Synthesis of Mono- and Difluoronaphthoic Acids

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Aryl carboxamides are useful structural units found in several biologically active compounds. Unlike their benzoic acid counterparts, fluorinated versions of naphthoic acids are relatively unknown. In connection with a recent project, we needed viable syntheses of several mono- and difluorinated naphthoic acids. Herein we describe the synthesis of 5-, 6-, 7-, and 8-fluoro-1-naphthalenecarboxylic acids and 5,7-, 5,8-, 6,7-, and 4,5-difluoro-1-naphthalenecarboxylic acids. The 5-fluoro derivative **1** was obtained from the corresponding 5-bromo compound via electrophilic fluorination of the lithio-intermediate. The rest of the monofluoro (**2**, **3**, and **4**) and the difluoro acids (**5**, **6**, and **7**) were prepared by a new, general route which entailed the elaboration of commercial fluorinated phenylacetic acids to 2-(fluoroaryl)glutaric acids with differential ester groups; selective hydrolysis to a mono acid, intramolecular Friedel−Crafts cyclization, and aromatization furnished the target structures. An alternative process to assemble a naphthalene skeleton is also presented for the difluoro acids **5** and **6**. Finally, 4,5-difluoro-1-naphthalenecarboxylic acid (**8**) was prepared expeditiously from 1,8-diaminonaphthalene by adapting classical reactions.

Introduction

Several biologically active natural products and pharmaceuticals contain substituted naphthoic acids or the derived amides as structural features of interest.[1] In connection with a recent project, we found that the naphthamide moiety that is required for eliciting a selective biological response is also rapidly metabolized. LCMS studies of the metabolites showed an M + 34 peak perhaps indicating arene oxide formation and hydrolysis. This was a major problem for the parent naphthamide but was much less significant for the 4-fluoro derivative (Figure 1), both prepared from commercially available 1-naphthalenecarboxylic acids.

Since it is reasonable to expect that such a process may occur more readily in the unsubstituted B-ring, we set out to prepare naphthamides that contain one or more fluorine atoms in the B-ring in order to block the oxidative metabolism. To this end, the fluorinated 1-naphthalenecarboxylic acids **1**−**8** were targeted (Figure 2).[2]

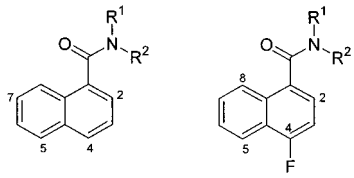

Figure 1.

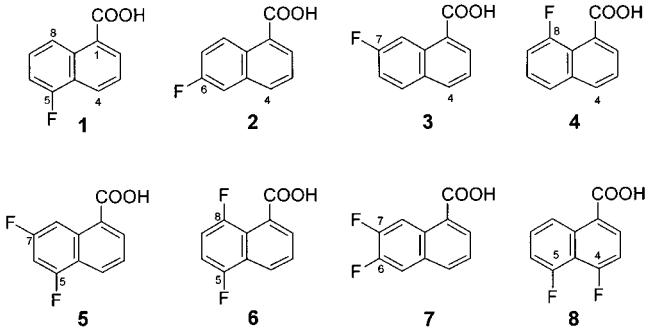

Figure 2.

Results and Discussion

In addition to direct modification of available naphthalene derivatives, other useful routes to substituted naphthalenes in general involve either the Diels−Alder reaction or the Michael addition/intramolecular cyclization sequence.[3] In the Diels−Alder route, the diene or the dienophile must be symmetrical to control regiochemistry. The Michael addition route has been mainly used to make naphthols with either a ketone or an ester functionality at the 2-position. A search for the desired 1-naphthoic acids **1**−**8** revealed that only the 6- and 7-fluoronaphthoic acids **2** and **3** were previously known.[4] The 5-bromo derivative **10** was prepared by a reported

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(1) (a) Lowe, J. A. U.S. Patent 4,891,375, 1990. (b) Hollinshead, S. P.; Huff, B. E.; WO 9 904 778, 1999. (c) Barnett, S. F.; Heimbrook, D. C. WO 9 910 523, 1999. (d) Ding, C. Z.; Bhide, R. S.; WO 9 918 951, 1999. (e) Kozlowski, J. A.; McCombie, S. W.; Tagat, J. R.; Vice, S. F. U. S. Patent 6,066,636. 2000.

(2) A preliminary account of this work has been presented as a poster: Tagat, J. R.; McCombie, S. W.; Nazareno, D. V.; Kozlowski, J. A.; Boyle, C. D.; Josien, H.; Wang, Y.; Zhou, G. *Abstracts of Papers*, 36th National Organic Chemistry Symposium, Madison, WI, 1999, NOS 259.

(3) Katritzky, A. R.; Zhang, G.; Xie, L. *J. Org. Chem.* **1997**, *62*, 721 (and references therein).

(4) (a) Fujita et al. *Agric. Biol. Chem.* **1961**, *25*, 719. (b) Adcock, W.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1967**, *89*, 386.

10.1021/jo0160322 CCC: $22.00
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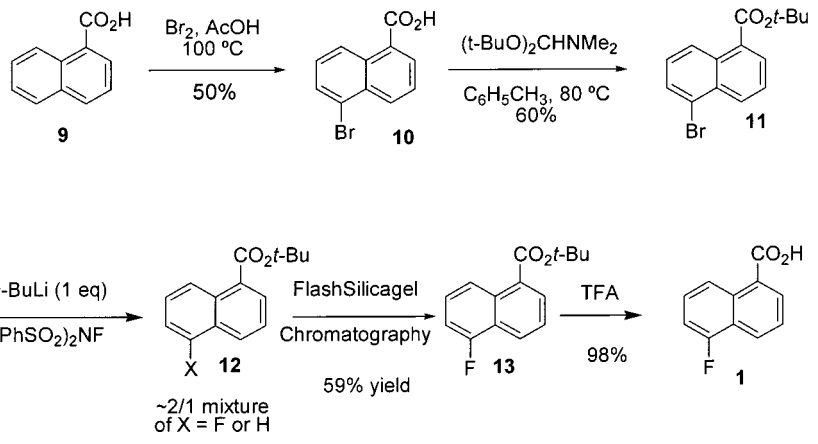
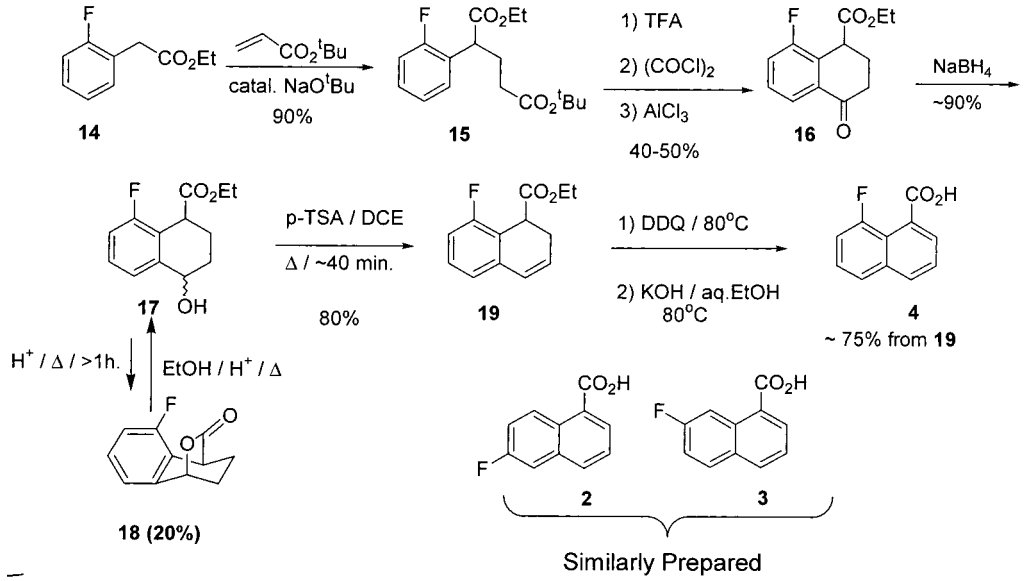
Scheme 1



