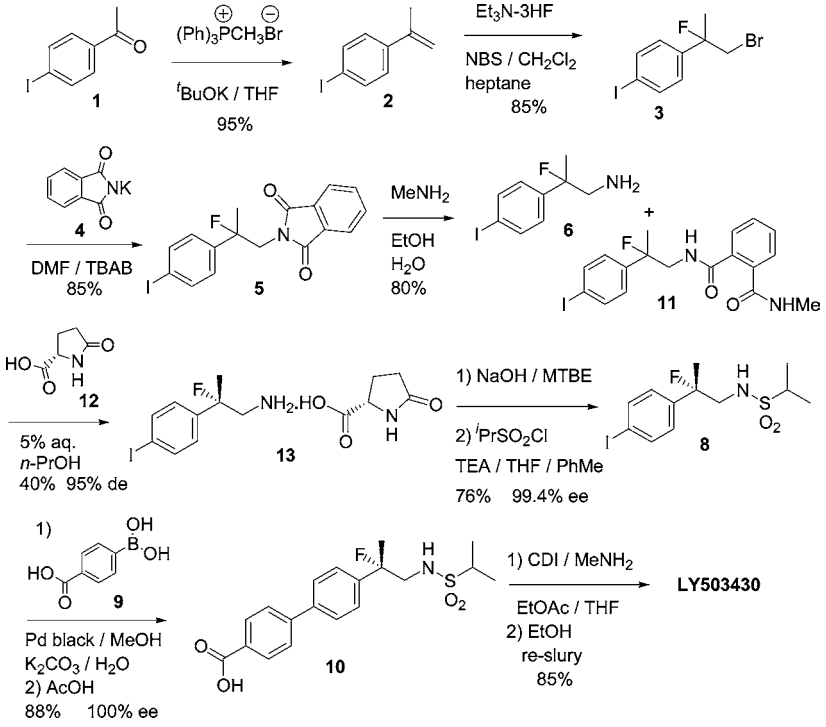
Scheme 2



tions were evaluated as substitutes. The use of carbonate and phosphate bases proved encouraging, but large excesses of isopropylsulfonyl chloride were necessary to achieve high conversion. Toluene and THF emerged as the solvents of choice for the sulfonylation, with a mixture of the two solvents giving better impurity suppression than either solvent by itself. The diastereomeric salt **13** was converted to its free base with aqueous NaOH, extracted into MTBE, dried with sodium sulfate, and concentrated to an oil. The oil was dissolved in a mixture of toluene and THF, cooled to 0−5 °C, and treated with TEA, followed by a slow addition of isopropylsulfonyl chloride to give about 95% conversion to sulfonamide **8**. The reaction was quenched with aqueous HCl, and after the organic phase was separated and dried with sodium sulfate, concentration gave a "technical grade" solid of about 90% pure sulfonamide **8**. Step 7 in the synthesis of LY503430 was a Suzuki coupling to establish the biphenyl linkage. The biphenyl motif in this chemistry renders the molecule very insoluble and makes any biphenyl-related impurities difficult to remove from the desired products **10** and LY503430. Therefore, the crude sulfonamide **8** was recrystallized from acetonitrile and water, which reduced the yield by 10 to 15%, but gave sulfonamide **8** with excellent purity. The isolated yields of purified sulfonamide **8** were consistently in the 76% range over four batches with enantiomeric excesses of >99%.

The conditions we received for running the Suzuki reaction to couple sulfonamide **8** to 4-carboxylphenylboronic acid **9** were as follows: $Pd(OAc)_2$, Ph_3P, and Na_2CO_3 in aqueous IPA at reflux for 3 h.[8] This reaction mixture was filtered through Celite and acidified with aqueous HCl to precipitate the acid **10** as a fine, slow-filtering solid with isolated yields of about 70% with <95% purity. A Suzuki reaction with similar coupling partners was being run in our department with palladium black as the catalyst, which was giving good results.[9] We applied the palladium black Suzuki reaction conditions to the coupling of sulfonamide **8** to boronic acid **9**. The sulfonamide **8** was combined with a slight subcess of the boronic acid **9** (0.99 equiv relative to the sulfonamide **8**), dissolved in aqueous MeOH containing K_2CO_3, catalytic palladium black was added, and the resulting mixture was heated to 63−68 °C for 1 h. These conditions gave >99% conversion of the boronic acid **9** (lower conversion levels and/or >0.99 equiv of **9** led to difficulty removing the boronic acid from the product acid **10**). The reaction mixture was filtered through Celite and the Celite rinsed with warm water to displace product **10**. The resulting clarified mixture was heated to 60−65 °C and acidified slowly with acetic acid to induce crystallization of very high purity, rapid filtering acid **10** in about 88% yield over five batches as the single desired enantiomer. The palladium levels in the isolated acid **10** typically ranged from 3 to 8 ppm.

