

# Synthesis and Properties of *gem*-(Difluorocyclopropyl)amine

## Derivatives of Bicyclo[n.1.0]alkanes

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## Experimental Section

**CAUTION!** Organomercury compounds are *extremely toxic*. Avoid skin contact, use heavy-duty protective gloves, and use all other safety precautions for handling of highly toxic materials!

**General:** Uncorrected melting points were determined with a Hoover capillary apparatus.  $^1\text{H}$  (300 or 500 MHz),  $^{13}\text{C}$  (75 or 125 MHz), and  $^{19}\text{F}$  (288 MHz) NMR spectra were recorded in  $\text{CDCl}_3$  unless noted. Electron impact mass spectra were obtained at 70 eV. High-resolution mass spectra (MS) were determined with EI or FAB [glycerol, thioglycerol, or *p*-nitrobenzyl alcohol (NBA)]. All chemicals and solvents were of reagent quality. All enamines, **1**, were made by the procedure of Stork et al.,<sup>1</sup> and were used immediately after distillation.

**General Procedure:** Powdered NaI (5.6 g, 37.2 mmol) was stirred and heated at 170 °C for 1 h under vacuum in a flask (250 mL) equipped with a Teflon valve, and the flask was allowed to cool to ambient temperature. A solution of enamine **1f** (2.0 g, 9.3 mmol) in dried THF (10 mL) and then a solution of  $\text{Hg}(\text{CF}_3)_2$  (3.15 g, 9.3 mmol) in dried THF (10 mL) were injected through a septum under an atmosphere of  $\text{N}_2$ . The reaction mixture was heated in an oil bath at 70 °C for 80 min and cooled to ambient temperature. Volatiles were concentrated, and the mixture was deposited on a column of silica gel. Chromatography (EtOAc/hexanes, 1:20) gave the difluorocyclopropylamine **2f** (2.2 g, 89%) as a pale-yellow oil. This material was dissolved in MeOH (10 mL), and conc.  $\text{HCl}/\text{H}_2\text{O}$  (3 mL) was added with stirring. Volatiles were evaporated in vacuo. A purified sample of **2f**•HCl was obtained by chromatography (EtOAc then MeOH) followed by recrystallization (EtOH/Et<sub>2</sub>O).

### Characterization Data:

**7,7-Difluoro-1-(morpholin-4-yl)bicyclo[4.1.0]heptane (2b).** Colorless oil:  $^1\text{H}$  NMR  $\delta$  1.15–1.82 (m, 8H), 1.84–2.02 (m, 1H), 2.57–2.62 (m, 4H), 3.61–3.70 (m, 4H);  $^{13}\text{C}$  NMR  $\delta$  15.1, 17.0, 20.4, 21.3, 25.0 (t,  $J = 8.8$  Hz), 46.2 (t,  $J = 9.9$  Hz), 48.0, 66.8, 116.5 (dd,  $J = 285.3, 293.7$  Hz);  $^{19}\text{F}$  NMR  $\delta$  141.9 (d,  $J = 151.7$  Hz, 1F), 142.9 (dd,  $J = 15.0, 151.7$  Hz, 1F). **2b**•HCl•H<sub>2</sub>O: mp 122–124 °C (THF); EI-MS  $m/z$  217 (4%, M<sup>+</sup>), 166, 91, 87; HRMS Calcd for C<sub>11</sub>H<sub>17</sub>F<sub>2</sub>NO: 217.1278, Found: 217.1277.

**8,8-Difluoro-1-(morpholin-4-yl)bicyclo[5.1.0]octane (2c).** Colorless oil:  $^1\text{H}$  NMR  $\delta$  1.06–2.10 (m, 10H), 2.23–2.30 (m, 1H), 2.64–2.82 (m, 4H), 3.54–3.69 (m, 4H);  $^{13}\text{C}$  NMR  $\delta$  23.1 (d,  $J = 4.6$  Hz), 23.4 (d,  $J = 4.6$  Hz), 28.2, 29.0, 32.5, 33.3 (t,  $J = 8.0$  Hz), 49.8, 53.6 (t,  $J = 9.2$

Hz), 67.3, 116.5 (dd,  $J = 287.6, 296.8$  Hz);  $^{19}\text{F}$  NMR  $\delta$  141.9 (dd,  $J = 15.0, 145.2$  Hz, 1F), 142.9 (d,  $J = 145.3$  Hz, 1F). **2c**•HCl: mp 163–165 °C (dec.) (EtOH/Et<sub>2</sub>O); EI-MS  $m/z$  231 (63%, M<sup>+</sup>), 216, 202, 188, 180 (100), 152; HRMS Calcd for C<sub>12</sub>H<sub>19</sub>F<sub>2</sub>NO: 231.1435, Found: 231.1433.

**9,9-Difluoro-1-(morpholin-4-yl)bicyclo[6.1.0]nonane (2d)**. Colorless oil:  $^1\text{H}$  NMR  $\delta$  1.24–1.76 (m, 11H), 1.90–1.96 (m, 1H), 2.07–2.11 (m, 1H), 2.71–2.86 (m, 4H), 3.59–3.70 (m, 4H); (d,  $J = 3.1$  Hz);  $^{13}\text{C}$  NMR  $\delta$  20.7, 22.2, 25.2, 25.7, 26.1, 27.5, 29.2 (t,  $J = 7.5$  Hz), 49.0, 50.4 (t,  $J = 8.8$  Hz), 67.8, 115.9 (t,  $J = 293.7$  Hz);  $^{19}\text{F}$  NMR  $\delta$  140.7 (br d,  $J = 151.7$  Hz, 1F), 145.4 (d,  $J = 151.7$  Hz, 1F). **2d**•HBr: mp 150–155 °C (dec.) (EtOH/THF); FAB-MS (glycerol)  $m/z$  246 (100 %, [M + H]<sup>+</sup>); HRMS Calcd for C<sub>13</sub>H<sub>22</sub>F<sub>2</sub>NO: 246.1669, Found: 246.1650.

**2,3-Benzo-7,7-difluoro-1-(morpholin-4-yl)bicyclo[4.1.0]heptane (2e)**. Crystals: mp 125–127 °C (toluene);  $^1\text{H}$  NMR (CD<sub>3</sub>OD)  $\delta$  1.51–1.59 (m, 2H), 2.16–1.26 (m, 1H), 2.18–1.36 (m, 1H), 2.46–2.54 (m, 1H), 2.64–2.80 (m, 3H), 2.97–3.06 (m, 2H), 3.30–3.32 (m, 1H), 3.63–3.78 (m, 4H), 7.17–7.21 (m, 1H), 7.24–7.31 (m, 2H), 7.40–7.44 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  20.3, 28.5, 30.1 (t,  $J = 9.5$  Hz), 49.5 (t,  $J = 11.4$  Hz), 49.6, 67.2, 116.4 (dd,  $J = 288.4, 296.8$  Hz), 126.2, 127.3, 127.6, 128.5, 129.9, 140.6;  $^{19}\text{F}$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$  135.8 (d,  $J = 143.1$  Hz, 1F), 136.6 (dd,  $J = 15.0, 143.1$  Hz, 1F); FAB-MS (NBA)  $m/z$  266 (75%, [M + H]<sup>+</sup>), 264 (100%); HRMS Calcd for C<sub>15</sub>H<sub>18</sub>F<sub>2</sub>NO: 266.1356, Found: 266.1371. **2e**•HCl (prepared by the general procedure) lost HCl upon heating to give mp and MS data identical to that of **2e**.

