An Efficient and Convenient Protocol for the Synthesis of 1,1-Difluoro-6-nitro-2,3-dihydro-1*H*-indene Derivatives

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Abstract: A convenient and efficient synthesis of *gem*-difluorinated compounds is reported. The synthetic route toward various 2-substituted and 3-substituted 1,1-difluoro-6-nitro-2,3-dihydro-1*H*-indene derivatives is described starting from commercially available indanone. The key *gem*-difluorination step is accomplished in good yield by treatment of in situ generated bromine fluoride (BrF) with a dithioketal. A plausible mechanism discussing the competition between substitution and elimination is provided to rationalize the outcome of the reactions of the 3-brominated compounds with different amines.

Key words: indanone, dithioketal, *gem*-difluorination, substitution, synthesis

The introduction of fluorine or fluorinated groups to compounds has been extensively studied in organic chemistry and medicinal chemistry in order to induce remarkable changes in the physical, chemical and biological properties relative to the non-fluorinated counterparts.[1–4] Among fluorinated compounds, those bearing a *gem*-difluoro group are very attractive. Many applications, for example, liquid crystals,[5] photostable n-type materials,[6] electron-transporting materials[7] and pharmaceuticals, have utilized *gem*-difluoro groups. One such example, 1,1-difluoro-2,3-dihydro-1*H*-indene (or 1,1-difluoroindane) is a valuable and widely used *gem*-difluoro framework in medicinal chemistry. Several compounds containing this moiety have been found to possess improved biological activity over their corresponding protonated analogues. For example, compound **A** is a CGRP receptor antagonist,[8] **B** is an antifungal agent,[9] **C** is an inhibitor of aldosterone synthase (CYP11B2),[10] and compound **D** is an MMP-13 inhibitor which acts as an antitumor agent[11] (Figure 1).

For a particular medicinal chemistry program, we needed to synthesize a series of compounds containing 1,1-difluoroindane analogues with substituted 6-nitro and 2- or 3-amino moieties, in which the 6-nitro group can be transformed into other versatile groups. Generally, fluorinating reagents such as (diethylamino)sulfur trifluoride (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor)[12,13] can be used to introduce difluoro groups via reactions with ketones, but few reports have been found describing the preparation of difluoroindanes.

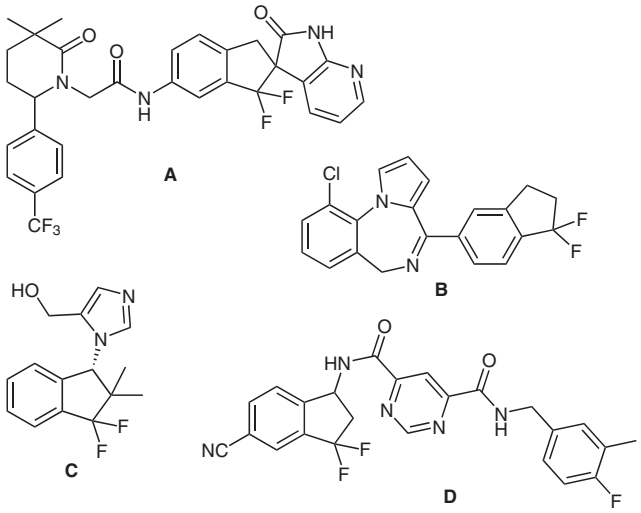

Figure 1 Structures of compounds **A**–**D** containing a *gem*-difluoroindane moiety

Thus it would appear challenging to establish a protocol for the synthesis of 3,6-disubstituted or 2,6-disubstituted 1,1-difluoroindanes. In this paper, we report an efficient and convenient route for the synthesis of 1,1-difluoro-6-nitro-2,3-dihydro-1*H*-indene derivatives.

Initially, we designed a retrosynthetic route (Scheme 1) using the difluorination of 3,6-disubstituted indanone with Deoxo-Fluor or DAST as the key step, but we found that this reaction failed as no significant reaction took place, whether in the presence of solvent or neat. Subsequently, an indirect difluorination method was used (Scheme 2), however, this proved unsatisfactory.

Starting with 1-indanone (**1**), nitration in the presence of sulfuric acid gave 6-nitroindanone **2** in 66% yield.[14] Next, dehydrogenation was conducted via silylenol ether formation followed by palladium-catalyzed oxidation.[15,16] The resulting enone **4** was reacted with *N*-methylpiperazine via a Michael addition to give the 3-amine substituted indanone **5** in high yield.[17] According to Scheme 2 we tried to react **5** directly with Deoxo-Fluor or DAST under a range of conditions, however, no *gem*-difluorination product was obtained. This may be due to the interference

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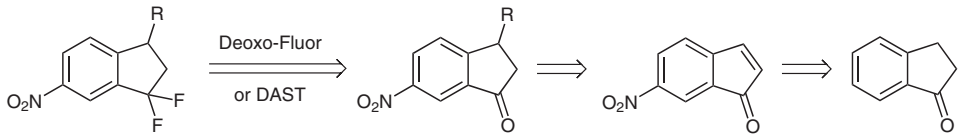


