Late-stage fluorination of bridged scaffolds: Chemoselective generation of a CHF group at three positions of the bicyclo[3.3.1]nonane system

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Supporting Information

Instruments and methods

All moisture-sensitive reactions were performed under an atmosphere of argon and using glassware pre-dried in an oven (100 °C). Thin-layer chromatography was performed on Merck 0.2 mm aluminium-backed silica gel 60 F_{254} plates and visualised by UV (254 nm) or by staining with potassium permanganate with subsequent heating. Flash column chromatography was performed using Merck 0.040-0.063 mm, 230-400 mesh silica gel. Evaporation refers to the removal of solvent under reduced pressure. Melting points were determined using a Büchi B-540 apparatus. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer; absorptions are quoted in wavenumbers. ^{1}H and ^{3}C NMR spectra were recorded on a Bruker DRX-400 (400 MHz) spectrometer and calibrated using residual undeuterated solvent as an internal reference; chemical shifts are in parts per million (δ) and coupling constants (J) are given in Hertz (Hz). The following abbreviations were used in signal assignments: singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), and multiplet (m). Equivocal assignments are denoted by an asterisk. High-resolution mass spectra (HRMS) were obtained using either an Agilent ESI-TOF (time of flight) mass spectrometer at 3500 V emitter voltage, or using a VG7070H mass spectrometer with Finigan Incos II data system at University College London.

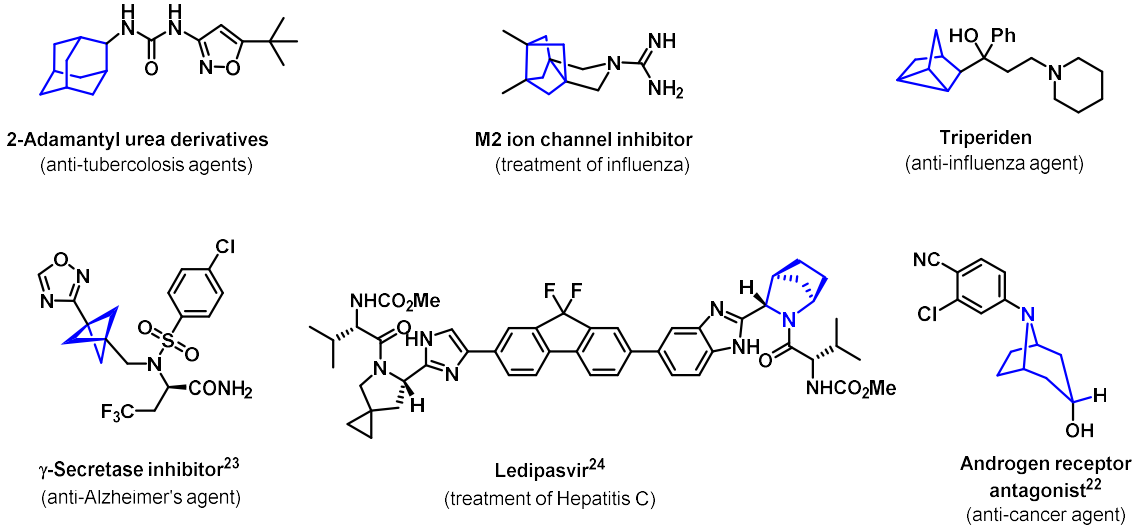
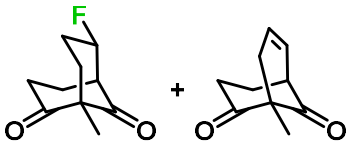


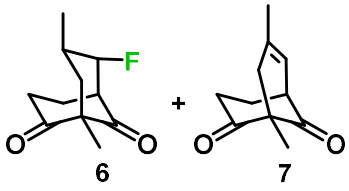
Figure S1. Representative bicyclo compounds with pharmaceutical activity.

Synthesized compounds

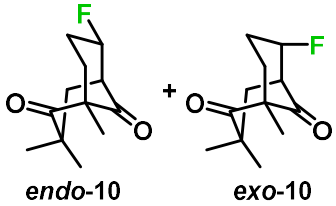


3 4

6-Fluoro-1-methylbicyclo[3.3.1]nonane-2,9-dione (3) and 1-methylbicyclo[3.3.1]non-6-ene-2,9-dione (4). To a stirring solution of 6-*exo*-hydroxy-1-methylbicyclo[3.3.1]nonane-2,9-dione (**2**) (0.073 g, 0.40 mmol) in dry dichloromethane (6 mL) at -78 °C DAST (0.322 g, 2.0 mmol) was added dropwise. The mixture was stirred at -78 °C for 1 h then quenched with water (5 mL) and the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated. Column chromatography (95:5 then 93:7 hexane:ethyl acetate) of the residue gave **3** (0.015 g, 20%) as a colourless oil; IR (film) ν_{max} 3000, 2968, 2925, 1720, 1700, 1275, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.82 (1H, ddt *J* = 48.3, *J*ax-ax = 11.2, *J*ax-eq = 5.6 Hz, 6-H), 3.42–3.33 (1H, m, 5-H), 2.62 (1H, ddd, $^2J_{HH}$ = 16.3, *J*ax-ax = 7.5, *J*ax-eq = 4.6 Hz, 3-Heq) 2.37 (1H, dtm, $^2J_{HH}$ = 16.3, *J*ax-ax = 9.5 Hz, 3-Hax), 2.21–2.09 (3H, m, 7-Heq, 4-Heq, 8-Hax), 2.04–1.94 (1H, m, 4-Hax), 1.85–1.69 (1H, m, 7-Hax), 1.37 (1H, tdm, $^2J_{HH}$ = 14.0, *J* = 4.8 Hz, 8-Heq), 1.15 (3H, s, 1-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211. 2 (C-2) 207.7 (d, $^3J_{CF}$ = 10.6 Hz, (C-9), 92.2 (d, J_{CF} = 188.2 Hz, C-6), 61.9 (C-1), 50.8 (d, $^2J_{CF}$ = 19.4 Hz, C-5), 38.5 (C-3), 33.5 (d, $^3J_{CF}$ = 11.6 Hz, C-8), 25.7 (d, $^2J_{CF}$ = 19.8 Hz, C-7), 16.2 (1-CH_3), 15.3 (d, $^3J_{CF}$ = 4.3 Hz, C-4). ^{19}F NMR (565 MHz, $CDCl_3$) δ -176.3. HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{14}FO_2$ calcd. 185.0972, found 185.0967; and **4** (0.036 g, 60%) as a colourless oil; IR (film) ν_{max} 3005, 2989, 1733, 1691, 1455, 1376, 1350, 1275, 1260, 1195, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (1H, ddd, *J* = 9.2, 3.6, 2.5, 7-H), 5.77 (1H, dm, *J* = 9.2 Hz, 6-H), 3.23–3.18 (1H, m, 5-H), 2.88–2.77 (1H, m, 3-Heq), 2.69 (1H, dd, $^2J_{HH}$ = 18.0 Hz, *J* = 4.0 Hz, 8-C*H*H), 2.57–2.49 (2H, m, 3-Hax, 8-CH*H*), 2.02–1.94 (1H, m, 4-Heq), 1.89–1.79 (1H, m, 4-Hax), 1.22 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.6 (C-9), 208.5 (C-2), 128.4 (C-6), 127.7 (C-7), 64.6 (C-1), 46.5 (C-5), 44.8 (C-8), 34.9 (C-3), 24.6 (C-4), 15.8 (CH_3). HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{13}O_2$ calcd. 165.0910, found 165.0913.

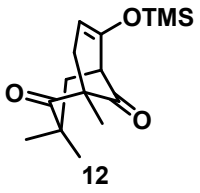


6-Fluoro-1,7-dimethylbicyclo[3.3.1]nonane-2,9-dione (6) and 1,7-dimethylbicyclo[3.3.1]non-6-ene-2,9-dione (7). To stirring solution of 6-hydroxy-1,7-dimethylbicyclo[3.3.1]nonane-2,9-dione (**5**) (0.050 g, 0.25 mmol, 80:20 *exo: endo* epimers) in dry dichloromethane (4 mL) at -78 °C DAST (0.080 g, 0.50 mmol) was added dropwise. The mixture was stirred at -78 °C for 1 h then quenched with water (5 mL) and the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated. Column chromatography (9:1 hexane:ethyl acetate) of the residue gave **6** (0.012 g, 24%) as a colourless oil; IR (film) ν_{max} 1733, 1705, 1451, 1263, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.75 (1H, ddd J = 47.8, Jeq-ax = 4.0, Jeq-eq = 2.0 Hz, 6-H), 3.22–3.15 (1H, m, 5-H), 2.60 (1H, dddd, ^2J = 16.4, Jeq-ax = 7.5, Jeq-eq = 3.9, Jeq-eq = 1.3 Hz, 3-Heq), 2.38 (1H, dt, $^2J_{HH}$ = 16.4, Jax-ax = 9.6 Hz, 3-Hax), 2.24–1.90 (4H, m, 4-Heq, 7-H, 8-CH_2), 1.72–1.61 (1H, m, 4-Hax), 1.15 (3H, s, 1-CH_3), 1.06 (3H, d, J = 6.6 Hz, 1-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.6 (C-2), 209.3 (C-9), 99.8 (d, J_{CF} = 178.7 Hz, C-6), 62.1 (C-1), 48.9 (d, $^3J_{CF}$ = 24.0 Hz, C-5), 43.7 (C-8), 37.6, (C-3), 29.7 (d, $^3J_{CF}$ = 20.1 Hz, C-7), 17.4 (d, $^3J_{CF}$ = 11.0 Hz, C-4), 16.5 (1-CH_3), 15.9 (d, J = 5.1 Hz, 7-CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -189.0. HRMS (ESI-TOF) $[M+H]^+$ $C_{11}H_{16}FO_2$ calcd. 199.1129, found 199.1123; and **7** (0.020 g, 45%) as a colourless oil; IR (film) ν_{max} 1732, 1693, 1444, 1232, 1193, 1085, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.47 (1H, dm, J = 6.0 Hz, 6-H), 3.13–3.09 (1H, m, 5-H), 2.86–2.75 (1H, m, 3-Heq), 2.59–2.42 (3H, m, 3-Hax, 8-CH_2), 1.99–1.92 (1H, m, 4-Hax), 1.86–1.75 (1H, m, 4-Heq), 1.72 (3H, s, 7-CH_3), 1.20 (3H, s, 1-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.7 (C-2), 209.3 (C-9), 135.7 (C-7), 123.0 (C-6), 63.9 (C-1), 49.0 (C-8), 46.0 (C-5), 34.9 (C-3), 25.2 (C-4), 21.7 (7-CH_3), 15.7 (1-CH_3). HRMS (ESI-TOF) $[M+H]^+$ $C_{11}H_{15}O_2$ calcd.179.1067, found 179.1058.