**8,8-Difluoro-1-[(N-benzyl)(N-methyl)amino]bicyclo[5.1.0]octane (2f)**. Colorless oil:  $^1\text{H}$  NMR  $\delta$  1.10–2.10 (m, 10H), 2.28 (s, 3H), 2.34–2.38 (m, 1H), 3.73 (d,  $J = 13.2$  Hz, 1H), 3.87 (d,  $J = 13.2$  Hz, 1H), 7.19–7.31 (m, 5H);  $^{13}\text{C}$  NMR  $\delta$  23.7 (d,  $J = 6.1$  Hz), 23.7 (d,  $J = 4.5$  Hz), 28.1, 29.2, 32.8, 34.3 (t,  $J = 8.4$  Hz), 37.7, 54.8 (t,  $J = 9.2$  Hz), 59.2, 117.9 (dd,  $J = 288.4, 296.0$  Hz), 126.8, 128.06, 128.12, 139.7;  $^{19}\text{F}$  NMR (Me<sub>2</sub>CO-*d*<sub>6</sub>)  $\delta$  140.4 (dd,  $J = 17.1, 145.2$  Hz, 1F), 142.2 (d,  $J = 145.2$  Hz, 1F). **2f**•HCl: mp 152–154 °C (dec.) (EtOH/THF); FAB-MS (glycerol)  $m/z$  266 (100%, [M + H]<sup>+</sup>), 185, 174; HRMS Calcd for C<sub>16</sub>H<sub>22</sub>F<sub>2</sub>N: 266.1720, Found: 266.1719.

**8,8-Difluoro-1-(N,N-dibenzylamino)bicyclo[5.1.0]octane (2g)**. Colorless oil:  $^1\text{H}$  NMR  $\delta$  0.81–1.95 (m, 10H), 2.34–2.41 (m, 1H), 3.81 (d,  $J = 13.9$  Hz, 2H), 3.93 (d,  $J = 13.7$  Hz, 2H), 7.14–7.32 (m, 10H);  $^{13}\text{C}$  NMR  $\delta$  23.7 (d,  $J = 3.8$  Hz), 26.1, 27.1, 28.0, 32.5, 33.4 (t,  $J = 8.4$  Hz), 53.8 (t,  $J = 9.5$  Hz), 56.5, 117.4 (t,  $J = 294.5$  Hz), 126.8, 127.9, 128.8, 139.8;  $^{19}\text{F}$  NMR  $\delta$  136.1 (dd,  $J = 17.1, 147.4$  Hz, 1F), 143.6 (d,  $J = 147.4$  Hz, 1F). **2g**•HCl: Orange oil: FAB-MS

(glycerol)  $m/z$  342 (80%,  $[M + H]^+$ ), 340, 288 (100%); HRMS Calcd for  $C_{22}H_{26}F_2N$ : 342.2033, Found: 342.2032.

**8,8-Difluoro-1-[(*N*-methyl)(*N*-phenyl)amino]bicyclo[5.1.0]octane (2h).** Pale-yellow oil:  $^1H$  NMR  $\delta$  1.18–1.29 (m, 1H), 1.36–1.45 (m, 1H), 1.50–1.61 (m, 3H), 1.65–1.73 (ddd,  $J = 7.3, 10.7, 17.6$  Hz, 1H), 1.91–2.01 (m, 2H), 2.15–2.23 (m, 1H), 2.28–2.37 (m, 1H), 3.08 (s, 3H), 6.68–6.78 (m, 3H), 7.23–7.28 (m, 2H);  $^{13}C$  NMR  $\delta$  23.5, 26.7, 26.8, 28.5, 32.1 (t,  $J = 9.1$  Hz), 32.2, 36.8, 51.5 (t,  $J = 10.3$  Hz), 112.6, 116.81 (dd,  $J = 293.0, 294.5$  Hz), 116.85, 128.8, 147.8;  $^{19}F$  NMR  $\delta$  135.9 (dd,  $J = 17.1, 147.4$  Hz, 1F), 143.4 (d,  $J = 147.4$  Hz, 1F); FAB-MS (thioglycerol)  $m/z$  252 (100%,  $[M + H]^+$ ); HRMS Calcd for  $C_{15}H_{20}F_2N$ : 252.1564, Found: 252.1564.

**8,8-Difluoro-1-(*N,N*-dipentylamino)bicyclo[5.1.0]octane (2i).** Colorless oil:  $^1H$  NMR  $\delta$  0.89 (t,  $J = 7.1$  Hz, 6H), 1.10–1.92 (m, 21H), 2.02–2.09 (m, 1H), 2.13–2.19 (m, 1H), 2.54–2.72 (m, 4H);  $^{13}C$  NMR  $\delta$  14.1, 22.7, 23.8 (d,  $J = 3.8$  Hz), 24.6, 27.2, 28.9, 29.6, 32.7, 33.3 (t,  $J = 8.4$  Hz), 51.0, 52.9, 53.8 (t,  $J = 8.7$  Hz), 117.8 (dd,  $J = 291.4, 294.5$  Hz);  $^{19}F$  NMR (DMSO- $d_6$ )  $\delta$  133.5 (dd,  $J = 18.2, 141.0$  Hz, 1F), 141.4 (d,  $J = 141.0$  Hz, 1F). **2i**•HBr: Orange oil: FAB-MS (thioglycerol)  $m/z$  300 (100%,  $[M - H]^+$ ); HRMS Calcd for  $C_{18}H_{32}F_2N$ : 300.2503, Found: 300.2517.

**Thermal Decomposition of 8,8-Difluoro-1-(morpholin-4-yl)bicyclo[5.1.0]octane (2c).** A sample of **2c** (2.10 g, 9.09 mmol) was heated at 170 °C for 24 h and treated as described for the conversion of **2d**  $\rightarrow$  **4d** to give **4c**. Careful concentration of the solution of the somewhat volatile 2-fluorocyclooct-2-enone (**4c**), and its treatment with 2,4-dinitrophenylhydrazine (300 mg, 1.52 mmol) gave the purified derivative (130 mg, 4% overall from **2c** after recrystallisation from  $CH_2Cl_2/EtOH$ ) as lustrous, bright-orange plates: mp 186–188 °C;  $^1H$  NMR  $\delta$  1.58–1.65 (m, 2H), 1.69–1.75 (m, 2H), 1.90–1.96 (m, 2H), 2.46–2.52 (m, 2H), 2.84–2.89 (m, 2H), 5.89 (dt,  $J = 8.5, 24.4$  Hz, 1H), 8.08 (d,  $J = 9.8$  Hz, 1H), 8.35 (dd,  $J = 2.4, 9.8$  Hz, 1H), 9.14 (d,  $J = 2.4$  Hz, 1H), 11.41 (s, 1H);  $^{13}C$  NMR  $\delta$  22.5, 23.6 (d,  $J = 8.4$  Hz), 23.7, 25.4, 26.3, 113.2 (d,  $J = 23.7$  Hz), 117.1, 123.2, 130.1, 138.7, 144.8, 149.3 (d,  $J = 18.3$  Hz), 155.5 (d,  $J = 244.9$  Hz);  $^{19}F$  NMR  $\delta$  111.3 (d,  $J = 23.5$  Hz, 1F); FAB-MS (thioglycerol)  $m/z$  323 (100%,  $[M + H]^+$ ), 345 (55%,  $[M + Na]^+$ ); HRMS Calcd for  $C_{14}H_{15}FN_4O_4Na$ : 345.0975, Found: 345.0983.

