

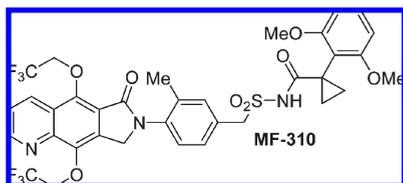
Remote Electronic Control in the Regioselective Reduction of Succinimides: A Practical, Scalable Synthesis of EP4 Antagonist MF-310

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A practical large-scale chromatography-free synthesis of EP4 antagonist **MF-310**, a potential new treatment for chronic inflammation, is presented. The synthetic route provided **MF-310** as its sodium salt in 10 steps and 17% overall yield from commercially available pyridine dicarboxylate **7**. The key features of this sequence include a unique regioselective reduction of succinimide **2** controlled by the electronic properties of a remote pyridine ring, preparation of cyclopropane carboxylic acid **3** via a Corey–Chaykovsky cyclopropanation, and a short synthesis of sulfonamide **5**.

Prostanoids are a group of lipid mediators that regulate numerous processes in the body. Prostaglandin E₂ (PGE₂) is the principal proinflammatory prostanoid and it plays crucial roles in several biological events such as neuronal function, female reproduction, vascular hypertension, tumorigenesis, kidney function, and inflammation.¹ PGE₂ mediates its various cellular functions through binding to the various subtypes of prostaglandin E receptors, namely EP4. This inhibition has recently been proposed as a new approach to the treatment of chronic ailments such as arthritis.² Our discovery efforts identified quinoline **MF-310** as a potent, selective inhibitor of the EP4 receptor and a promising lead

in the treatment of chronic inflammation.³ To support preclinical and clinical development of this compound, we sought to develop a scalable synthesis of **MF-310**. We describe herein a chromatography-free preparation of EP4 antagonist **MF-310** on multikilogram scale that features the use of an electronically controlled regioselective succinimide reduction.

The retrosynthetic analysis of **MF-310** suggests a logical first disconnection between succinimide **2** and cyclopropane carboxylic acid **3** (Scheme 1). Succinimide **2** could be accessed through a condensation of quinoline anhydride **4** with sulfonamide **5**. This strategy was attractive since it would allow for a convergent synthesis, starting from easily accessible, commercially available, starting materials **6**, **7**, and **8**. The success of this approach hinges on the ability to differentiate between the two electronically biased carbonyl groups of the succinimide moiety **2**.

The synthesis of sulfonamide intermediate **5** is outlined in Scheme 2. Although there are several methods available for the preparation of sulfonamides from sulfonyl chlorides and amines or sulfinic acid salts (prepared from organolithium or Grignard reagents) and an electrophilic nitrogen source,⁴ in our hands the methodology described by Wang⁵ produced higher yield and purity material on large scale. Therefore, under phase transfer catalysis conditions, the S_N2 displacement of benzylic bromide **8** with methyl 3-mercaptopropionate provided thioether **9** in 95% yield. The crude reaction mixture was taken directly into the tungsten-catalyzed oxidation, which afforded sulfone **10** in 95% yield.^{6,7} Intermediate **11** can be prepared when sulfone **10** is treated with sodium methoxide in methanol. However, careful monitoring of the reaction revealed that **11** was thermally unstable under anhydrous conditions and would extrude SO₂ upon

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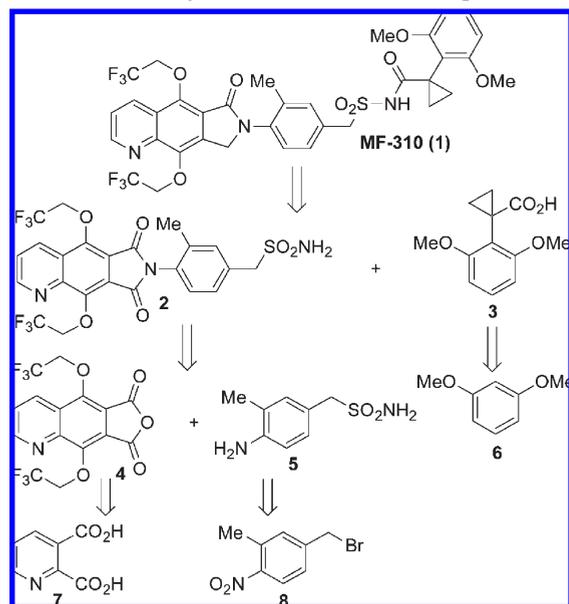
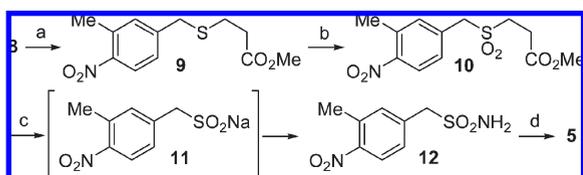
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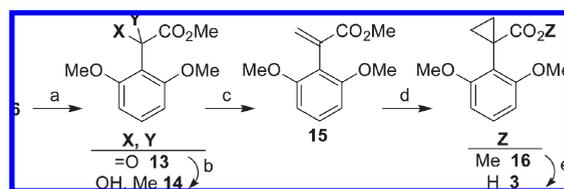
SCHEME 1. Retrosynthetic Plan for EP4 Antagonist MF-310