The last step in the synthesis of LY503430 was an amide coupling that used diphenylphosphinic chloride with *N*-methylmorpholine in THF to effect the coupling of methylamine with the acid **10**.[10] The workup involved an aqueous acidic wash, followed by an aqueous basic wash, drying the organic phase with $MgSO_4$, and removing the solvent to give the amide LY503430 as a crude solid. The crude LY503430

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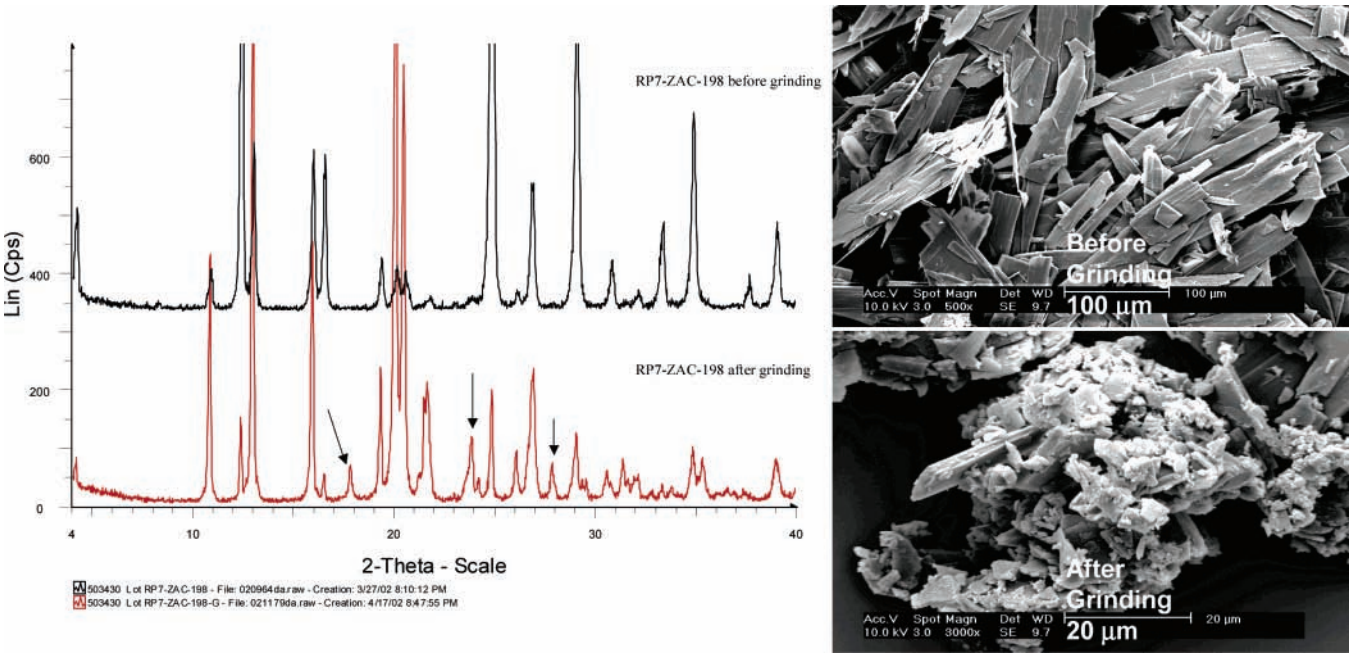

Figure 1. **Lath morphology of LY503430 gave rise to preferred orientation issues when gathering the XRPD (X-ray powder diffraction) data. Example of an XRPD pattern of LY503430 before and after grinding the sample to exemplify the preferred orientation issue. The "ground" sample's XRPD pattern in red has diffraction peaks that were not present prior to grinding.**

was purified by recrystallization from acetone/water (1/ 4) employing 130 volumes (mL/g) of solvent. We found that the combination of 1,1′-carbonyldiimidazole (CDI) as the coupling agent with EtOAc as the reaction solvent had some operational advantages over the existing diphenylphosphinic chloride procedure.[11] The acid **10** was combined with CDI in EtOAc at 23 °C to give a slurry, which became homogeneous as the corresponding imidazolide was formed. Eventually the imidazolide crystallized from solution, but warming the mixture to 40 °C redissolved the imidazolide to give a homogeneous solution. We took this opportunity to polish filter the mixture prior to crystallizing the final product. Slow subsurface introduction of a 2 M solution of methylamine in THF to the imidazolide caused LY503430 to crystallize from solution (if the methylamine was introduced into the headspace of the reactor, it would react with the carbon dioxide produced from the CDI degradation, and the carbonate of methylamine deposited as a white solid on the reactor walls). After filtration, the resulting wet cake was further purified by employing an EtOH re-slurry, affording LY503430 with excellent chemical purity. This protocol avoided a workup and unnecessary drying of the "technical" grade API, which was being handled with a high level of containment. The LY503430 was afforded in 85% yield, with 99.8 wt % potency by HPLC, and the undesired enantiomer of LY503430 not detectable.