Scheme 2



procedure.[5] It was converted to the *tert*-butyl ester **11** by Widmer's method.[6] Halogen−metal exchange followed by quenching with an electrophilic fluorinating agent[7] gave a 2:1 mixture of the 5-F/5-H products. They were separated by careful chromatography and the 5-fluoro ester **13** was treated with trifluoroacetic acid to obtain 5-fluoro-1-naphthalenecarboxylic acid **1** (Scheme 1).

The inherent problems in the Br → F exchange as noted for the synthesis of **1** prompted us to choosefluorine-containing starting materials for an alternative route. Thus, base-catalyzed Michael addition of appropriately (*o*-, *m*-, *p*-) fluorinated phenylacetic esters (**14**) to *tert*-butyl acrylate gave 2-(fluorophenyl)glutaric esters **15** (90%) with differential ester groups. Selective cleavage of the *tert*-butyl ester and Friedel−Crafts cyclization of the derived acid chloride produced the tetralone **16** (∼50%). During the reductive elimination of **16** to a dihydronaphthalene (**19**), longer reaction times (>1 h) gave significant amounts of the bicyclic lactone **18** which was reconverted to **17**. DDQ-mediated aromatization and saponification of the ethyl ester completed the synthesis. In this seven-step sequence, only the tetralones **16** and the penultimate naphthalene ester required chromatographic purification. The mono-fluoro-1-naphthalenecarboxylic acids **2**, **3**, and **4** were obtained in 25−30% overall yield (Scheme 2).

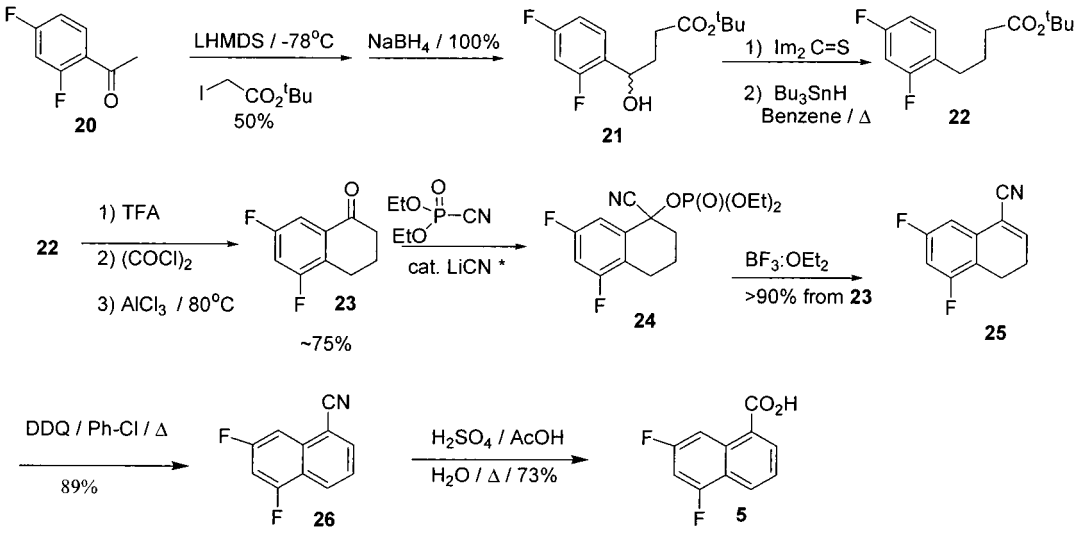
The slightly higher cost of difluorophenyl acetic acids as starting materials in a sequence analogous to Scheme 2 led us to explore the use of difluoroacetophenones as precursors in a similar strategy for preparing difluoronaphthoic acids (Scheme 3). 2,4-Difluoroacetophenonewas elaborated to the 4-arylbutanoic acid derivative **22,**[8] which was cyclized to the tetralone **23** (∼30% overall yield) in the usual manner. Cyanohydrin formation[9] and a two-step aromatization process provided the naphthonitrile **26**. Hydrolysis of **26** under strongly acidic conditions afforded the target 5,7-difluoro-1-naphthalenecarboxylic acid **5**.

On the other hand, the 5,8-difluoro-1-naphthonitrile **28** prepared by a similar sequence of reactions from 2,5-difluoroacetophenone **27** could only be partially hydrolyzed under acidic or basic conditions, stopping at the stage of the amide **29** (Scheme 4). However, we were able to reduce the naphthonitrile **28** to the corresponding

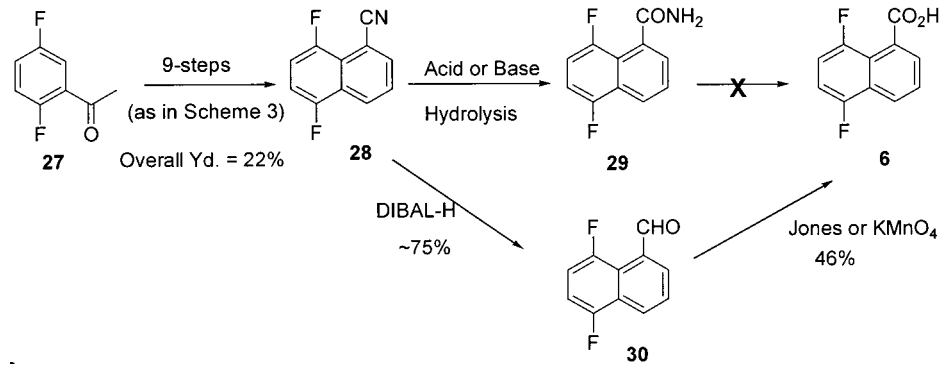
(5) Short, W. F.; Wang, H. *J. Chem. Soc.* **1950**, 991.
(6) Widmer, U. *Synthesis* **1983**, 135.
(7) Differding, E.; Ofner, H. *Synlett* **1991**, 187.