SCHEME 2. Synthesis of Sulfonamide 5^a

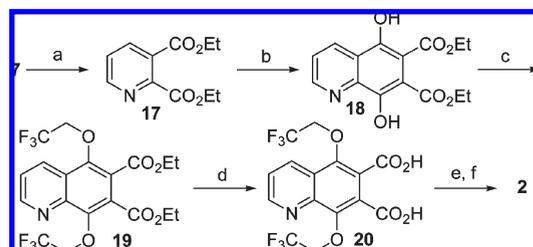
^aReagents and conditions: (a) $\text{HS}(\text{CH}_2)_2\text{CO}_2\text{Me}$, K_2CO_3 , *n*-Bu₄NBr, PhMe, 95%; (b) H_2O_2 , NaWO_4 , *n*-Bu₄N SO_4 , PhMe/water, 45 °C, 95%; (c) (1) NaOMe, MeOH, 0 °C, (2) $\text{H}_2\text{NOSO}_3\text{H}/\text{KOAc}$, water, 77%; (d) H_2 (80 psi), PtO_2 , 1,4-dioxane/ H_2O , 45 °C, 78%.

aging at ambient temperature to afford 2,4-dimethylnitrobenzene. On large scale this was avoided by monitoring the temperature during the deprotonation step by a portion-wise addition of base, followed by an in situ subsequent reaction with aqueous hydroxylamine-*O*-sulfonic acid to afford nitro sulfonamide **12** in 77% yield.⁸ Finally, PtO_2 -catalyzed reduction afforded 1.25 kg of requisite aniline **5** in 78% yield (Scheme 2).

Cyclopropane carboxylic acid **3** was prepared in 5 steps from dimethoxybenzene **6** (Scheme 3). Ortho metalation of 1,3-dimethoxybenzene with *n*-BuLi, followed by formation of the corresponding cuprate and quenching with methyl oxalylchloride afforded the aryl oxalate **13** in 81% yield. The methyl-ester analogues were used in place of the ethyl option as this afforded more crystalline intermediates, facilitating purification. Although a Wittig olefination of **13** was possible, rejection of the triphenylphosphine oxide byproduct proved difficult on larger scale. Therefore, the olefination of ketone **13** was replaced with a two-step Me_3Al addition and acid-catalyzed dehydration sequence to provide acrylate **15** in 74% yield over 2 steps. The success of the subsequent Corey–Chaykovsky cyclopropanation⁹ was found to

SCHEME 3. Synthesis of Cyclopropane Carboxylic Acid 3^a

^aReagents and conditions: (a) *n*-BuLi, CuI, ClCOCO_2Me , 81%; (b) Me_3Al , DCE, 78%; (c) *p*-TsOH, PhMe, 95%; (d) Me_3SOI , *t*-BuOK, DMSO, 95%; (e) TMSOK, THF, 65 °C, 95%.