X-ray powder diffraction (XRPD), used to evaluate the crystal phase composition of LY503430, showed considerable lot-to-lot variability in both the relative peak intensities and the number of diffraction peaks, which raised a concern that polymorphs might be present. Solid state ^{13}C NMR spectra (not shown) collected for lots of LY503430, which gave different XRPD patterns, were virtually identical, suggesting that preferred orientation effects complicated the XRPD analysis. The crystals of LY503430 had a lath habit, lacking in the third dimension as illustrated in Figure 1. This crystal morphology can lead to preferred orientation issues when conducting XRPD analyses.

To determine if preferred orientation complicated the XRPD analysis, a lot of LY503430 was lightly ground using an agate mortar and pestle, and an XRPD pattern was collected. As shown in Figure 1, the diffraction peak intensities, before (in black) and after (in red), were dramatically affected by the grinding process. The black arrows in Figure 1 point to new diffraction peaks in the XRPD pattern that were not present prior to grinding. These results confirmed the effects of preferred orientation; however, phase transformations induced by even light grinding could not be ruled out as a possible cause for the appearance of the new diffraction peaks. Therefore, to unambiguously show that a single crystalline form of LY503430 was present, thin crystals of acceptable quality for X-ray structure analysis were grown from EtOH−H_2O, and the crystal structure was solved. From the crystal structure, a theoretical powder pattern was calculated. Aside from a slight shifting of a few of the diffraction peaks due to the different temperatures at which the simulated and experimental data were obtained (148 K vs ambient temperature, respectively), there is excellent agreement between the simulated pattern and the experimental pattern of the ground material, Figure 2. This result confirms that *all* of the peaks observed in the different LY503430 powder patterns were due to a single crystalline phase. The absolute stereochemistry of LY503430 was also confirmed in the single crystal X-ray analysis using the sulfur atom as the asymmetric reference.[12]

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(12) X-ray data in the Supporting Information.

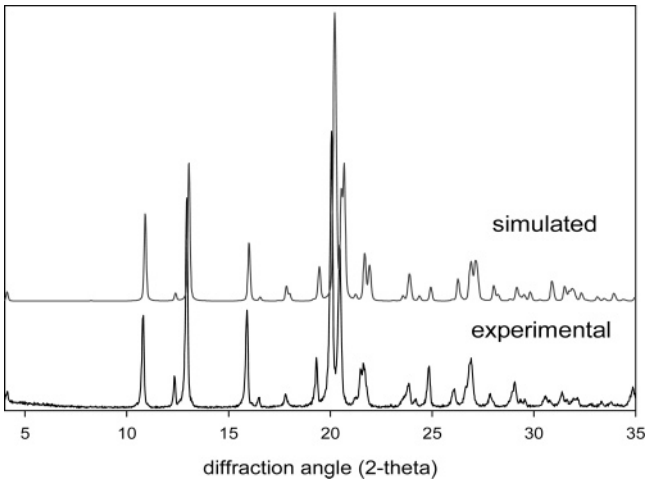

Figure 2.

Conclusion

The diastereomeric salt resolution based synthesis of LY503430 was developed and performed in a pilot plant and kilo lab in eight isolated stages with an overall yield of 11.6%. A total of 2.19 kg of LY503430 was produced to fund phase I clinical evaluation.

Experimental Section

Analytical Methods for the Scheme 2 Synthesis of LY503430. *GC conditions for the first stage of the synthesis:* column: J & W DB 1701 (30 m × 0.25 μm); carrier gas: He, 1.1 mL @ 40 °C; injection: 1.0 μL @ 250 °C, split 50:1; temperature program: 40−280 °C at 15 °C/min, hold at final temperature for 15 min; detection FID @ 300 °C; sample prep: ∼5 mg/mL in CH_2Cl_2. Peaks: alkene **2** at 9.9 min, fluorobromo adduct **3** at 13.2 min, Phthalimide adduct **5** at 22.6 min, amine **6** at 12.2 min.

*CE chiral assay for diastereomeric salt **13**:* column: 48 cm long × 50 μm i.d. uncoated capillary; temperature: 30 °C; detection: 232 nm; voltage: +25 kV; buffer: 25 mM citrate/tris pH 2.5 + 2.5 mM $18C_6H_4$ + 1.5 mM DM β CD; injection: 50 mbar × 2 s; sample prep: ∼0.4 mg/mL in 1:1 (v:v) CH_3CN:H_2O. Peaks: enantiomers of amine **6** at 18.3 (*S*-enantiomer) and 19.4 (*R*-enantiomer) minutes.

*HPLC potency assay for diastereomeric salt **13**:* column: Zorbax SB-phenyl 250 nm × 4.6 mm; temperature: 25 °C; detection: UV 229 nm; injection: 20 μL; eluent: isocratic, 30% CH_3CN (w/0.05% TFA): 70% Milli-Q H_2O (w/ 0.05% TFA); sample prep: ∼0.1 mg/mL in 1:1 (v:v) CH_3CN:H_2O. Peaks: amine **6** at 6.2 min.

