JOC Article

Preparation of 8-Amido-2-dimethylamino-1,2,3,4-tetrahydro-2-dibenzofurans and Several Fluorinated Derivatives via [3,3]-Sigmatropic Rearrangement of *O*-Aryloximes

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Methodology to prepare 8-amido-2-amino-1,2,3,4-tetrahydro-2-dibenzofurans, analogues with a fluorine substituent incorporated in the 6-, 7-, and 9-positions, and a difluorinated analogue with fluorines in the 6- and 9-positions is described. The tetrahydrodibenzofuran ring systems are prepared by acid-catalyzed [3,3]-sigmatropic rearrangement of *O*-aryloximes. Regioselective reactions to prepare the requisite *O*-aryloxime intermediates from commercially available fluorobenzene derivatives are discussed.

Introduction

Serotonin (**1**, 5-hydroxytryptamine, 5-HT; Figure 1) is a prominent neurotransmitter with diverse physiological actions in both the central and peripheral nervous systems. Seven families of serotonin receptors (5-HT_1−5-HT_7) and 14 distinct serotonin receptor subtypes have been identified in the mammalian central nervous system.[1] The identification of selective agonists and antagonists for the diverse serotonin receptor subtypes has been an active area of investigation.

Serotonin 1F agonists have demonstrated potential for the treatment of migraine headaches.[2] Previously, tetrahydrocarbazole **2** (LY344864; Figure 1) was demonstrated to be a potent and selective serotonin 1F receptor agonist.[2a] In connection with a program to discover novel and selective 5-HT_{1F} agonists, tetrahydrodibenzofuran analogues **3** were selected as targets.[3] The synthesis of

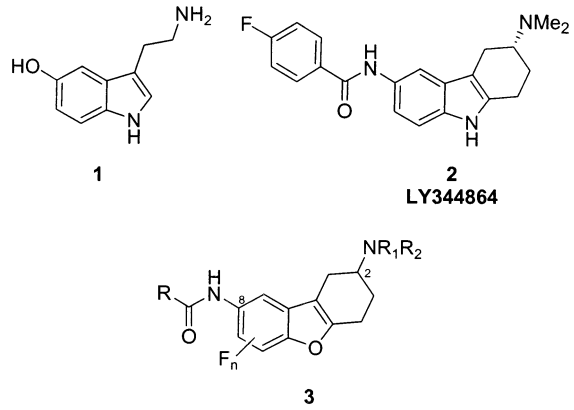

FIGURE 1.

the parent tetrahydrodibenzofuran ring system as well as syntheses to selectively incorporate fluorine atoms into the 6-, 7-, and 9-positions and to create a difluorinated analogue with fluorine atoms in the 6- and 9-positions were explored. Herein the details for the syntheses of these ring systems are described.

The incorporation of fluorine atoms into molecules alters their physical and biological characteristics and has been a popular strategy for studying structure activity relationships in medicinal chemistry.[4] Recently, a series of fluorinated tryptamines has been prepared to study the pharmacological effects of fluorination.[5] In this study, fluorine substitution at different positions around

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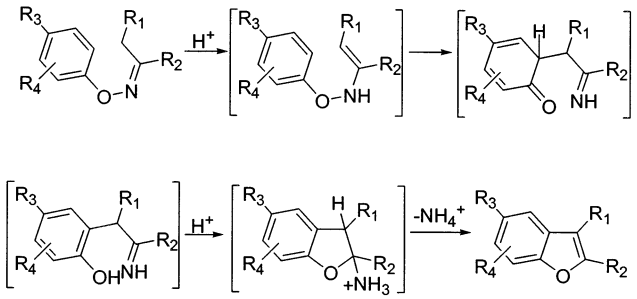


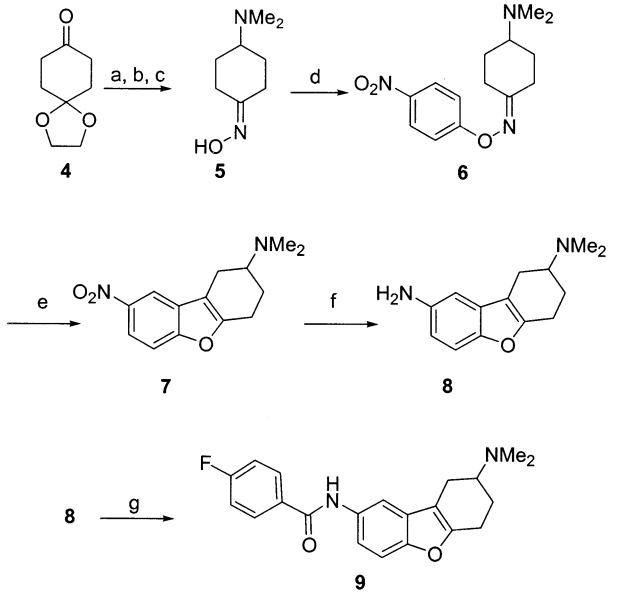
FIGURE 2.

the aromatic ring led to interesting changes in selectivity, affinity, and functional activity at $5HT_{1A,2A,2C}$ receptors as well as differing behaviorial effects in animal models. In a separate study, the synthesis of potential in vivo precursors to fluorinated norepinephrines has been reported.[6] Access to several fluorinated tetrahydrodibenzofuran analogues **3** would allow for a systematic study of the effects of ring fluorination on the binding selectivity at serotonin receptors as well as effects on the metabolism, distribution, and biological activity of the molecules.

One potential approach for the preparation of the benzofuran derivatives of interest involves the acid-catalyzed cyclization of *O*-aryloximes (Figure 2).[7] The transformation is analogous to the well-known Fischer indole synthesis. A plausible reaction mechanism is shown in Figure 2. The reaction proceeds through a [3,3]-sigmatropic rearrangement followed by condensation to form the benzofuran ring. On the basis of the proposed mechanism, an electron-donating group substituted on the aromatic ring would favor the [3,3]-sigmatropic rearrangement. Conversely, electron-withdrawing substitution will inhibit the [3,3]-sigmatropic rearrangement process. Limited literature reports seem to be consistent with this mechanism.[7] Our proposed targets, however, have strong electron-withdrawing fluorine atom(s) on the aromatic ring and fluorine substituents often can have a strong impact on reactivity through complex electronic effects.[8] These fluorinated systems presented a major hurdle for our effort in synthesizing these analogues. These challenges, however, also provided us opportunities to find new acid catalysts to promote the effective [3,3]-sigmatropic rearrangement. In the end, this synthetic approach proved well-suited to access the desired tetrahydrodibenzofuran derivatives (**3**) of interest to the program.

The starting *O*-aryloximes are generally prepared by the following two methods: (1) reaction of the anion of an oxime and an aryl halide containing a suitable electron-withdrawing group or the use of a tricarbonylchromium complex to activate aryl halides without the presence of an electron-withdrawing group[7h] or (2) condensation of the aryloxyamine with the corresponding ketone. The commercial availability of aryloxyamines is quite limited, however. Substituted aryloxyamines can be prepared by amination of the corresponding phenol,[7g,9] copper-mediated cross-coupling with arylboronic acids and *N*-hydroxyphthalimide,[10] or through addition of oximes to arylchromium complexes.[11]

SCHEME 1[a]



[a] (a) Me_2NH in THF, CH_2Cl_2, $Na(OAc)_3BH$, rt 18 h. (b) 6 M HCl, reflux 1 h, 66% (2 steps). (c) $NH_2OH-HCl$, EtOH, reflux 3 h, 87%. (d) KH, 18-crown-6 (4 mol %), THF, 1-fluoro-4-nitrobenzene, 0 °C to rt, 2 h, 90%. (e) 1 M HCl in acetic acid, 90−110 °C 7.5 h, 95%. (f) 10% Pd/C, MeOH, H_2, 12 h, 85%. (g) 4-Fluorobenzoyl chloride, Et_3N, THF, rt 16 h, 60%.