6-Fluoro-1,3,3-trimethylbicyclo[3.3.1]nonane-2,9-dione (10). To a stirring solution of 6-hydroxy-1,3,3-trimethylbicyclo[3.3.1]nonane-2,9-dione (**9**) (0.030 g, 0.14 mmol) in dry dichloromethane (4 mL) at -78 °C DAST (0.115 g, 0.71 mmol) was

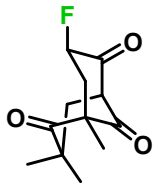
added dropwise. The mixture was stirred at -78 °C for 1 h then quenched with water (5 mL) and the aqueous layer extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated. Column chromatography (95:5 then 93:7 hexane:ethyl acetate) of the residue gave **10** (0.011 g, 38%) as a 65:35 mixture of *exo*-**10**:*endo*-**10**; IR (film) ν_{max} 3018, 1643, 1603, 1379, 1275, 1260, 1226, 1187 cm^{-1}; *exo*-**10**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.94 (1H, ddq, $^2J_{HF}$ = 47.4, *J*eq-ax = 4.5, *J*eq-eq = 1.6 Hz, 6-H), 3.25–3.17 (1H, m, 5-H), 2.25–2.18 (1H, m, 7-Heq), 2.11–1.91 (3H, m, 4-Heq, 7-Hax, 8Heq), 1.65–1.45 (1H, m, 4-Hax), 1.29–1.24 (1H, m, 8-Hax), 1.22 (3H, s, 3-CH_3), 1.15 (3H, s, 3-CH_3), 0.99 (3H, s, 1-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.7 (C-2), 210.9 (C-9), 97.6 (d, J_{CF} = 177.7 Hz, C-6), 60.2 (C-1), 49.1 (d, $^2J_{CF}$ = 22.7 Hz, C-5), 45.5 (C-3), 38.4 (C-7), 34.1 (d, $^3J_{CF}$ = 9.4 Hz, C-8), 26.2 (3-CH_3), 24.7 (3-CH_3), 24.65 (C-4), 18.7 (1-CH_3); ^{19}F NMR (565 MHz, $CDCl_3$) δ -174.9; *endo*-**10**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (1H, dm, J_{HF} = 58.0, Hz, 6-H), 3.33–3.30 (1H, m, 5-H), 2.25-2.18 (1H, m, 7-Heq), 2.11–1.91 (3H, m, 4-Heq, 7-Hax, 8-Heq), 1.91–1.85 (1H, m, 4-Hax), 1.22 (3H, s, 3-CH_3), 1.15 (3H, s, 3-CH_3), 0.99 (3H, s, 1-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$, part assignments) δ 215.7 (C-2), 210.9 (C-9), 97.6 (d, J_{CF} = 177.7 Hz, C-6), ^{19}F NMR (565 MHz, $CDCl_3$) δ -163.8. HRMS (ESI-TOF) $[M+H]^+$ $C_{12}H_{18}FO_2$ calcd. 213.1285, found 213.1288.



12

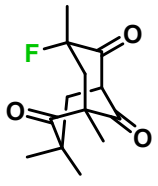
1,3,3-Trimethyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione (12). To a stirring solution of 1,3,3-trimethylbicyclo[3.3.1]nonane-2,6,9-trione (**11**) (0.050 g, 0.24 mmol) in dry dichloromethane (6 mL) at 0 °C was added Et_3N (0.109 g, 1.08 mmol). The mixture was stirred for 5 min, then TMSOTf (0.192 g, 0.86 mmol) was added and the mixture was stirred at 0 °C for a further 10 min. The ice-bath was then removed, and the mixture was allowed to warm to 20 °C, then heated at 45 °C for 3 h. After allowing to cool to 20 °C sat. aqueous $NaHCO_3$ (5 mL) was added, and the aqueous layer extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated to give **12** (0.064 g, 95%) as colourless oil; IR (film) ν_{max} 2965, 2925, 1706, 1470, 1277, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.72 (1H, dd, *J* = 5.5, 2.0 Hz, 7-H), 3.03 (1H, d, *J* = 7.5 Hz, 5-H), 2.72 (1H, dd, *J* = 16.0, 5.6 Hz, 8-Heq/ax), 2.11–2.03 (2H, m, 8-Hax/eq, 4-Hax), 1.96 (1H, dd, *J* = 13.5, 7.5 Hz, 4-Heq), 1.26 (3H, s, 1-CH_3), 1.18 (3H, s, 3-CH_3), 1.04 (3H, s, 3-CH_3), 0.20 (9H, s, $OSi(CH_3)_3$). HRMS

(ESI-TOF) $[M+H]^+$ $C_{15}H_{25}O_3Si$ calcd. 281.1567, found 281.1567.



13

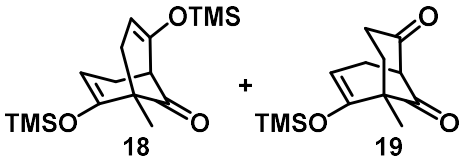
7-Fluoro-1,3,3-trimethylbicyclo[3.3.1]nonane-2,6,9-trione (13). To a stirring solution of 1,3,3-trimethyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione (**12**) (0.037 g, 0.13 mmol) in dry acetonitrile (2 mL) was added selectfluor in one portion (0.093 g, 0.26 mmol) at 25 °C. After stirring the mixture for 16 h water (2 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated to give **13** (0.018 g, 58%) as a colourless oil; IR (film) ν_{max} 2918, 1850, 1729, 1703, 1462, 1270, 1239, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.96 (1H, ddd, J_{HF} = 46.5, *J*ax-ax = 12.4, *J*ax-eq = 7.6 Hz, 7-H), 3.92 (1H, ddd, *J* = 11.0, 4.5, 1.2 Hz, 5-H), 2.75 (1H, ddd, $^2J_{HH}$ = 12.4, $^3J_{HF}$ = 7.6, *J*eq-ax = 2.5 Hz, 8-Heq), 2.33 (1H, dd, $^2J_{HH}$ = 15.2, *J*eq-eq = 11.0 Hz, 4-Heq), 1.76 (1H, dd, $^2J_{HH}$ = 15.2 Hz, 4-Hax), 1.63 (1H, apparent q, $^2J_{HH}$ = *J*ax-ax = $^3J_{HF}$ = 12.4 Hz, 8-Hax), 1.39 (3H, s, 1-CH_3), 1.20 (3H, s, 3-CH_3), 1.08 (3H, s, 3-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.0 (C-2), 201.9 (C-9), 198.0 (d, $^2J_{FC}$ = 15.0 Hz, C-6), 86.9 (d, J_{FC} = 195.4 Hz, C-7), 62.0 (C-5), 58.5 ($^3J_{FC}$ = 8.5 Hz, C-1), 45.1 (C-3), 37.9 (d, $^3J_{FC}$ = 20.5 Hz, C-8), 35.5 (C-4), 26.1 (3-CH_3), 24.6 (3-CH_3), 18.6 (1-CH_3); ^{19}F NMR (565 MHz, $CDCl_3$) δ -198.0. HRMS (ESI-TOF) [M]+ $C_{12}H_{15}FO_3$ calcd. 226.1005, found 226.1007.