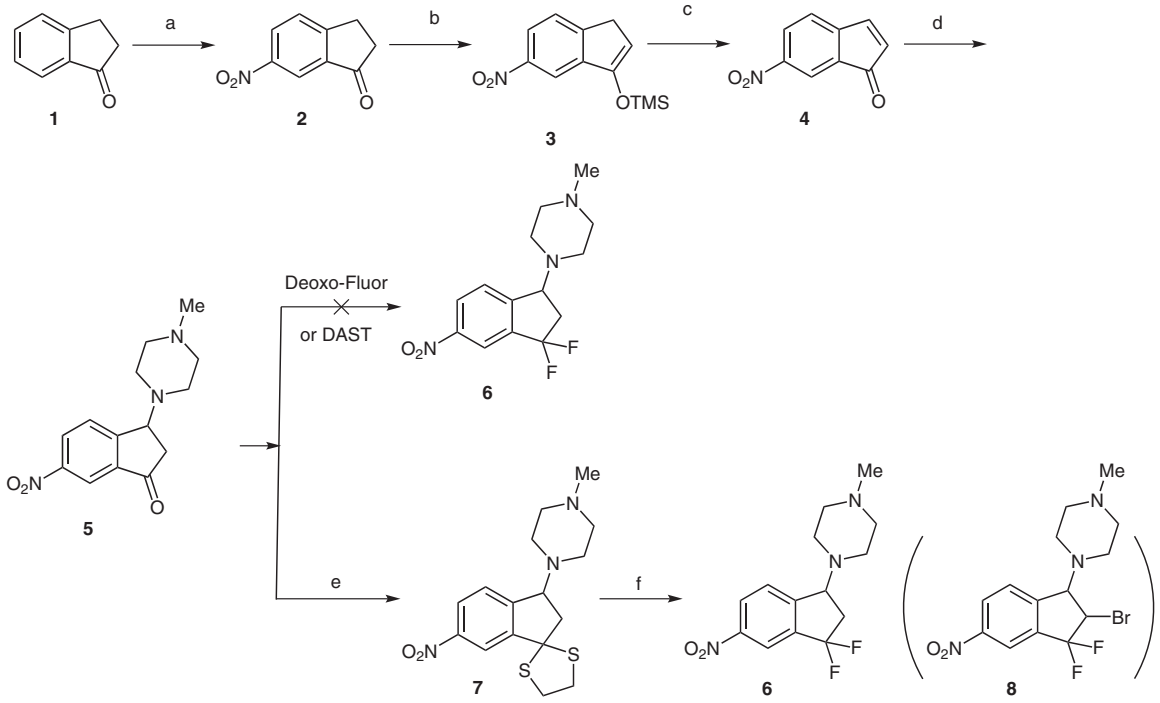
Scheme 1 Retrosynthetic analysis of 1,1-difluoro-6-nitro-2,3-dihydro-1*H*-indene derivatives

of the 3-amino group and/or the 6-nitro group in substrate **5**. It was therefore envisaged that indirect *gem*-difluorination might be a better proposition than direct *gem*-difluorination. Thus, dithioketal **7** was treated with bromine fluoride (BrF), generated in situ from 1,3-dibromo-5,5-dimethylhydantoin (DBH) and hydrogen fluoride–pyridine (HF–Py) in dichloromethane.[18]

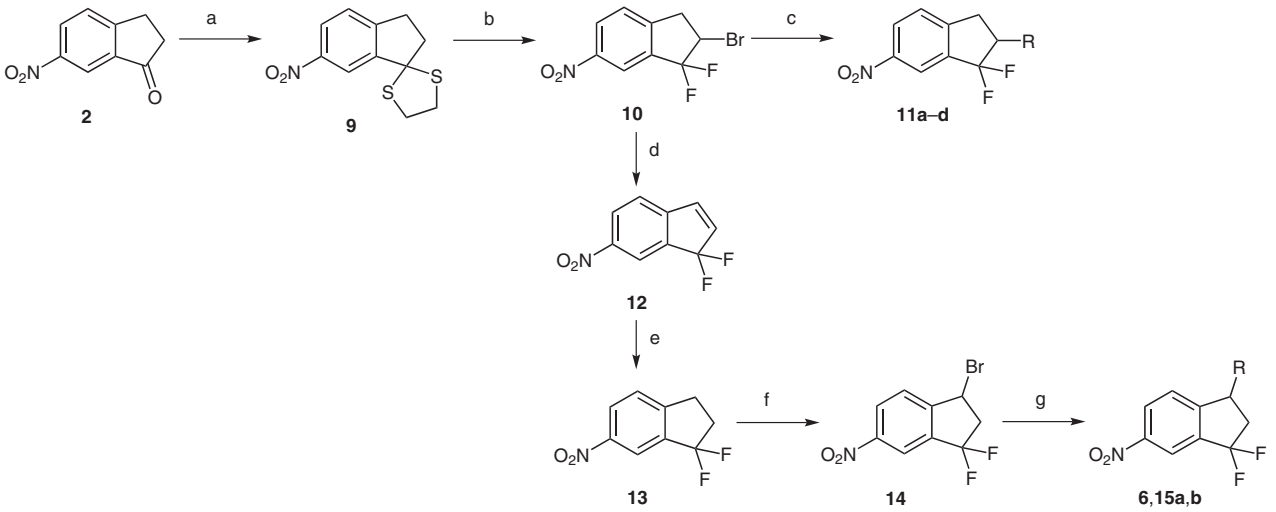
Unfortunately, only about a 10% yield of the desired 1,1-difluorindane **6** was obtained along with a considerable amount of by-product **8**.[19]

An alternative synthetic route was adopted to overcome the interference of the 3-amino group, in which the in situ generated bromine fluoride was used as the difluorination reagent, given the reaction efficiency and reagent cost (Scheme 3). As Deoxo-Fluor failed to react with compound **2**, this might indicate that the 6-nitro group in **2** plays a deactivating role in this reaction. Dithioketalization of compound **2** was subsequently conducted by heating ethane-1,2-dithiol with **2** in toluene at reflux temperature in the presence of *p*-toluenesulfonic acid (PTSA) as the catalyst, using a Dean–Stark apparatus, and the yield of the expected product **9** was almost quantitative. This method was more efficient than those described in the literature, which usually employed boron trifluoride–diethyl ether complex or aluminum trichloride.[20–24] To our surprise, treatment of dithioketal **9** with 1,3-dibromo-5,5-dimethylhydantoin and hydrogen fluoride–pyridine afforded only a trace amount of **13**. Instead, the brominated derivative **10** was obtained as the major product in 88% yield. We attempted to use *N*-iodosuccinimide as the halide source in order to avoid bromination at the *ortho*-position,[19] but the reaction failed (no product formation). In addition, unlike those conditions described in the literature,[18] we found that more than four equivalents of 1,3-dibromo-5,5-dimethylhydantoin were necessary to promote complete reaction (Table 1). The obtained 2-bromo-1,1-difluoroindane (**10**) was easily converted into different 2-amino analogues (**11a–d**) through substitution of the bromine with different amines; the products might be useful for our biological screening studies.