(8) Attempted deoxygenation of **21** using $EtSiH_3$/TFA resulted in the formation of 5-(2,4-difluorophenyl)-γ-butyrolactone.
(9) Harusawa, S.; Yoneda, R.; Kurihara, T.; Hamada, T.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 427.

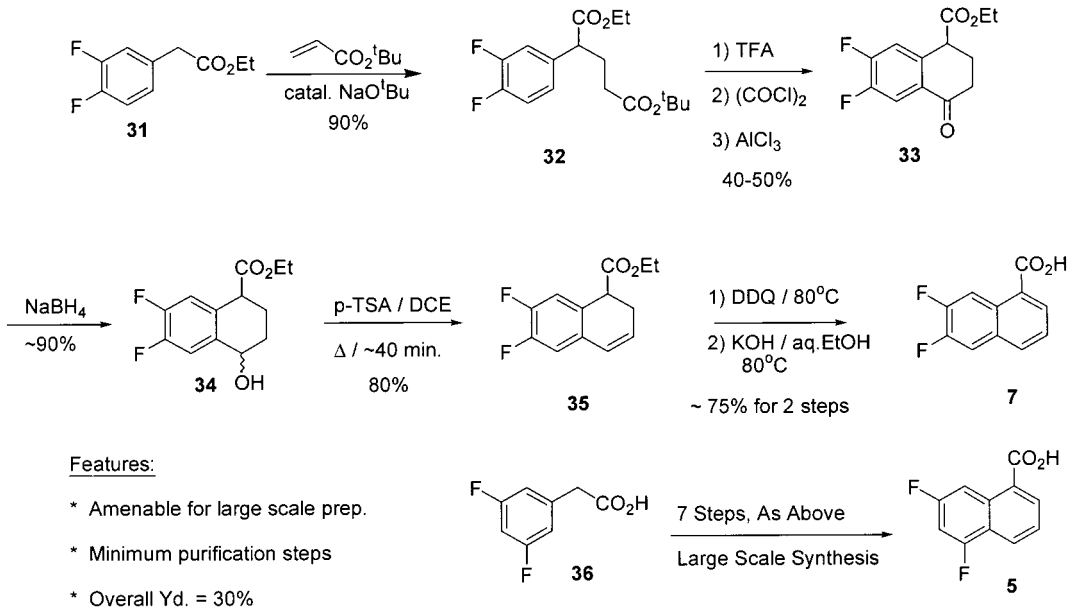
Scheme 3



Scheme 4



Scheme 5



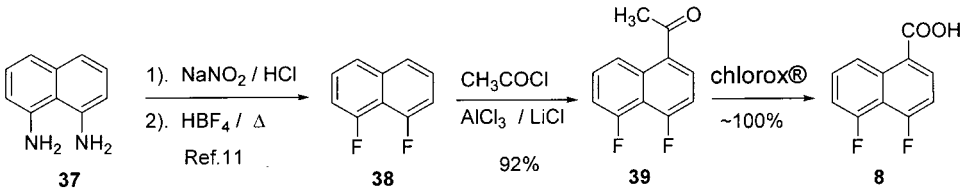
aldehyde (**30**) and then oxidize it to the desired 5,8-difluoro-1-naphthalencarboxylic acid **6**.

The lower cost of the starting difluoroacetophenones was off set by the extra steps needed to introduce the acidic group and the additional chromatographic purification needed in the above sequence. We, therefore, revisited the first route starting with **31** and prepared the 6,7-difluoro-1-naphthoic acid **7** (Scheme 5).[10] Later, this sequence of reactions was also used to prepare the difluoro-1-naphthalenecarboxylic acids **5** and **6** (2−10 g).

The final target, 4,5-difluoro-1-naphthoic acid (**8**) was

(10) In this route, the Friedel−Crafts cyclization of **32** gave only the 6,7-difluoro-1-tetralone (**33**) and none of the alternative 7,8-difluoro-1-tetralone as confirmed by NOE experiments.

Scheme 6



assembled from the inexpensive 1,8-diaminonaphthalene (**37**) by a short sequence. Thus, diazotization of **37** and reaction with fluoroboric acid yielded the 1,8-difluoro naphthalene **38**.[11] Acetylation and oxidation[12] afforded 4,5-difluoro-1-naphthalenecarboxylic acid **8** (Scheme 6).

In summary, we have described general, scalable methods for the preparation of four monofluoro and four difluoro-1-naphthoic acids from readily available precursors. The wide spread occurrence of naphthamides and other naphthoic acid derivatives in biologically active substances warrants the general utility of the title compounds described in this paper.[13]

Experimental Section

General. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by the Physical−Analytical Chemistry department, Schering-Plough Research Institute, on either a Leeman CE 440 or a Fisons EA 1108 elemental analyzer. Mass spectra were recorded using either Extrel 401 (Chemical Ionization), JEOL or MAT-90 (FAB), VG ZAB−SE (SIMS) or Finnigan MAT-CH-5 (Electron Impact) spectrometer. The ^{1}H and ^{13}C NMR spectra were obtained on either Varian Gemini-300 (300 MHz, ^{1}H; 75.5 MHz ^{13}C) or XL-400 (400 MHz ^{1}H; 100 MHz ^{13}C) and are reported as ppm downfield from Me_4Si with number of protons, multiplicities, and coupling constants in hertz indicated in parentheses. For ^{13}C NMR, a Nalorac probe was used. The compound purity was checked using thin-layer chromatography (TLC) and LC/MS analysis using Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Allech platinum C18, 3 mμ, 33 mm × 7 mm ID. Abbreviations used: dichloromethane (DCM), tetrahydrofuran (THF), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDCI), 1-hydroxybenzotriazole (HOBt), flash silica gel chromatography (FSGC).

5-Bromo-1-naphthalenecarboxylic Acid, 1,1-Dimethylethyl Ester (11). A suspension of 5-bromo-1-naphthoic acid[5] **10** (2.00 g, 7.97 mmol) in toluene (12 mL) was heated to 80 °C. *N*,*N*-Dimethylformamide di-*tert*-butyl acetal (7.6 mL, 31.9 mmol) was added dropwise, and the resulting mixture was heated at 80 °C for an additional 30 min. After cooling to room temperature, the organic solution was washed consecutively with H_2O, saturated aqueous $NaHCO_3$, and brine. The solution was dried over sodium sulfate and concentrated in vacuo, resulting in 1.2 g of desired product **11** as a yellow oil (49% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (d, J = 8.4 Hz, 1H), 8.45 (d, J = 8.8 Hz, 1H), 8.09 (d, J = 7.2 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.59 (dd, J = 7.2, 8.8 Hz, 1H), 7.42 (dd, J = 7.6, 8.4 Hz, 1H), 1.67 (s, 9H). HRMS calculated for $C_{15}H_{16}BrO_2$ (MH^+): 307.0329, found 307.0334.