*HPLC chiral assay for sulfonamide **8**:* column: Chiralpak AD, 250 × 4.6 mm, 30 °C; detection: UV 230 nm; eluent: 95:5 v/v hexane/IPA; flow: 1.0 mL/min; injection: ∼20 μL; sample prep: ∼0.3 mg/mL 1:1 v/v IPA/hexane. Peaks: enantiomers of sulfonamide **8** at 16.6 (*S*-enantiomer) and 28.0 (*R*-enantiomer) min.

*HPLC potency assay for sulfonamide **8**:* column: Zorbax SB-phenyl 250 nm × 4.6 mm; temperature: 25 °C; detection: UV 232 nm; injection: 20 μL; eluent: isocratic, 55% CH_3CN (w/0.05% TFA): 45% Milli-Q H_2O (w/ 0.05% TFA); sample prep: ∼0.5 mg/mL in 1:1 (v:v) CH_3CN:H_2O.

*HPLC chiral and potency assay for acid **10**:* column: ChiralPak AD, 250 nm × 4.6 mm; temperature: 30 °C; detection: UV 270 nm; injection: 20 μL; flow rate: 1.0 mL/min; eluent: 85:15 (v:v) hexane (w/ 0.2% AcOH):IPA (w/0.2% AcOH). Peaks: enantiomers of acid **10** at 20.0 (*S*-enantiomer) and 26.6 (*R*-enantiomer) min.

*HPLC chiral and potency assay for acid **LY503430**:* column: ChiralPak AD, 250 nm × 4.6 mm; temperature: 30 °C; detection: UV 270 nm; injection: 20 μL; flow rate: 1.0 mL/min.; eluent: 80:20 (v:v) hexane:IPA. Peaks: enantiomers of acid **10** at 10.7 (*S*-enantiomer) and 15.1 (*R*-enantiomer) min.

2-[2-Fluoro-2-(4-iodo-phenyl)-propyl]-isoindole-1,3-dione (5). *Step 1.* Under a nitrogen atmosphere, a reactor was charged with THF (35 L) followed by 4-iodoacetophenone **1** (5.298 kg, 21.53 mol) at 20−25 °C. Methyltriphenylphosphonium bromide (8.492 kg, 23.77 mol) was added to the reaction mixture, followed by a 20% ^{t}BuOK in THF solution (14.6 kg, 25.85 mol) addition over about 0.5 h, between 20 and 30 °C. The reaction mixture was cooled to 22 °C and stirred for about 1.5 h. Subsequent GC analysis of the reaction mixture indicated complete consumption of the 4-iodoacetophenone **1**. Heptane (30 L) was charged to a quench vessel followed by DI water (45 L). The reaction was charged to the quench vessel over about 0.5 h, between 20 and 30 °C (no exotherm observed), and the resulting mixture was agitated for about 0.5 h. Agitation was stopped, and the phases were allowed to separate over about 0.5 h. The bottom aqueous phase was removed, and a 1% aqueous NaCl solution (45 L) was charged to the organic mixture. The resulting mixture was agitated for about 0.25 h and held to separate for about 0.5 h (20−25 °C). The bottom aqueous phase was removed, the reactor was set up for vacuum distillation (40−55 °C under 250−375 mmHg vacuum), and 50 L of distillate was removed, producing a triphenylphosphine oxide slurry in heptane. The reactor contents were cooled to 0−5 °C over about 0.5 h to further precipitate triphenylphosphine oxide. The contents of the reactor were passed through a filter into a second reactor to remove precipitated triphenylphosphine oxide, and the oxide waste cake was washed with cold heptane (20 L, 0−5 °C) to give an end volume of 43 L.

Step 2. CH_2Cl_2 (20 L) and triethylamine trihydrofluoride (7.998 kg, 49.61 mol) were charged to the alkene **2** heptane mixture between 20 and 25 °C, and the resulting mixture was cooled to 0−5 °C. *N*-Bromosuccinimide (4.184 kg, 23.51 mol) was charged to the reaction mixture in one portion, producing an exotherm which was controlled with jacket cooling (set to 0−5 °C). After the exotherm subsided, the reaction mixture was heated to 20−25 °C over about 1.0 h. After about 4.0 h of stirring the reaction mixture at 20−25 °C, GC indicated 7.9 area % of alkene **2** remaining (<2 area % of alkene **2** was the criteria for reaction completion). An additional portion of *N*-bromosuccinimide (0.80 kg, 4.50 mol) was added, and after about 1.0 h the GC area % of alkene **2** was 1.8. (Note: GC area % criteria of alkene **2** can be met in <3.0 h with 1.2 equiv of NBS charged initially). An aqueous ammonia solution was prepared by

combining DI water (15 L) and "strong (28−30%)" aqueous ammonia solution (8 L). The reaction mixture was added to the aqueous ammonia solution over about 0.5 h, in a temperature range of 20−30 °C. The resulting mixture was agitated for about 1.0 h, and the phases were allowed to separate for about 0.5 h. The bottom phase (pH 10) was removed, and DI water (21 L) was charged to the organic layer. The resulting mixture was agitated for 0.25 h, and the phases were allowed to separate for about 0.5 h (bottom phase removed). $MgSO_4$ (2.1 kg) was charged to the organic phase, and the resulting mixture agitated for about 1.0 h between 20 and 25 °C. The $MgSO_4$ was filtered off and washed with CH_2Cl_2 (20 L). The resulting organic mixture was concentrated via distillation (30−60 °C under 150−275 mmHg vacuum) to an end volume of about 20 L. DMF (20−25 L) was charged to the organic mixture, and a second vacuum distillation performed (45−75 °C under 75−150 mmHg vacuum) to a final volume of about 34 L. The DMF solution of fluorobromo adduct **3** (36.4 kg) was collected in a drum, and a 90% yield (based on forward processing lab data) was assumed for the first two steps.