Results and Discussion

The synthetic approach to the parent 8-amido-2-amino-1,2,3,4-tetrahydro-2-dibenzofuran scaffold is shown in Scheme 1. Reductive amination of ketone **4** with dimethylamine and sodium triacetoxyborohydride, followed by acidic hydrolysis of the ketal, provided 4-dimethylaminocyclohexanone in good yield. 4-Dimethylaminocyclohexanone was converted to oxime **5**.[12] Arylation of oxime **5** with KH, catalytic 18-crown-6, and 1-fluoro-4-nitrobenzene provided *O*-aryloxime **6** in good yield. Cyclization of *O*-aryloxime **6** in 1.0 M hydrogen chloride in acetic acid at reflux provided tetrahydrodibenzofuran **7** in 95% yield. The nitro group of **7** was reduced by hydrogenation in the presence of palladium on carbon to provide amine **8**. Acylation of **8** with 4-fluorobenzoyl chloride afforded amide **9**, a tetrahydrodibenzofuran analogue of LY344864 (**2**).[13]

(5) (a) Blair, J. B.; Kurrasch-Orbaugh, D.; Marona-Lewicka, D.; Cumbay, M. G.; Watts, V. J.; Barker, E. L.; Nichols, D. E. *J. Med. Chem.* **2000**, *43*, 4701. (b) Laban, U.; Kurrasch-Orbaugh, D.; Marona-Lewicka, D.; Nichols, D. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 793.

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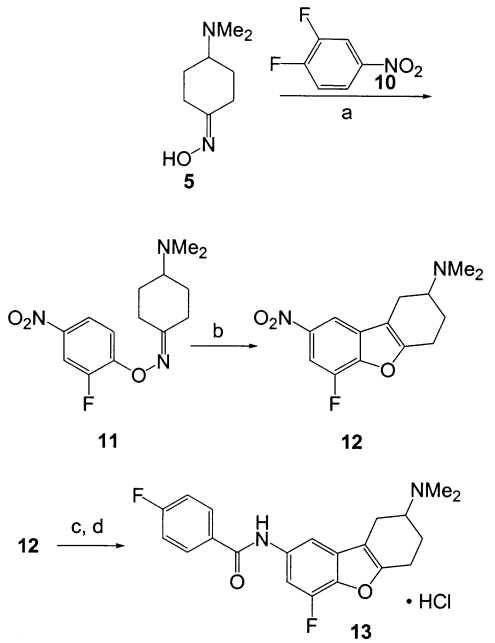
SCHEME 2[a]



[a] (a) KH, 18-crown-6 (4 mol %), THF, 0 °C, 86%. (b) Conditions: see Table 1. (c) Pd/C, H_2, THF, 42 psi, rt 2 h, 76%. (d) 4-Fluorobenzoyl chloride, Et_3N, rt 12 h, 77%.

Next, efforts were focused on the selective incorporation of fluorine atoms into the aromatic portion of the tetrahydrodibenzofuran ring system. The synthesis of fluorinated tetrahydrodibenzofurans has not been described in the literature. Analogous routes, as described above, starting from the appropriate commercially available fluorobenzene derivatives were explored for their preparation.

For the preparation of the 6-fluoro-tetrahydrodibenzofuran analogue **13**, condensation of oxime **5** with 1,2-difluoro-4-nitrobenzene (**10**) provided *O*-aryloxime **11** in good yield (Scheme 2). The acid-catalyzed cyclization of **11**, which contains an electron-withdrawing fluoro substituent ortho to the oxygen of the oxime, was anticipated to require much more vigorous conditions when compared with the cyclization of desfluoro derivative **6**. Additionally, electronic dipole effects due to the *o*-fluorine substituent may destabilize the required conformation for [3,3]-sigmatropic rearrangement. In the related acid-catalyzed Fischer indole reaction, electron-withdrawing substituents have been shown to reduce the rate of cyclization.[14] Also, byproducts derived from [3,3]-sigmatropic rearrangement to the substituted side of the aromatic ring have been observed in the Fischer indole reaction. In a study of the [3,3]-sigmatropic rearrangement of aryloximes to benzofuran derivatives, byproducts derived from cyclization onto an ortho tosyloxy group were reported.[7g]

Various conditions for the cyclization of **11** were explored (Table 1). Refluxing 1 M hydrogen chloride in acetic acid (Entry 1), conditions that worked well for the cyclization of desfluoro derivative **6**, did not provide any significant amount of desired product **12**. Attempted cyclization using both refluxing formic acid as well as conducting the reaction in a sealed flask in formic acid at 135 °C also did not provide a significant amount of **12** (entries 2 and 3). Refluxing with polyphosphoric acid in toluene gave no product **12** (entry 4). The best conditions found for this transformation were the use of acetic acid saturated with HCl at 140 °C in a sealed flask (entry 5); these conditions afforded a 47% yield of **12**. All of aryloxime **11** was consumed in the reaction and several other byproducts from the reaction were not able to be characterized. A few other conditions using sulfuric acid were explored (entries 6−8) in an attempt to lower the reaction temperature and avoid the use of a sealed flask. The best results were achieved with sulfuric acid (10 vol %) in acetic acid at reflux, which provided a 25% yield of **12**. Hydrogenation of the nitro group of **12** with palladium on carbon followed by acylation with 4-fluorobenzoyl chloride provided the final amide **13**.

TABLE 1. Reaction Conditions and Observations for Conversion of 11 to 12

entry	conditions	yield/comment
1	1 M HCl/AcOH, reflux	trace product
2	formic acid, reflux, 1 h	trace product
3	formic acid, 135 °C, sealed tube, 1 h	trace product
4	polyphosphoric acid, toluene, reflux	no product
5	HCl (sat.)/AcOH, 140 °C, 1 h	47%
6	10% H_2SO_4/ethanol, reflux, 2 h	14%
7	10% H_2SO_4/water, reflux, 2 h	no product
8	10% H_2SO_4/AcOH, reflux, 1 h	25%

Incorporation of fluorine substituents in the 7- and 9-positions of the 1,2,3,4-tetrahydrodibenzofuran ring system was explored next. It was envisioned that both derivatives could be prepared from a nonregioselective cyclization of a common intermediate 3-fluoroaryloxime derivative (see intermediates **15a**−**c**, Scheme 3). Two regioisomeric products can be envisioned in the reaction of oxime **5** with difluorinated benzene compounds **14a**−**c**. Products derived from substitution of the 4-fluoro substituent would provide the desired products **15a**−**c,** while substitution of the 2-fluoro substituent would provide an undesired product **16a**−**c**.

Arylation of oxime **5** with 2,4-difluoronitrobenzene (**14a**) using the reaction conditions of KH and 18-crown-6 gave a 3:97 ratio of **15a** and **16a** in favor of the undesired regioisomer derived from displacement of the 2-fluoro substituent (Scheme 3, Table 2). A literature report describes the regioselective addition of potassium *N*-Boc-4-piperidinoxide to the 4-position of 2,4-difluorobenzonitrile.[15] However, in our case, arylation of the potassium salt of oxime **5** with 2,4-difluorobenzonitrile (**14b**) resulted in a 35:65 ratio of **15b** and **16b**, still in favor of substitution of the 2-fluoro substituent. When the arylation of oxime **5** with benzonitrile **14b** was conducted without the use of 18-crown-6, the ratio of **15b** and **16b** was not significantly altered.

Since our synthesis required the para regioisomer **15a**−**c**, we looked for more regioselective conditions for

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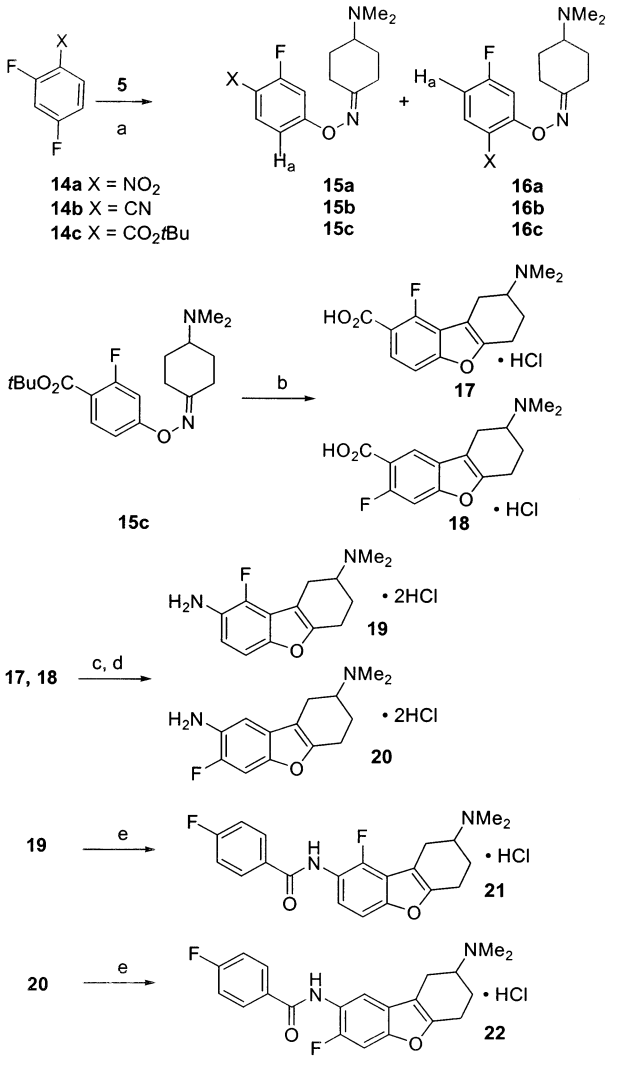
SCHEME 3[a]



[a] (a) Conditions: see Table 2. (b) sat. anhyd HCl in HOAc, sealed flask, 120 °C 2 h, 70%, **17** + **18** (1:1.5 ratio). (c) $(PhO)_2P(O)N_3$, Et_3N, *t*-BuOH, reflux 24 h, 47%. (d) TFA, chromatographic separation of regioisomers, **19**, 31%; **20**, 34%. (e) 4-Fluorobenzoyl chloride, Et_3N, rt 6 h, **21**, 60%; **22**, 80%.