5-Fluoro-1-naphthalenecarboxylic Acid, 1,1-Dimethylethyl Ester (13). A stirred solution of **11** (0.42 g; 1.4 mmol) in THF (14 mL) was cooled to −78 °C under nitrogen. *n*-Butyllithium (1.6 M in hexanes, 1.1 mL, 1.8 mmol) was added, and the resulting solution was stirred for 1.5 min, followed by addition of *N*-fluorobenzenesulfonimide (0.86 g; 2.7 mmol). After stirring for 30 min, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous component was extracted with Et_2O, and the combined organics were dried over magnesium sulfate and concentrated in vacuo. The crude product **12** was identified by ^{1}H NMR as a 2/1 mixture of 5-F/5-H compounds. FSGC (toluene as eluent) resulted in 157 mg of **13** (46% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 8.4 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.13 (dd, J = 1.0, 7.2 Hz, 1H), 7.52 (m, 2H), 7.19 (ddd, J = 1.0, 8.4, 10.0 Hz, 1H), 1.68 (s, 9H). MS (M-*t*-Bu): 191 (100%).

5-Fluoro-1-naphthalenecarboxylic Acid (1). Trifluoroacetic acid (0.3 mL, 3.9 mmol) was added to a stirred methylene chloride (4 mL) solution of **13** (96.5 mg, 0.39 mmol) at room temperature. After stirring for several hours, the solution was concentrated in vacuo and stored under high vacuum for 12 h, yielding 73 mg of pure **1** (98% yield). ^{1}H NMR (400 MHz, CD_3OD): δ 8.73 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 8.8 Hz, 1H), 8.27 (d, J = 7.6 Hz, 1H), 7.63 (dd, J = 7.2, 8.4 Hz, 1H), 7.56 (m, 1H), 7.26 (dd, J = 7.2, 10.0 Hz, 1H). Anal. Calcd for $C_{11}H_7FO_2$: C, 69.47, H, 3.71. Found: C, 69.32; H, 3.76.

2-(2-Fluorophenyl)pentanedioic Acid, 5-(1,1-Dimethylethyl)-1-ethyl Ester (15). *o*-Fluorophenyl ethyl acetate (**14**) was prepared from commercially available *o*-fluorophenylacetic acid. *tert*-Butyl acrylate was added to a solution of **14** (6.3 g; 34.62 mmol) in 30 mL of *tert*-butyl alcohol cooled in a cold water bath (5 °C) and treated with oil-free sodium hydride (0.3 g). After the initial effervescence ceased, the resulting clear, pale yellow solution was stirred at 5 °C for 30 min and allowed to warm to room temperature (45 min). The reaction mixture was quenched with 1 mL of glacial acetic acid. The organic products were extracted into ether and washed with water (4×), 10% aqueous $NaHCO_3$ solution, and brine. Concentration in vacuo gave 10 g of a crude product. FSGC (5% ether−hexane) served to isolate compound **15** (7.6 g; 83% yield) as colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.20 (t, J = 7.0 Hz, 3H), 1.43 (s, 9H), 2.05 (m, 1H), 2.2 (t, J = 7.0 Hz, 2H), 2.35 (m, 1H), 3.96 (t, J = 7.5 Hz, 1H), 4.15 (m, 2H), 7.0−7.15 (m, 2H), 7.2−7.35 (m, 2H).

8-Fluoro-1, 2,3,4-tetrahydro-4-oxo-1-naphthalenecarboxylic Acid, Ethyl Ester (16). (a) 4-(Ethyl)-3-(2-fluorophenyl)-1-glutaric acid: Trifluoroacetic acid (TFA; 10 mL) was added to a solution of **15** (6.6 g; 21.29 mmol) in 25 mL of CH_2Cl_2 and stirred at room temperature until the starting material was fully consumed (∼7 h). The solvent and most of the TFA were removed in vacuo. The residue was dissolved in ethyl acetate (100 mL) and washed with water (4×) and brine. After concentrating in vacuo, the residue was evaporated with toluene (2 × 10 mL) to remove the last traces of TFA. The residue was concentrated overnight under high vacuum to afford 5.35 g (∼100%) of the monoacid as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.2 (t, J = 7 Hz, 3H), 2.1 (m, 1H), 2.3−2.45 (m, 3H), 3.95 (t, J = 7 Hz, 1H), 4.15 (m, 2H), 7.0−7.15 (m, 2H), 7.15−7.35 (m, 2H) and 8.25 (br-s, 1H).

(b). Formation of the acid chloride and cyclization to the title compound (**16**): Oxalyl chloride (2.3 mL; 25.8 mmol) was added to a solution of the mono-acid (5.3 g) prepared above and dimethylformamide (0.3 mL) in 30 mL of DCM at 0 °C. The reaction mixture was stirred at ice-bath temperature for 45

(11) Mallory, F. B.; Mallory, C. W.; Fedarko, M.-C. *J. Am. Chem. Soc.* **1974**, *96*, 3536.

(12) Bachmann, W. E.; Cronyn, M. W.; Struve, W. S. *J. Org. Chem.* **1947**, *12*, 603.

(13) For examples of fluorinated naphthamides prepared from all of the new fluoronaphthoic acids described in this paper and their effects on pharmacokinetic parameters, see: Boyle, C. D.; Chackalamannil, S.; Clader, J. C.; Greenlee, W. J.; Josien, H. B.; Kaminski, J. J.; Kozlowski, J. A.; McCombie, S. W.; Nazareno, D. V.; Tagat, J. R.; Wang, Y.; Zhou, G.; Billard, W.; Binch, H., III; Crosby, G.; Cohen-Williams, M.; Coffin, V. L.; Cox, K. A.; Grotz, D. E.; Duffy, R.; Ruperto, V.; Lachowicz, J. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2311.

min and then at room temperature for 1.5 h. The solvent and acidic byproducts were removed on a rotary evaporator. Finally, the residue was concentrated under high vacuum to yield 6.3 g (~100%) of a colorless oil.

The 4-ethyl-3-(2-fluorophenyl)-1-glutaroyl chloride prepared above was dissolved in 50 mL of DCM, and solid aluminum chloride (6.6 g; 50 mmol) was added quickly. After the initial effervescence, a clear yellow solution is formed and it was heated to reflux for 6 h. The deep burgundy slurry that resulted was cooled to room temperature and diluted with ethyl acetate. The reaction was quenched with 2 M hydrochloric acid solution (100 mL) to leave a turbid yellow solution. The layers were separated, and the organic layer was washed with 2 M HCl aqueous solution (3 × 100 mL) until it was almost clear and finally with water and brine. Concentration left a deep red liquid which was purified by FSGC (20% ethyl acetate in hexane) to obtain 2.1 g (42%) of the tetralone **16** as a pale yellow syrup. ^{1}H NMR ($CDCl_3$): δ 1.2 (t, J = 7 Hz, 3H), 2.3−2.45 (m, 1H), 2.5−2.8 (m, 3H), 4.1−4.3 (m, 3H), 7.26 (dd, J = 2.7, 8 Hz, 1H), 7.37 (dd, J = 2.5, 8 Hz, 1H) and 7.87 (d, J = 8 Hz).