In order to convert 2-bromo-1,1-difluoroindane (**10**) into 3-bromo analogue **14**, it was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford difluoride **12** in more than 90% yield via elimination of hydrogen bromide.[20]



Scheme 2 *Reagents and conditions*: (a) KNO_3, concd H_2SO_4, 0 °C, 1 h, 66%; (b) TMSOTf, Et_3N, toluene, 0 °C, 0.5 h; (c) $Pd(OAc)_2$, CH_2Cl_2, MeCN, r.t., 2 h, 46% from **2**; (d) *N*-methylpiperazine, THF, r.t., 18 h, 61%; (e) ethane-1,2-dithiol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –15 °C to r.t., overnight, 56%; (f) DBH, HF–Py, CH_2Cl_2, –70 °C to r.t., overnight, 18%.



Scheme 3 Synthesis of 1,1-difluoro-6-nitro-2,3-dihydro-1*H*-indene derivatives. *Reagents and conditions*: (a) ethane-1,2-dithiol, PTSA, toluene, reflux, 12 h, 99%; (b) DBH, HF–Py, CH_2Cl_2, –70 °C to r.t., overnight, 85%; (c) amine, K_2CO_3, DMF, r.t., 4 h, 77–90%; (d) DBU, CH_2Cl_2, r.t., 2 h, 94%; (e) 2-nitrobenzenesulfonyl chloride, hydrazine hydrate, MeCN, 0 °C to r.t., 18 h, 84%; (f) NBS, AIBN, CCl_4, reflux,18 h, 65%; (g) amine, K_2CO_3, DMF, r.t., 4 h, 36–59%.

Table 1 Fluorodesulfurization of Dithioketal **9** Using DBH/HF–Py

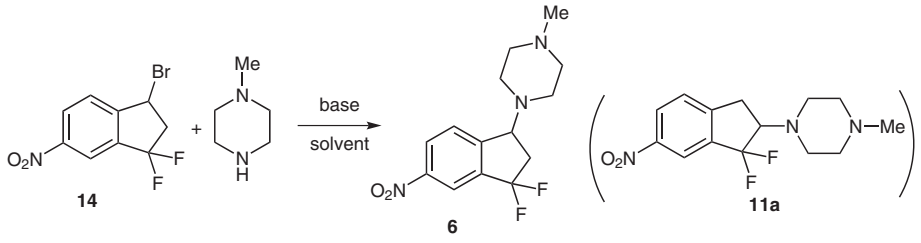
Entry	DBH (equiv)[a]	Yield of **10** (%)[b]
1	1	23
2	2	48
3	4	88

[a] With respect to dithioketal **9**.
[b] Yield of isolated product.

As the double bond and nitro group of **12** would be reduced simultaneously by catalytic hydrogenation, we utilized the diimide generated from 2-nitrobenzenesulfonylhydrazide for selective reduction of the double bond. Compound **12** was treated with 2-nitrobenzenesulfonyl chloride and hydrazine hydrate,[25] leading to reduced difluoride **13** in good yield. The subsequent bromination of compound **13** with *N*-bromosuccinimide (NBS) successfully afforded intermediate 3-bromo analogue **14** (Scheme 3).[26]

On treatment of compound **14** with *N*-methylpiperazine, 1-(1,1-difluoro-2,3-dihydro-6-nitro-1*H*-inden-3-yl)-4-methylpiperazine (**6**) was obtained, but only in 50% yield;

Table 2 Nucleophilic Substitution of Bromide **14** under Different Reaction Conditions



Entry	Base	Solvent	Temp	Yield (%)[a]	
				6	**11a**
1	Et_3N	CH_2Cl_2	r.t.	–	–
2[b]	Et_3N	THF	r.t. to reflux	–	–
3	*N*-methylpiperazine	DMF	r.t.	–	–
4[c]	K_2CO_3	DMF	r.t.	50	8
5[d]	K_2CO_3	DMF	r.t.	58	7

[a] Yield of isolated product.
[b] Bromide **14** was converted into **12** when the mixture was heated at reflux temperature.
[c] Bromide **14** was added to a suspension of *N*-methylpiperazine and K_2CO_3 in DMF at r.t.
[d] *N*-Methylpiperazine was added to a suspension of **14** and K_2CO_3 in DMF at r.t.

this was lower than that of the transformation of bromide **10** into **11a**. Interestingly, amine **11a** (structure confirmed by ^{1}H NMR and HRMS) was obtained as a by-product in this reaction. In order to improve the yield of **6**, different reaction conditions were explored and the results are outlined in Table 2. The best yield of **6** was achieved when *N*-methylpiperazine was added to a suspension of bromide **14** and potassium carbonate (K_2CO_3) in *N*,*N*-dimethylformamide (DMF) at room temperature (58%, Table 2, entry 5). It is interesting that a lower yield was obtained by changing the sequence of addition of compound **14** and *N*-methylpiperazine (50%, Table 2, entry 4).