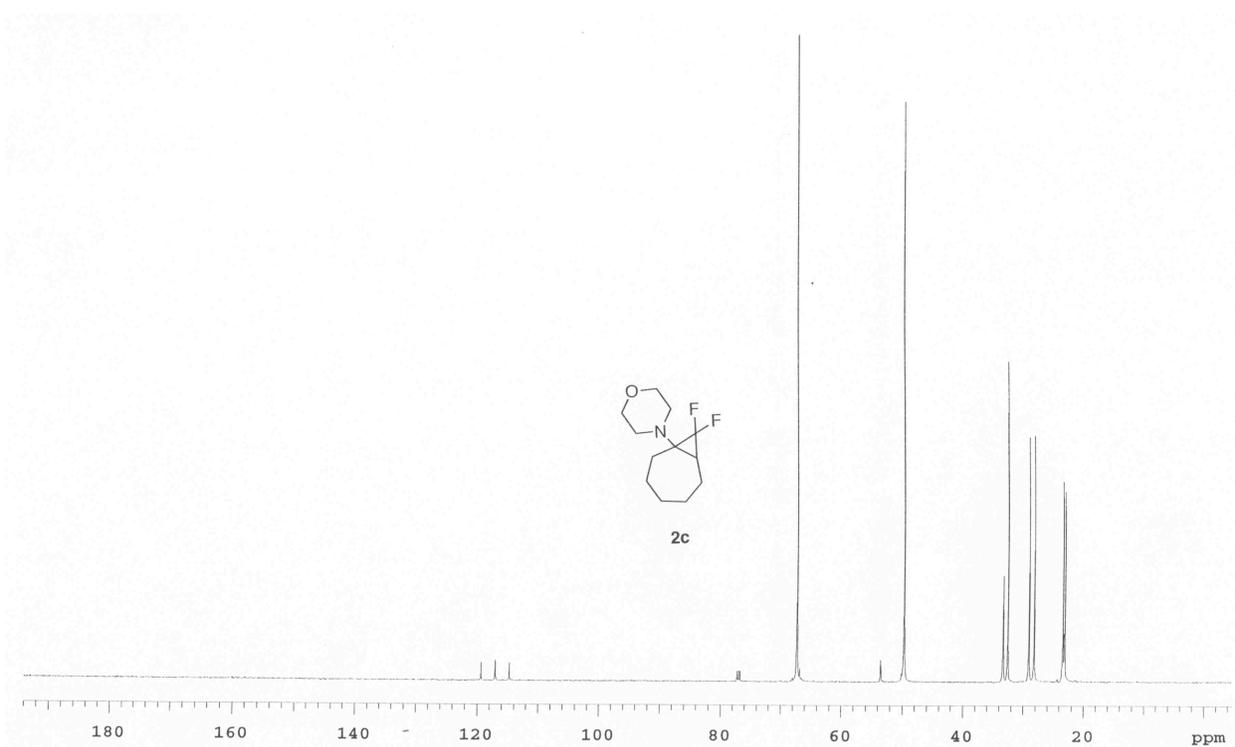
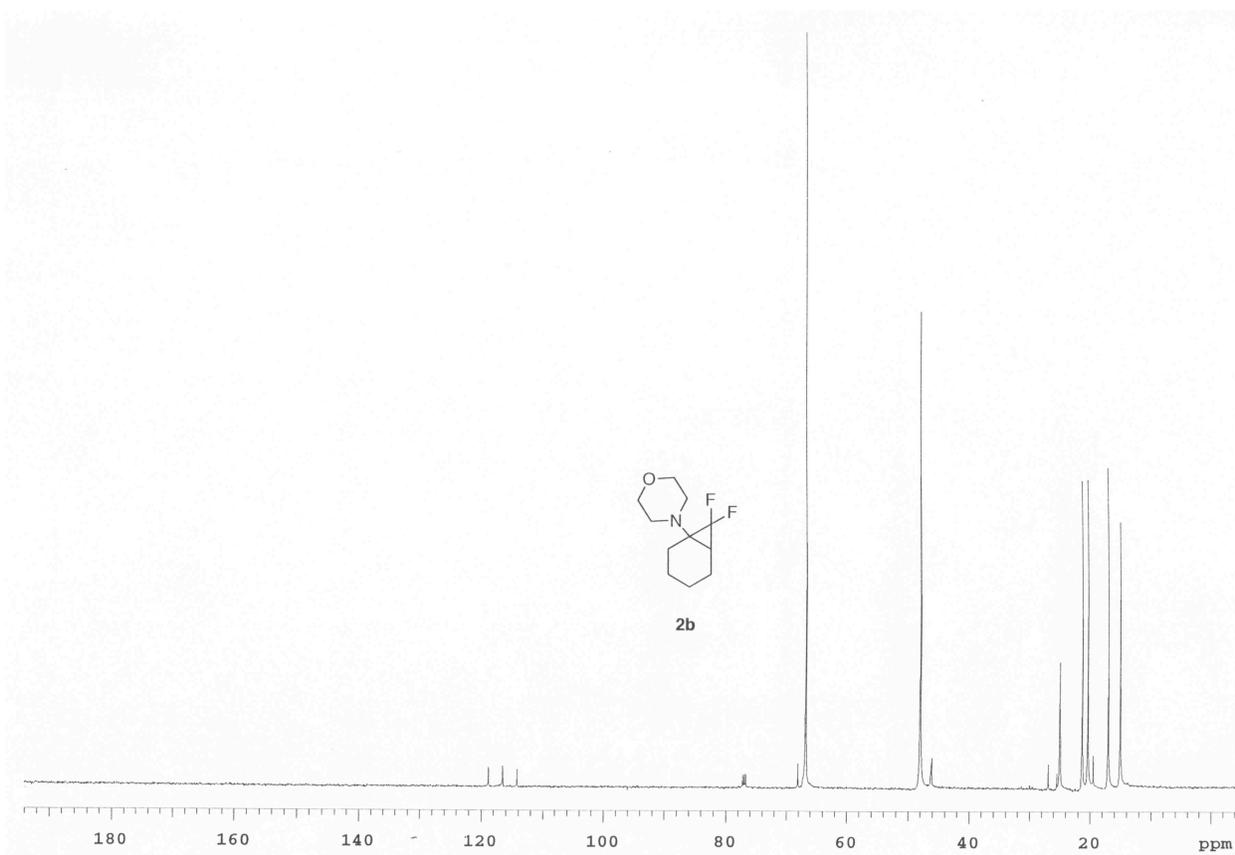
**Thermal Decomposition of 9,9-Difluoro-1-(morpholin-4-yl)bicyclo[6.1.0]nonane (2d).** Compound **2d** (700 mg, 2.86 mmol) was heated at 100 °C for 1 h in a glass tube equipped