8-Fluoro-1, 2, 3, 4-tetrahydro-4-hydroxy-1-naphthalenecarboxylic Acid, Ethyl Ester (17). A solution of sodium borohydride (0.21 g; 5.52 mmol) in 4 mL of water was added to a solution of the tetralone **16** (1.1 g; 4.66 mmol) in 2 mL of THF and 2 mL of ethanol. The reaction mixture was stirred at room temperature for 6 h when TLC indicated absence of starting material. The reaction was quenched with 1 N citric acid and the product was isolated by extractive workup in DCM. The carbinol **17** (~2:1 mixture of epimers) was obtained as a colorless oil (1.05 g; ~100%). ^{1}H NMR ($CDCl_3$): δ 1.2 (t, J = 7 Hz, 3H), 1.8−2.15 (m, 4H), 2.25 (m, 2H), 3.85 (t, J = 6 Hz, 1H), 4.1−4.25 (m, 2H), 4.72 (t, J = 6 Hz, 1H), 6.96 (t, J = 9 Hz, 1H) and 7.2−7.35 (m, 2H).

8-Fluoro-1, 2-dihydro-1-naphthalenecarboxylic Acid, Ethyl Ester (19). The above carbinol **17** was dissolved in 10 mL of 1,2-dichloroethane, treated with *p*-toluenesulfonic acid (20 mg), and heated at reflux for 1 h. TLC indicated the consumption of starting material to form a nonpolar, UV-active spot. The reaction mixture was cooled to room temperature, diluted with DCM, and washed with saturated $NaHCO_3$ solution, water, and brine. The product was purified by FSGC (5−10% EtOAc−hexane) to obtain the olefin **19** (0.65 g; 67%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, J = 7 Hz, 3H), 2.55 (m, 1H), 2.89−2.98 (dd, J = 2.5, 2.8 Hz, dd, J = 2.6, 6 Hz, 1H), 4.0−4.2 (m, 3H), 6.0 (m, 1H), 6.45 (dd, J = 2, 9.6 Hz, 1H), 6.86−7.0 (m, 2H) and 7.16−7.23 (m, 1H).

8-Fluoro-1-naphthalenecarboxylic Acid (4). Solid 2,3-dichloro-5,6-dicyano-1,4-benzo quinone (DDQ; 0.73 g; 3.2 mmol) was added to a solution of the dihydronaphthalene **19** (0.65 g; 2.95 mmol) in 6 mL of 1,2-dichoroethane. The reaction mixture was heated to reflux for 16 h and cooled to room temperature, and the unreacted DDQ was quenched with cyclohexadiene. The reaction mixture turned from a dark brown to muddy tan slurry. After concentration, the residue was dissolved in a minimum amount of DCM. FSGC of the crude reaction mixture (25% ether−hexane) provided 8-fluoro-1-ethyl naphthoate (0.45 g; 71%) as a yellow foam. ^{1}H NMR ($CDCl_3$): δ 1.42 (t, J = 7 Hz, 3H), 4.45 (q, J = 7, 14 Hz, 2H), 7.2−7.26 (dd, J = 3, 12 Hz, 1H), 7.45 (m, 1H), 7.52 (d, J = 8 Hz, 1H), 7.60 (d, J = 16 Hz, 1H), 7.68 (J = 8 Hz, 1H) and 7.92 (d, J = 16 Hz, 1H).

To a solution of the ethyl ester isolated above in 6 mL of ethanol was added 2 mL of 1 M aqueous solution of sodium hydroxide, and the reaction was heated at reflux for 24 h. After being cooled to room temperature, the reaction mixture was acidified with 1 M HCl solution. Extractive workup in DCM served to isolate 8-fluoro-1-naphthalenecarboxylic acid (**4**) as a cream-colored solid (0.33 g; 84%). mp: 140 °C. ^{1}H NMR ($CDCl_3$): δ 7.27 (m, 1H), 7.45−7.6 (m, 2H), 7.7 (d, J = 9 Hz, 1H), 7.8 (d, J = 9 Hz, 1H) and 8.0 (d, J = 9 Hz, 1H). CI MS (MH^+) = 191 (100%). HRMS calculated for $C_{11}H_8O_2F$: 191.0508. Found 191.0503. Anal. Calcd for $C_{11}H_7O_2F$: C, 69.37; H, 3.71; F, 9.99. Found: C, 68.94; H, 3.95; F, 9.74.

7-Fluoro-1-naphthalenecarboxylic Acid (3).[4b] Preparation similar to **4**. mp: 245 °C. ^{1}H NMR (DMSO-d_6): δ 7.45−7.65 (m, 2H), 8.13 (m, 1H), 8.20−8.35 (m, 2H) and 8.67 (d, J = 13 Hz, 1H).

6-Fluoro-1-naphthalenecarboxylic Acid (2).[4a] Preparation similar to **4**. ^{1}H NMR: 7.45 (dt, J = 2.7, 9.4 Hz, 1H), 7.6 (q, J = 7.5, 16 Hz, 2H), 8.1 (d, J = 8 Hz, 1H), 8.2 (d, J = 7.3 Hz, 1H) and 9.05 (dd, J = 5.7, 9.4 Hz, 1H).

4-(2,4-Difluorophenyl)-4-hydroxy-butanoic Acid, 1,1-Dimethylethyl Ester (21). A solution of 2,4-difluoroacetophenone **20** (7 g; 45.45 mmol) in 50 mL of dry THF was added to a solution of freshly prepared lithium hexamethyldisilazide in dry THF (50 mmol in 50 mL) at −78 °C and stirred for 30 min. The resulting yellow solution of the enolate was added into a solution of *tert*-butyl iodoacetate (12.1 g; 50 mmol) in 50 mL of dry THF at −78 °C over 15 min. The amber-colored reaction mixture was allowed to warm to room temperature over 3 h and quenched with saturated aqueous NH_4Cl solution. Extractive workup in ether gave 14 g of a clear orange liquid. FSGC (5% ether−hexane) yielded 6 g (~50%) of the monoalkylated keto-ester and 1.2 g (~10%) of the dialkylated keto-ester.

A solution of sodium borohydride (0.6 g; 16 mmol) in 5 mL of water was added to a solution of the keto-ester (4.3 g; 16 mmol) prepared in the first step in 40 mL of THF. The reaction was allowed to proceed at room temperature for 2.5 h and quenched with 2 M tartaric acid solution. The organic product was extracted into DCM and washed with water, 10% $NaHCO_3$ solution, and brine. Concentration in vacuo gave 4.35 g (~100%) of the hydroxy ester **21** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9H), 2.05 (q, J = 3, 9 Hz, 2H), 2.4 (t, J = 6 Hz, 2H), 2.5 (br-s, OH), 5.03 (t, J = 6 Hz, 1H), 6.75 (dt, J = 2, 10 Hz, 1H), 6.9 (t, J = 9.5 Hz, 1H) and 7.5 (q, J = 6, 12 Hz, 1H). Anal. Calcd for $C_{14}H_{18}F_2O_3$: C, 61.76; H, 6.66; F, 13.95. Found: C, 61.58; H, 6.78; F, 13.61.