When *N*-methylpiperazine was added to a suspension of compound **14** and potassium carbonate in *N*,*N*-dimethylformamide, the amount of deeply colored impurities was reduced, and the yield of the desired substituted product **6** was increased (Table 2, entry 5). Notably, when the reaction was heated at reflux temperature in tetrahydrofuran, the eliminated product **12** was found to be the major product (Table 2, entry 2), while no reaction occurred at room temperature (Table 2, entries 1 and 3).

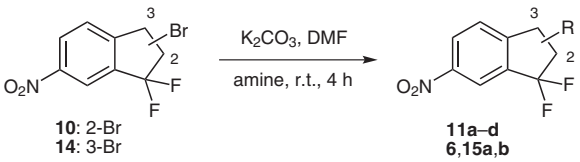
The lower yield of **6** was anticipated because of the existence of the 6-nitro group. Compound **14** may undergo partial elimination to give **12** under the basic conditions, and then **12** will react with *N*-methylpiperazine to give predominately amine **11a** via a Michael addition, due to the electron-withdrawing effect of the 6-nitro group (Scheme 4). In order to examine this plausible mechanism, compound **12** was reacted with *N*-methylpiperazine in *N*,*N*-dimethylformamide to provide **11a** in 86% yield. Therefore, the elimination occurred in competition with the substitution in the reaction of *N*-methylpiperazine with 3-brominated compound **14**.

Finally, different amines underwent substitution with compounds **10** or **14** to afford 6-nitro-1,1-difluoroindanes derivatives. The structures of the products and the obtained yields are listed in Table 3. When the amine was pyrrolidine, compound **15b** was obtained in only 36% yield accompanied by a 25% yield of **11c**, perhaps due to the higher basicity of pyrrolidine (pK_a = 11.27) relative to morpholine (pK_a = 8.36) and *N*-methylpiperazine (pK_a = 9.14). As a result, compound **14** was liable to undergo elimination to give **12** under these conditions.

Additionally, three dithioketalized indanones (**16**–**18**), prepared from 4-nitro-1-indanone, 6-chloro-1-indanone and 1-indanone, were selected to investigate the broad application of this protocol (DBH and HF–Py) to afford *gem*-difluorinated products. The preliminary results are shown in the Table 4. According to the results, this method could be applied to other indane derivatives to afford 2-bromo-1,1-difluoroindane derivatives, and not only for 6-nitroindanone. However, the effect of the substituent on the phenyl moiety needs to be further researched in order to obtain a clear picture on the possible applications of this protocol.

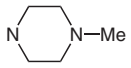
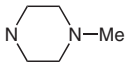
In summary, we have described an efficient and convenient method for the synthesis of 1,1-difluoro-6-nitro-2,3-dihydro-1*H*-indene derivatives with different amino groups located at the 2- or 3-positions. Commercially available indanone was used as the starting material and the key step, *gem*-difluorination, was achieved by treatment of the intermediate dithioketal with in situ generated bromine fluoride. On the other hand, DAST and Deoxo-Fluor failed to fluorinate directly the ketone carbonyl using 6-nitroindanone derivatives, probably due to deactivation by the 6-nitro group.

Table 3 Synthesis of 1,1-Difluoro-6-nitro-2,3-dihydro-1*H*-indene Derivatives

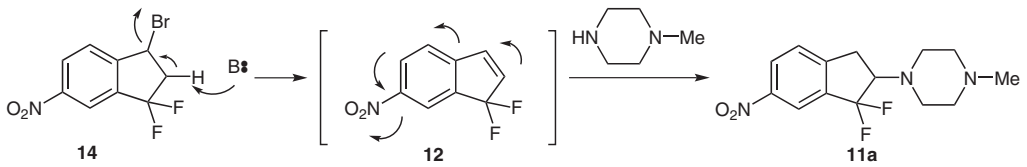


10: 2-Br
14: 3-Br

11a–d
6,**15a**,**b**

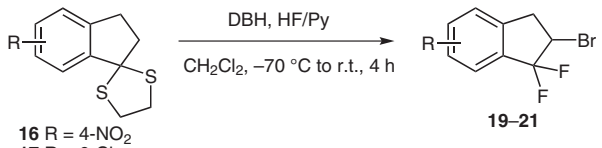
Product	Position	R	Yield (%)[a]
11a	2		90
11b	2		77
11c	2		88
11d	2		79
6	3		58
15a	3		59
15b	3		36

[a] Yield of isolated product.



Scheme 4 The mechanism for the formation of by-product **11a**

Table 4 Synthesis of 2-Bromo-1,1-difluoro-2,3-dihydro-1*H*-indene Derivatives

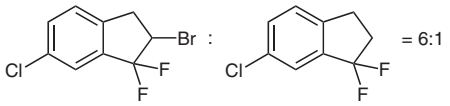


16 R = 4-NO_2
17 R = 6-Cl
18 R = H

19–21

Product	R	Yield (%)[a]
19	4-NO_2	74
20	6-Cl	73[b]
21	H	52

[a] Yield of isolated product.
[b] The product was a mixture as shown below; the ratio was 6:1 according to the ^{1}H NMR spectrum.



All reagents and solvents were purchased from commercial sources unless otherwise indicated. CH_2Cl_2 and DMF were purified using a PURE SOLV device (Innovative Technology); MeCN was HPLC grade and stored over 4 Å molecular sieves. All reactions were monitored by thin-layer chromatography (TLC) using Qingdao Haiyang plates, and the components were made visual with UV light (254 nm). Purification was performed by flash column chromatography on silica gel (Qingdao Haiyang, 300–400 mesh). Melting points were determined on a Yanaco MP-J3 melting point apparatus. IR spectra were recorded on a Nicolet 5700 FTIR spectrometer. ^{1}H NMR spectra were obtained on Varian Mercury-300 and 400 MHz spectrometers, ^{13}C NMR spectra were obtained on Inova-500 (at 125 MHz), Varian Mercury-400 (at 100 MHz) and Varian Mercury-300 (at 75 MHz) spectrometers, and ^{19}F NMR spectra were obtained on Varian Mercury-400 (at 376 MHz) and Bruker-500 (at 470 MHz) spectrometers, in $CDCl_3$ as the solvent. Chemical shifts and coupling constants were recorded in units of ppm and Hz, respectively. High-resolution mass spectra were recorded using a Thermo Exactive Orbitrap plus mass spectrometer (ESI). EI-MS and HR-EIMS data were measured using a Micromass Autospec Ultima-TOF spectrometer.