16

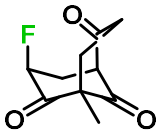
7-Fluoro-1,3,3,7-tetramethylbicyclo[3.3.1]nonane-2,6,9-trione (16). To a stirring solution of 1,3,3-trimethylbicyclo[3.3.1]non-6-ene-2,6,9-trione **(14)** (0.050 g, 0.22 mmol) in dry dichloromethane (3 mL) at 0 °C was added Et_3N (0.101 g, 1.0 mmol). The mixture was stirred for 5 min, then TMSOTf (0.177 g, 0.80 mmol) was added and the mixture was stirred at 0 °C for a further 10 min. The ice-bath was then removed, and the mixture was allowed to warm to 20 °C, then heated at 45 °C for 16 h. After allowing to cool to 20 °C sat. aqueous $NaHCO_3$ (5 mL) was added, and the aqueous layer extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with water (10 mL), dried over

Na_2SO_4, filtered and evaporated. Column chromatography (petroleum ether then 97:3 petroleum ether:ethyl acetate) of the residue gave 1,3,3,7-tetramethyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione **15** (0.030 g, 46%) as a colourless oil of which (0.025 g, 0.08 mmol) was immediately placed in a flame-dried round-bottom flask and dry acetonitrile (3 mL) and selectfluor (0.060 g, 0.16 mmol) added at 25 °C. The resulting solution was stirred at 25 °C for 3 d after which water (2 mL) was added and the aqueous layer extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated to give **16** (0.011 g, 57%) as a colourless oil; IR (film) ν_{max} 2925, 2845, 1732, 1707, 1455, 1383 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.60 (1H, dt, *J*eq-eq = 8.4, *J*eq-eq = 2.4 Hz, 5-H), 2.60–2.45 (1H, dm, $^3J_{HF}$ = 36.0, *J* = 14.8 Hz, 8-Heq), 2.44–2.38 (1H, dd, *J* = 13.6 Hz, 1.6 Hz, 4-Hax), 2.14–2.03 (2H, m, 4-Heq, 8-Hax), 1.46 (3H, d, $^3J_{HF}$ = 22.1 Hz, 7-CH_3), 1.35 (3H, s, 1-CH_3), 1.12 (3H, s, 3-CH_3), 1.09 (3H, s, 3-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.3 (C-2), 204.2 (C-9), 202.3 (d, $^2J_{FC}$ = 25.8 Hz, (C-6), 95.5 (d, J_{FC} = 170.8 Hz, (C-7), 60.0 (C-1), 57.5 (C-5), 45.9 (C-3), 45.6 (d, $^2J_{FC}$ = 3.7 Hz, C-8), 36.6 (C-4), 28.5 (3-CH_3), 26.6 (3-CH_3), 20.1 (1-CH_3), 19.7 (d, J_{FC} = 23.4 Hz, 7-CH_3); ^{19}F NMR (565 MHz, $CDCl_3$) δ -141.0.



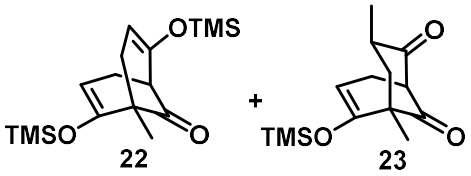
1-Methyl-2,6-bis((trimethylsilyl)oxy)bicyclo[3.3.1]nona-2,6-ene-2,9-dione (18) and 1-methyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione (19). To a stirring solution of 1-methylbicyclo[3.3.1]nonane-2,6,9-trione **17** (0.040 g, 0.22 mmol) in dry dichloromethane (3 mL) at 0 °C was added Et_3N (0.066 g, 0.66 mmol) was then added. The mixture was stirred for 5 min, then TMSOTf (0.120 g, 0.54 mmol) was added and the mixture was stirred at 0 °C for a further 10 min. The ice-bath was then removed, and the mixture was allowed to warm to 20 °C, then heated at 45 °C for 2 h. After allowing to cool to 20 °C sat. aqueous $NaHCO_3$ (5 mL) was added, and the aqueous layer extracted with dichloromethane (3 x 12 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated. Column chromatography of the residue (hexane then 95:5 hexane:ethyl acetate) gave **18** (0.020 g, 28%) as an oil; IR (film) ν_{max} 2959, 1734, 1658, 1253, 1181, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.81–4.77 (2H, m, 3-H, 7-H), 2.80 (1H, d, *J* = 4.8 Hz, 5-H), 2.50–2.41 (2H, m, 4-Heq, 8-Heq), 2.35 (1H, dm, *J* = 16.4 Hz, 4-Hax), 2.00 (1H, m, 8-Hax), 1.53 (3H, s, 1-CH_3), 0.18 (9H, $OSi(CH_3)_3$), 0.17 (9H, $OSi(CH_3)_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1 (C-9), 152.4 (C-2), 150.2 (C-6), 101.7 (C-3/C-7), 99.8 (C-7/C-3), 51.3 (C-5), 50.5 (C-1), 36.4 (C-8), 28.2 (C-4), 16.3 (1-CH_3), 0.38 ($OSi(CH_3)_3$), 0.35 ($OSi(CH_3)_3$). HRMS (ESI-TOF) [M+H] $C_{16}H_{29}O_3Si_2$ calcd. 325.1650, found 325.1658; and **19** (0.005 g, 10%) as an oil; IR (film) ν_{max} 3003, 2978, 1709, 1270 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (1H, dd, *J* = 5.2, 2.4 Hz, 3-H), 3.38 (apparent d, *J*eq-ax = 6.4 Hz, 5-H), 2.69–2.61 (2H, m, 4-Heq, 7-Heq), 2.51 (1H, ddt, $^2J_{HH}$ = 17.0 Hz, *J*ax-eq = 5.6, *J*eq-eq = 1.6 Hz, 7-Hax), 2.39 (1H, ddd, $^2J_{HH}$ = 17.1, *J*ax-ax = 5.1, *J*ax-eq = 1.6 Hz, 4-Hax), 2.10 (1H, ddd, $^2J_{HH}$ = 13.7, *J*ax-ax = 8.0 Hz, *J* =1.7 Hz, 8-Hax), 1.47 (1H, m, 8-Heq), 1.24 (3H, s, 1-CH_3), 0.24 (9H, s, ($OSi(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.8 (C-9), 205.3 (C-6), 150.7 (C-2), 100.2 (C-3), 63.6 (C-5), 51.0 (C-1), 36.8 (C-7), 30.4 (C-8), 29.4 (C-4), 16.5 (1-CH_3), 0.32 ($OSi(CH_3)_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{13}H_{21}O_3Si$ calcd. 253.1254, found 253.1259.



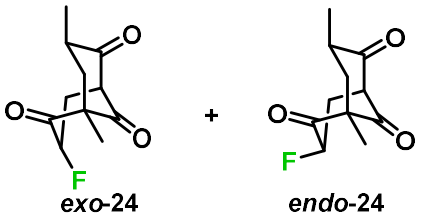
20

3-Fluoro-1-methylbicyclo[3.3.1]nonane-2,6,9-trione (20). To a stirring solution of 5-methyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione **19** (0.005 g, 0.02 mmol) in dry acetonitrile (2 mL) was added selectfluor (0.014 g, 0.04 mmol) at 25 °C. After stirring the mixture for 16 h water (3 mL) was added and the aqueous layer extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give **20** (0.0035 g, 90%) as a colourless oil; IR (film) ν_{max} 2919, 1719, 1456, 1270, 1109, 1020 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (1H, dtd, J_{HF} = 47.7 Hz, *J*ax-eq = 7.5 Hz ^4J = 1.6 Hz, 3-H), 3.64 (1H, dd, *J* = 6.8, 3.3 Hz, 5-H), 2.64–2.50 (2H, m, 7-CH_2), 2.46–2.36 (2H, m, 4-CH_2), 2.25 (1H, ddd, $^2J_{HH}$ = 14.0 Hz, *J*ax-eq = 7.3, *J*eq-eq = 5.0 Hz, 8-Heq), 1.74 (1H, ddd, $^2J_{HH}$ = 13.9, *J*ax-ax = 9.7, *J*ax-eq = 7.7 Hz, 8-Hax), 1.40 (3H, s, 1-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.8 (C-6), 202.5 (d, $^2J_{CF}$ = 17.6 Hz, C-2), 200.9 (C-9), 89.0 (d, J_{CF} = 184.5 Hz, C-3), 61.5 (C-1), 60.9 (d, $^3J_{CF}$ = 4.6 Hz, C-5), 36.4 (C-7), 30.2 (C-8), 29.0 (d, $^2J_{CF}$ = 22.5 Hz, C-4), 16.9 (1-CH_3); ^{19}F NMR (565 MHz, $CDCl_3$) δ -187.13. HRMS (ESI-TOF) $[M+H]^+$ $C_{10}H_{11}FO_3$ calcd. 199.0765, found 199.0771.