TABLE 2. Reaction Conditions for the Conversion of 14a–c to 15a–c and 16a–c

entry	starting material	conditions	ratio 15:16
1	**14a**	KH, 18-crown-6 (cat.), THF	3:97
2	**14b**	KH, 18-crown-6 (cat.), THF	35:65
3	**14c**	KH, 18-crown-6 (cat.), THF	55:45
4	**14c**	Bu_4NHSO_4, tol/50% aq NaOH, rt 2 h (38%, **15c**)	85:15

its preparation. Arylation of oxime **5** with *tert*-butyl 2,4-difluorobenzoate (**14c**) using the reaction conditions of KH and 18-crown-6 provided a 55:45 ratio of **15c** and **16c**. Presumably, the more sterically hindered *tert*-butyl ester provided additional selectivity for substitution of the 4-fluoro substituent. In attempts to optimize this reaction further, a number of reaction conditions were explored where the temperature, solvent, and counterion were independently varied; however, no significant changes in the ratio of the arylation products **15c** and **16c** were observed in these experiments. A large boost in selectivity was observed when the arylation was conducted by utilizing phase-transfer conditions with tetrabutylammonium sulfate as catalyst. These conditions resulted in a significantly improved 85:15 ratio of **15c** and **16c** in favor of substitution at the 4-fluoro substituent. The desired *O*-aryloxime **15c** was isolated in 38% yield after silica gel chromatography. Phase-transfer-catalyzed nucleophilic aromatic substitution reactions of various fluorinated benzene derivatives have been described, but the effect of phase transfer conditions versus other conditions on regioselectivity was not described.[16] Substitution at the 2-fluoro position of **14c**, adjacent to the lipophilic *tert*-butyl ester, may be disfavored due to steric repulsion with the large lipophilic tetrabutylammonium counterion that is associated with the oxime anion.

The structures of **15a–c** and **16a–c** were assigned on the basis of the coupling constants in their corresponding ^{1}H NMR spectra. For **15a–c**, H_a (see Scheme 3) was observed as a dd, whereas for **16a–c**, H_a was observed as a ddd, consistent with what would be expected.

Cyclization of **15c** with saturated, anhydrous HCl in acetic acid again required elevated temperature of 120 °C in a sealed flask to give a 1:1.5 ratio of regioisomers **17** and **18**. A regioisomeric mixture of products was anticipated on the basis of related literature for forming benzofuran and indole derivatives.[7g,14] Convenient separation of the two regioisomeric carboxylic acids **17** and **18** could not be achieved.

Curtius rearrangement on the mixture of carboxylic acids **17** and **18** in *tert*-butyl alcohol provided the corresponding *tert*-butylcarbamates; these intermediates were converted to amines **19** and **20** after treatment with TFA. At this stage the regioisomers **19** and **20** were separable by chromatography on silica gel. The structures of **19** and **20** were assigned on the basis of the coupling constants in their ^{1}H NMR spectra. Separate conversion of amines **19** and **20** to the amides **21** and **22** proceeded under standard conditions.

The preparation of the 6,9-difluorinated tetrahydrodibenzofuran scaffold started with the conversion of 2,4,5-trifluorobenzoic acid (**23a**) to *tert*-butyl ester **23b** (Scheme 4). Arylation of *tert*-butyl ester **23b** with oxime **5** under phase-transfer conditions led to the selective formation of the 4-substituted aryloxime **24**; none of the corresponding regioisomer derived from substitution of the 2-fluoro substituent was observed. The inductive effect of the 5-fluoro substituent apparently helps to direct the alkylation to the 4-position of benzoate **23b**. Analysis of the ^{19}F NMR spectrum of **24** gave a coupling constant of 15.2 Hz, typical of *p*-F's in a substituted aromatic ring.[17]

Cyclization of **24** with saturated, anhydrous HCl in acetic acid at 135 °C in a sealed flask followed by reesterification with methanol led to **25** in moderate yields. The inductive electron-withdrawing effect of two fluoro substituents apparently further diminished the cyclization yield when compared with the monofluoro and desfluoro derivatives. Attempts to cyclize **24** using alter-

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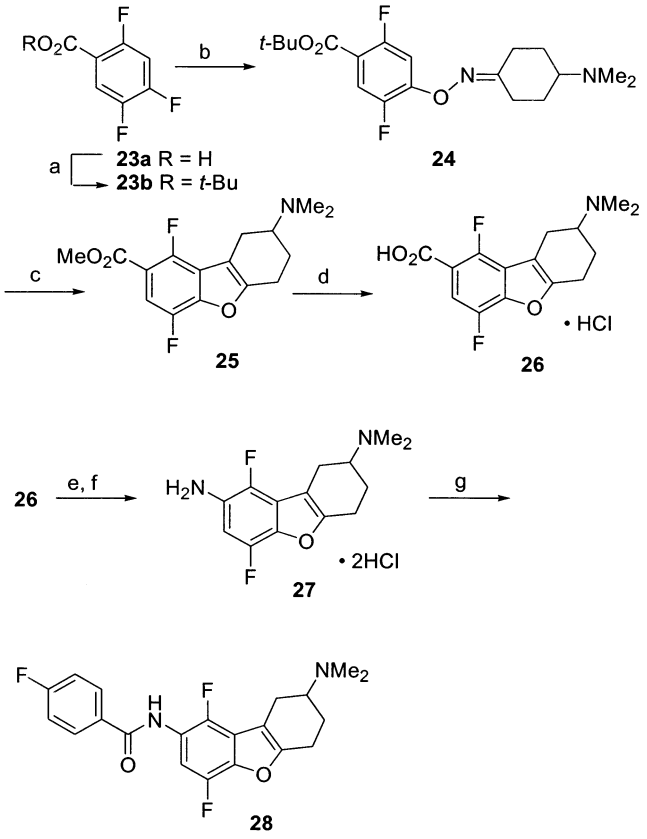
SCHEME 4[a]



[a] (a) *t*-BuOH, Boc_2O, DMAP, 30 °C 24 h, 70%. (b) **5**, Bu_4NHSO_4, toluene/NaOH (50% w/w aq), rt 1 h, 64%. (c) (i) sat. anhyd HCl in HOAc, 135 °C, sealed flask, 1 h. (ii) MeOH, pTSA (1.2 equiv), reflux 36 h, 20%. (d) 2 M NaOH, MeOH/H_2O (10:1), rt 12 h; 2 N HCl, 83%. (e) $(PhO)_2P(O)N_3$, Et_3N, *t*-BuOH, reflux 7 h, 26%. (f) HCl, MeOH, 0 °C to rt, 80%. (g) 4-Fluorobenzoyl chloride, Et_3N, rt 12 h, 66%.

native conditions including anhydrous HCl in ethanol, 10% H_2SO_4 in ethanol, concentrated aqueous HCl, and 10% trifluoroacetic acid in toluene resulted in no improvement in yield. Conversion of the initially formed carboxylic acid to methyl ester **25** was required for the efficient purification. Subsequent hydrolysis of **25** to carboxylic acid **26** proceeded efficiently. Curtius rearrangement of **26** to form the *tert*-butylcarbamate followed by treatment with HCl provided amine **27**. Transformation of amine **27** to amide **28** proceeded smoothly.