Step 3. A reactor was charged with a DMF solution of fluorobromo adduct **3** (61.6 kg, 28.87 mol), and the mixture was held at 20−25 °C. To this mixture was added potassium phthalimide **4** (8.1 kg, 43.73 mol) followed by tetrabutylammonium bromide (0.94 kg, 2.92 mol). The reaction mixture was heated to 150−155 °C and was sampled for area % conversion after 3.0 h (1.7 area % fluorobromo adduct **3**), and sampled again after 4.0 h (0.62 area % fluorobromo adduct **3**). The reaction mixture was cooled to 38−42 °C over about 1.0 h, and DI water (95 L) was added to the reaction mixture at 38−42 °C over 2.0 h. The resulting mixture was cooled to 20−25 °C over 0.5 h and stirred for 1.0 h. The thick solids produced during the water addition required a manual scrape with a clean spatula to remove them from the walls of the reactor for filtration. The filter cake was washed with DI water (25 L) and dried at 45−55 °C under vacuum to constant weight; 12.47 kg of crude phthalimide adduct **5** was isolated as a tan solid.

1-Iodo-4-isopropenyl-benzene (2): ^{1}H NMR (500 MHz, DMSO-d_6), δ 2.01 (s, 3H), 5.14 (s, 1H), 5.47 (s, 1H), 7.32 (d, 2H, J = 8.5 Hz), 7.72 (d, 2H, J = 8.5 Hz).

1-(2-Bromo-1-fluoro-1-methyl-ethyl)-4-iodo-benzene (3): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74−1.81 (d, 3H, J = 21.27 Hz), 3.54−3.65 (m, 2H), 7.10−7.13 (d, 2H, J = 8.5 Hz), 7.71−7.74 (d, 2H, J = 8.5 Hz).

2-[2-Fluoro-2-(4-iodo-phenyl)-propyl]-isoindole-1,3-dione (5): (sample was recrystallized from IPA) mp (DSC) (5 °C/min) onset 133.17 °C, peak 134.83 °C. IR (neat) 3471, 3069, 2991, 2938, 1777, 1711, 1615, 1589 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.65 (d, 3H, J = 23.2 Hz), 3.97−4.02 (m, 2H), 7.21 (d, 2H, J = 8.5 Hz), 7.71 (d, 2H, J = 8.5 Hz), 7.85−7.90 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.4, 46.4, 94.3, 96.5, 123.2, 126.7, 131.3, 134.5, 137.0, 141.4, 167.4. ^{19}F NMR (282 MHz, DMSO-d_6) δ −129.2. Anal. Calcd for $C_{17}H_{13}FINO_2$: C, 49.90; H, 3.20; N, 3.42. Found: C, 49.95; H, 3.19; N, 3.27.

2-Fluoro-2-(4-iodo-phenyl)-propylamine (*S*)-(−)-(2)-Pyrrolidone-5-carboxylic Acid Salt (13). *Step 1.* A reactor was charged with ethanol (50 L) followed by the crude phthalimide adduct **5** (8.0 kg, 70.8 wt %, ∴5.6 kg, 13.69 mol). At 20−25 °C, a 40% aqueous solution of methylamine (28.8 kg or 32 L, 370.90 mol) was charged to the reaction mixture and the reactor sealed. After 24.0 h, the reaction was sampled, and 30 area % of the bis-secondary amide **11** was present by HPLC. After a further 2.0 h, a second sample was taken, and the bis-secondary amide **11** was present at the 29 area % level by HPLC. Due to the lack of forward reaction, the reaction temperature was increased to 32 °C. After an additional 24.0 h, the reaction was sampled and 0.6 area % of the bis-secondary amide **11** was present by HPLC (criteria <1 area %). A reduced pressure distillation was performed (40−60 °C under 100−150 mmHg) to remove 55 kg of distillate. MTBE (56 L) was charged to the reactor between 15 and 30 °C, followed by 1 M HCl (48 L). The resulting mixture was mixed for 10 min, and the phases were allowed to separate for 35 min. The lower aqueous phase containing amine **6** was removed, the organic phase was extracted with DI water (32 L), and the aqueous phases were combined. MTBE (50 L) was charged to the aqueous phase, the resulting mixture was agitated for 17 min, and the phases were allowed to separate for 20 min. The aqueous bottom phase containing amine **6** was drained, and this MTBE extraction was repeated. The aqueous phase had a pH of 5.32, causing the desired product amine **6** to be extracted into the MTBE. Therefore, the combined organic phases were extracted with 1 M HCl (26 L), and the resulting aqueous phase was combined with the initial aqueous phase giving a new pH of 1.2. This aqueous phase was extracted with MTBE (2 × 40 L). Fresh MTBE (48 L) was charged to the aqueous phase, followed by 5 M NaOH (6.4 kg) over 20 min (20 °C) to adjust the pH from 1.2 to 8.5. The organic phase was removed, and the aqueous phase was back-extracted with MTBE (48 L). The combined organic phases containing amine **6** were concentrated via atmospheric pressure distillation to afford 19.68 kg of amine **6** as an MTBE stock solution (19.31 wt %; ∴3.8 kg of amine **6**; 86.3% yield).