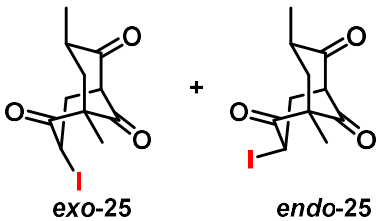


1,7-Dimethyl-2,6-bis((trimethylsilyl)oxy)bicyclo[3.3.1]nona-2,6-dien-9-one (22) and 1,7-Dimethyl-2-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione (23). To a stirring solution of 1,7-*exo*-dimethylbicyclo[3.3.1]nonane-2,6,9-trione **21** (0.090 g, 0.46 mmol) in dry dichloromethane (5 mL) at 0 °C was added Et_3N (0.140 g, 1.38 mmol). The mixture was stirred for 5 min, then TMSOTf (0.245 g, 1.1 mmol) was added and the mixture was stirred at 0 °C for a further 10 min. Then the ice-bath was then removed and the mixture heated at 45 °C for 3 h. After allowing to cool to 20 °C sat. aqueous $NaHCO_3$ (5 mL) was added, and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated. Column chromatography (petroleum ether then 95:5 petroleum ether:ethyl acetate) of the residue gave 1,7-dimethyl-2,6-bis((trimethylsilyl)oxy)bicyclo[3.3.1]nona-2,6-dien-9-one **22** (0.018 g, 11%) as a colourless oil; R_f 0.76 (petroleum ether:ethyl acetate, 80:20); IR (film) ν_{max} 1723, 1420, 1262, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (1H, dd, *J* = 5.6, 2.0 Hz, 3-H), 2.83 (1H, d, *J*eq-ax = 4.8 Hz, 5-H), 2.47 (1H, ddd, $^2J_{HH}$ = 16.4, *J*ax-eq = 5.2, *J*ax-eq = 1.6 Hz, 4-Heq), 2.41–2.34 (2H, m, 4-Hax, 8-Heq), 2.01 (1H, dd, $^2J_{HH}$ = 16.4, *J*eq-eq = 1.2, 8-Hax), 1.56 (3H, s, 7-CH_3), 1.12 (3H, s, 1-CH_3), 0.18 (18H, s, 2 x $OSi(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9 (C-9), 152.4 (C-2), 141.9 (C-6), 111.5 (C-7), 99.5 (C-3), 64.2 (C-1), 50.9 (C-5), 42.8 (C-8), 28.2 (C-4), 16.2 (1-CH_3), 15.7 (7-CH_3), 0.8 ($OSi(CH_3)_3$), 0.3 ($OSi(CH_3)_3$); HRMS (ESI-TOF) $[M+H]^+$ $C_{17}H_{31}O_3Si_2$ calcd. 339.1806, found 339.1807, and 1,7-dimethyl-2-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione **23** (0.045 g, 36%) as a colourless oil; R_f 0.6 (petroleum ether:ethyl acetate, 80:20); IR (film) ν_{max} 2955, 2931, 2849, 1728, 1702, 1653, 1452, 1252, 1225, 1048, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (1H, dd, *J* = 4.8, 2.4 Hz, 3-H), 3.47 (1H, apparent d, *J*eq-*endo* = 6.4 Hz, 5-H), 2.80-2.72 (2H, m, 7-CH), 2.71–2.62 (1H, ddd, $^2J_{HH}$ = 17.2, *J*ax-eq = 6.8 Hz, *J*eq-eq = 2.0 Hz, 4-Hax), 2.53–2.40 (1H, m, 8-Heq), 2.34 (1H, ddd, $^2J_{HH}$ = 17.2, *J*eq-eq = 4.8, *J*eq-eq = 0.8 Hz, 4-Heq), 2.20 (1H, dd, $^2J_{HH}$ = 13.2 Hz, *J*ax-eq = 7.2 Hz, 8-Hax), 1.20 (3H, s, 1-CH_3), 1.12 (3H, d, *J* = 6.8 Hz, 7-CH_3), 0.24 (9H, s, $OSi(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9 (C-9), 204.8 (C-6), 151.3 (C-2), 100.0 (C-3), 63.5 (C-5), 51.7 (C-1), 40.6 (C-7), 39.9 (C-8), 29.1 (C-4), 16.4 (1-CH_3), 13.4 (7-CH_3), 0.3 ($OSi(CH_3)_3$). HRMS (ESI-TOF) $[M+H]^+$ $C_{14}H_{23}O_3Si$ calcd.

267.1411, found 267.1413.



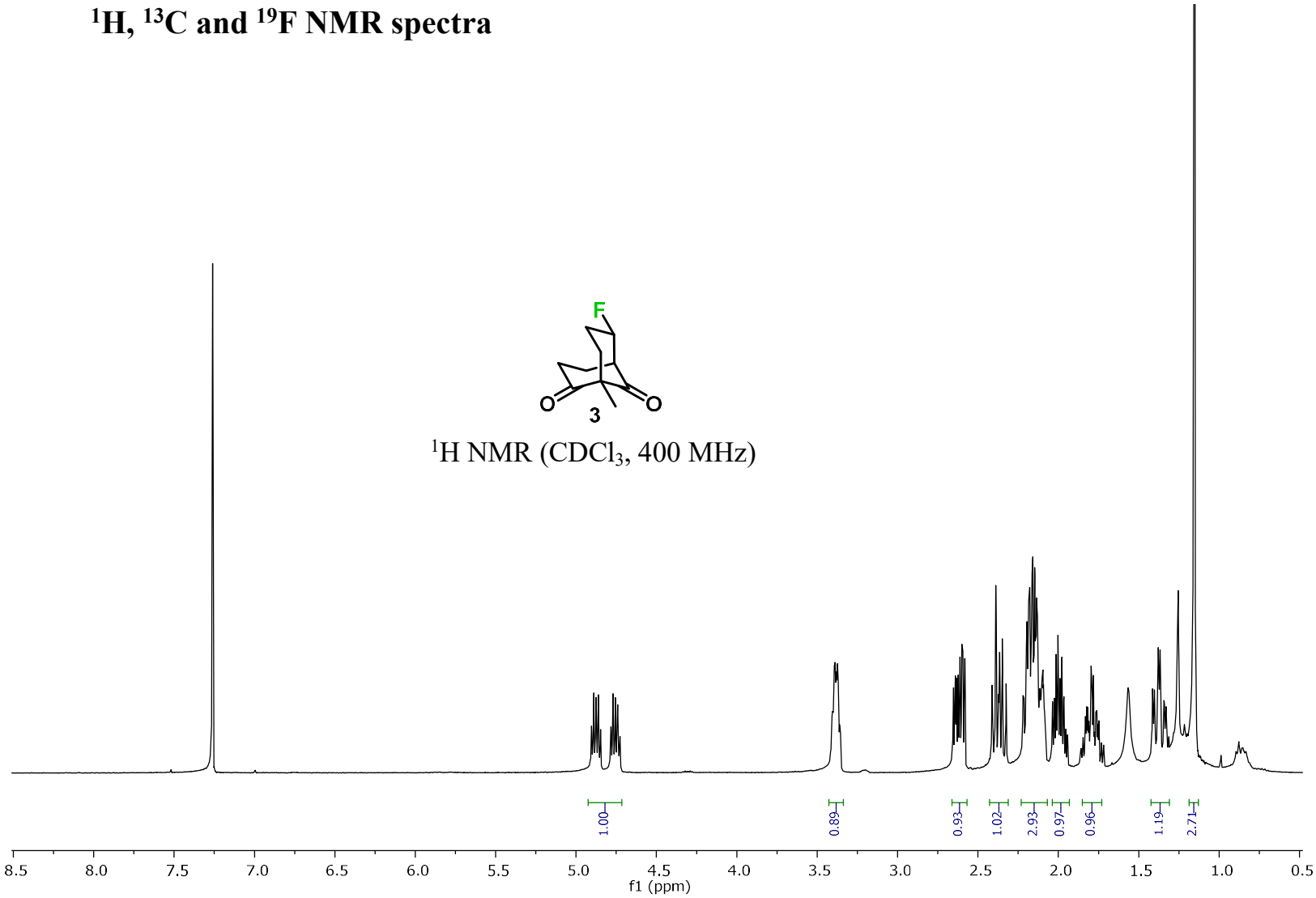
3-Fluoro-1,7-dimethylbicyclo[3.3.1]nonane-2,6,9-trione (24). To a stirring solution of 3,5-dimethyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione (**22**) (0.020 g, 0.08 mmol) in dry acetonitrile (2 mL) was added selectfluor in one portion (0.056 g, 0.16 mmol) at 25 °C. After stirring the mixture for 16 h water (2 mL) was added and the aqueous layer extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (3 x10 mL), dried over Na_2SO_4, filtered and evaporated to give **24** (0.013 g, 81%) as a 75:25 of ***exo*-24**:***endo*-24**, R_f 0.23 (petroleum ether: ethyl acetate, 80:20); IR (film) ν_{max} 2916, 1721, 1642, 1452, 1218, 1022, 995 cm^{-1}; ***exo*-24**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.05 (1H, dt, J_{HF} = 48.4, *J*ax-eq = *J*eq-eq = 4.8 Hz, 3-H), 3.74 (1H, td, *J* = 9.2, 2.0 Hz, 5-H), 2.70–2.50 (2H, m, 8-CH_2), 2.51–2.36 (2H, m, 4-CH_2), 2.35–2.25 (1H, m, 7-H), 1.38 (3H, s, 1-CH_3), 1.13 (3H, d, *J* = 6.5 Hz, 7-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.0 (C-9), 203.9 (d, $^2J_{CF}$ = 19.7 Hz, C-2), 200.2 (C-6), 89.7 (d, J_{CF} = 180.4 Hz, C-3), 63.3 (C-1), 61.4 (C-5), 40.4 (C-7), 39.6 (d, $^2J_{CF}$ = 4.6 Hz, C-4), 37.2 (C-8), 17.1 (1-CH_3), 14.2 (7-CH_3); ^{19}F NMR (565 MHz, $CDCl_3$) δ -183.0; ***endo*-24**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (1H, ddd, J_{HF} = 46.7, *J*ax-ax = 11.8, *J*ax-eq = 7.6 Hz, 3-H), 3.70 (1H, m, 5-H), 2.51-2.36 (2H, m, 4-CH_2), 2.35-2.25 (1H, m, 7-H), 2.18 (1H, tdd, $^2J_{HH}$ = 17.2, *J*ax-ax = 6.8, *J*ax-eq = 2.0 Hz, 8-Heq), 2.05–1.96 (1H, m, 8-Hax), (3H, s, 1-CH_3), 1.11 (3H, d, *J* = 6.8 Hz, 7-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.8 (C-9), 206.8 (C-2), 203.4 (C-6), 87.1 (d, J_{CF} = 192.2 Hz, C-3), 77.4 (C-1), 63.4 (d, $^3J_{CF}$ = 26.8 Hz, C-5), 40.6 (C-7), 28.7 (d, $^2J_{CF}$ = 22.8 Hz, C-4), 21.6 (C-8), 16.3 (1-CH_3), 14.4 (7-CH_3); ^{19}F NMR (565 MHz, $CDCl_3$) δ -195.8; HRMS (ESI-TOF) $[M+H]^+$ $C_{11}H_{14}FO_3$ calcd. 213.0921, found 213.093.