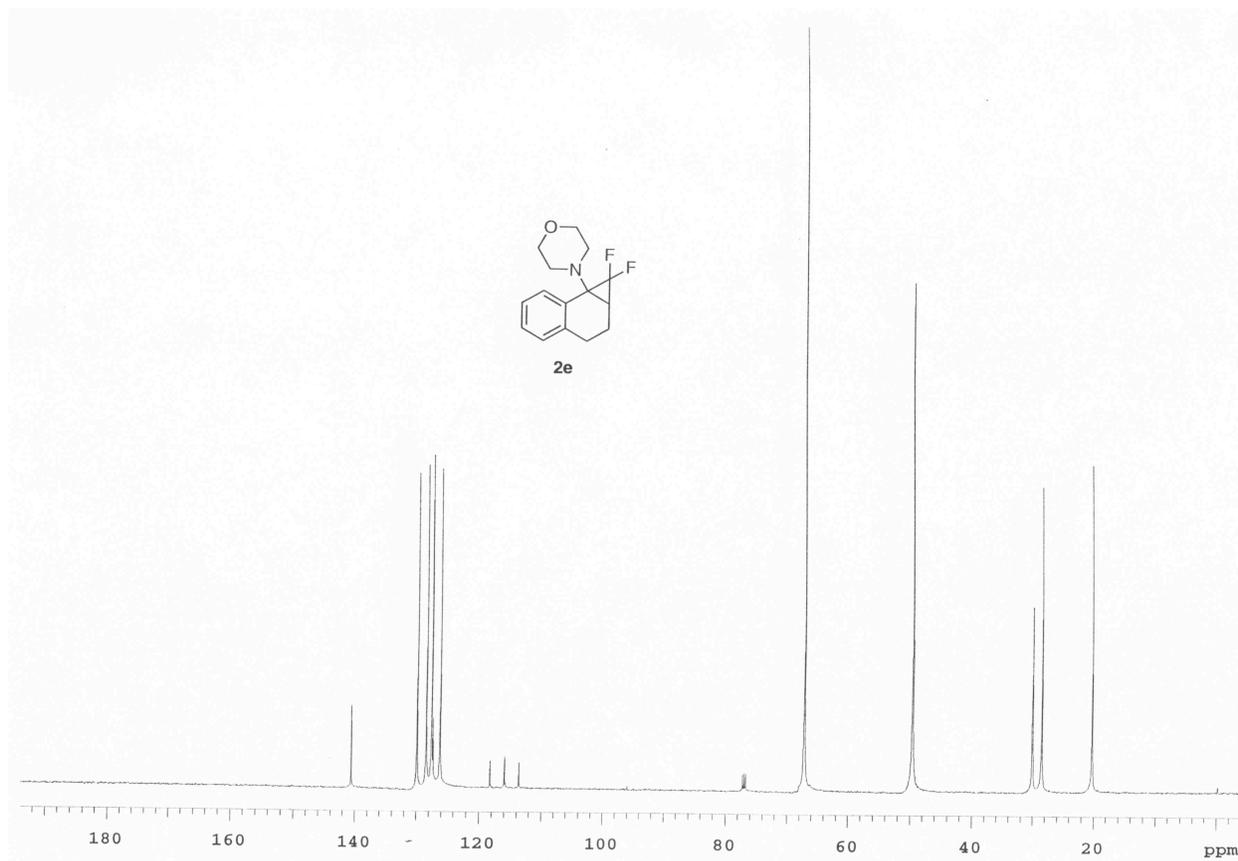
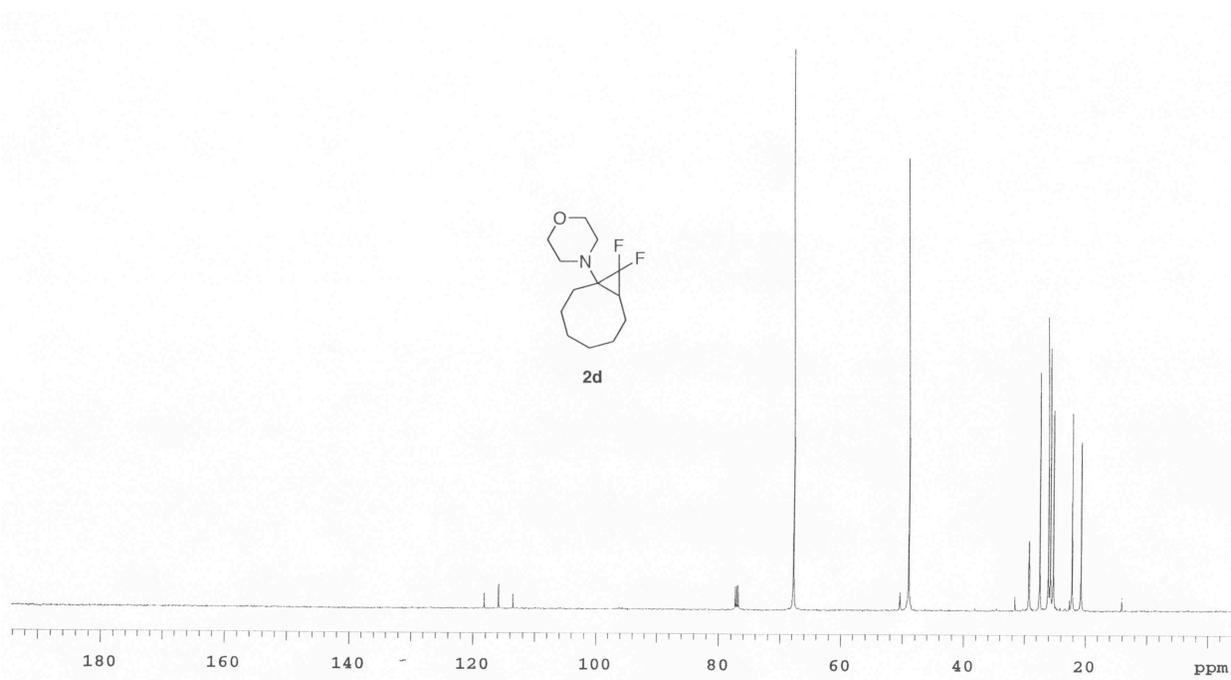
with a Teflon valve. The purple residue contained 2-fluoro-3-(4-morpholin-1-yl)-1,3-cyclononadiene (**3d**) and 2-fluorocyclonon-2-enone (**4d**) in a 3:1 ratio (NMR). The residue was dissolved in MeOH (5 mL) and stirred with 5% HCl/H<sub>2</sub>O (5 mL) for 15 min. Volatiles were removed in vacuo, and the residue was partitioned (EtOAc/H<sub>2</sub>O). Volatiles were evaporated from the organic phase, and the residue was chromatographed (EtOAc/hexanes, 1:3) to give **4d** (320 mg, 72%) as a pale-yellow oil whose spectral data were in harmony with literature values, and a sample was converted into its 2,4-dinitrophenylhydrazone. Thus, 2,4-dinitrophenylhydrazine (430 mg, 2.18 mmol) was suspended in MeOH (8 mL), and conc. H<sub>2</sub>SO<sub>4</sub>/H<sub>2</sub>O (0.9 mL) was added. The resulting mixture was filtered with a cotton plug, and the filtrate was collected in a flask containing **4d** (200 mg, 1.28 mmol) in MeOH (3 mL). After 1 h, filtration gave crystals that were recrystallized several times (CH<sub>2</sub>Cl<sub>2</sub>/EtOH) to give the purified derivative (200 mg, 48%) as lustrous, bright-orange plates: mp 165–167 °C; <sup>1</sup>H NMR δ 1.50–1.64 (m, 6H), 1.92–1.98 (m, 2H), 2.38–2.46 (m, 2H), 2.78–2.86 (m, 2H), 5.72 (dt, *J* = 9.8, 24.9 Hz, 1H), 8.07 (d, *J* = 9.8 Hz, 1H), 8.35 (dd, *J* = 2.4, 9.8 Hz, 1H), 9.14 (d, *J* = 2.4 Hz, 1H), 11.41 (s, 1H); <sup>13</sup>C NMR δ 22.3 (d, *J* = 8.4 Hz), 23.4, 25.10, 25.13, 26.2, 27.9, 112.8 (d, *J* = 23.7 Hz), 117.0, 123.1, 130.0, 138.7, 144.6, 149.8 (d, *J* = 22.1 Hz), 155.0 (d, *J* = 242.6 Hz); <sup>19</sup>F NMR δ 109.3 (d, *J* = 23.5 Hz, 1F); EI-MS *m/z* 336 (100%, M<sup>+</sup>), 319, 299; HRMS Calcd for C<sub>15</sub>H<sub>17</sub>FN<sub>4</sub>O<sub>4</sub>: 336.1233, Found: 336.1241.