In conclusion, a unified synthetic strategy was developed to prepare 8-amido-2-(dimethylamino)-1,2,3,4-tetrahydro-2-dibenzofurans and several aryl ring fluorinated analogues. To enable this strategy, conditions were developed to prepare the requisite intermediate *O*-aryloximes through a regioselective addition of oxime **5** to various fluorinated benzene compounds containing appropriate electron-withdrawing groups. Modified acidic conditions were developed to allow cyclization of the fluorinated *O*-aryloximes through a [3,3]-sigmatropic rearrangement to the desired tetrahydrodibenzofuran intermediates. These intermediates were then elaborated to 8-amido-2-(dimethylamino)tetrahydrodibenzofurans for biological testing.

Experimental Section

General Methods. Melting points are uncorrected. ^1H NMR spectra were recorded at 300 MHz. ^{19}F NMR spectra were recorded at 282 MHz. Elemental analyses were performed at Quantitative Technologies Inc. (Whitehouse, NJ). HPLC analyses were performed on a Waters Symmetry C18 reverse phase column (4.6 × 250 mm, flow rate 1 mL/min, detection at 254 nm) using the following gradient elution: 95:5 H_2O/CH_3CN + 0.1% TFA for 5 min and then a linear gradient elution to 0:100 H_2O/CH_3CN + 0.1% TFA over 20 min. All reactions were performed under a dry N_2 atmosphere. Analytical TLC was performed on silica gel GF (Analtech) or silica gel 60 F_{254} (EM Science) plates. Flash column chromatography was performed with silica gel 60 (230−400 mesh, EM Science).

4-Dimethylaminocyclohexanone Oxime (5). Ketone **4** (200 g, 1.28 mol) was dissolved in methylene chloride (900 mL), after which glacial acetic acid (7.33 mL, 0.128 mol) and a 2 M solution of dimethylamine in tetrahydrofuran (800 mL, 1.60 mol) was added. The reaction was cooled to less than 10 °C, after which sodium triacetoxyborohydride (100 g, 0.47 mol) was slowly added. After 25 min, additional sodium triacetoxyborohydride (290 g, 1.37 mol) was added. The reaction was allowed to stir while warming to room temperature overnight, after which it was cooled in an ice water bath. Water (1.5 L) was added, and the reaction was adjusted to pH 9 with solid potassium carbonate. The aqueous layer was extracted with chloroform (5 × 1 L), and the combined organic extracts were dried over magnesium sulfate, filtered, and evaporated under reduced pressure to afford the intermediate ketal as a dark green oil: R_f 0.25 (89:10:1 CH_2Cl_2/MeOH/NH_4OH); ^1H NMR ($CDCl_3$) δ 1.60 (m, 4H), 1.83 (m, 4H), 2.37 (s, 6H), 2.48 (m, 1H), 3.94 (s, 4H). The crude ketal was diluted with water (100 mL), and 6 M hydrochloric acid (1200 mL) was added slowly over 30 min. The reaction was heated to reflux for 1 h, after which it was cooled in an ice bath. Solid potassium carbonate was slowly added to adjust the pH to 10. A white solid appeared, which was filtered off and discarded. The reaction was then extracted with chloroform (10 × 500 mL), and the combined organic layers were dried over magnesium sulfate, filtered, and evaporated under reduced pressure to afford a red-brown oil. Distillation under reduced pressure (0.5 mmHg, 48 °C) afforded 4-dimethylaminocyclohexanone as a colorless oil (119 g, 66% over two steps): R_f 0.25 (89:10:1 CH_2Cl_2/MeOH/NH_4OH); ^1H NMR ($CDCl_3$) δ 1.85 (m, 4H), 2.05 (m, 4H), 2.33 (s, 6H), 2.49 (m, 1H). To a solution of 4-dimethylaminocyclohexanone (119 g, 840 mmol) in anhydrous ethanol (1.6 L) was added hydroxylamine hydrochloride (52.6 g, 756 mmol). After vigorous stirring, anhydrous pyridine (229 mL, 2.84 mol) was added. The reaction was heated to reflux for 3 h, after which the reaction was allowed to cool to room temperature while stirred overnight. The reaction was then evaporated under reduced pressure to give a pale green solid, which was subjected to high vacuum at 50 °C for 1 h. The solid was then dissolved in water (350 mL) and washed with methylene chloride (2 × 200 mL). The organic extracts were then discarded. The aqueous layer was then adjusted to pH 10 with solid potassium carbonate and extracted with chloroform (9 × 800 mL). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated under reduced pressure to afford **5** as a white solid (115 g, 87%): mp 77−80 °C; R_f 0.20 (90:10:0.5 CH_2Cl_2/MeOH/NH_4OH); ^1H NMR ($CDCl_3$) δ 1.51 (m, 2H), 1.85−2.06 (m, 3H), 2.11 (m, 1H), 2.29 (s, 6H), 2.43 (m, 2H), 3.20 (m, 1H), 7.19 (s, 1H); APCI MS *m*/*z* 157 [M + H]$^+$. Anal. Calcd for $C_8H_{16}N_2O$: C, 61.51; H, 10.32; N, 17.93. Found: C, 61.22; H, 10.34; N, 17.97.

4-Dimethylaminocyclohexanone *O*-(4-Nitrophenyl)-oxime (6). A suspension of potassium hydride (3.24 g, 28.3 mmol, 35% in mineral oil, prewashed with hexanes) in THF (60 mL) was cooled to 0 °C and a solution of **5** (3.99 g, 25.5 mmol) in THF (20 mL) was added over 5 min. After the reaction temperature was maintained at 0 °C for 1 h, 1-fluoro-4-nitrobenzene (4.00 g, 28.3 mmol) and 18-crown-6 (0.224 g,

0.849 mmol) were added. After 1 h, the ice was removed and the reaction was left to slowly warm to room temperature. After stirring for 2 h, the reaction was quenched with saturated aqueous sodium chloride (60 mL). The aqueous layer was extracted with chloroform (3 × 150 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH/NH_4OH (95:5:0.5) to afford **6** (6.35 g, 90%) as an off-white solid: mp 60−63 °C; R_f 0.27 (95:5:0.5 CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.64 (m, 2H), 2.02 (m, 2H), 2.15−2.35 (m, 2H), 2.31 (s, 6H), 2.48 (m, 1H), 2.67 (m, 1H), 3.28 (m, 1H), 7.25 (d, J = 9.3 Hz, 2H), 8.20 (d, J = 9.3 Hz, 2H); APCI MS m/z 278 $[M + H]^+$. Anal. Calcd for $C_{14}H_{19}N_3O_3$: C, 60.64; H, 6.91; N, 15.15. Found: C, 60.35; H, 6.96; N, 14.79.

Dimethyl(8-nitro-1,2,3,4-tetrahydrodibenzofuran-2-yl)amine (7). A mixture of **6** (1.50 g, 5.41 mmol) in 1.0 M HCl in acetic acid (20 mL) was heated to 90 °C for 2.5 h. To the reaction mixture was added 1.0 M HCl in acetic acid (10 mL) and the temperature was increased to 110 °C. After 5 h the reaction mixture was cooled to room temperature and the excess solvent removed under reduced pressure. Water (40 mL) was added and the resulting solution was basified with 10% aqueous potassium carbonate to pH 10 (pH paper). The aqueous layer was extracted with chloroform (3 × 70 mL) and the combined organic layers were dried over magnesium sulfate, filtered, and evaporated. The residue was purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH/NH_4OH (96:4:0.5), which gave **7** (1.34 g, 95%) as an off-white solid: mp 68−72 °C; R_f 0.54 (95:5:0.5 CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.86 (m, 1H), 2.25 (m, 1H), 2.41 (s, 6H), 2.64 (m, 1H), 2.74−2.96 (m, 4H), 7.44 (d, J = 9.0 Hz, 1H), 8.14 (dd, J = 2.3, 9.0 Hz, 1H), 8.34 (d, J = 2.3 Hz, 1H); CI MS (methane) m/z 261 $[M + H]^+$. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.21; H, 6.08; N, 10.50.