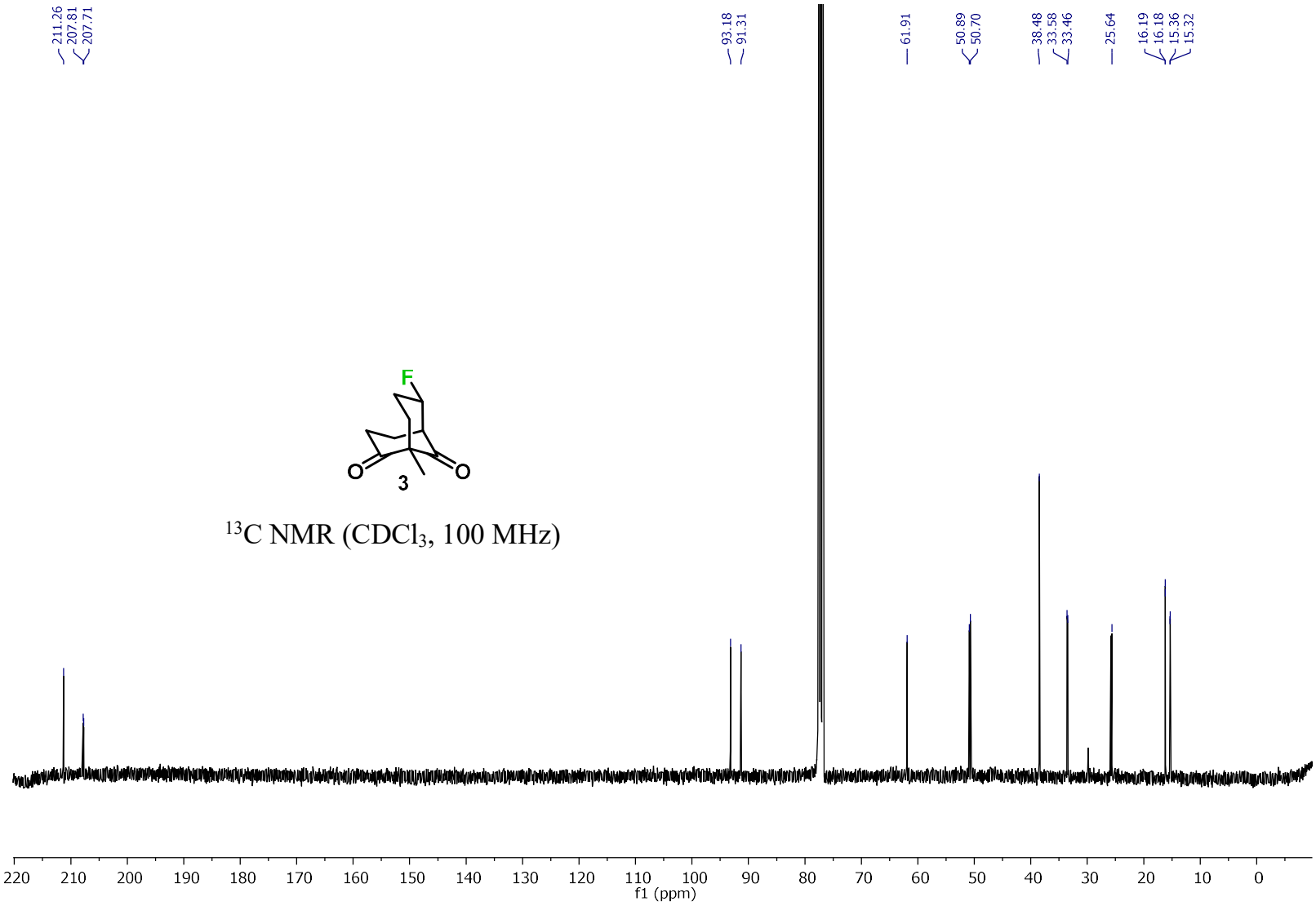
3-Iodo-1,7-dimethylbicyclo[3.3.1]nonane-2,6,9-trione (25). To a stirring solution of 3,5-dimethyl-6-((trimethylsilyl)oxy)bicyclo[3.3.1]non-6-ene-2,9-dione (**22**) (0.018 g, 0.06 mmol) in dry acetonitrile (2 mL) was added *N*-iodosuccinimide in

one portion (0.022 g, 0.10 mmol) at 25 °C, and the mixture stirred at 25 °C for 48 h. Then sat. aqueous NH_4Cl (5 mL) was added and the aqueous layer extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and evaporated to give **25** (0.015 g, 80%) as a 80:20 mixture of ***exo*-25**:***endo*-25**; IR (film) ν_{max} 2939, 1715, 1452, 1230, 1108 cm^{-1}; ***exo*-25**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, dd, *J*ax-eq = 6.3 Hz, *J*eq-eq = 2.2 Hz, 3-H), 3.87 (1H, dd, *J* = 10.2, 2.0 Hz, 5-H), 2.85 (1H, dd, $^2J_{HH}$ = 16.8, *J*ax-eq = 10.2 Hz, 4-Hax), 2.66 (1H, ddd, $^2J_{HH}$ = 16.8 Hz, *J*ax-eq = 6.3 Hz, *J*eq-eq = 2.0 Hz, 4-Heq), 2.56–2.45 (2H, m, 7-CH_2), 2.40 (1H, dd, $^2J_{HH}$ = 13.1 Hz, *J*ax-eq =7.0 Hz, 8-Heq), 1.61 (3H, s, 1-CH_3), 1.33–1.22 (1H, m, 8-Hax), 1.07 (3H, d, *J* = 6.4 Hz, 7-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6 (C-2), 204.2 (C-6), 201.0 (C-9), 62.0 (C-5), 61.2 (C-1), 41.0 (C-8), 38.6 (C-7), 31.5 (C-4), 21.8 (C-3), 21.2 (1-CH_3), 13.7 (7-CH_3); ***endo*-25**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (1H, dd, *J*eq-ax = 12.0, *J*eq-eq = 3.6 Hz, 3-H), 3.87 (1H, dd, *J* = 10.2, 2.0 Hz, 5-H); ^{13}C NMR (101 MHz, $CDCl_3$, part assignment) δ 206.6, 203.2, 202.8, 61.5, 60.6.

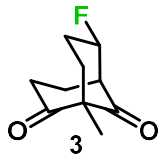
^{1}H, ^{13}C and ^{19}F NMR spectra



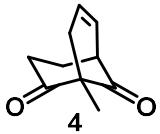
^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 100 MHz)



^{19}F NMR ($CDCl_3$, 376 MHz)