6-Nitro-2,3-dihydro-1*H*-inden-1-one (2)
A solution of KNO_3 (10.1 g, 0.1 mol) in concd H_2SO_4 (30 mL) was added dropwise to a mixture of 1-indanone (13.2 g, 0.1 mol) and concd H_2SO_4 (80 mL) at 0 °C over 40 min. Following addition, the mixture was stirred at 0 °C for 1 h, then poured onto ice (500 g). The resulting precipitate was collected by filtration, washed with H_2O and dried in air. The crude product was purified by chromatography on silica gel (PE–EtOAc, 70:30) to give a colorless solid.

Yield: 11.6 g (66%); mp 71–72 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (s, 1 H), 8.44 (d, *J* = 8.4 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 3.28 (t, *J* = 6.4 Hz, 2 H), 2.83 (t, *J* = 6.4 Hz, 2 H).[14]

6′-Nitro-2′,3′-dihydrospiro([1,3]dithiolane-2,1'-indene) (9)
A solution of **2** (8.85 g, 50 mmol), ethane-1,2-dithiol (4.6 mL, 55 mmol) and PTSA (1.72 g, 10 mmol) in toluene (100 mL) was heated at reflux temperature for 12 h using a Dean–Stark apparatus. The cooled solution was washed with 10% NaOH (100 mL), and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered, and purified by chromatography on silica gel (9–18% EtOAc in PE) to give a yellow oil.

Yield: 12.5 g (99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 3.57–3.61 (m, 2 H), 3.47–3.52 (m, 2 H), 3.05 (t, *J* = 6.8 Hz, 2 H), 2.76 (t, *J* = 6.8 Hz, 2 H).[27]

2-Bromo-1,1-difluoro-6-nitro-2,3-dihydro-1*H*-indene (10)
A solution of 1,3-dibromo-5,5-dimethylhydantoin (DBH) (21.2 g 74 mmol) in anhydrous CH_2Cl_2 (100 mL) was cooled to –70 °C in a dry ice–acetone bath. HF–Py (22.2 mL, 70%) was added dropwise at a temperature below –65 °C under Ar, and the mixture stirred at –70 °C for 30 min. A solution of **9** (4.7 g, 18.5 mmol) in CH_2Cl_2 (20 mL) was added dropwise and the mixture stirred at –70 °C for 4 h, and then at r.t. overnight. The mixture was poured into NaOH (2 M, 200 mL) containing 39% $NaHSO_3$ (30 mL) solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layer washed with brine (30 mL), dried over Na_2SO_4, filtered, and purified by chromatography on silica gel (3% EtOAc in PE) to give a yellow solid.

Yield: 4.39 g (85%); mp 46–47 °C.

IR (KBr): 3110, 3089, 1525, 1353, 1083, 1062, 742, 735, 656 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (s, 1 H), 8.38 (d, *J* = 8.4 Hz, 1 H), 7.49 (d, *J* = 8.4 Hz, 1 H), 4.61–4.68 (m, 1 H), 3.71 (dd, *J* = 7.2 and 17.2 Hz, 1 H), 3.37 (dd, *J* = 6.4 and 17.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.19, 147.21 (t, $^3J_{C–F}$ = 6.3 Hz), 135.79 (t, $^2J_{C–F}$ = 26.3 Hz), 127.28, 126.37, 123.38 (t, $^1J_{C–F}$ = 250.0 Hz), 119.44, 47.38 (dd, $^2J_{C–F}$ = 23.8 and 23.8 Hz), 39.06.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –91.97 (d, *J* = 248.2 Hz), –99.75 (d, *J* = 244.4 Hz).

HRMS (EI, 70 eV): *m*/*z* $[M]^+$calcd for $C_9H_6BrF_2NO_2$: 276.9550; found: 276.9528.

1-(1,1-Difluoro-2,3-dihydro-6-nitro-1*H*-inden-2-yl)-4-methylpiperazine (11a)
To a stirred suspension of **10** (0.83 g, 3 mmol) and K_2CO_3 (0.49 g, 3.6 mmol) in DMF (15 mL) was added dropwise *N*-methylpiperazine (0.3 g, 3 mmol) at r.t. The mixture was stirred under Ar for 4 h, and then poured into H_2O (30 mL). After extraction with CH_2Cl_2 (3 × 20 mL), the combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, and purified by chromatography on silica gel (3–9% MeOH in CH_2Cl_2) to afford a brown solid.

Yield: 0.8 g (90%); mp 100–101 °C.

IR (KBr): 3103, 2970, 1537, 1351, 1088, 1052, 740, 680 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (s, 1 H), 8.32 (d, *J* = 8.4 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 3.24–3.36 (m, 2 H), 3.07–3.13 (m, 1 H), 2.87 (br s, 2 H), 2.72 (m, 2 H), 2.57 (m, 4 H), 2.33 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.94, 147.01 (t, $^3J_{C–F}$ = 6.3 Hz), 137.60 (t, $^2J_{C–F}$ = 23.8 Hz), 126.82, 126.35, 125.72 (t, $^1J_{C–F}$ = 250.0 Hz), 119.22, 70.12 (t, $^2J_{C–F}$ = 20.0 Hz), 54.81, 51.39, 45.96, 33.19 (d, $^3J_{C–F}$ = 7.5 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –94.68 (d, *J* = 253.8 Hz), –98.54 (d, *J* = 241.9 Hz).