SCHEME 4. Synthesis of Succinimide 2^a

^aReagents and conditions: (a) EtOH, H_2SO_4 , reflux, 78%; (b) diethyl succinate, NaOEt, EtOH/PhMe, reflux, 69%; (c) (1) $\text{CF}_3\text{CH}_2\text{OTf}$, K_2CO_3 , DMF, 70 °C, (2) water, 94%; (d) 5 N NaOH, THF, reflux, 100%; (e) TFAA, PhMe, 0 °C, 89%; (f) (1) sulfonamide **5**, TFA, THF, reflux, (2) heptane, 84%.

depend on the rapid addition of acrylate to a mixture of *t*-BuOK and Me_3SOI (i.e., addition time of < 3 min) and in maintaining the internal temperature near 40 °C. This protocol provided cyclopropane ester **16** in 95% yield. Intermediate **16** could be isolated and purified by a direct recrystallization from the reaction mixture by adding water. The final hydrolysis step to provide 1.79 kg of cyclopropane carboxylic acid **3** was performed with TMSOK,¹⁰ which reached completion in 3 h in contrast to a hydroxide-mediated protocol that required 3 days to achieve >95% conversion.

Succinimide **2** was prepared in 6 steps from commercially available pyridine dicarboxylate **7** (Scheme 4). After a Fisher esterification to prepare the diethyl ester of 2,3-pyridine dicarboxylate **17** and a Claisen condensation with diethyl succinate to afford the requisite dihydroxyquinoline **18**, the crude reaction mixture was solvent switched from toluene to DMF and used directly in the alkylation step with $\text{CF}_3\text{CH}_2\text{OTf}$. At the end of the alkylation step, intermediate **19** was isolated in 51% yield from pyridine dicarboxylate **7** (3 steps) and high purity (>98A%)¹¹ by a slow crystallization of the crude reaction mixture from DMF:water. A subsequent hydrolysis of **19** from NaOH in THF provided diacid **20** in quantitative yield. While prolonged reaction time at 80 °C with Ac_2O as a solvent did allow for the successful dehydration to form anhydride **4**, a protocol with 5 equiv of TFAA in toluene at 0 °C was preferred for large-scale preparation. This protocol allowed for a dramatic rate enhancement (99% conversion in 30 min) and the residual TFAA was easily removed by distillation. Finally, clean conversion to succinimide **2** from anhydride **4** and sulfonamide **5** was

(8) No experiments were conducted to determine the pK_a values or the order of deprotonation. However, we believe it to be reversible.

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(11) A% indicates the area percent observed on a HPLC trace at 220 nm. Yields are reported relative to an HPLC standard.

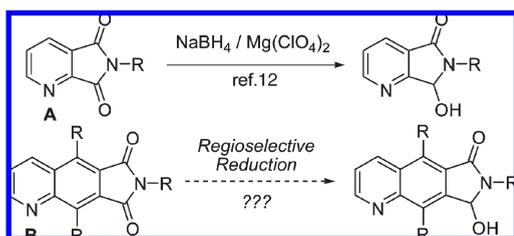


FIGURE 1. Regioselective azaphthalimide reduction.

achieved with 5 equiv of TFA in THF. The product could be precipitated out by the addition of heptane as an antisolvent providing 5.34 kg of **2** in 84% yield. It should be noted that **2** was isolated as a 3:2 THF solvate, which influenced the efficacy of the next transformation (vide infra). The THF could be removed by heating the material under vacuum at temperatures above 110 °C (Scheme 4).

The next challenge to be addressed was the critical regioselective succinimide reduction. The regioselective reduction of azaphthalimides having the general structure **A** (Figure 1) has been described by using $Mg(ClO_4)_2$ in conjunction with $NaBH_4$,¹² however, we are not aware of examples in the literature of this type of selectivity being extended to substrates such as **B** with an aryl spacer between the pyridine and succinimide functionalities. While chelation between the pyridine nitrogen atom and the proximal carbonyl has been invoked by Goto et al.¹² to explain the selectivity observed with the reduction of **A** in the presence of Mg^{2+} ions, this is not possible with compounds such as **B** where any observed selectivity would arise from differences in electronics between the two carbonyls.