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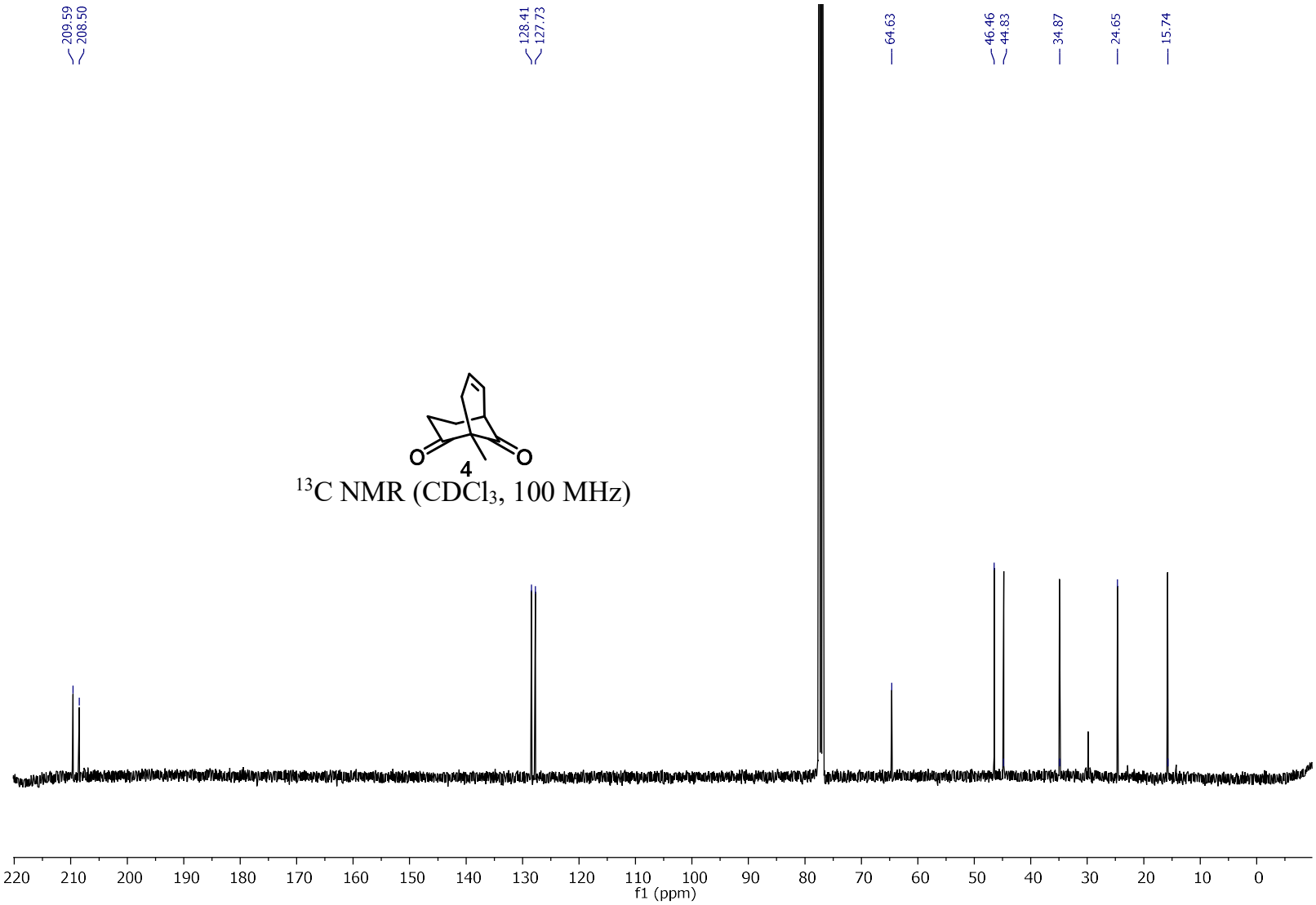
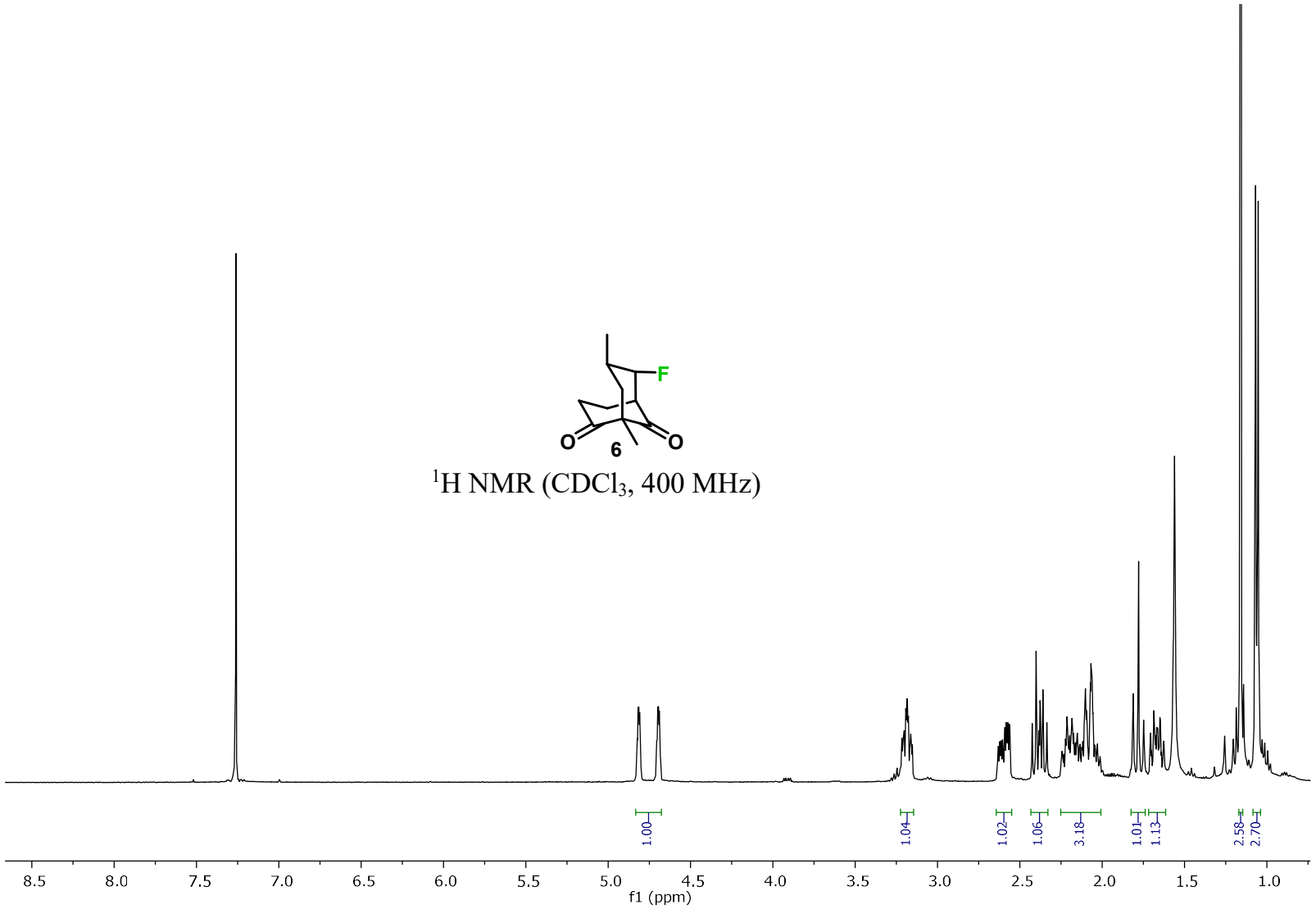
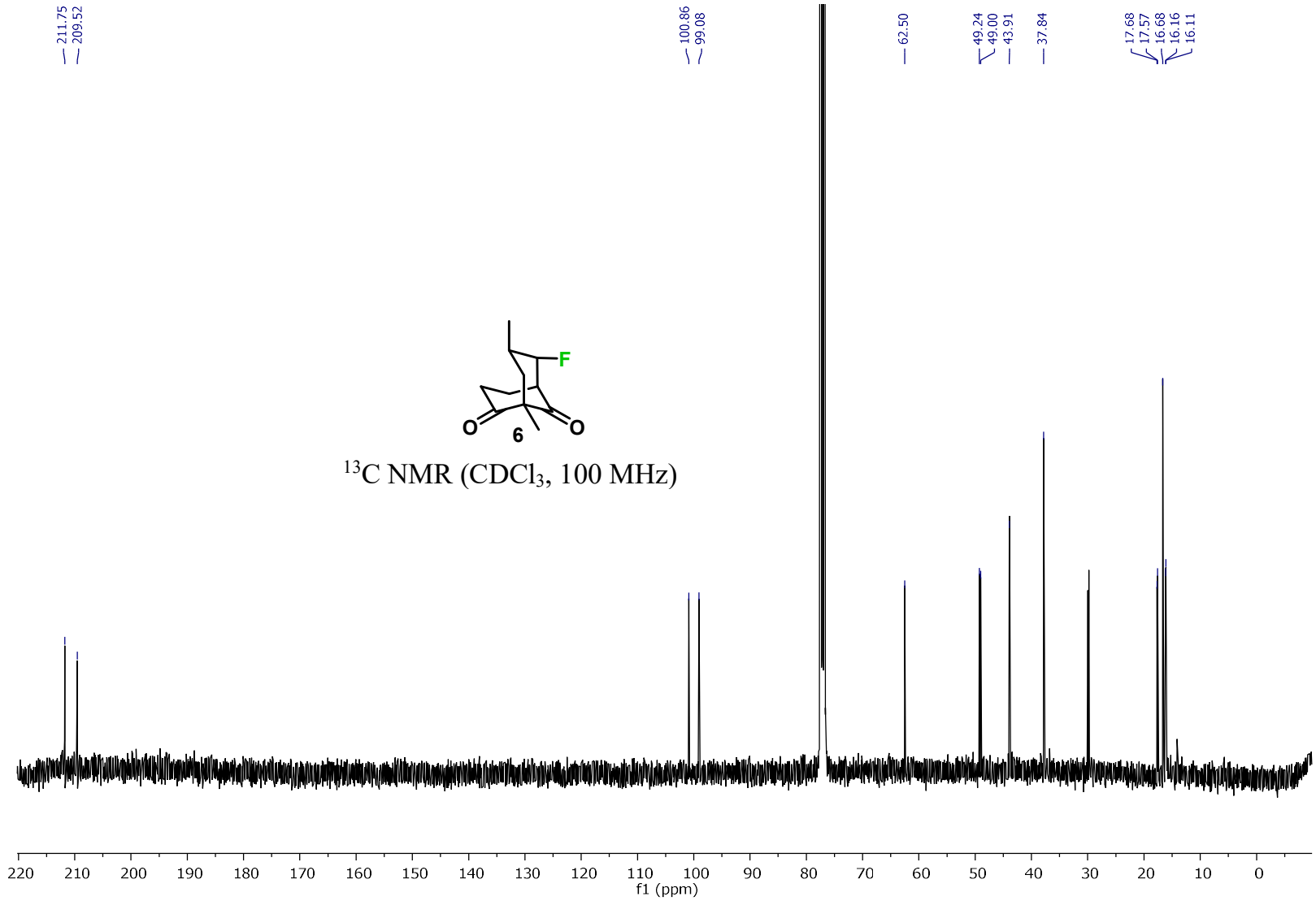
^{1}H NMR ($CDCl_3$, 400 MHz)



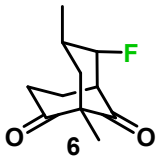
^{13}C NMR ($CDCl_3$, 100 MHz)



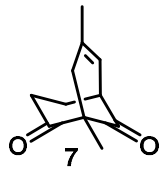
^{1}H NMR ($CDCl_3$, 400 MHz)