N^2,N^2-Dimethyl-1,2,3,4-tetrahydrodibenzofuran-2,8-diamine (8). To 10% palladium-on-carbon (50% wet with water, 165 mg) under a nitrogen atmosphere was added methanol (30 mL) followed by **7** (275 mg, 1.06 mmol). The reaction mixture was stirred under a hydrogen atmosphere (1 atm) for 12 h. The catalyst was removed by filtration through Celite and the solution was evaporated to give the crude amine, which was purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH/NH_4OH (98:2:0.5), which gave **8** (209 mg, 85%) as a clear viscous oil: R_f 0.25 (80:10:0.5 CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 1H), 2.16 (m, 1H), 2.40 (s, 6H), 2.45−2.57 (m, 1H), 2.69−2.90 (m, 4H), 3.55 (br s, 2H), 6.57 (dd, J = 2.3, 8.5 Hz, 1H), 6.70 (d, J = 2.3 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H); CI MS (methane) m/z 231 $[M + H]^+$.

Dimethyl[8-(4-fluorobenzamide)-1,2,3,4-tetrahydrodibenzofuran-2-yl]amine (9). Amine **8** (63 mg, 0.274 mmol) was dissolved in tetrahydrofuran (5 mL) and to this solution was added triethylamine (1.5 mL) followed by 4-fluorobenzoyl chloride (0.05 mL, 0.42 mmol). After stirring for 1 h, the volatiles were removed under reduced pressure, and the residue was taken up in dichloromethane (5 mL) and stirred with dilute aqueous sodium carbonate solution. After stirring for 16 h, the dichloromethane layer was separated and the aqueous layer extracted with fresh dichloromethane. The dichloromethane extracts were combined, dried over sodium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography eluting with $CHCl_3$/MeOH/NH_4OH (95:5:0.25). Fractions containing product were combined and concentrated under reduced pressure. The resulting residue was crystallized from toluene/hexane to provide **9** (58 mg, 60%) as a crystalline solid in two crops: mp 137−138 °C; R_f 0.49 (90:10:0.5 CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR (CD_3OD) δ 2.18 (m, 1H), 2.46 (m, 1H), 2.90−3.08 (m, 3H), 3.02 (s, 6H), 3.20 (m, 1H), 3.77 (m, 1H), 7.25 (m, 2H), 7.39 (m, 2H), 8.00 (m, 3H); APCI MS m/z 353 $[M + H]^+$. Anal. Calcd for $C_{21}H_{21}FN_2O_2$: C, 71.57; H, 6.01; N, 7.95; F, 5.39. Found: C, 71.36; H, 5.86; N, 7.72; F, 5.25.

4-Dimethylaminocyclohexanone *O*-(2-Fluoro-4-nitrophenyl)oxime (11). A suspension of potassium hydride (8.06 g, 70.4 mmol, 35% in mineral oil, prewashed with hexanes) in THF (4 mL) was cooled to 0 °C and a solution of **5** (10.0 g, 64.0 mmol) in THF (400 mL) was added over 10 min. After the reaction temperature was maintained at 0 °C for 1.5 h, 1,2-difluoro-4-nitrobenzene (7.8 mL, 70 mmol) and 18-crown-6 (0.628 g, 2.38 mmol) were added. After 30 min, the ice was removed and the reaction was left to slowly warm to room temperature. After stirring for 2 h, the reaction was quenched with saturated aqueous sodium chloride (300 mL). The organic layer was concentrated and redissolved in methylene chloride (300 mL). The aqueous layer was extracted with methylene chloride (4 × 200 mL). The combined organic extracts were washed with water (300 mL), dried over potassium carbonate, filtered, and concentrated. The residue was purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH/NH_4-OH (96:4:1) to afford **11** (16.3 g, 86%) as an off-white solid: mp 60−62 °C; R_f 0.24 (95:5:0.5 CH_2Cl_2/MeOH/ NH_4OH); ^{1}H NMR (DMSO-d_6) δ 1.52 (m, 2H), 1.92 (m, 2H), 2.20 (s, 6H), 2.30−2.60 (m, 4H), 3.12 (m, 1H), 7.69 (t, J = 8.7 Hz, 1H), 8.14 (dd, J = 2.4, 8.6 Hz, 1H), 8.23 (dd, J = 2.4, 10.9 Hz, 1H); CI MS (methane) m/z 296 $[M + H]^+$. Anal. Calcd for $C_{14}H_{18}$-FN_3O_3: C, 56.94; H, 6.14; N, 14.23. Found: C, 57.13; H, 6.06; N, 14.18.

(6-Fluoro-8-nitro-1,2,3,4-tetrahydrodibenzofuran-2-yl)-dimethylamine (12). To a mixture of **11** (3.00 g, 10.1 mmol) in acetic acid (20 mL) was added gaseous HCl until it was saturated. The contents were closed in a sealed tube and heated to 140 °C for 1 h. The mixture was cooled to room temperature and evaporated. The residue was redissolved in ethanol and evaporated twice. The residue was partitioned between water and methylene chloride and basified with potassium carbonate (solid) to pH 10. The layers were separated, and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried over potassium carbonate, filtered, and evaporated. The residue was purified by silica gel column chromatography eluting with CH_2-Cl_2/MeOH/NH_4OH (98:2:0.5), which gave **12** (1.32 g, 47%) as a solid: mp 88−90 °C; ^{1}H NMR ($CDCl_3$) δ 1.89 (m, 1H), 2.23 (m, 1H), 2.42 (s, 6H), 2.65 (m, 1H), 2.70−3.05 (m, 4H), 7.91 (dd, J = 2.5, 10.4 Hz, 1H), 8.19 (d, J = 2.5 Hz, 1H); APCI MS m/z 279 $[M + H]^+$. Anal. Calcd for $C_{14}H_{15}FN_2O_3$: C, 60.43; H, 5.43; N, 10.07. Found: C, 60.45; H, 5.37; N, 9.91.

Dimethyl[8-(4-fluorobenzamide)-6-fluoro-1,2,3,4-tetrahydrodibenzofuran-2-yl]amine Hydrochloride (13). To 10% palladium-on-carbon (622 mg) under a nitrogen atmosphere was added THF (180 mL), followed by **12** (2.43 g, 8.74 mmol). The solution was shaken on a Parr apparatus with 42 psi of hydrogen for 2 h. The catalyst was removed by filtration through and the solution was evaporated to give the crude amine, which was dissolved in methanol and treated with ethereal HCl, followed by evaporation to give the dihydrochloride salt (2.12 g, 76%) as an off-white solid: mp 160 °C dec; R_f 0.48 (89:10:1 CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR (CD_3OD) δ 2.20 (m, 1H), 2.49 (m, 1H), 3.02 (s, 6H), 3.00−3.30 (m, 4H), 3.80 (m, 1H), 7.14 (dd, J = 1.6, 10.7 Hz, 1H), 7.41 (d, J = 1.6 Hz, 1H); HPLC Analysis >99%, t_R 14.0 min; APCI MS m/z 249 $[M + H]^+$. Anal. Calcd for $C_{14}H_{17}FN_2O$·1.9HCl·1.0H_2O: C, 50.11; H, 6.28; N, 8.35; Cl, 20.07. Found: C, 49.86; H, 6.44; N, 8.08; Cl, 20.48. To a solution of the free base (437 mg, 1.76 mmol) in CH_2Cl_2 (5 mL) were added 4-fluorobenzoyl chloride (0.230 mL, 1.94 mmol) and Et_3N (0.270 mL, 1.94 mmol), and the mixture was stirred at room temperature overnight. The reaction was concentrated under reduced pressure and the residue was purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH/NH_4OH (98:2:0.5), which gave the free base of **13**. The free base was dissolved in methanol, treated with ethereal HCl, followed by evaporation to afford **13** (552 mg, 77%) as the hydrochloride salt: mp 250 °C dec;

R_f 0.69 (89:10:1 CH_2Cl_2/MeOH/NH_4OH); ^1H NMR (DMSO-d_6) δ 2.05 (m, 1H), 2.45 (m, 1H), 2.84 (s, 6H), 2.80−3.00 (m, 3H), 3.13 (m, 1H), 3.70 (m, 1H), 7.39 (t, J = 8.7 Hz, 2H), 7.59 (d, J = 13.3 Hz, 1H), 7.93 (s, 1H), 8.07 (dd, J = 5.5, 8.6 Hz, 2H), 10.49 (s, 1H), 10.96 (br s, 1H); HPLC Analysis >99%, t_R 17.9 min; APCI MS m/z 371 $[M + H]^+$. Anal. Calcd for $C_{21}H_{20}F_2N_2O_2 \cdot 1.0HCl \cdot 0.5H_2O$: C, 60.65; H, 5.33; N, 6.74; Cl, 8.53. Found: C, 60.69; H, 5.26; N, 6.68; Cl, 8.76.