HRMS (ESI–TOF): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{18}F_2N_3O_2$: 298.1362; found: 298.1359.

A solution of *N*-methylpiperazine (20 mg, 0.2 mmol) and difluoride **12** (39 mg, 0.2 mmol) in DMF (1 mL) was stirred at r.t. for 3 h. The mixture was poured into H_2O (20 mL), extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layer washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated to afford a brown solid (51 mg, 86%). The identity of the product (**11a**) was con-

firmed from ^{1}H NMR spectroscopy and TLC, and by comparison with a sample of **11a** prepared from **10** as described above.

4-(1,1-Difluoro-2,3-dihydro-6-nitro-1*H*-inden-2-yl)morpholine (11b)
The product was prepared according to the procedure described for compound **11a**, using morpholine as the nucleophile.

Yield: 65 mg (77%); yellow solid; mp 146–147 °C.

IR (KBr): 3100, 3081, 1525, 1357, 1084, 1051, 742, 678 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (s, 1 H), 8.36 (d, *J* = 7.6 Hz, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 3.83 (br s, 4 H), 3.29–3.36 (m, 2 H), 3.15 (m, 1 H), 2.86 (br s, 2 H), 2.72 (br s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.01, 146.78, 137.37 (t, $^2J_{C–F}$ = 25.0 Hz), 126.92, 126.40, 125.72 (t, $^1J_{C–F}$ = 250.0 Hz), 119.25, 70.30 (t, $^2J_{C–F}$ = 20.0 Hz), 66.66, 51.96, 32.85 (d, $^3J_{C–F}$ = 6.3 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –94.73 (d, *J* = 253.8 Hz), –98.78 (d, *J* = 249.1 Hz).

HRMS (ESI–TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}F_2N_2O_3$: 285.1045; found: 285.1043.

1-(1,1-Difluoro-2,3-dihydro-6-nitro-1*H*-inden-2-yl)pyrrolidine (11c)
The product was prepared according to the procedure described for compound **11a**, using pyrrolidine as the nucleophile.

Yield: 70 mg (88%); brown solid; mp 95–96 °C.

IR (KBr): 3100, 2976, 1526, 1353, 1087, 1055, 745, 678 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (s, 1 H), 8.33 (d, *J* = 8.4 Hz, 1 H), 7.46 (d, *J* = 8.4 Hz, 1 H), 3.16–3.29 (m, 3 H), 2.86 (d, *J* = 6.0 Hz, 2 H), 2.76 (d, *J* = 6.0 Hz, 2 H), 1.90 (br s, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.85, 147.44 (t, $^3J_{C–F}$ = 6.3 Hz), 137.59 (t, $^2J_{C–F}$ = 26.3 Hz), 126.72, 126.35, 123.37 (t, $^1J_{C–F}$ = 250.0 Hz), 119.26, 69.77 (t, $^2J_{C–F}$ = 20.0 Hz), 52.68, 34.70 (d, $^3J_{C–F}$ = 5.0 Hz), 23.27.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –98.71 (d, *J* = 253.8 Hz), –99.33 (d, *J* = 249.1 Hz).

HRMS (ESI–TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}F_2N_2O_2$: 269.1096; found: 269.1096.

1,1-Difluoro-2,3-dihydro-*N*-isopropyl-6-nitro-1*H*-inden-2-amine (11d)
The product was prepared according to the procedure described for compound **11a**, using isopropylamine as the nucleophile.

Yield: 60 mg (79%); yellow solid; mp 79–80 °C.

IR (KBr): 3106, 2967, 1528, 1350, 1077, 1051, 741, 677 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1 H), 8.31 (d, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 3.82–3.90 (m, 1 H), 3.67 (dd, *J* = 7.2 and 16.8 Hz, 1 H), 3.25 (br s, 1 H), 2.75–2.81 (m, 1 H), 1.16 (br s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.82, 147.70 (t, $^3J_{C–F}$ = 6.3 Hz), 137.30 (t, $^2J_{C–F}$ = 26.3 Hz), 126.64, 126.38, 125.31 (t, $^1J_{C–F}$ = 248.8 Hz), 119.32, 61.34 (t, $^2J_{C–F}$ = 22.5 Hz), 46.50, 36.28 (d, $^3J_{C–F}$ = 5.0 Hz), 23.68, 22.10.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –100.66 (d, *J* = 272.6 Hz), –101.26 (d, *J* = 258.5 Hz).

HRMS (ESI–TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}F_2N_2O_2$: 257.1096; found: 257.1095.

1,1-Difluoro-6-nitro-1*H*-indene (12)
To a solution of **10** (2.22 g, 8.0 mmol) in CH_2Cl_2 (30 mL) was added dropwise DBU (1.92 mL, 13 mmol) at r.t. The mixture was stirred at r.t. under Ar for 2 h and then washed with HCl (2 M, 30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layer washed with brine (20 mL), dried over Na_2SO_4, and purified by chromatography on silica gel (6–9% EtOAc in PE) to afford a yellow solid.

Yield: 1.48 g (94%); mp 47–48 °C.

IR (KBr): 3153, 3102, 1578, 1525, 1345, 1055, 1030, 742, 730 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29–8.31 (m, 2 H), 7.32 (d, *J* = 7.6 Hz, 1 H), 6.88 (d, *J* = 6.0 Hz, 1 H), 6.46 (d, *J* = 6.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.80, 146.51 (t, $^3J_{C–F}$ = 5.0 Hz), 138.79 (t, $^2J_{C–F}$ = 26.3 Hz), 135.77 (t, $^3J_{C–F}$ = 8.8 Hz), 134.68 (t, $^2J_{C–F}$ = 26.3 Hz), 127.94, 123.99 (t, $^1J_{C–F}$ = 243.8 Hz), 122.64, 117.75.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –75.49 (d, *J* = 263.2 Hz), –107.37 (d, *J* = 263.2 Hz).