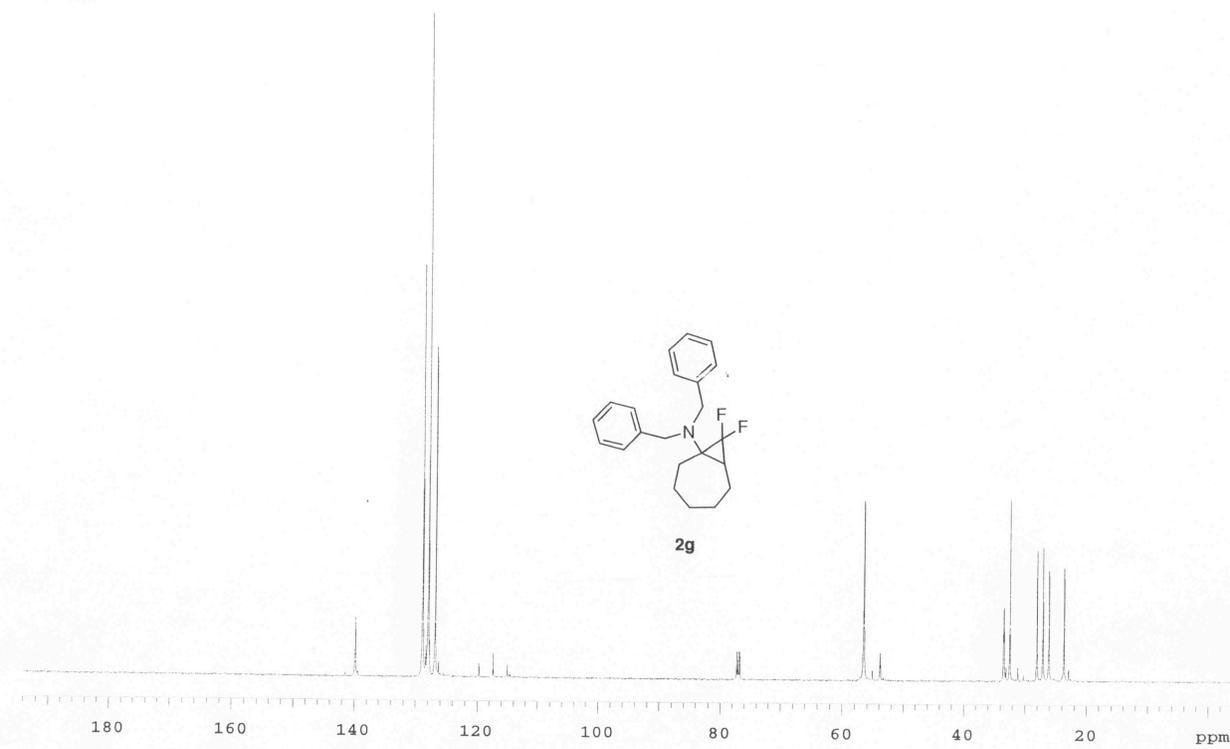
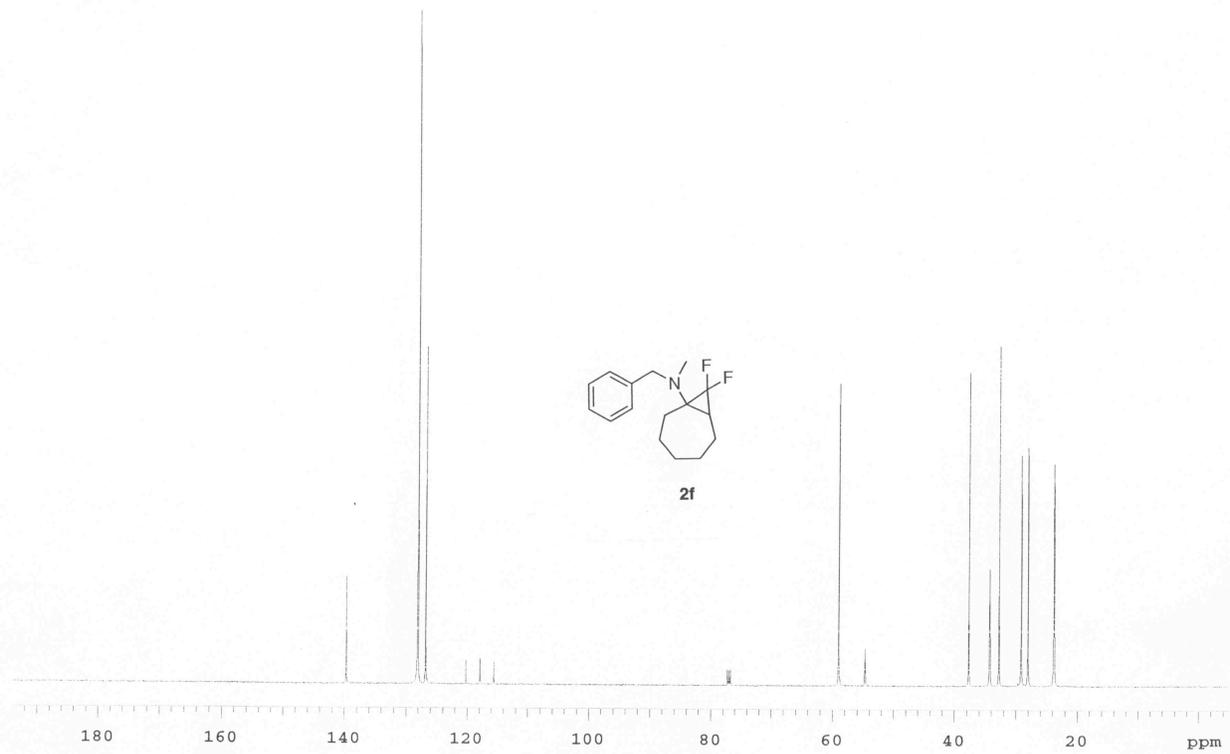
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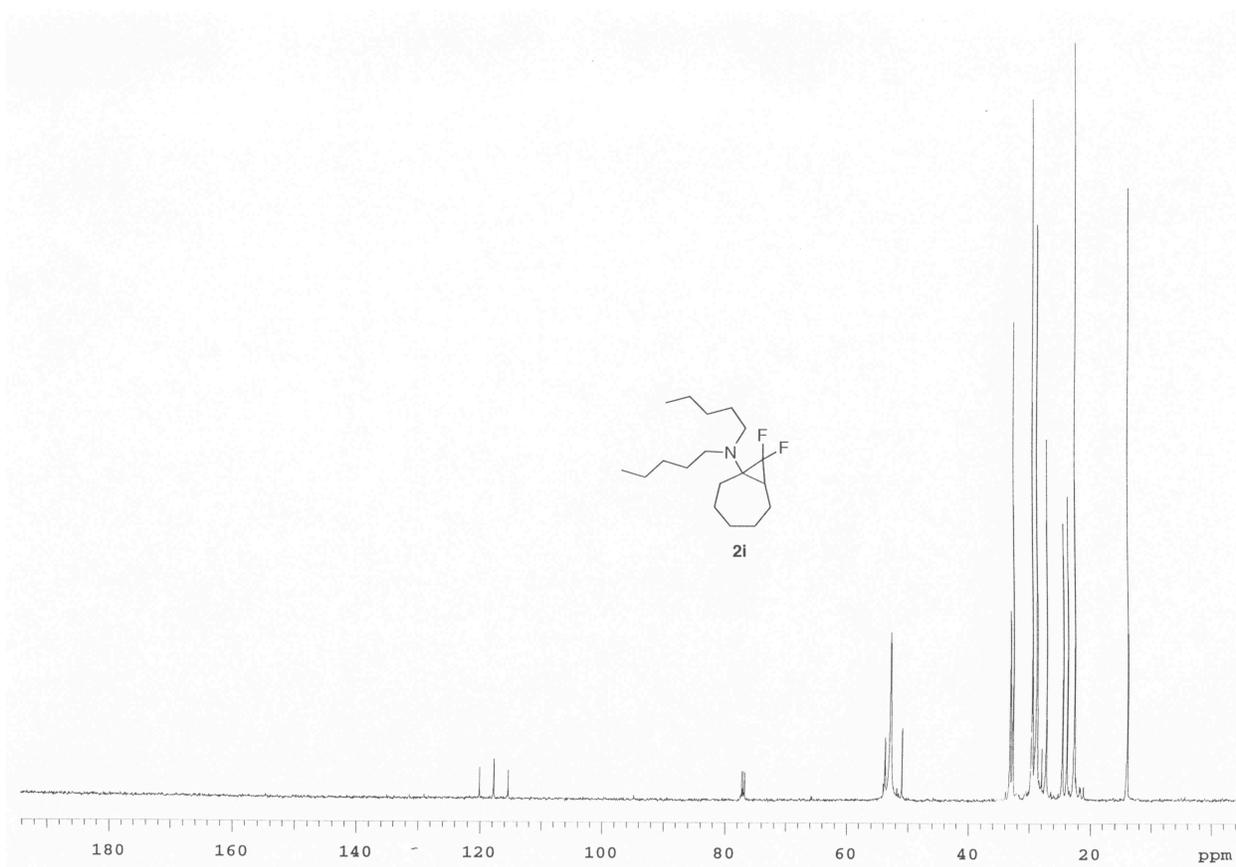
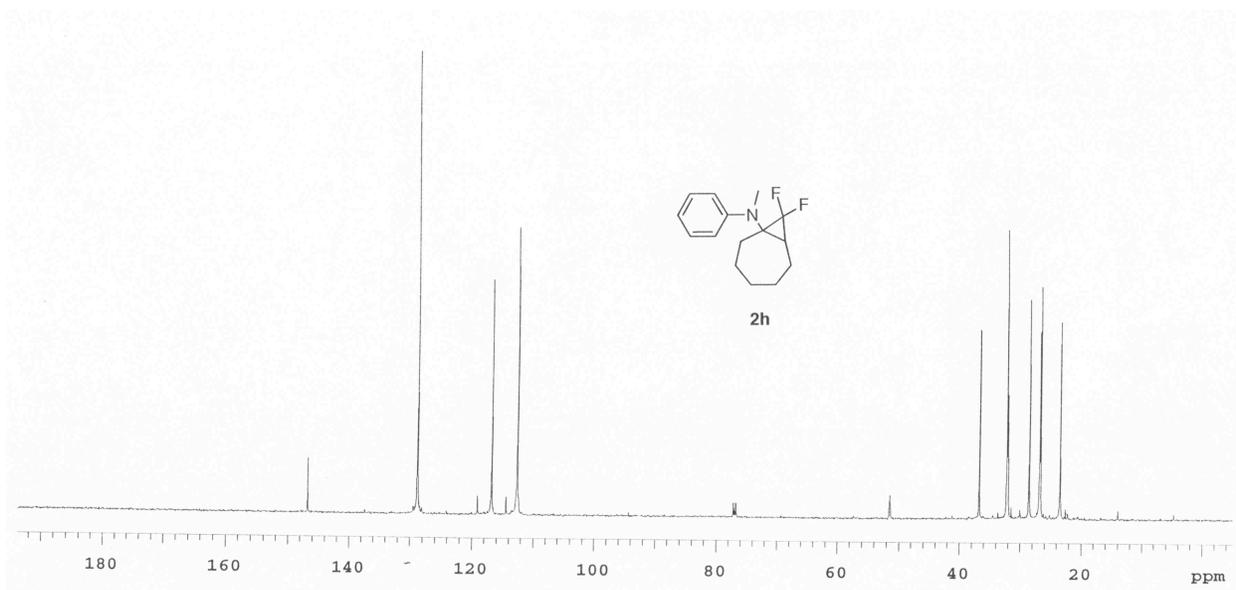
(1) Stork, G.; Brizollara, A.; Landesman, H.; Szmuszkovich, J.; Terrell, R. *J. Org. Chem.* **1963**, *85*, 207-221.