4-Dimethylaminocyclohexanone *O*-(3-Fluoro-4-nitrophenyl)oxime (15a) and 4-Dimethylaminocyclohexanone *O*-(5-Fluoro-2-nitrophenyl)oxime (16a). Using the same reaction conditions as described for the preparation of **6**, an inseparable mixture of **15a** and **16a** (88%) in a ratio of 3:97 was obtained. Characterization data for **15a**: ^1H NMR ($CDCl_3$) δ 1.55−1.71 (m, 3H), 1.95−2.08 (m, 2H), 2.16−2.38 (m, 7H), 2.46 (m, 1H), 2.65 (m, 1H), 3.24, (m, 1H), 6.98 (ddd, J = 1.1, 2.4, 9.3 Hz, 1H), 7.14 (dd, J = 2.5, 13.0 Hz, 1H), 8.13 (m, 1H). Characterization data for **16a**: ^1H NMR ($CDCl_3$) δ 1.55−1.71 (m, 3H), 1.95−2.08 (m, 2H), 2.16−2.38 (m, 7H), 2.46 (m, 1H), 2.65 (m, 1H), 3.39 (m, 1H), 6.73 (ddd, J = 2.7, 7.2, 9.2 Hz, 1H), 7.51 (dd, J = 2.7, 10.8 Hz, 1H), 8.05 (dd, J = 5.9, 9.2 Hz, 1H). Inseparable mixture of **15a** and **16a**: R_f 0.46 (90:10:0.5 CH_2Cl_2/MeOH/NH_4OH); CIMS (methane) m/z 296 $[M + H]^+$. Anal. Calcd for $C_{14}H_{18}FN_3O_3 \cdot 0.15H_2O$: C, 56.28; H, 6.05; N, 13.99. Found: C, 56.42; H, 6.19; N, 14.10.

4-(4-Dimethylaminocyclohexylideneaminooxy)-2-fluorobenzonitrile (15b) and 2-(4-Dimethylaminocyclohexylideneaminooxy)-4-fluorobenzonitrile (16b). Using the same reaction conditions as described for the preparation of **6**, an inseparable mixture of **15b** and **16b** (54%) in a ratio of 35:65 was obtained. Characterization data for **15b**: ^1H NMR ($CDCl_3$) δ 1.56−1.71 (m, 3H), 1.94−2.09 (m, 2H), 2.14−2.31 (m, 7H), 2.45 (m, 1H), 2.64 (m, 1H), 3.24 (m, 1H), 6.98 (dd, J = 1.7, 8.7 Hz, 1H), 7.10 (dd, J = 2.2, 11.1 Hz, 1H), 7.50 (dd, J = 7.3, 8.7 Hz, 1H). Characterization data for **16b**: ^1H NMR ($CDCl_3$) δ 1.56−1.71 (m, 3H), 1.94−2.09 (m, 2H), 2.14−2.31 (m, 7H), 2.45 (m, 1H), 2.64 (m, 1H), 3.36 (m, 1H), 6.73 (ddd, J = 2.5, 7.9, 8.6 Hz, 1H), 7.32 (dd, J = 2.4, 10.8 Hz, 1H), 7.52 (dd, J = 6.0, 8.6 Hz, 1H). Inseparable mixture of **15b** and **16b**: R_f 0.49 (90:10:0.5 CH_2Cl_2/MeOH/NH_4OH); CIMS (methane) m/z 276 $[M + H]^+$. Anal. Calcd for $C_{15}H_{18}FN_3O \cdot 0.1H_2O$: C, 65.00; H, 6.44; N, 15.10. Found: C, 65.01; H, 6.62; N, 15.16.

4-(4-Dimethylaminocyclohexylideneaminooxy)-2-fluorobenzoic Acid *tert*-Butyl Ester (15c) and 2-(4-Dimethylaminocyclohexylideneaminooxy)-4-fluorobenzoic Acid *tert*-Butyl Ester (16c). To a solution of *tert*-butyl alcohol (300 mL) were added 2,4-difluorobenzoic acid (10.0 g, 63.3 mmol), di-*tert*-butyl dicarbonate (27.6 g, 126 mmol), and 4-(dimethylamino)pyridine (2.30 g, 18.9 mmol). The solution was stirred for 48 h, diluted with ethyl acetate (750 mL), and washed with 1 M HCl (2 × 250 mL) and saturated sodium bicarbonate (2 × 250 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated to give the *tert*-butyl 2,4-difluorobenzoate (11.6 g, 86%): ^1H NMR ($CDCl_3$) δ 1.58 (s, 9H), 6.80−6.92 (m, 2H), 7.89 (dd, J = 8.4, 15.1 Hz, 1H). To a well-stirred solution of the *tert*-butyl 2,4-difluorobenzoate (31.0 g, 144 mmol) in toluene (960 mL) were sequentially added tetrabutylammonium hydrogen sulfate (12 g, 58 mmol), **5** (15 g, 96 mmol), and 50% aqueous NaOH (385 mL). The solution was stirred for 2 h and then poured into water (1 L) and extracted with ethyl acetate (500 mL). The aqueous layer was extracted with chloroform (2 × 750 mL). The combined organic extracts were washed with water (750 mL), dried over sodium sulfate, and concentrated to give a 85:15 mixture of **15c** and **16c**. The mixture was purified by medium-pressure silica gel chromatography using a gradient elution of CH_2Cl_2/MeOH/Et_3N (98:1:1 to 95:4:1), which gave 12.8 g (38%) of the desired isomer **15c**: ^1H NMR ($CDCl_3$) δ 1.58 (s, 9H), 1.91−2.08 (m, 2H), 2.10−2.36 (m, 4H), 2.31 (s, 6H), 2.47 (m, 1H), 2.65 (m, 1H), 3.28 (m, 1H), 6.90 (dd, J = 2.3, 8.7 Hz, 1H), 6.97 (dd, J = 2.3 12.8 Hz, 1H), 7.82 (dd, J = 8.6, 8.7 Hz, 1H). **16c**: ^1H NMR ($CDCl_3$) δ 1.58 (s, 9H), 2.02 (m, 2H), 2.14−2.36 (m, 4H), 2.31 (s, 6H), 2.47 (m, 1H), 2.66 (m, 1H), 3.45 (m, 1H), 6.65 (ddd, J = 2.6, 7.7, 8.7 Hz, 1H), 7.32 (dd, J = 2.6, 11.4 Hz, 1H), 7.78 (dd, J = 6.7, 8.7 Hz, 1H). Partially separable mixture of **15c** and **16c**: R_f 0.22 (95:5:0.5 CH_2Cl_2/MeOH/NH_4OH); APCI MS m/z 351 $[M + H]^+$. Anal. Calcd for $C_{19}H_{27}FN_2O_3$: C, 65.12; H, 7.77; N, 7.99. Found: C, 65.02; H, 7.81; N, 7.86.

Dimethyl(9-fluoro-8-carboxy-1,2,3,4-tetrahydrodibenzofuran-2-yl)amine Hydrochloride (17) and Dimethyl-(7-fluoro-8-carboxy-1,2,3,4-tetrahydrodibenzofuran-2-yl)amine Hydrochloride (18). To a solution of 1 M HCl in acetic acid (7.5 mL) at 0 °C was added **15c** (1.00 g, 2.85 mmol), which formed a precipitate. The mixture was warmed to room temperature to give a solution. HCl(g) was bubbled through the solution for 3 min until saturated. The solution was sealed in a pressure tube and heated to 120 °C for 2 h. The mixture was cooled in an ice bath, and hexanes were added. The resultant precipitate was isolated by filtration and recrystallized from methanol to give a white solid. The mother liquor was treated with ether to obtain a second crop. The combined crops were dried under vacuum to give a 1.5:1 mixture of **18** and **17** (630 mg, 70%) as the hydrochloride salts in the form of an off-white solid: ^1H NMR (CD_3OD) δ 2.19 (m, 1H), 2.20−2.30 (s, 1H), 2.43 (s, 1H), 2.66 (m, 1H), 3.01 (s, 6H), 2.92−3.10 (m, 3H), 3.79 (m, 1H), 7.31 (m, 1H), 7.85 (m, 0.4H), 8.09 (d, J = 7.1 Hz, 0.6H); MS m/z 278 $[M + H]^+$.