A number of reduction conditions of succinimide **2** were evaluated in order to identify a selective protocol for the preparation of regioisomer **21** over **22** (Table 1). Of the reductants tested, lithium thexylborohydride (LTB) and diisobutylaluminum hydride (DIBAL) showed promising selectivities (entries 5 and 6). While the reduction with LTB showed good yield and selectivity (80% yield, dr = 5:1, entry 5), the limited commercial availability of the reducing agent precluded the use of this protocol on larger scale. On the other hand, DIBAL afforded a low yield of the desired regioisomer, but with greater selectivity (35% yield, dr = 10:1, entry 6), probably due to a preferential binding to one of the carbonyls. In toluene, a relatively large excess of DIBAL (4.7 equiv) was required to achieve complete conversion of the starting material, with modest yield (entry 6). In addition to the regioisomer **22** (7A%),¹¹ an over reduced byproduct **23** (9A%)¹¹ was also formed during this reaction due to the large excess of DIBAL required to achieve complete conversion of **2**. Presumably, some of the excess reagent may be necessary to deprotonate the sulfonamide, as well as for coordination to the other Lewis basic sites in the molecule. In an effort to minimize the requirements in DIBAL, a variety of sacrificial nonreductive Lewis acids were screened. While the number of equivalents of DIBAL could be reduced by using an additional Lewis acid such as Et_2Zn or Et_3Al (entries 7 and 8), this resulted only in a marginal improvement in yields. A variety of solvents were evaluated for this reaction and the use of chlorobenzene led to a significant improvement in the HPLC

TABLE 1. Regioselective Reductions of Succinimide **2**

| Entry | Conditions | Additive | 21 : 22 | Yield (%) ^a |
|--------------------|----------------------------|-------------------|-----------------------|------------------------|
| 1 | Red-Al, PhMe, r.t. | --- | 1 : 1 | n.d. |
| 2 | $Zn(BH_4)_2$, THF, 60 °C | --- | 1.5 : 1 | n.d. |
| 3 | $LiBH_4$, THF, 0 °C | --- | 2 : 1 | n.d. |
| 4 | BH_3 -DMS, THF, r.t. | --- | 2 : 1 | n.d. |
| 5 | LTB, DCM, r.t. | --- | 5 : 1 | 80 |
| 6 ^b | DIBAL (4.7 eq), PhMe, 0 °C | --- | 10 : 1 | 35 |
| 7 ^b | DIBAL (3.7 eq), PhMe, 0 °C | Et_2Zn (1.5 eq) | 12 : 1 | 45 |
| 8 ^b | DIBAL (2.0 eq), PhMe, 0 °C | Et_3Al (1.2 eq) | 12 : 1 | 45 |
| 9 ^b | DIBAL (3.4 eq), PhCl, 0 °C | --- | 11 : 1 | 67 |
| 10 ^b | DIBAL (3.4 eq), PhCl, 0 °C | THF (1.5 eq) | 11 : 1 | 55 |
| 11 ^{b, c} | DIBAL (3.4 eq), PhCl, 0 °C | THF (0.7 eq) | 11 : 1 | 76 |
| 12 ^b | DIBAL (3.4 eq), PhCl, 0 °C | THF (0.3 eq) | 11 : 1 | 75 |

^a Isolated yields
^b By-product **23** was also observed
^c 3 Kg scale

profile of the reaction with a substantial improvement in the yield (67%) with 3.4 equiv of DIBAL (entry 9). In this solvent, there was no advantage of adding Et_3Al or Et_2Zn . While the use of THF as a solvent led to a number of unidentified side products and low yields, we were pleased to find that the reduction of the partial THF solvate of **2**, isolated from the aniline/anhydride condensation, led to higher yields of **21** (entry 12 vs. 9). Although we remain uncertain of the exact role of THF on the reduction of **2**, the optimum amount required is 0.7 equiv (entries 10–12). Furthermore, during the course of this reaction we have observed an increase in ratios of regioisomers (**21** vs. **22**).¹³ We believe that **22** is preferentially converted to **23** under these conditions therefore slightly increasing the final ratio of the reaction. Finally, on 3.07 kg scale, the excess hydride in the reaction mixture was quenched with acetone in order to minimize hydrogen gas evolution during aqueous workup. An extraction with a 3 M solution of tartaric acid was performed at 45 °C in order to remove aluminum salts and minimize emulsions in the workup of this reaction. The isolated product **21** was shown to be 76A%, with the major impurities being the regioisomer **22** (7A%)¹¹ and the over-reduction product **23** (12A%).^{11,14}

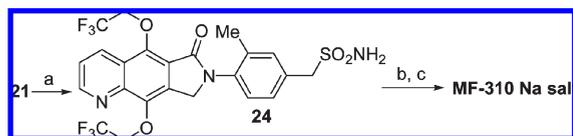
Completion of the synthesis for MF-310 is outlined in Scheme 5. The crude hydroxy lactam **21** (4.00 kg) was further reduced to lactam **24** with 5 equiv of triethylsilane dissolved in a mixture of CH_2Cl_2 and TFA (1:1) and refluxed for 5 h.¹⁵ This procedure afforded a 90% yield of the lactam **24**. Treatment with activated charcoal was necessary at this stage to remove the dark color and increase the purity profile from 70A% to 75A% as shown by HPLC analysis. The purity of lactam **24** was further increased with two subse-

(13) Ratios of **21:22** as a function of conversion of **2**: 20% (7:1), 65% (9:1), 100% (11:1).