(2) Blanco, L.; Rousseau, G. *Bull. Soc. Chim. Fr.* **1985**, *3*, 455-462.

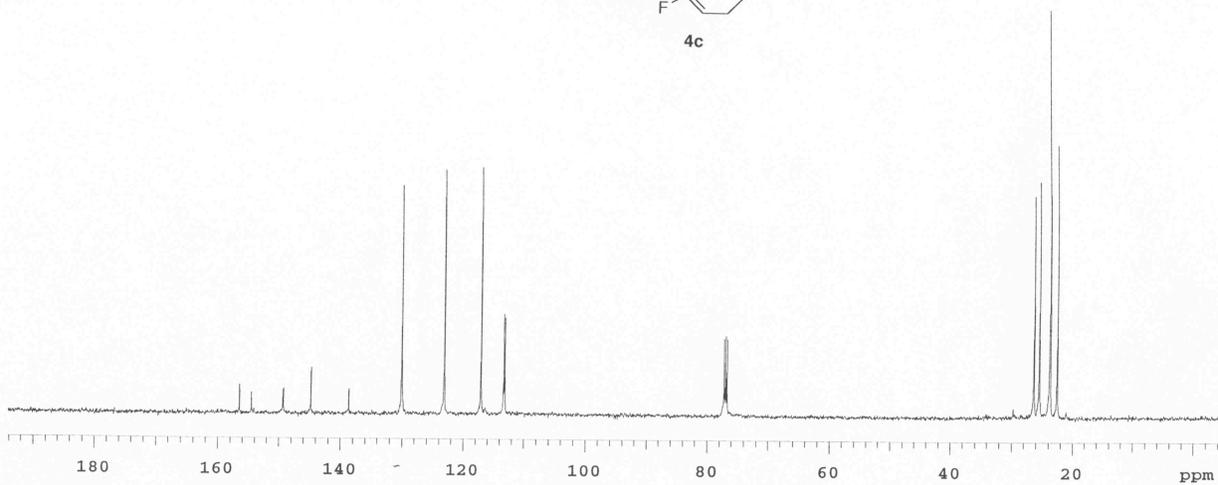
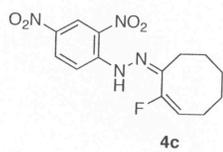
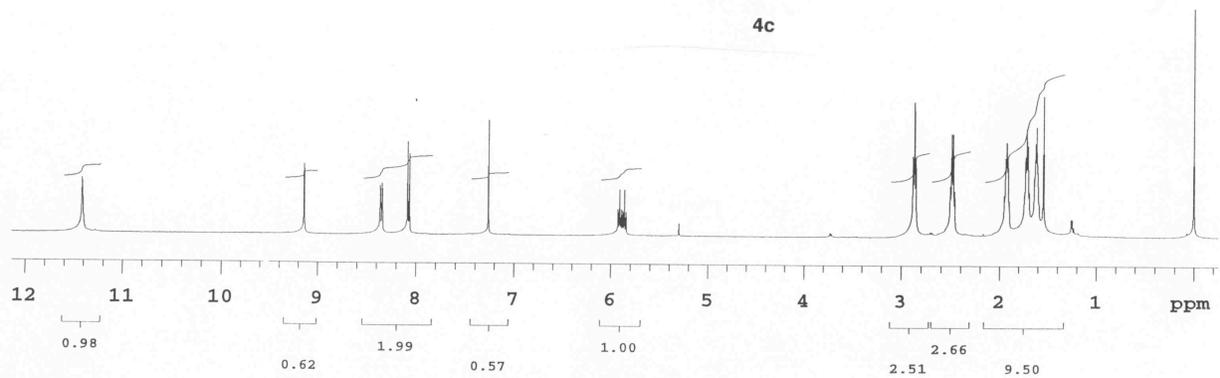
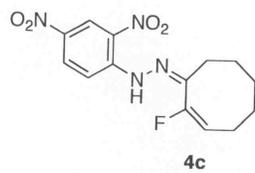