Step 2. The amine **6** that was produced in the pilot plant as a stock solution in MTBE was taken into the kilo lab. A portion of the amine **6** MTBE stock solution was concentrated via distillation on a rotovapor at 30−40 °C to give 1.61 kg (5.77 mol; this mass is used for "equivalent" and "volume" calculations) of amine **6** as an oil (stored under vacuum for 15.25 h). In a separate flask, **12** (*S*)-(−)-(2)-pyrrolidone-5-carboxylic acid (0.336 kg, 2.60 mol) was dissolved in 95/5 v/v *n*-propanol/DI water (4.03 L) between 40 and 50 °C. The amine **6** was dissolved in 95/5 v/v *n*-propanol/DI water (8.06 L) at 20−30 °C, and the resulting mixture was heated to 65−70 °C. The warm (40−50 °C) aqueous *n*-propanol solution of **12** was added to the warm (69 °C) amine **6** aqueous *n*-propanol mixture over 3.5 h. Initial nucleation was observed after 2.7 L of the acid solution was added, and a large amount of solids were present after the addition was complete. After the acid addition was

complete, the reaction mixture was held at 69 °C for 1.0 h and was subsequently cooled to 60 °C over 1.0 h. The mixture was held at 60 °C for 1.5 h, at which point the power to the mantle was switched off, and the reaction mixture was allowed to cool to ambient temperature (25 °C, 17.0 h) with the mantle in place. A sample of the solids was taken and washed with IPA for de determination (94.2% de; criterion >90% de). After the de criterion was met, the batch was filtered and washed with IPA (8 L) between 20 and 30 °C. The crystalline salt **13** was dried under vacuum between 57 and 62 °C to constant weight (0.814 kg isolated; 39.5% yield based on acid **12** with >94% de).

2-Fluoro-2-(4-iodo-phenyl)-propylamine (6): ^{1}H NMR (500 MHz, DMSO-d_6), δ 1.39 (bs, 2H, NH_2), 1.55 (d, 3H, J = 23.0 Hz), 2.84 (2H, m), 7.15 (d, 2H, J = 8.0), 7.71 (d, 2H, J = 8.0).

2-Fluoro-2-(4-iodo-phenyl)-propylamine (*S*)-(−)-(2)-pyrrolidone-5-carboxylic acid salt (13): mp (DSC) (5 °C/min) onset 184.62 °C, peak 187.30 °C. $[\alpha]^{22}_D$ 9.3 (c = 1.0, MeOH). IR (neat) 3220, 2186, 1688, 1649, 1544 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.57 (d, 3H, J = 23.0 Hz), 1.91−2.1 (m, 1H), 2.04−2.18 (m, 3H), 2.22−2.32 (m, 1H), 2.87−2.98 (m, 2H), 3.99−4.02 (m, 1H), 7.16 (d, 2H, J = 8.0 Hz), 7.63 (bs, 1H), 7.72 (d, 2H, J = 8.0 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.9, 24.5, 28.9, 50.4, 55.0, 93.1, 97.5, 126.6, 136.7, 142.6, 174.1, 175.5. ^{19}F NMR (282 MHz, DMSO-d_6) δ −152.0. Anal. Calcd for $C_9H_{11}FIN{\cdot}C_5H_7NO_3$: C, 41.19; H, 4.44; N, 6.86. Found: C, 41.25; H, 4.48; N, 6.79.