4-(2,4- Difluorophenyl)butanoic Acid, 1,1-Dimethylethyl Ester (22). A solution of the hydroxy ester **21** (4.3 g; 15.8 mmol) in 40 mL of dry DCM was treated with 4-(dimethylamino)pyridine (0.1 g) and freshly obtained thiocarbonyl diimidazole (4.2 g; 23.7 mmol). The reaction mixture was stirred at room temperature until TLC showed disappearance of the alcohol to form a more polar spot (~20 h). The reaction mixture was diluted with DCM and washed with water and brine. The crude orange oily product was passed through a short column of FSG (25% EtOAc−hexane) to isolate the xanthate derivative as a pale yellow oil (5.5 g; 92%). ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9H), 2.25−2.45 (m, 4H), 2.5(m, 1H), 6.65 (m, 1H), 6.9 (m, 1H), 7.05 (s, 1H), 7.35 (m, 1H), 7.65 (s, 1H) and 8.35 (s, 1H).

Tributyltin hydride (5.7 mL; 21.2 mmol) and a catalytic amount of AIBN were added to a solution of the xanthate derivative made above in dry toluene (50 mL). The colorless reaction mixture was heated at reflux for 1.5 h when TLC indicated complete conversion of the starting material to a less polar spot. The reaction mixture was diluted with EtOAc, washed with water, and brine. Concentration to turbid yellow oil (~5 g) and FSGC (neat hexane followed by 25% EtOAc−hexane) of the crude product gave the deoxygenated 4-arylbutanoic acid ester **22** (3.25 g; 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9H), 1.9 (m, 2H), 2.25 (t, J = 9 Hz, 2H), 2.65 (t, J = 8 Hz, 2H), 6.8 (m, 2H) and 7.1 (q, J = 7, 12 Hz, 1H). Anal. Calcd for $C_{14}H_{18}F_2O_2$: C, 65.61; H, 7.08; F, 14.83. Found: C, 64.98; H, 6.97; F, 14.40.

5,7-Difluoro-3,4-dihydro-1-(2*H*)-naphthalenone (23). Liberation of the acid from **22**: A solution of the *tert*-butyl ester **22** prepared above was dissolved in a mixture of DCM (15 mL) and trifluoroacetic acid (5 mL) and stirred at room temperature for 4 h. After removing the solvent and most of TFA on the rotary evaporator, the residue was dissolved in DCM and extracted with 1 M sodium hydroxide solution. Acidification of the aqueous layer and extractive workup in DCM gave 4-(2,4-difluorophenyl)butanoic acid as 2.2 g (88%) of colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.98 (m, 2H), 2.4 (t, J = 5.8 Hz, 2H), 2.7 (t, J = 5.7 Hz, 2H), 6.8 (m, 2H) and 7.17 (q, J = 4, 9 Hz, 1H).

Friedel−Crafts Reaction. The above acid was converted to the acid chloride by treatment with oxalyl chloride (2.5 mL) in DCM containing a trace of DMF followed by concentration in vacuo. Solid $AlCl_3$ was added to a solution of the acid chloride prepared above in 40 mL of DCM and heated at reflux for 4 h. The reaction was then cooled in an ice bath and quenched with 2 M HCl solution, and the layers were separated. The DCM layer was washed with water and brine. Concentration gave ∼ 2 g of a semisolid. FSGC (1:1 ether−hexane) afforded 1.55 g (74%) of the 5,7-difluorotetralone **23** as a white solid. mp: 80 °C. ^{1}H NMR ($CDCl_3$): δ 2.1−2.3 (m, 2H), 2.7 (t, J = 8 Hz, 2H), 2.95 (t, J = 7 Hz, 2H), 7.0 (m, 1H) and 7.55 (d, J = 9 Hz, 1H). Anal. Calcd for $C_{10}H_8F_2O$: C, 65.93; H, 4.43; F, 20.86. Found: C, 66.08; H, 4.41; F, 20.74.

5,7-Difluoro-3,4-dihydro-1-naphthalenecarbonitrile (25). A solution of the above tetralone **23** (1.5 g; 8.24 mmol) in 15 mL of dry THF was stirred with lithium cyanide (0.81 g; 24.6 mmol) and diethyl cyanophosphonate (3.75 mL; 24.6 mmol) for 10 min. Extractive workup in ethyl acetate gave ∼4 g of red-brown oil. The cyanohydrin **24** obtained above was dissolved in benzene (25 mL) and stirred with boron trifluoride etherate (3 mL; 24. 6 mmol) for 20 h. The mixture was diluted with more benzene and the reaction mixture quenched with water. The organic product was extracted with EtOAc and washed with water and brine. Concentration gave ∼2 g of a brown gum which was purified by FSGC (20−50% ether−hexane) to yield **25** (1.47 g; 93%) as an off-white solid. mp: 68 °C. ^{1}H NMR ($CDCl_3$): δ 2.55 (m, 2H), 2.9 (t, J = 8 Hz, 2H), 6.8 (dt, J = 2, 10 Hz, 1H), 7.0 (s, 1H) and 7.0−7.1 (t, J = 10 Hz, 1H). Anal. Calcd for $C_{11}H_7F_2N$: C, 69.11; H, 3.69; N, 7.33; F, 19.87. Found: C, 68.95; H, 3.58; N, 7.28; F, 19.83.

5,7-Difluoro-1-naphthalenecarbonitrile (26). DDQ (2.04 g; 9 mmol) was added to a solution of **25** in chlorobenzene (30 mL), and the resulting red heterogeneous mixture was heated at reflux for 16 h. TLC indicated a slightly less polar, fluorescent spot. Unreacted DDQ was quenched with 3 mL of cyclohexadiene. The resulting brown slurry was directly subjected to FSGC (hexane then 5% ether−hexane) to give 1.25 g (89%) of the naphthonitrile **26** as fibrous white solid. mp: 106 °C. ^{1}H NMR ($CDCl_3$): δ 7.15 (dt, J = 2, 10 Hz, 1H), 7.6 (t, J = 9 Hz, 1H), 7.75 (d, J = 9 Hz, 1H), 8.0 (d, J = 8 Hz, 1H) and 8.35 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{11}H_5F_2N$: C, 69.84; H, 2.66; F, 20.09; N, 7. 41. Found: C, 69.74; H, 2.55; F, 20.24; N, 7.46.

5,7-Difluoro-1-naphthalenecarboxylic Acid (5). The naphthonitrile **26** (0.5 g; 2.65 mmol) was dissolved in 5 mL of glacial acetic acid, 4 mL of concentrated sulfuric acid, and 2 mL of water and heated at reflux for 20 h. The heterogeneous reaction mixture was cooled to room temperature and poured into ice−water. Upon stirring vigorously, a precipitate formed which was collected by filtration, washed with water until clear, and dried in vacuo to leave 0.4 g (73%) of the desired naphthoic acid **5** as beige solid. mp: 260 °C (dec). ^{1}H NMR: δ 7.0 (dt, J = 2, 10 Hz, 1H), 7.5 (t, J = 9 Hz, 1H), 8.25 (d, J = 8 Hz, 1H), 8.4 (d, J = 8 Hz, 1H) and 8.65 (d, J = 10 Hz, 1H). Anal. Calcd for $C_{11}H_6F_2O_2$: C, 63.47; H, 2.91; F, 18.25. Found: C, 63.29; H, 2.95; F, 17.91.