9-Fluoro-N^2,N^2-dimethyl-1,2,3,4-tetrahydrodibenzofuran-2,8-diamine dihydrochloride (19) and 7-Fluoro-N^2,N^2-dimethyl-1,2,3,4-tetrahydrodibenzofuran-2,8-diamine dihydrochloride (20). A mixture of **17** and **18** (1.80 g, 5.73 mmol) was dissolved in *tert*-butyl alcohol (18 mL) and dioxane (18 mL). Diphenylphosphoryl azide (1.5 mL, 7.0 mmol) and triethylamine (1.80 mL, 12.9 mmol) were added, and the mixture was heated to reflux for 24 h. The mixture was evaporated and purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH/NH_4OH (95:5:1) to afford 0.926 g (47%) of a mixture of *tert*-butyl carbamates: ^1H NMR (CD_3OD) δ 1.40−1.60 (m, 1H), 1.51 (s, 9H), 1.83 (m, 1H), 2.23 (m, 1H), 2.41 (s, 6H), 2.59 (m, 1H), 2.70−2.90 (m, 3H), 3.00 (m, 1H), 6.77 (t, 0.4H), 7.12−7.22 (m, 1H), 7.34 (m, 0.6H); CIMS (methane) m/z 349 $[M + H]^+$. To a solution of the mixture of *tert*-butyl carbamates (900 mg, 2.58 mmol) in methylene chloride (15 mL) was added trifluoroacetic acid (1.5 mL). The solution was stirred at room temperature for 4 h and evaporated. The two regioisomers were separated by silica gel chromatography, eluting with CH_2Cl_2/MeOH/NH_4OH (95:5:1), to give the free bases of **19** (200 mg, 31%) and **20** (220 mg, 34%). The dihydrochloride salts were prepared by dissolving the free bases in methanol and treating with ethereal HCl, followed by evaporation. **19**: mp 267−272 °C; R_f 0.53 (90:10:1 CH_2Cl_2/CH_3OH/ NH_4OH); ^1H NMR (CD_3OD) δ 2.17 (m, 1H), 2.48 (m, 1H), 3.01 (s, 6H), 3.00−3.17 (m, 3H), 3.30−3.40 (m, 1H), 3.81 (m, 1H), 7.33 (dd, J = 7.5, 8.7 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H); HPLC Analysis 98.8%, t_R 11.6 min; APCI MS m/z 249 $[M + H]^+$. Anal. Calcd for $C_{14}H_{17}FN_2O \cdot 1.95HCl \cdot 0.6H_2O$: C, 50.79; H, 6.16; N, 8.46; Cl, 20.88. Found: C, 50.99; H, 6.40; N, 7.87; Cl, 20.73. **20**: mp 238−240 °C; R_f 0.41 (90:10:1 CH_2Cl_2/CH_3OH/NH_4OH); ^1H NMR (CD_3OD) δ 2.17 (m, 1H), 2.40 (m, 1H), 3.01 (s, 6H), 2.90−3.40 (m, 4H), 3.75 (m, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 10.5 Hz, 1H); HPLC Analysis >99%, t_R 12.5 min; CIMS (methane) m/z 249 $[M + H]^+$. Anal. Calcd for $C_{14}H_{17}FN_2O \cdot 1.7HCl \cdot 0.75H_2O$: C, 51.93; H, 6.29; N, 8.65; Cl, 18.61. Found: C, 51.73; H, 6.09; N, 8.32; Cl, 18.33.

Dimethyl[8-(4-fluorobenzamide)-9-fluoro-1,2,3,4-tetrahydrodibenzofuran-2-yl]amine Hydrochloride (21). To a solution of free base **19** (52 mg, 0.21 mmol) in methylene chloride (1.5 mL) were added 4-fluorobenzoyl chloride (32 μL, 0.27 mmol) and triethylamine (40 μL, 0.29 mmol). The solution was stirred for 5.5 h at room temperature, diluted with methylene chloride (50 mL), and washed with 10% K_2CO_3 (50 mL). The aqueous layer was extracted with methylene chloride (3 × 25 mL). The combined organic layers were dried over sodium sulfate, filtered, and evaporated. The solid was recrys-

tallized from methylene chloride and diethyl ether. The resulting solid was dissolved in methanol, the solution was clarified by filtration, and then 2 M HCl in ether was added with stirring. The reaction was filtered and the white solid was dried under vacuum at 76 °C overnight to give 47 mg (60%) of free base **21**. The free base was dissolved in methanol, treated with ethereal HCl, followed by evaporation to afford hydrochloride salt **21**: mp 155−160 °C dec; R_f 0.41 (90:10:0.5 CH_2Cl_2/CH_3OH/NH_4OH);^{1}H NMR (CD_3OD) δ 2.16 (m, 1H), 2.42 (m, 1H), 3.01 (s, 6H), 3.00−3.14 (m, 2H), 3.30−3.40 (m, 2H), 3.79 (m, 1H), 7.23−7.37 (m, 4H), 8.03 (dd, J = 5.3, 8.5 Hz, 2H); HPLC Analysis >99%, t_R 19.9 min; APCI MS m/z 371 $[M + H]^+$. Anal. Calcd for $C_{21}H_{20}F_2N_2O_2 \cdot 1.1HCl \cdot 1.6H_2O$: C, 57.41; H, 5.57; N, 6.38; Cl, 8.88. Found: C, 57.17; H, 5.61; N, 6.24; Cl, 9.11.

Dimethyl[8-(4-fluorobenzamide)-7-fluoro-1,2,3,4-tetrahydrodibenzofuran-2-yl]amine Hydrochloride (22). The title compound was prepared from free base **20** (60 mg, 0.242 mmol), 4-fluorobenzoyl chloride (32 μL, 0.27 mmol), and triethylamine (40 μL, 0.29 mmol) in methylene chloride (1.5 mL) to give free base **22** as a white solid (71 mg, 80%) using a method substantially equivalent to that described for **21**. The free base was dissolved in methanol, treated with ethereal HCl, followed by evaporation to afford hydrochloride salt **22**: mp 250 °C dec; R_f 0.43 (90:10:0.5 CH_2Cl_2/CH_3OH/NH_4OH); ^{1}H NMR (CD_3OD) δ 2.16 (m, 1H), 2.41 (m, 1H), 3.01 (s, 6H), 3.00−3.40 (m, 4H), 3.77 (m, 1H), 7.27 (t, J = 8.6 Hz, 2H), 7.39 (d, J = 9.9 Hz, 1H), 7.80 (d, J = 7.4 Hz, 1H), 8.04 (dd, J = 5.4, 8.5 Hz, 2H); HPLC Analysis 97.9%, t_R 20.4 min; APCI MS m/z 371 $[M + H]^+$. Anal. Calcd for $C_{21}H_{20}F_2N_2O_2 \cdot 1.1HCl \cdot 1.0H_2O$: C, 58.86; H, 5.43; N, 6.54; Cl, 9.10. Found: C, 58.98; H, 5.47; N, 6.49; Cl, 9.47.

4-(4-Dimethylaminocyclohexylideneaminooxy)-2,5-difluorobenzoic Acid *tert*-Butyl Ester (24). To a solution of 2,4,5-trifluorobenzoic acid (**23a**, 10.0 g, 56.8 mmol) in *tert*-butyl alcohol (280 mL) were added di-*tert*-butyl dicarbonate (32.1 g, 114 mmol) and 4-(dimethylamino)pyridine (0.694 g, 5.68 mmol). The solution was stirred for 24 h, diluted with ethyl acetate (600 mL), and washed with 1 N HCl (2 × 75 mL) and saturated aqueous sodium bicarbonate (2 × 75 mL). The organic layer was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography, eluting with hexanes/EtOAc (99:1) to afford 9.22 g (70%) of the *tert*-butyl 2,4,5-trifluorobenzoate (**23b**): R_f 0.48 (98:2 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 9H), 6.96 (ddd, J = 6.3, 9.9, 9.9 Hz, 1H), 7.70 (ddd, J = 6.6, 9.0, 15.6 Hz, 1H); APCI MS, m/z 175 $[M - C_4H_9]^+$. To a well-stirred solution of tetrabutylammonium hydrogen sulfate (2.36 g, 6.96 mmol) in 50% w/w aqueous sodium hydroxide (70 mL) was added **5** (2.72 g, 17.4 mmol), followed by a solution of *tert*-butyl 2,4,5-trifluorobenzoate (5.66 g, 24.0 mmol) in toluene (175 mL). After stirring for 1 h, the reaction mixture was diluted with ice-cold water (150 mL) and toluene (150 mL). The organic layer was separated and the aqueous layer was extracted with toluene (150 mL). The combined organic extracts were dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography, eluting with CH_2Cl_2/MeOH/NH_4OH (95:5:0.5) to afford 4.09 g (64%) of oxime **24**: mp 37−39 °C; R_f 0.24 (90:10:1 CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.45−1.70 (m, 2H), 1.58 (s, 9H), 1.92−2.09 (m, 2H), 2.15−2.32 (m, 2H), 2.31 (s, 6H), 2.42 (m, 1H), 2.64 (m, 1H), 3.30 (m, 1H), 7.27 (dd, J = 6.5, 12.3 Hz, 1H), 7.58 (dd, J = 6.7, 11.5 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ −111.90 (d, J = 15.2 Hz, 1F), −140.96 (d, J = 15.2 Hz, 1F); APCI MS m/z 369 $[M + H]^+$.