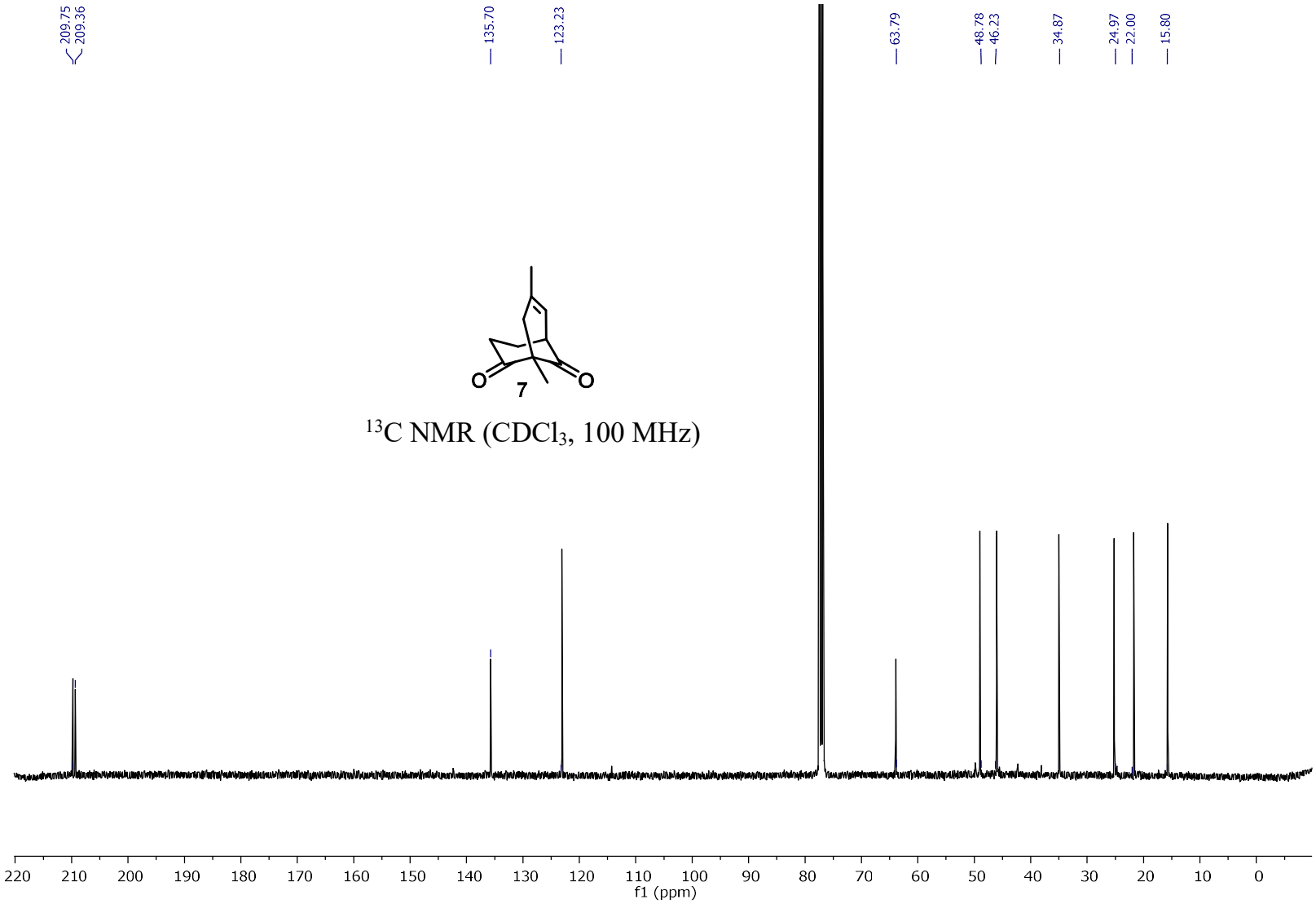
^{13}C NMR ($CDCl_3$, 100 MHz)



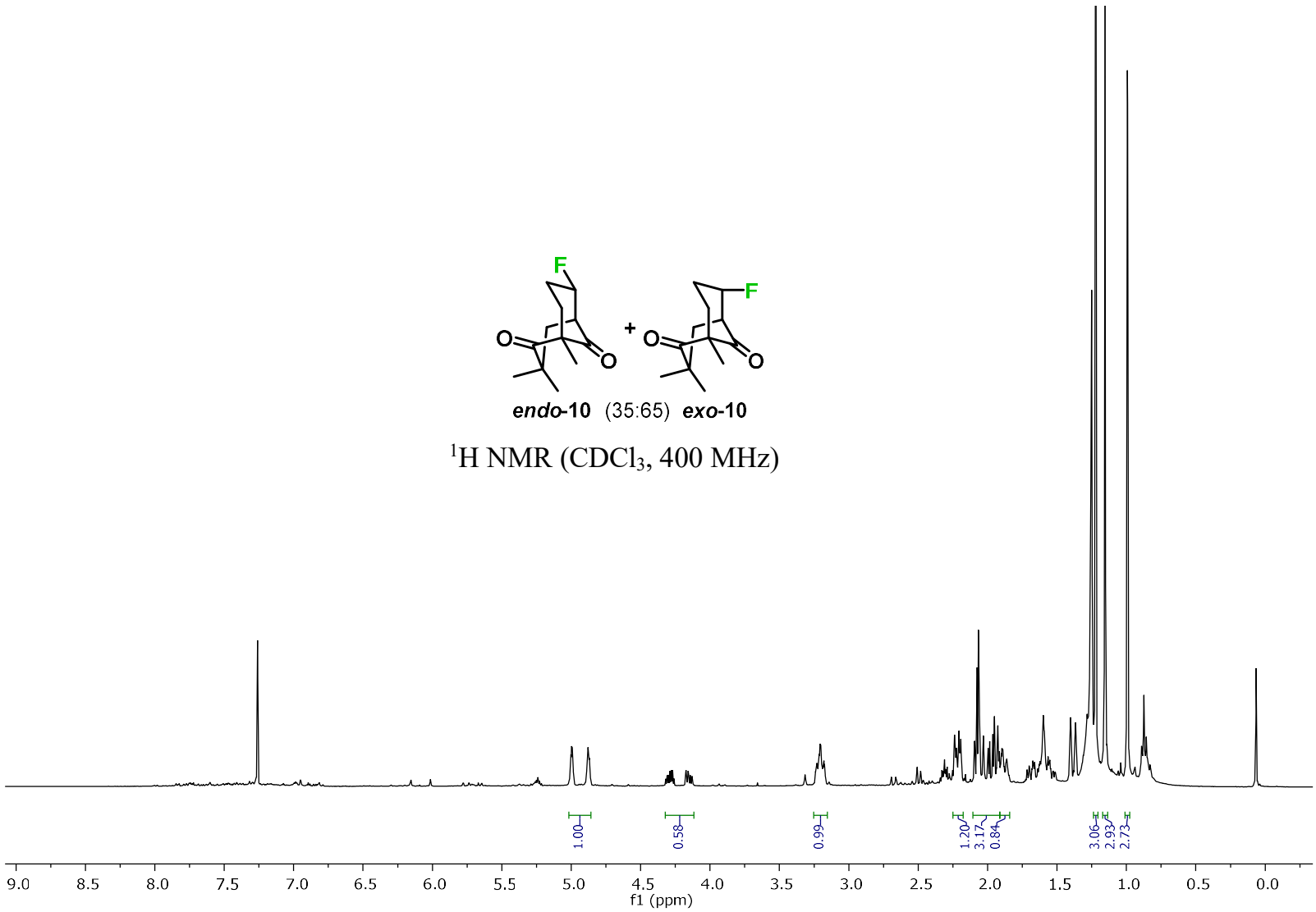
^{19}F NMR ($CDCl_3$, 376 MHz)



^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 100 MHz)


F
O
O
+
O
F
O
endo-10 (35:65) exo-10
1H NMR (CDCl3, 400 MHz)
1.00
0.58
0.99
1.20
3.17
0.84
3.06
2.93
2.73
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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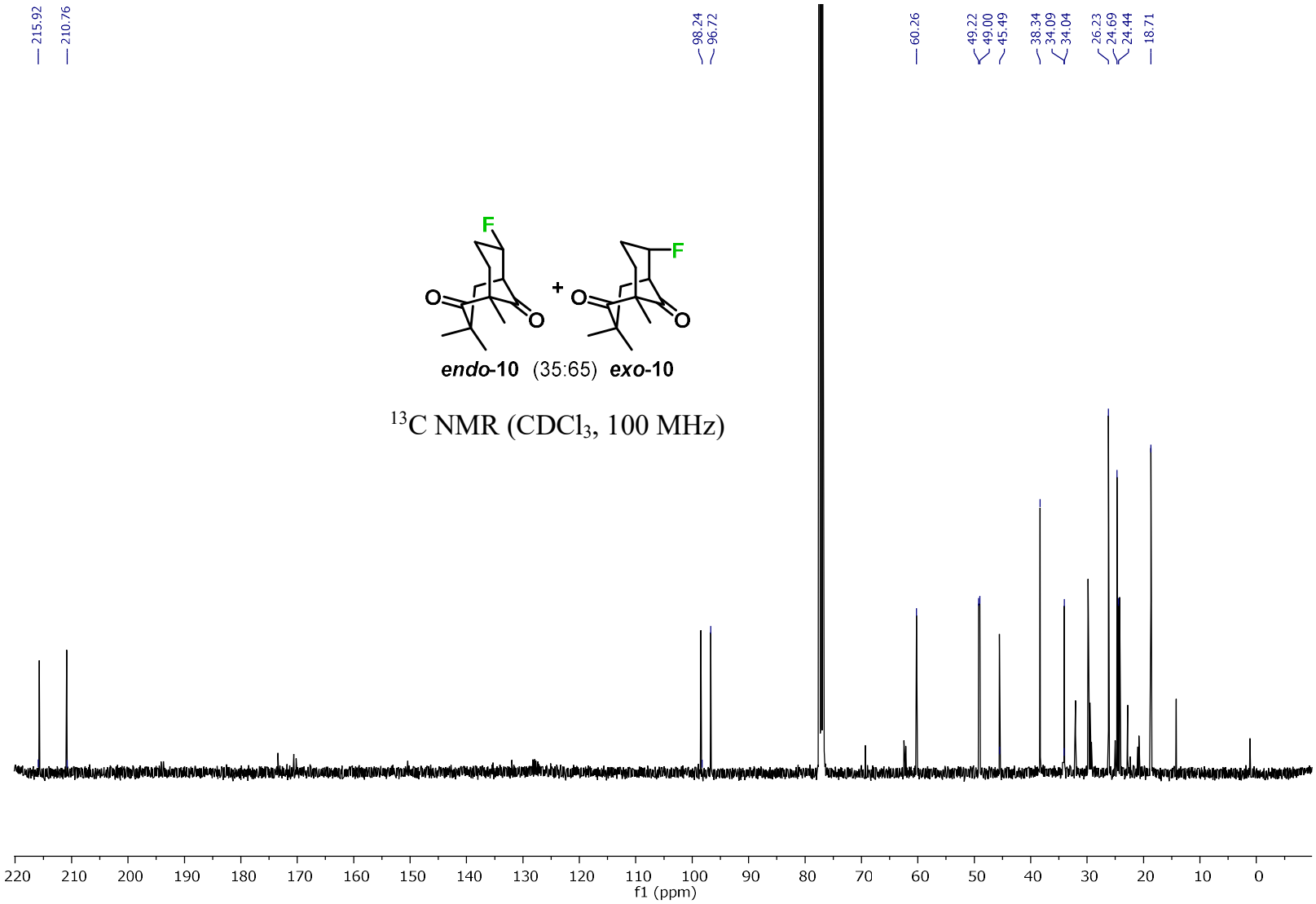
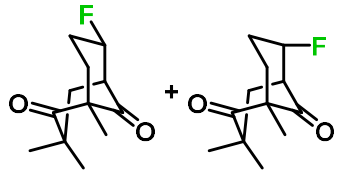
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