5,8-Difluoro-1-naphthalenecarbonitrile (28). Commercially available 2,5-difluoroacetophenone **27** (5.9 g; 37.82 mmol) was alkylated with *tert*-butyl iodoacetate (10 g; 41.60 mmol) and the resulting keto-ester reduced with sodium borohydride to furnish *tert*-butyl 4-hydroxy-4 (2,5-difluorophenyl)butyrate (50% overall) exactly as described for compound **21**. This material was processed as described above for target **26** to obtain 1.1 g (22% overall yield) of 5,8-difluoro-1-naphthonitrile (**28**) as a fibrous white solid. mp: 119 °C. ^{1}H NMR: δ 7.25 (m, 2H), 7.7 (t, J = 8 Hz, 1H), 8.05 (d, J = 8 Hz, 1H) and 8.35 (d, J = 10 Hz, 1H). CI MS (MH^+): 190. Anal. Calcd for $C_{11}H_5F_2N$: C, 69.84; H, 2.66; N, 7.41; F, 20.09. Found: C, 69.66; H, 2.51; N, 7.41; F, 20.05.

5,8-Difluoro-1-naphthalenecarboxylic Acid (6). Diisobutylaluminum hydride (1 M in toluene; 6.4 mL) was added to a solution of the nitrile **28** (1 g; 5.29 mmol) in toluene (10 mL) at −78 °C, stirred for 2 h, and then allowed to warm to room temperature. Excess DIBAL-H was destroyed by the addition of ethyl acetate. The reaction mixture was diluted with more ethyl acetate and quenched with 2 N aqueous HCl solution. The organic product was extracted into ethyl acetate and washed with water and brine. Concentration and purification (FSGC using 10% ether−hexane) afforded 0.75 g (75%) of 5,8-difluoro naphthaldehyde **30**. ^{1}H NMR ($CDCl_3$): δ 7.25 (m, 2H), 7.75 (t, J = 8 Hz, 1H), 8.4 (dd, J = 6, 14 Hz, 1H) and 11.0 (s, 1H).

5,8-Difluoro naphthaldehyde **30** (0.75 g; 3.9 mmol) was dissolved in 10 mL of acetone and treated with a solution of $KMnO_4$ (1.26 g) in 5 mL of water and 5 mL of acetone and stirred at 40 °C for 6 h. Inorganic salts were removed by filtration. The filtrate was concentrated, redissolved in DCM (50 mL), and washed with water and brine. Concentration in vacuo gave 0.4 g (∼50%) of 5,8-difluoro-1-naphthalenecarboxylic acid **6** as beige solid. mp: 260 °C (dec). CI MS (MH^+): 209. ^{1}H NMR ($CDCl_3$): δ 7.2 (m, 2H), 7.65 (t, J = 7 Hz, 1H), 7.85 (d, J = 8 Hz, 1H) and 8.25 (d, J = 9 Hz, 1H). Anal. Calcd for $C_{11}H_6F_2O_2$: C, 63.47; H, 2.91; F, 18.25. Found: C, 63.29; H, 3.32; F, 18.07.

2-(3,4-Difluorophenyl)pentanedioic Acid, 5-(1,1-Dimethylethyl)-1-ethyl Ester (32). 3,4-Difluorophenyl ethyl acetate **31** (4 g; 20 mmol) prepared quantitatively from its commercial acid was dissolved in 20 mL of *tert*-butyl alcohol and treated with *tert*-butyl acrylate (2.5 mL) in a cold water bath (5 °C). Oil-free sodium hydride (0.14 g) was added, and the reaction mixture was stirred at 5 °C for 15 min and at ambient temperature for 1.5 h. TLC (15% ether−hexane) indicated the complete formation of a slightly more polar spot. The reaction was quenched with 2 mL of acetic acid, and the product was extracted with ether and washed with water, 10% $NaHCO_3$ solution, and brine. Concentration in vacuo gave 6.23 g (95%) of **32** as yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, J = 6 Hz, 3H), 1.47 (s, 9H), 2.0 (m, 1H), 2.2 (t, J = 7 Hz, 1H), 2.25−2.4 (m, 1H), 3.6 (t, J = 6 Hz, 1H), 4.15 (m, 2H), 7.0 (br-s, 1H) and 7.05−7.2 (m, 2H). Anal. Calcd for $C_{17}H_{22}F_2O_4$: C, 62.18; H, 6.75; F, 11.57. Found: C, 62.13; H, 6.76; F, 11.84.

6,7-Difluoro-1, 2, 3, 4-tetrahydro-4-oxo-1-naphthalenecarboxylic Acid, Ethyl Ester (33). Trifluoroacetic acid (10 mL) was added to a solution of the diester **32** (5 g; 15.24 mmol) in 10 mL of DCM and stirred at ambient temperature for 1.5 h. The solvent and acid were removed on the rotary evaporator; the residue was dissolved in DCM and washed with water and brine. Concentration gave 3.9 g (95%) of the carboxylic acid as a yellow gum. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, J = 6 Hz, 3H), 2.0−2.2 (m, 1H), 2.2−2.4 (m, 1H), 2.3−2.5 (m, 2H), 3.6 (t, J = 7 Hz, 1H), 4.15 (m, 2H), 6.95−7.05 (br-s, 1H) and 7.05−7.25 (m, 2H).

The glutaric acid monoester obtained above was dissolved in DCM (20 mL) and treated with two drops of DMF and oxalyl chloride (1.9 mL; 21.6 mmol). After stirring at ambient temperature for 2 h, the solvent and unreacted acid chloride were removed on the rotary evaporator. Traces of acidic vapors were removed by further evaporating with ethyl acetate, and the residue was dried under high vacuum.

Aluminum chloride (3.8 g; 28.67 mmol) was added to a solution of the acid chloride prepared above in 50 mL of DCM and stirred at ambient temperature for a day. The reaction was quenched by slow addition of 2 N HCl solution and product isolated by extractive workup in DCM. FSGC (10−20% ether in hexane) served to purify the less polar tetralone **33** which was isolated as an amber oil (2.43 g; 52%). ^{1}H NMR ($CDCl_3$): δ 1.3 (t, J = 6 Hz, 3H), 2.2−2.45 (m, 1H), 2.45−2.65 (m, 1H), 2.68 (t, J = 4 Hz, 1H), 2.9 (dt, J = 4, 14 Hz, 1H), 3.9 (t, J = 5 Hz, 1H), 4.2 (q, J = 6, 12 Hz, 2H), 7.1−7.25 (dd, J = 8, 10 Hz, 1H), 7.87 (dd, J = 8, 10 Hz, 1H). Anal. Calcd for $C_{13}H_{12}F_2O_3$: C, 61.42; H, 4.76; F, 14.95. Found: C, 61.51; H, 4.76; F, 15.20.