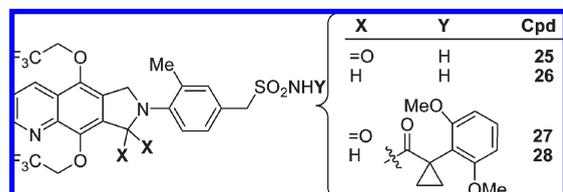
(14) A total of 5A% of minor unidentified byproduct was also observed.

(15) Only the alcohol functionality is reduced by the Et_3Si /TFA conditions providing products **24**, **25**, and **26**.

(12) Goto, T.; Konno, M.; Saito, M.; Sato, R. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1205.

SCHEME 5. Synthesis of MF-310^a

^aReagents and conditions: (a) (1) Et₃SiH, TFA, DCE, 90%, (2) MeOH/0.1 N HCl recrystallization, 83%, (3) CH₃CN/0.1 N HCl recrystallization, 88%; (b) (1) **3**, EDC-HCl, DMAP, CH₃CN, 92%, (2) CH₃CN/0.1 N HCl recrystallization, 81%; (c) NaOH, H₂O, THF, heptane, 91%.

SCHEME 6. Byproducts **25**, **26**, **27**, and **28** Observed

quent crystallizations: once from MeOH/0.1 N HCl and once from CH₃CN/0.1 N HCl with 83% and 88% recovery, respectively. This afforded material which was 89A% with 4A% of both regioisomer **25** and isoindoline **26**.¹¹ Coupling sulfonamide **24** with cyclopropane carboxylic acid **3** using EDC-HCl in CH₃CN afforded a 92% yield of MF-310 free acid,¹⁶ which was recrystallized from CH₃CN by using 0.1 N HCl as an antisolvent to afford 3.25 kg of material that was shown to be 97A%, contaminated with 1.6A% of regioisomer **27** and 0.9A% of **28** (Scheme 6).¹¹

A number of conditions were evaluated in an effort to identify a practical approach to the salt formation. A series of water miscible solvents were examined by using basic aqueous solutions as antisolvents. Surprisingly, many of these conditions returned the free acid. For example, dissolving the free acid MF-310 in DME and adding 0.1 N NaOH effected slow precipitation of the free acid in ~80% recovery. The nature of this material was characterized by X-ray powder diffraction and ¹H NMR. We were pleased to find that dissolving the free acid in THF and adding 1.3 equiv of 5 N NaOH allowed for the isolation of the sodium salt of MF-310. Heptane was added as an antisolvent and the resulting suspension was filtered to afford 2.15 kg of the sodium salt of MF-310 in 87% yield (98A%). The material was contaminated with low levels of the sodium salts of **27** (1.1A%) and **28** (0.6A%).¹¹

In conclusion, a practical large-scale chromatography-free synthesis of EP4 antagonist MF-310, a potential new treatment for chronic inflammation, was developed. The synthetic route provided MF-310, as its sodium salt, in 10 steps and 17% overall yield from commercially available pyridine dicarboxylate **7**. The key features of this sequence include a unique regioselective reduction of succinimide **2** controlled by the electronic effects of a remote pyridine ring, preparation of cyclopropane carboxylic acid **3** through a Corey-Chaykovsky cyclopropanation, and a short synthesis of sulfonamide **5**. This approach was used to successfully produce > 2.0 kg of MF-310 Na salt.

(16) Measured pK_a for MF-310 is 5.6.