HRMS (EI, 70 eV): *m*/*z* [M]$^+$ calcd for $C_9H_5F_2NO_2$: 197.0288; found: 197.0269.

1,1-Difluoro-6-nitro-2,3-dihydro-1*H*-indene (13)
A solution of **12** (1.97 g, 10 mmol) and 2-nitrobenzenesulfonyl chloride (4.42 g, 20 mmol) in MeCN (50 mL) was cooled to 0 °C under Ar. To this stirred solution was added hydrazine hydrate (1.94 mL, 40 mmol) dropwise over 30 min. The mixture was stirred at r.t. for 18 h, then poured into H_2O (100 mL) and extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, and purified by chromatography on silica gel (5% EtOAc in PE) to afford a yellow oil.

Yield: 1.68 g (84%).

IR (neat): 3100, 3080, 1530, 1351, 1092, 1060, 943, 741, 595 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40 (s, 1 H), 8.33 (d, *J* = 8.4 Hz, 1 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 3.13–3.18 (m, 2 H), 2.63–2.77 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.86 (t, $^3J_{C–F}$ = 6.0 Hz), 148.03, 138.62 (t, $^2J_{C–F}$ = 27.0 Hz), 128.87 (t, $^1J_{C–F}$ = 243.0 Hz), 126.72, 126.65, 119.14, 35.96 (t, $^2J_{C–F}$ = 25.0 Hz), 28.05.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –86.94, –123.80.

HRMS (EI, 70 eV): *m*/*z* [M]$^+$ calcd for $C_9H_7F_2NO_2$: 199.0445; found: 199.0438.

3-Bromo-1,1-difluoro-6-nitro-2,3-dihydro-1*H*-indene (14)
A mixture of **13** (1.77 g, 8.88 mmol), NBS (1.9 g, 10.7 mmol) and AIBN (0.15 g, 0.89 mmol) in CCl_4 (50 mL) was heated at reflux temperature under Ar for 18 h. After removal of the solid and evaporation of the solvent under vacuum, the residue was purified by chromatography on silica gel (5% EtOAc in PE) to give a yellow solid.

Yield: 1.6 g (65%); mp 50–51 °C.

IR (KBr): 3107, 3078, 1525, 1350, 1092, 1057, 740, 600 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42–8.44 (m, 2 H), 7.71 (d, *J* = 8.4 Hz, 1 H), 5.43–5.47 (m, 1 H), 3.31–3.43 (m, 1 H), 3.00–3.11 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.95 (t, $^3J_{C–F}$ = 6.3 Hz), 149.14, 137.33 (t, $^2J_{C–F}$ = 27.5 Hz), 127.60, 127.52, 125.88 (t, $^1J_{C–F}$ = 246.3 Hz), 118.94, 47.60 (t, $^2J_{C–F}$ = 25.0 Hz), 40.21 (dd, $^3J_{C–F}$ = 2.5 and 2.5 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –86.32 (d, *J* = 253.8 Hz), –88.81 (d, *J* = 253.8 Hz).

MS (EI, 30 eV): *m*/*z* 277 and 279 [M]$^+$ (1:1 ratio), 258 and 260 [M – F]$^+$ (1:1 ratio), 198 [M – Br]$^+$, 179 [M – Br – F]$^+$, 151 [M – Br – NO_2]$^+$, 133 [M – Br – F – NO_2]$^+$.

1-(1,1-Difluoro-2,3-dihydro-6-nitro-1*H*-inden-3-yl)-4-methylpiperazine (6)
A solution of *N*-methylpiperazine (0.1 g, 1 mmol) in DMF (1 mL) was added dropwise to a suspension of **14** (0.14 g, 0.5 mmol) and

K_2CO_3 (0.1 g, 1 mmol) in DMF (2 mL) at r.t., and the resulting mixture was stirred under Ar for 4 h. The mixture was poured into H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with HCl (2 M, 20 mL). The aqueous layer was neutralized with sat. $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried over Na_2SO_4, and purified by chromatography on silica gel (3% MeOH in CH_2Cl_2) to afford the title product as a pale yellow solid along with **11a** as a by-product (11 mg, 7%).

Yield: 86 mg (58%); mp 105–106 °C.

IR (KBr): 3106, 2975, 1527, 1349, 1112, 1095, 741, 685 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.41 (s, 1 H), 8.37 (d, *J* = 8.1 Hz, 1 H), 7.67 (d, *J* = 8.4 Hz, 1 H), 4.56–4.59 (m, 1 H), 2.62–2.77 (m, 4 H), 2.47 (br s, 6 H), 2.31 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.66 (t, $^3J_{C-F}$ = 5.0 Hz), 148.83, 138.30 (t, $^2J_{C-F}$ = 27.5 Hz), 126.70, 126.66 (t, $^1J_{C-F}$ = 247.5 Hz), 118.90, 64.48 (t, $^3J_{C-F}$ = 2.5 Hz), 55.12, 45.94, 35.05 (t, $^2J_{C-F}$ = 22.5 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –85.45 (d, *J* = 253.8 Hz), –86.02 (d, *J* = 253.8 Hz).

HRMS (ESI–TOF): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{18}F_2N_3O_2$: 298.1362; found: 298.1359.

4-(1,1-Difluoro-2,3-dihydro-6-nitro-1*H*-inden-3-yl)morpholine (15a)

The product was prepared according to the procedure described for compound **6**, using morpholine as the nucleophile.