(*R*)-Propane-2-sulfonic Acid [2-Fluoro-2-(4-iodo-phenyl)-propyl]-amide (8). A reactor was charged with MTBE (5.5 L) followed by salt **13** (1.1 kg, 2.69 mol) between 15 and 30 °C. A 1 N NaOH solution (5.06 L) was added over 12 min at 19−20 °C to the agitated reaction mixture (stirred for 23 min, and the phases were allowed to separate for 4 min). The aqueous phase was removed and back-extracted with a further 5.5 L of MTBE (agitated for 5 min, allowed to separate for 3 min). The organic phases were combined and dried over sodium sulfate (1.0 kg) for 18 min. The solvent was removed via distillation on a rotovapor at 35 °C under vacuum. The free amine oil weighed 747 g (2.68 mol, 99.5% yield for the free base step), which was the mass used to calculate the reagent equivalents for the sulfonamide preparation. The free amine was dissolved in toluene (3.75 L) and THF (3.75 L) between 10 and 30 °C. The reaction mixture was cooled to −5−5 °C, and treated with triethylamine (1.353 kg, 13.37 mol) followed by the addition of isopropylsulfonyl chloride (670 g, 4.71 mol) over 51 min. The reaction mixture was stirred between 5 and 3 °C for 1.5 h and was subsequently sampled for HPLC analysis (result: 95.3 area % **8**; criteria >93 area % **8**). The reaction mixture was warmed to 10 °C, treated with cold 1 N HCl (5.6 L), and agitated for 18 min. The phases separated in 15 min, and the bottom aqueous phase was removed. The organic phase was washed with an additional 5.6 L of cold 1 N HCl (agitated 5 min, separated 4 min), followed by a 1 N NaOH (5.6 L) wash (agitated 5 min, separated 6 min). The organic phase was finally washed with DI water (5.6 L) (agitated 5 min, separated 5 min). The organic phase was dried over sodium sulfate (1.0 kg), and the solvent was removed on a rotovapor at 45 °C under vacuum to give crude **8** (949 g, 93.59 area % by HPLC) as a solid. The crude **8** was dissolved in CH_3CN (3.3 L) between 77 and 82 °C, and DI water (2.6 L) was added to the mixture over 1.0 h at 78 °C. The resulting mixture (cloudy) was held at 76−78 °C for 19 min, and cooled to 43.5 °C over 2.5 h to promote crystallization. The mixture was cooled further to 28 °C over 0.5 h, and then to 1.8 °C over 2.0 h. The batch was filtered, washed with DI water (3.0 L), and dried under vacuum at 55−65 °C to constant weight. The **8** (790 g, 76.5% isolated yield, ∼99 area % and 99.44% ee by HPLC) was isolated as a crystalline solid.

(*R*)-Propane-2-sulfonic acid [2-fluoro-2-(4-iodo-phenyl)-propyl]-amide (8): mp (DSC) (5 °C/min) onset 142.5 °C, peak 143.2 °C. $[\alpha]^{22}_D$ 25.1 (c = 1.0, MeOH). IR (neat) 3323, 2997, 2940, 1586 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6, 60 °C) δ 1.12 (d, 3H, J = 2.2 Hz), 1.14 (d, 3H, J = 2.2 Hz), 1.58 (d, 3H, J = 23.0 Hz), 3.02 (Sep, 1H, J = 6.8 Hz), 3.28−3.45 (m, 2H), 7.18 (d, 2H, J = 8.0 Hz), 7.31 (t, 1H, J = 6.5 Hz, NH), 7.73 (d, 2H, J = 8.0 Hz). ^{13}C NMR (75 MHz, DMSO-d_6, 60 °C) δ 16.2, 24.1, 51.4, 52.0, 94.0, 96.8, 127.0, 137.0, 141.9. ^{19}F NMR (282 MHz, DMSO-d_6, 60 °C) δ -131.3. Anal. Calcd for $C_{12}H_{17}FINO_2S$: C, 37.41; H, 4.44; N, 3.64. Found: C, 37.41; H, 4.44; N, 3.66.

(*R*)-4′-[1-Fluoro-1-methyl-2-(propane-2-sulfonylamino)-ethyl]-biphenyl-4-carboxylic acid (10). Under an N_2 atmosphere, the sulfonamide **8** (627 g, 1.63 mol) was charged to a reactor followed by the boronic acid **9** (267.4 g, 1.61 mol). To the mixture was added potassium carbonate (449.9 g, 3.36 mol) followed by MeOH (9.40 L) and DI water (1.88 L), between 15 and 35 °C. Palladium black (5.20 g, 48.8 mmol) was added to the reaction mixture, and the temperature was increased to 63−68 °C for 1.0 h (HPLC <1 area % **9**). The reaction mixture was cooled to 50−60 °C, filtered through Hyflo Super-Cel (430 g), and the Hyflo Super-Cel was rinsed with warm (50−60 °C) DI water (2.5 L) to displace desired product. The resulting clarified mixture was heated to 60−65 °C, and acetic acid (627 mL) was added dropwise over 1.0 h. The initial portion of the acid addition caused CO_2 evolution (addition controlled) as the residual potassium carbonate/bicarbonate was consumed. As the acid addition proceeded, the product **10** began to crystallize. After the acid addition was complete, the mixture was held for 10 min at 65 °C and was subsequently cooled to 35 °C over 1.25 h. The resulting mixture was cooled to 4 °C over 1.0 h and held for 0.5 h. The batch was filtered, washed with DI water (2 × 3.1 L) and cold MeOH (2 × 1.57 L), and dried under vacuum at 55−65 °C to constant weight. The **10** (543.47 g, 88.0% isolated yield, ∼99 area % and 100% ee by HPLC) was isolated as a crystalline solid.