Experimental Section

1-(3-Methyl-4-nitrophenyl)methanesulfonamide (12). A 100 L reaction vessel equipped with a N₂ inlet, thermocouple, mechanical stirrer, and an addition funnel was charged with methanol (41.6 L) and cooled to 0 °C. Then, a solution of NaOMe 30 wt % in MeOH (4.32 L, 23.28 mol) and sulfone **10** (5.85 kg, 19.40 mol) was charged and the resulting slurry was aged for 2.5 h. Next, a solution of NH₂OSO₃H (5.49 kg, 48.50 mol) and KOAc (5.14 kg, 52.40 mol) in water (27.7 L) was added to the reaction mixture over 1.5 h while keeping the internal temperature < 5 °C and then allowed to slowly warm to rt overnight. The resulting slurry is filtered and the solids washed with water (2 × 8 L) in a pressure filter. After transfer to a filter pot, the solids are washed with additional water (4 × 8 L) followed by toluene (3 × 8 L) and dried on a frit under a nitrogen atmosphere for 20 h, followed by tray drying in a vacuum oven at 24 °C and 8 Torr for an additional day: 7.19 kg of **12** at 48 wt % was isolated (14.98 mol, 77% yield): ¹H NMR (400 MHz, MeOD-*d*₄) δ 7.96 (d, *J* = 8.3 Hz, 1H), 7.50–7.46 (m, 2H), 4.82 (s, 3H), 4.40 (s, 2H), 2.58 (s, 3H); ¹³C NMR (100 MHz, MeOD-*d*₄) δ 150.7, 137.5, 136.4, 134.7, 130.7, 125.8, 61.0, 20.3; IR (CHCl₃) 3368, 3261, 3020, 2988, 1614, 1519, 1339, 1297, 1269, 1215, 1172, 1155, 1130, 931, 843, 756, 669 cm⁻¹; HRMS ESI (*m/z*) [M + H]⁺ calcd for C₈H₁₁N₂O₄S 231.0434, found 231.0436.

1-{4-[8-Hydroxy-6-oxo-5,9-bis(2,2,2-trifluoroethoxy)-6,8-dihydro-7H-pyrrolo[3,4-g]quinolin-7-yl]-3-methylphenyl}methanesulfonamide (21). A 100 L reaction vessel equipped with an N₂ inlet, thermocouple, mechanical stirrer, and an addition funnel was charged with the succinimide **2** (3.07 kg, 5.12 mol), chlorobenzene (60 L), and THF (125 mL, 1.54 mol). The mixture was cooled to -8 °C and a solution of 1.5 M DIBAL in toluene (11.6 L, 17.4 mol) was added over 1.5 h causing the internal temperature to rise to -4 °C. The mixture was aged 15 min. Acetone (3 L) was added over 5 min with the internal temperature rising to 3 °C. The mixture was aged 30 min and then transferred into an extractor containing aqueous 3 M tartaric acid (30 L). The internal temperature rose to 35 °C. The mixture was warmed to 45 °C and aged 30 min. The layers were separated and the aqueous layer was back extracted with MTBE (15 L). The crude organic solutions were filtered through a pad of Solka Floc and washed with chlorobenzene (3 × 4 L). The combined organic layers were assayed at 2.24 kg (76% yield) with a 11:1 mixture of regioisomers. The desired hydroxyl lactam was 76A%. ¹H NMR (500 MHz, acetone-*d*₆) δ 9.10 (d, *J* = 4.14 Hz, 1H), 8.76 (d, *J* = 8.6 Hz, 1H), 7.77 (dd, *J* = 8.6, 4.3 Hz, 1H), 7.46–7.36 (m, 3H), 6.60 (d, *J* = 8.3 Hz, 1H), 6.24 (s, 2H), 6.16 (d, *J* = 8.3 Hz, 1H), 5.33–5.16 (m, 3H), 5.06–4.94 (m, 1H), 4.37 (s, 2H), 2.30 (s, 3H); ¹³C NMR (100 MHz, acetone-*d*₆) δ 163.6, 152.7, 148.5, 146.2, 145.1, 138.3, 136.1, 134.3, 134.0, 133.3, 131.9, 129.9, 129.0, 126.0, 124.9 (q, *J* = 277 Hz), 124.8 (q, *J* = 277 Hz), 123.3, 117.9, 82.8, 72.5 (q, *J* = 35 Hz), 71.0 (q, *J* = 35 Hz), 60.9, 18.4; ¹⁹F NMR (377 MHz, acetone-*d*₆) δ -78.9 (t, *J* = 8.7 Hz), -78.8 (t, *J* = 8.9 Hz); IR (neat) 1685, 1500, 1372, 1263, 1153, 1094, 1040, 959 cm⁻¹; HRMS ESI (*m/z*) [M + H]⁺ calcd for C₂₃H₂₀N₃O₆F₆S 580.0965, found 580.0971; mp 128.3–130.2 °C.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.