Yield: 50 mg (59%); brown solid; mp 83–84 °C.

IR (KBr): 3101, 3049, 1533, 1350, 1113, 1097, 744, 682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.38–8.41 (m, 2 H), 7.69 (d, *J* = 6.8 Hz, 1 H), 4.56 (br s, 1 H), 3.73 (br s, 4 H), 2.68–2.76 (m, 2 H), 2.57 (br s, 2 H), 2.39 (br s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.19, 148.89, 138.39 (t, $^2J_{C-F}$ = 27.5 Hz), 126.74, 126.57 (t, $^1J_{C-F}$ = 243.8 Hz), 118.94, 66.99, 64.80 (d, $^3J_{C-F}$ = 2.5 Hz), 48.86, 34.93 (t, $^2J_{C-F}$ = 22.5 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –85.35 (d, *J* = 253.8 Hz), –85.53 (d, *J* = 253.8 Hz).

HRMS (ESI–TOF): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{15}F_2N_2O_3$: 285.1045; found: 285.1046.

1-(1,1-Difluoro-2,3-dihydro-6-nitro-1*H*-inden-3-yl)pyrrolidine (15b)

The product was prepared according to the procedure described for compound **6**, using pyrrolidine as the nucleophile. By-product **11c** (20 mg, 25%) was also obtained.

Yield: 29 mg (36%); yellow oil.

IR (neat): 3100, 2965, 1533, 1352, 1111, 1095, 740, 685 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.39 (s, 1 H), 8.35 (d, *J* = 8.4 Hz, 1 H), 7.67 (d, *J* = 8.4 Hz, 1 H), 4.73 (br s, 1 H), 2.69–2.81 (m, 4 H), 2.49–2.59 (m, 2 H), 1.00 (br s, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.40, 148.57, 137.95 (t, $^2J_{C-F}$ = 27.0 Hz), 126.86, 126.64 (t, $^1J_{C-F}$ = 243.0 Hz), 126.53, 118.84, 60.76, 48.82, 36.25 (t, $^2J_{C-F}$ = 20.0 Hz), 23.63.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –85.72.

HRMS (ESI–TOF): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{15}F_2N_2O_2$: 269.1096; found: 269.1093.

2-Bromo-1,1-difluoro-4-nitro-2,3-dihydro-1*H*-indene (19)

The product was prepared according to the procedure described for compound **10**.

Yield: 1.02 g (74%); yellow oil.

IR (neat): 3101, 1533, 1354, 1073, 1013, 818, 743, 727, 674 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.4 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.64 (t, *J* = 8.0 Hz, 1 H), 4.60–4.68 (m, 1 H), 4.17 (dd, *J* = 6.0 and 18.4 Hz, 1 H), 3.73 (dd, *J* = 6.0 and 18.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.92, 137.52 (t, $^2J_{C-F}$ = 27.0 Hz), 136.69 (t, $^3J_{C-F}$ = 6.8 Hz), 129.75, 129.52, 127.63, 123.43 (dd, $^1J_{C-F}$ = 246.0 and 249.8 Hz), 46.72 (dd, $^2J_{C-F}$ = 23.3 and 29.3 Hz), 39.69.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.84 (d, *J* = 263.2 Hz), –98.53 (d, *J* = 263.2 Hz).

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_9H_6BrF_2NO_2$: 276.9550; found: 276.9553.

2-Bromo-6-chloro-1,1-difluoro-2,3-dihydro-1*H*-indene (20)

The product was prepared according to the procedure described for compound **10**.

Yield: 394 mg (73%); yellow oil.

IR (neat): 3068, 1476, 1309, 1252, 1011, 885, 820, 775, 716, 665 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (s, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.22–7.24 (m, 1 H), 4.53–4.62 (m, 1 H), 3.55 (dd, *J* = 7.2 and 16.4 Hz, 1 H), 3.23 (dd, *J* = 7.2 and 16.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.65 (t, $^3J_{C-F}$ = 6.0 Hz), 135.65 (t, $^2J_{C-F}$ = 25.5 Hz), 134.00, 132.37, 126.39, 123.77, 123.68 (t, $^1J_{C-F}$ = 243.0 Hz), 47.85 (dd, $^2J_{C-F}$ = 24.8 and 28.5 Hz), 38.46.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.85 (d, *J* = 196.6 Hz), –100.53 (d, *J* = 196.6 Hz).

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_9H_6BrClF_2$: 267.9289; found: 267.9297.

2-Bromo-1,1-difluoro-2,3-dihydro-1*H*-indene (21)

The product was prepared according to the procedure described for compound **10**.

Yield: 240 mg (52%); yellow oil.

IR (neat): 3080, 3039, 1467, 1295, 1257, 1065, 997, 835, 770, 731, 639 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 7.5 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 1 H), 7.39 (t, *J* = 7.8 Hz, 1 H), 7.28 (d, *J* = 7.8 Hz, 1 H), 4.52–4.64 (m, 1 H), 3.57 (dddd, *J* = 2.1, 7.8 and 15.9 Hz, 1 H), 3.73 (dd, *J* = 7.5 and 15.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.30 (t, $^3J_{C-F}$ = 6.8 Hz), 134.06, 132.07, 128.13, 125.04, 124.41 (t, $^1J_{C-F}$ = 248.3 Hz), 123.42, 48.16 (dd, $^2J_{C-F}$ = 24.8 and 28.5 Hz), 38.90 (d, $^3J_{C-F}$ = 3.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –89.96 (d, *J* = 263.2 Hz), –100.82 (d, *J* = 263.2 Hz).

HRMS (EI, 70 eV): *m*/*z* $[M]^+$ calcd for $C_9H_7BrF_2$: 231.9699; found: 231.9709.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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