Dimethyl(6,9-difluoro-8-carboxymethyl-1,2,3,4-tetrahydrodibenzofuran-2-yl)amine (25). A solution of oxime **24** (6.00 g, 16.2 mmol) in acetic acid (120 mL) was saturated with HCl by bubbling HCl(g) through the solution for 8 min. The solution was sealed in a pressure tube and heated to 135 °C for 1 h. The mixture was cooled to room temperature and the acetic acid was removed under reduced pressure. Ethanol (2 × 100 mL) was added and the solvent again removed under reduced pressure. The resulting orange solid was suspended in a mixture of diethyl ether (50 mL) and ethanol (50 mL). The suspension was cooled to 0 °C and the solid was collected by filtration and dried under vacuum (50 °C) for 12 h to give 2.85 g (53%) of impure **26**. The crude acid was dissolved in methanol (100 mL) and 4-toluenesulfonic acid (2.00 g, 10.5 mmol) was added. This reaction mixture was refluxed for 36 h. After cooling to room temperature, the methanol was removed under reduced pressure. The reaction mixture was diluted with methylene chloride (100 mL) and water (75 mL) and the pH adjusted to 9 with 10% aqueous potassium carbonate. The aqueous layer was extracted with methylene chloride (2 × 50 mL), and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The reaction residue was purified by silica gel column chromatography, eluting with CH_2Cl_2/MeOH/NH_4-OH (97:3:0.5) to afford 1.01 g (20%) of methyl ester **25**: mp 89−92 °C; R_f 0.46 (94:6:0.5 CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.85 (m, 1H), 2.16 (m, 1H), 2.41 (s, 6H), 2.70−3.10 (m, 5H), 3.96 (s, 3H), 7.53 (dd, J = 6.5, 9.5 Hz, 1H); APCI MS m/z 310 $[M + H]^+$. Anal. Calcd for $C_{16}H_{17}F_2NO_3 \cdot 0.1H_2O$: C, 61.77; H, 5.57; N, 4.50. Found: C, 61.55; H, 5.35; N, 4.40.

8-Dimethylamino-1,4-difluoro-6,7,8,9-tetrahydrodibenzofuran-2-carboxylic Acid Hydrochloride (26). To a solution of methyl ester **25** (1.07 g, 3.46 mmol) in methanol/water (10:1, 22 mL) was added 2 N NaOH (2 mL). After stirring of the reaction overnight, the reaction mixture was acidified to pH 0 with 2 N HCl and then cooled to 0 °C. The solid was collected by filtration and washed with cold water (2 × 3 mL) and acetone (3 mL). After drying of the solid under vacuum (50 °C) for 12 h, acid **26** (949 mg, 83%) was obtained as a white solid: mp 318−322 °C; R_f 0.18 (70:30:1.5 CH_2Cl_2/MeOH/ NH_4-OH); ^{1}H NMR (DMSO-d_6) δ 2.00 (m, 1H), 2.42 (m, 1H), 2.75−3.40 (m, 4H), 2.84 (s, 6H), 3.65 (m, 1H), 7.60 (dd, J = 6.4, 9.3 Hz, 1H), 10.90 (br s, 1H); APCI MS m/z 296 $[M + H]^+$. Anal. Calcd for $C_{15}H_{15}F_2NO_3 \cdot 1.0HCl \cdot 0.7H_2O$: C, 52.32; H, 5.09; N, 4.07; Cl, 10.30. Found: C, 52.24; H, 4.71; N, 4.00; Cl, 10.55.

6,9-Difluoro-N^2,N^2-dimethyl-1,2,3,4-tetrahydrodibenzofuran-2,8-diamine Dihydrochloride (27). Diphenylphosphoryl azide (0.44 mL, 2.0 mmol) was added dropwise to a suspension of **26** (0.64 g, 1.9 mmol) and triethylamine (0.56 mL, 4.0 mmol) in *tert*-butyl alcohol (8 mL) and the mixture was heated to reflux. After 7 h, the reaction was cooled to room temperature and poured into ice water. Methylene chloride was added and the biphasic mixture was filtered. The solid consisted of unreacted starting material that was resubjected to the reaction conditions. All of the combined organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified twice on silica gel eluting with a gradient of CH_2Cl_2/MeOH (98:2 to 95:5) to afford the *tert*-butyl carbamate (0.18 g, 26%): ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 9H), 1.83 (m, 1H); 2.19 (m, 1H), 2.42 (s, 6H), 2.72−3.05 (m, 5H), 6.59 (br s, 1H), 7.76 (m, 1H); CIMS (methane) m/z 367 $[M + H]^+$.

A 2.0 M HCl in ether solution (9 mL) was added to a solution of the *tert*-butyl carbamate (184 mg, 0.502 mmol) in MeOH (5 mL) cooled in an ice bath. After the addition was complete, the reaction was warmed to room temperature overnight. The reaction was concentrated under reduced pressure and the crude material was purified by silical gel column chromatography eluting with CH_2Cl_2/MeOH/NH_4OH (95:5:0.5), which afforded 108 mg (80%) of the free amine. The free amine was further treated with ethereal HCl and concentrated under reduced pressure to give dihydrochloride salt **27** as an off-white solid: mp 285−288 °C dec; R_f 0.46 (95:5:0.5 CH_2Cl_2/MeOH/ NH_4OH); ^{1}H NMR (CD_3OD) δ 2.17 (m, 1H), 2.46 (m, 1H), 3.01 (s, 6H), 2.94−3.14 (m, 3H), 3.31 (m, 1H), 3.78 (m, 1H), 6.97 (m, 1H); HPLC 97.8%, t_R 13.7 min; CIMS (methane) m/z 267 $[M + H]^+$. Anal. Calcd for $C_{14}H_{16}F_2N_2O \cdot 1.9HCl \cdot 0.6H_2O$: C,

48.55; H, 5.56; N, 8.09; Cl, 19.45. Found: C, 48.90; H, 5.52; N, 7.92; Cl, 19.11.

Dimethyl[8-(4-fluorobenzamide)-7,9-difluoro-1,2,3,4-tetrahydrodibenzofuran-2-yl]amine (28). 4-Fluorobenzoyl chloride (0.015 mL, 0.13 mmol) was added dropwise to a solution of free base **27** (0.030 g, 0.11 mmol) and triethylamine (0.024 mL, 0.17 mmol) in methylene chloride (5 mL) cooled in an ice bath. After the addition was complete, the reaction was warmed to room temperature overnight. The reaction was partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with methylene chloride (2 × 25 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified three times by silica gel column chromatography eluting with CH_2Cl_2/MeOH/NH_4OH (95:5:0.5), which gave **28** (0.029 g, 66%) as an off-white solid: R_f 0.66 (95:5:0.5 CH_2Cl_2/MeOH/NH_4OH); ^{1}H NMR (CD_3OD, complex mixture of rotamers) δ 1.85 (m, 1H), 2.24 (m, 1H), 2.40 (s, 6H), 2.62−3.09 (m, 4H), 3.53 (m, 1H), 7.10−7.22 and 7.40−7.45 (m, 3H), 7.80−7.86 (m, 2H); HPLC 96.8%, t_R 19.8 min; APCI MS m/z 389 $[M + H]^+$.

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Supporting Information Available: Copies of the ^{1}H NMR spectra for **5**, **6**, **7**, **8**, **9**, **11**, **12**, **13**, **15a**/**16a**, **15b/16b**, **14c**, **15c/16c**, **15c**, **17/18**, **19**, **20**, **21**, **22**, **23b**, **24**, **25**, **26**, **27**, **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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