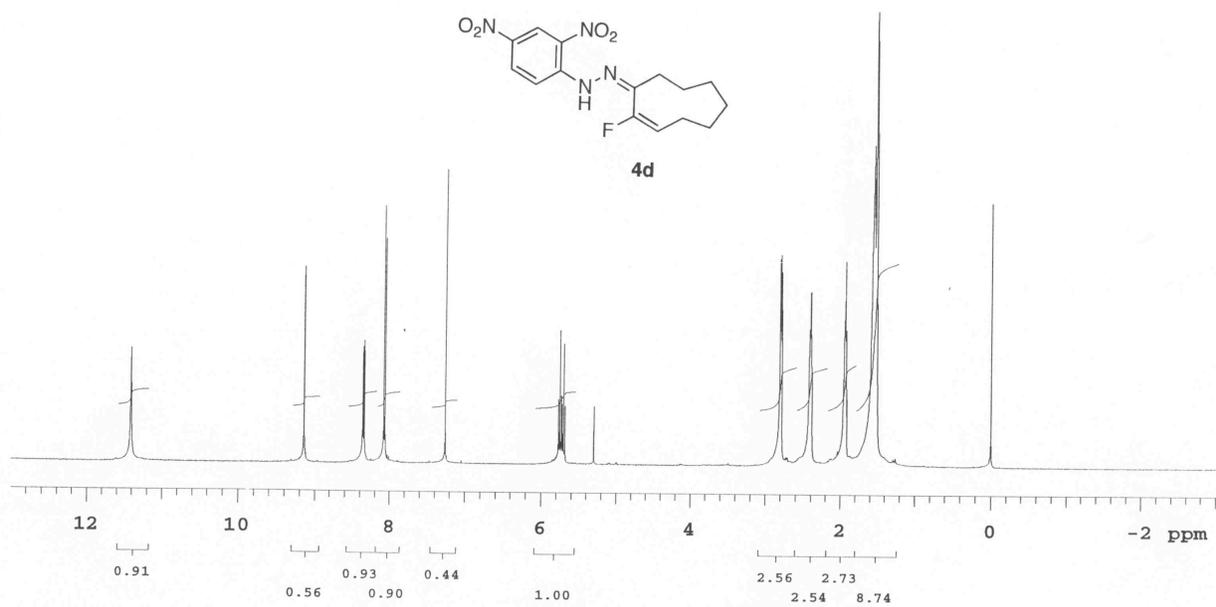




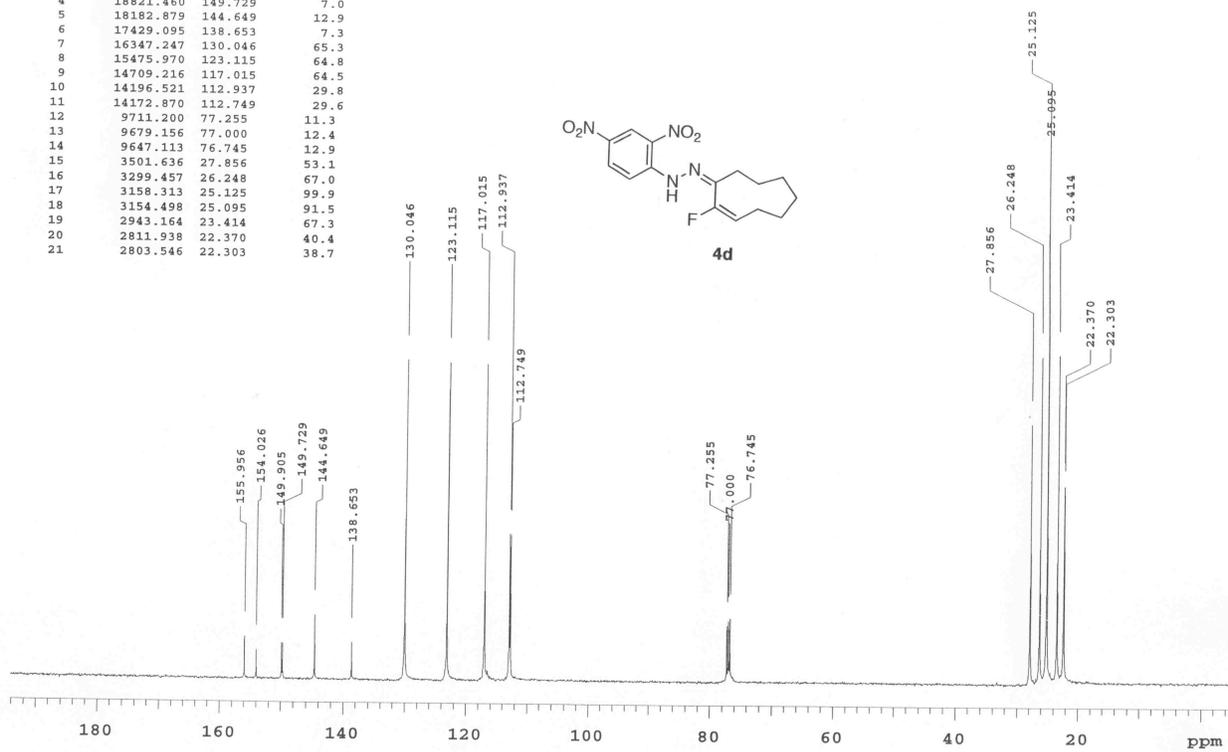


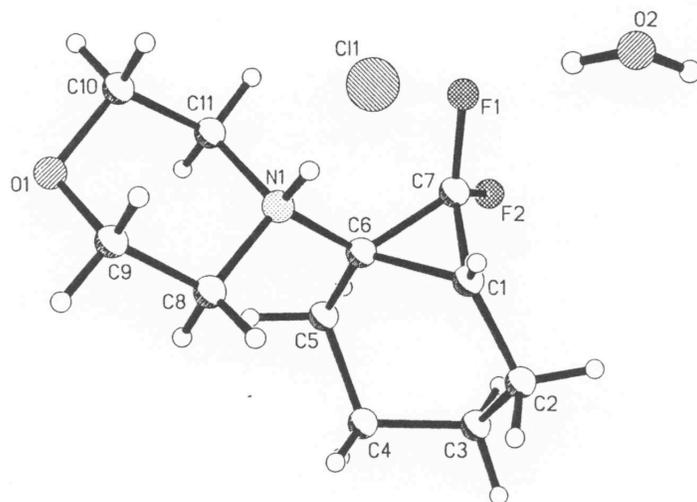
S10



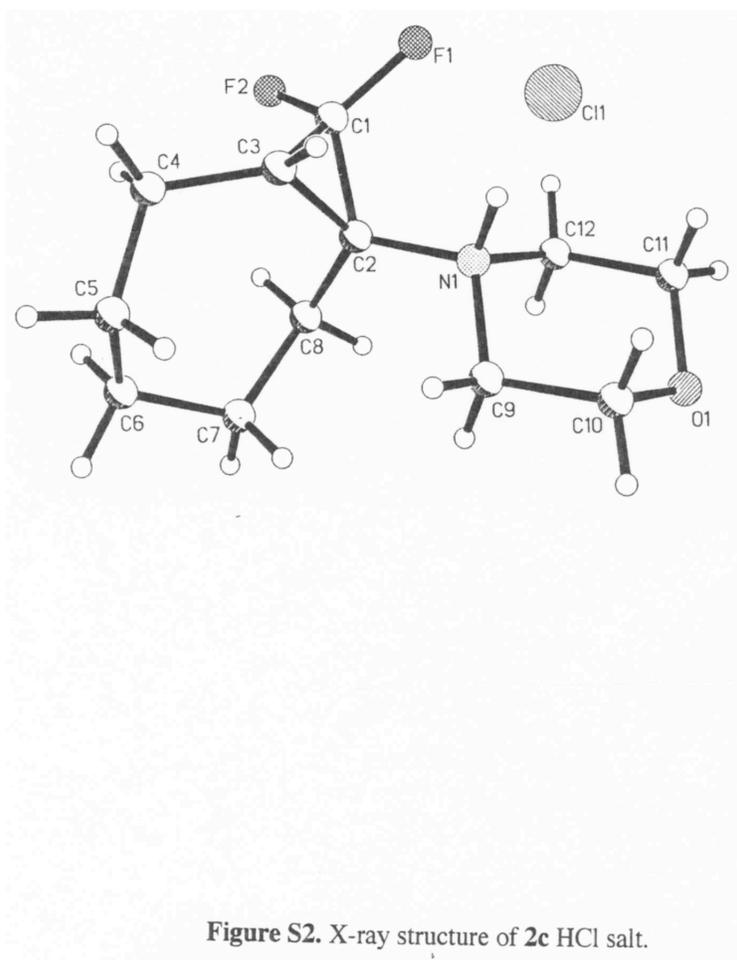


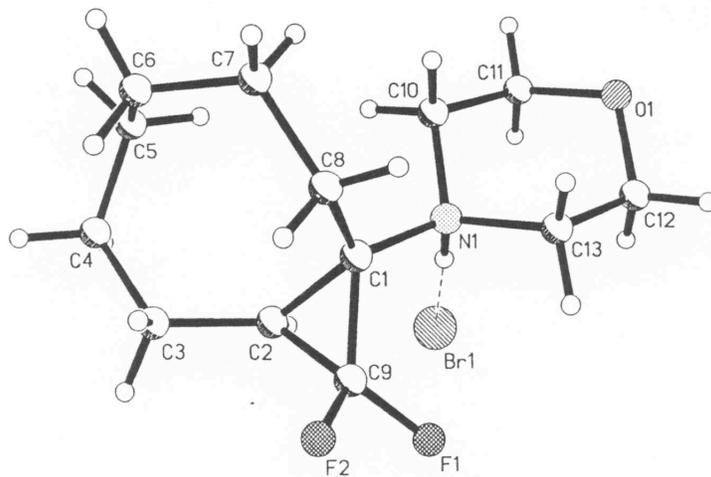
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6	17429.095	138.653	7.3
7	16347.247	130.046	65.3
8	15475.970	123.115	64.8
9	14709.216	117.015	64.5
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11	14172.870	112.749	29.6
12	9711.200	77.255	11.3