(*R*)-4′-[1-Fluoro-1-methyl-2-(propane-2-sulfonylamino)-ethyl]-biphenyl-4-carboxylic acid (10): mp (DSC) (5 °C/min) onset 183.51 °C, peak 185.00 °C. $[\alpha]^{22}_D$ 30.2 (c = 1.0, MeOH). IR (neat) 3202, 2989, 1700, 1607 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13 (d, 3H, J = 2.2 Hz), 1.16 (d, 3H, J = 2.2 Hz), 1.65 (d, 3H, J = 23.0 Hz), 3.03 (Sep, 1H,

J = 6.8 Hz), 3.33−3.48 (2H, m), 7.36 (t, 1H, NH, J = 6.4 Hz), 7.50 (d, 2H, J = 8.2 Hz), 7.75 (d, 2H, J = 8.2 Hz), 7.80 (d, 2H, J = 8.2 Hz), 8.00 (d, 2H, J = 8.2 Hz), 12.98 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.2, 24.1, 51.5, 52.0, 96.8, 125.2, 126.8, 129.8, 130.0, 138.4, 142.1, 143.7, 167.1. ^{19}F NMR (282 MHz, DMSO-d_6) δ −130.8. Anal. Calcd for $C_{19}H_{22}FNO_4S$: C, 60.14; H, 5.84; N, 3.69; S, 8.45. Found: C, 60.30; H, 5.86; N, 3.69; S, 8.45.

(*R*)-4′-[1-Fluoro-1-methyl-2-(propane-2-sulfonylamino)-ethyl]-biphenyl-4-carboxylic acid methylamide (LY503430). Under an N_2 atmosphere, the carboxylic acid **10** (1.30 kg, 3.43 mol) was charged to a reactor followed by CDI (1,1′-carbonyldiimidazole) (611.1 g, 3.77 mol). To the mixture was added EtOAc (13 L), and the resulting slurry was stirred at about 22 °C for 1.5 h. After the mixture had stirred for 1.0 h, it had become homogeneous (imidazolide intermediate), and a sample was taken for conversion check by preparing a derivative (2 drops of reaction quenched into 2 mL of 2 M methylamine in THF) (HPLC < 1 area % **10**). The reaction mixture was warmed to 40−50 °C to maintain homogeneity and polish filtered through an inline stainless steel Swagelock filter with a new 15 μm filter element into a second reactor. Two molar methylamine in THF (2.06 L, 4.11 mol) was added subsurface (to avoid carbonate formation) through the Swagelock filter into the reaction mixture between 40 and 50 °C over 19 min. The product **LY503430** began to precipitate during the methylamine addition. After the methylamine addition, the resulting slurry was stirred for 1.16 h with the temperature reducing from 48 to 23 °C. The mixture was cooled to 5 °C over 0.5 h and stirred for 1.5 h with an ending temperature of 0 °C. The product was filtered and washed with 0−5 °C EtOAc (6.5 L). House vacuum was pulled on the filter cake for 1.0 h, and the resulting product was transferred to a reactor for an EtOH re-slurry. Filtered EtOH (13 L) was added to the **LY503430** wet cake and the temperature was increased from 14 to 75 °C over 45 min, and held for 1.25 h. The heating mantle was removed (75 °C), and the mixture was allowed to cool to room temperature and stir overnight (24 °C). The product **LY503430** was filtered between 20 and 30 ° and washed with filtered EtOH (3.35 L). The wet cake was dried under vacuum at 60 °C, until constant weight. The isolated **LY503430** was ground to remove lumps with a mortar and pestle, affording 1.135 kg (84.4% yield, 99.82 wt % purity and 100% ee by HPLC) of colorless crystalline solid. Mp (DSC) (5 °C/min) onset 186.42 °C, peak 187.06 °C. $[\alpha]^{22}_D$ 31.0 (c = 1.0, MeOH). IR (neat) 3321, 3286, 2994, 2944, 2882, 1634, 1545, 1451 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13 (d, 3H, J = 2.2 Hz), 1.15 (d, 3H, J = 2.2 Hz), 1.66 (d, 3H, J = 22.7 Hz), 2.80 (d, 3H, J = 4.5 Hz), 3.04 (Sep, 1H, J = 6.8 Hz), 3.38−3.54 (m, 2H), 7.37 (t, 1H, J = 6.4 Hz, NH), 7.49 (d, 2H, J = 8.3 Hz), 7.74 (d, 2H, J = 5.0 Hz), 7.82 (d, 2H, J = 5.0 Hz), 7.92 (d, 2H, J = 8.3 Hz), 8.48 (q, 1H, J = 4.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.2, 24.1, 26.3, 51.7, 52.0, 97.2, 125.2, 126.5, 127.1, 127.6, 133.4, 138.5, 141.9, 166.2. ^{19}F NMR (282 MHz, DMSO-d_6) δ −130.8. Anal. Calcd for $C_{20}H_{25}FN_2O_3S$: C, 61.20; H, 6.42; N, 7.13; S, 8.16. Found: C, 61.11; H, 6.38; N, 7.07; S, 8.11.

Supporting Information Available

X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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