6,7-Difluoro-1, 2-dihydro-1-naphthalenecarboxylic Acid, Ethyl Ester (35). Sodium borohydride (0.39 g; 10.3 mmol) in 5 mL of water was added to a solution of the tetralone **33** (2.43 g; 9.4 mmol) in 25 mL of THF and stirred at ambient temperature for 5 h. The reaction was quenched with 2 N hydrochloric acid and stirred for 20 min. Extractive workup in DCM gave the 4-hydroxynaphthalene ester **34** (∼2:1 mixture of epimers) as yellow oil (2.4 g; ∼100%). ^{1}H NMR

($CDCl_3$): δ 1.3 (t, J = 6 Hz, 3H), 1.8−1.95 (m, 1H), 1.95−2.15 (m, 2H), 2.2−2.4 (m, 1H), 3.7 (t, J = 4 Hz, 1H), 3.75 (t, J = 3 Hz, 0.5H), 4.2 (q, J = 6, 9 Hz, 2H), 4.65 (t, J = 5 Hz, 1H), 4.7(t, J = 3 Hz, 0.5H), 7.05 (dd, J = 6, 10 Hz, 1H) and 7.25−7.45 (m, 1H).

The hydroxy ester **34** was dissolved in dichloroethane (20 mL), treated with *p*-toluenesulfonic acid (0.1 g), and heated at reflux for 1 h. The reaction mixture was cooled to room temperature, diluted with DCM, and washed with water, 10% $NaHCO_3$ solution, and brine. Concentration and FSGC (10−50% ether in hexane) afforded **35** (1.65 g; 74%) as colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, J = 7 Hz, 3H), 2.45−2.6 (m, 1H), 2.8−2.9 (two t, J = 5 Hz, 1H), 3.7 (t, J = 6 Hz, 1H), 4.15 (q, J = 6, 12 Hz, 2H), 6.0 (m, 1H), 6.35 (d, 10 Hz, 1H), 6.85 (dd, J = 7, 9 Hz, 1H) and 7.0 (dd, J = 7, 9 Hz, 1H). Anal. Calcd for $C_{13}H_{12}F_2O_2$: C, 60.93; H, 5.51; F, 14.83. Found: C, 60.81; H, 5.46; F, 14.58.

6,7-Difluoro-1-naphthalenecarboxylic Acid (7). DDQ (1.83 g; 8.06 mmol) was added to a solution of the dihydronaphthalene ester **35** (1.6 g; 6.72 mmol) in 15 mL of chlorobenzene and heated at reflux for 20 h. Excess DDQ was destroyed with 1,4-cyclohexadiene (5 mL) forming a turbid tan solution. The turbid tan solution was directly subjected to FSGC. Eluting with hexane removed chlorobenzene, and the nonpolar product was isolated by eluting further with 10% ether in hexane. Concentration gave 6,7-difluoro-1-ethylnaphthoate (1.49 g; 94%) as colorless film. ^{1}H NMR ($CDCl_3$): δ 1.48 (t, J = 6 Hz, 3H), 4.5 (q, J = 5, 8 Hz, 2H), 7.5 (t, J = 6 Hz, 1H), 7.6 (dd, J = 2, 9 Hz, 1H), 7.9 (d, J = 8 Hz, 1H), 8.23 (d, J = 8 Hz, 1H) and 8.85 (dd, J = 7, 10 Hz, 1H). FAB MS (MH^+): 237. Anal. Calcd for $C_{13}H_{10}F_2O_2$: C, 66.10; H, 4.27; F, 16.09. Found: C, 66.15; H, 4.15; F, 16.23.

The naphthalene ester (1.4 g; 5.93 mmol) was dissolved in 10 mL of ethanol. Aqueous potassium hydroxide solution (1 N; 10 mL) was added and heated at reflux for 8 h. The reaction mixture was cooled to ambient temperature and carefully quenched with 2 M hydrochloroic acid. The product was extracted into DCM (50 mL) and washed with water and brine. Concentration gave 1 g (81%) of 6,7-difluoro-1-naphthalenecarboxylic acid (**7**) as a white solid. mp: 260 °C (dec). ^{1}H NMR ($CDCl_3$): δ 7.5 (t, J = 6 Hz, 1H), 7.6 (dd, J = 2, 9 Hz, 1H), 7.9 (d, J = 8 Hz, 1H), 8.3 (d, J = 8 Hz, 1H) and 9.0 (dd, J = 7, 10 Hz, 1H). Anal. Calcd for $C_{11}H_6F_2O_2$: C, 63.47; H, 2.91; F, 18.25. Found: C, 63.66; H, 2.98; F, 18.49.

The above sequence of reactions (Scheme 5) was also used to convert 3,5-difluorophenyl acetic acid **36** to 5,7-difluoro-1-naphthalenecarboxylic acid **5** (5−10 g).

1-(4,5-Difluoro-1-naphthalenyl)ethanone (39). Commercial 1,8-diaminonaphthalene was converted to 1,8- difluoronaphthalene by the method of Mallory.[11] To a mixture of aluminum chloride (2.18 g; 16.39 mmol) and lithium chloride (0.35 g) was added a solution of 1,8-difluoronaphthalene (0.9 g; 5.5 mmol) and acetyl chloride (0.4 mL; 5.6 mmol) in 15 mL of 1,2-dichloroethane at −35 °C. After stirring for 1 h at low temperature, the reaction mixture was allowed to warm to room temperature and stirred for several hours. The reaction was carefully quenched with 5% hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water, 1 N sodium hydroxide, and brine and dried. Concentration gave the naphthaleno-ketone **39** (1.04 g; 92%) as a dark brown solid. ^{1}H NMR ($CDCl_3$): δ 2.75 (s, 3H), 7.1−7.3 (m, 2H), 7.6 (dd, J = 3, 8 Hz, 1H), 8.0 (t, J = 3 Hz, 1H) and 8.65 (d, J = 7 Hz, 1H).

4,5-Difluoro-1-naphthalenecarboxylic Acid (8). A mixture of 1-acetyl-4,5-difluoro naphthalene **39** (0.28 g; 1.36 mmol), 15 mL of commercial chlorox, and 0.15 g of NaOH was refluxed for 1 h. The reaction mixture was cooled to room temperature and filtered. To the filtrate 1 g of sodium hydrogen sulfite was added, followed by 5% hydrochloric acid until the pH was 1. The organic product was extracted with ethyl acetate, washed with water and brine, and concentrated. The 4,5-difluoro-1-naphthoic acid **8** was obtained as a white solid (0.28 g, ∼100%). mp: 182 °C (dec). ^{1}H NMR ($CDCl_3$): δ 3.0 (br-s, 1H), 7.0−7.15 (m, 2H), 7.4−7.5 (dd, J = 3, 8 Hz, 1H), 8.2 (t, J = 3 Hz, 1H) and 8.8 (d, J = 7 Hz, 1H). CI MS (MH^+): 209. FAB MS: M^+ = 208. FAB HR MS calculated for $C_{11}H_6F_2O_2$ 208.0336, found 208.0334.

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Supporting Information Available: ^{1}H NMR spectra of all the intermediates and the mono- and difluoro-1-naphthalene carboxylic acids (**1**−**8**) described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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