13	9679.156	77.000	12.4
14	9647.113	76.745	12.9
15	3501.636	27.856	35.1
16	3299.457	26.248	67.0
17	3158.313	25.125	99.9
18	3154.498	25.095	91.5
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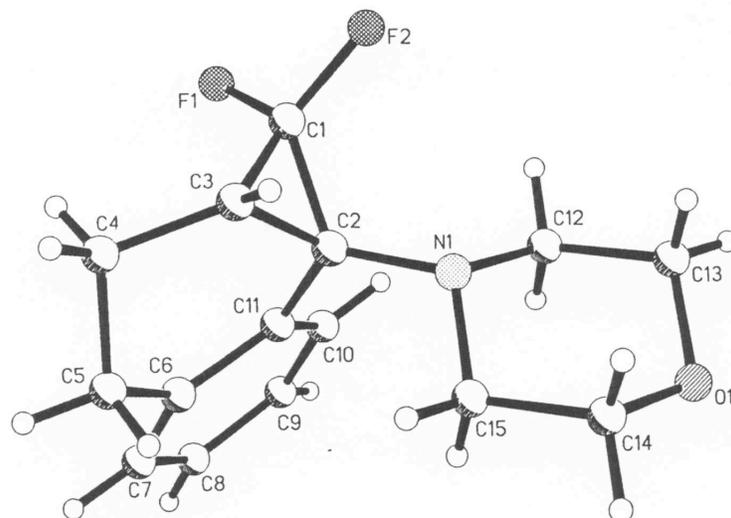


**Figure S1.** X-ray structure of **2b** HCl salt.

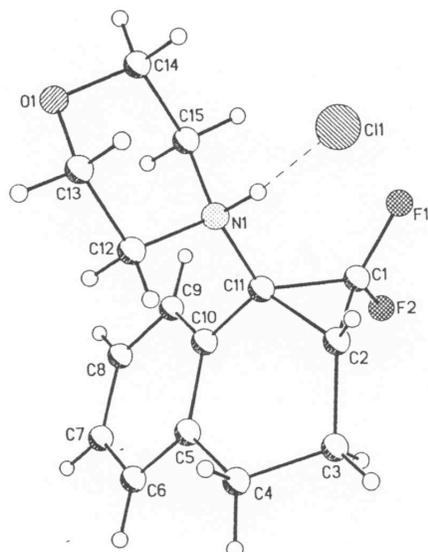




**Figure S3.** X-ray structure of **2d** HBr salt.



**Figure S4.** X-ray structure of **2e**.



**Figure S5.** X-ray structure of **2e** HCl salt.