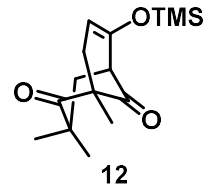
***endo*-10** (35:65) ***exo*-10**

^{13}C NMR ($CDCl_3$, 100 MHz)



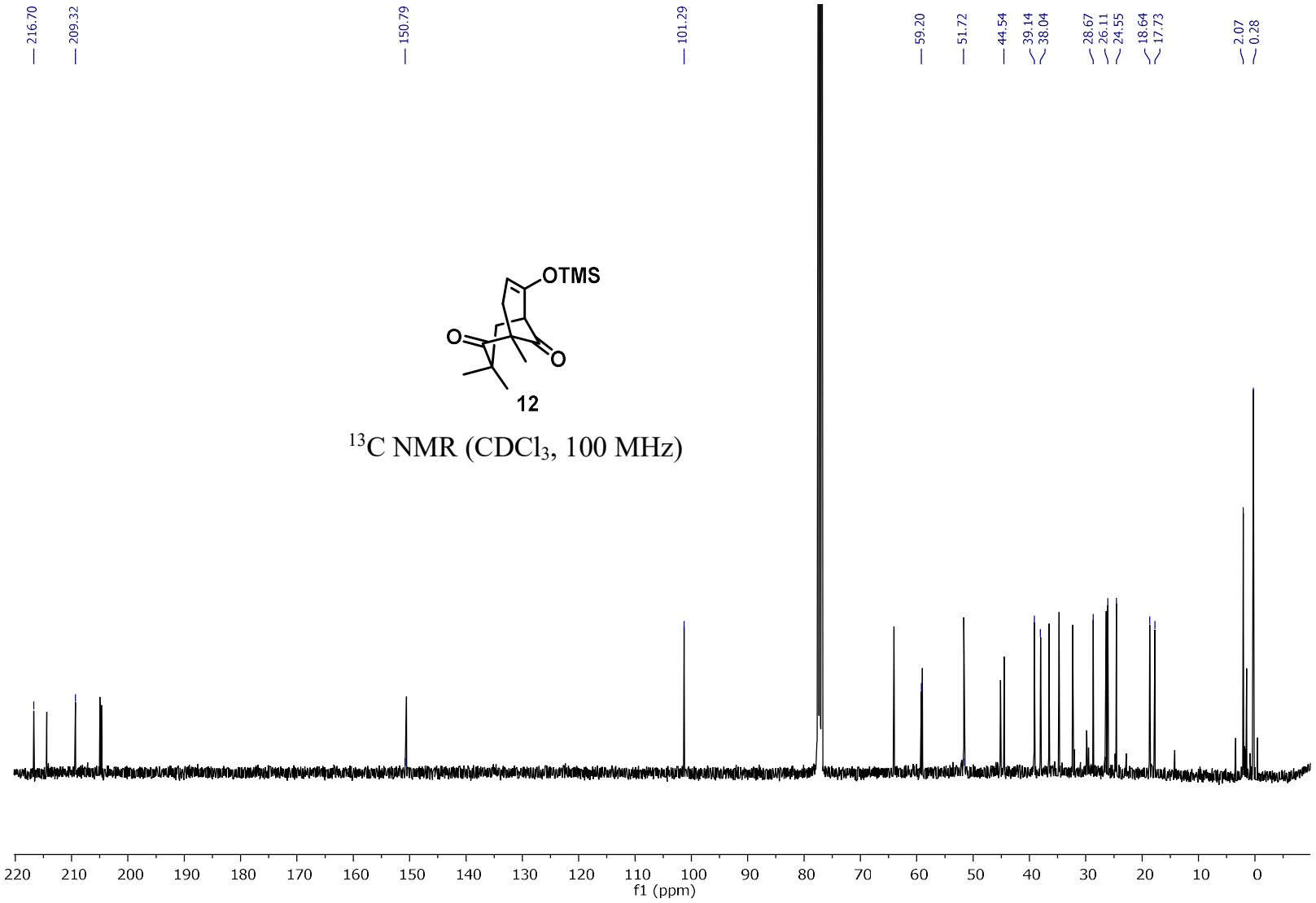
***endo*-10** (35:65) ***exo*-10**

^{19}F NMR ($CDCl_3$, 376 MHz)



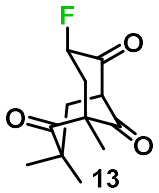
12

^{1}H NMR ($CDCl_3$, 400 MHz)



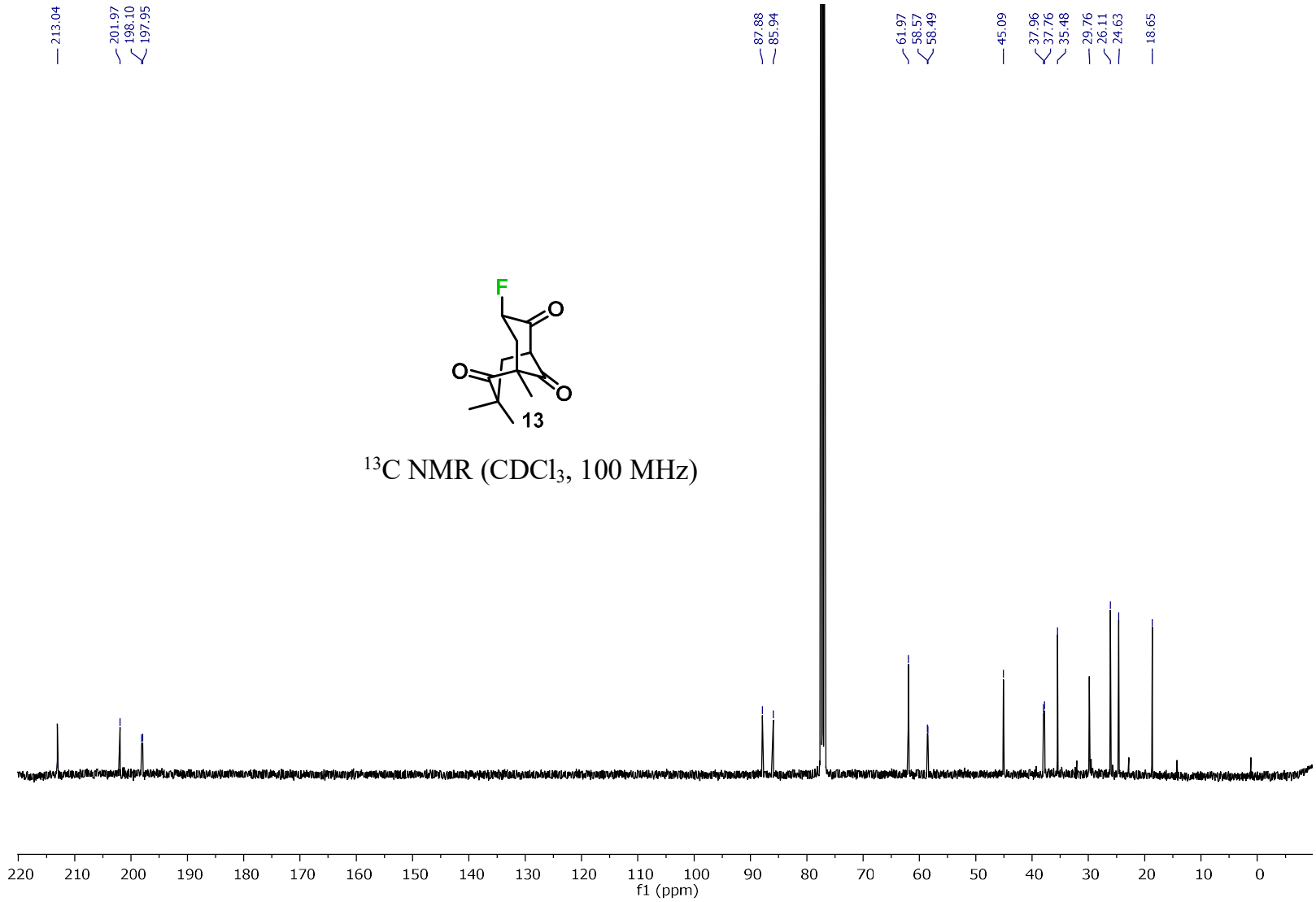
12

^{13}C NMR ($CDCl_3$, 100 MHz)

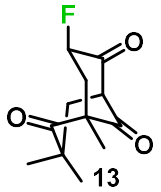


13

^{1}H NMR ($CDCl_3$, 400 MHz)

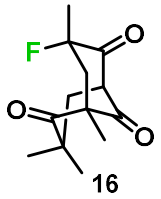


^{13}C NMR ($CDCl_3$, 100 MHz)



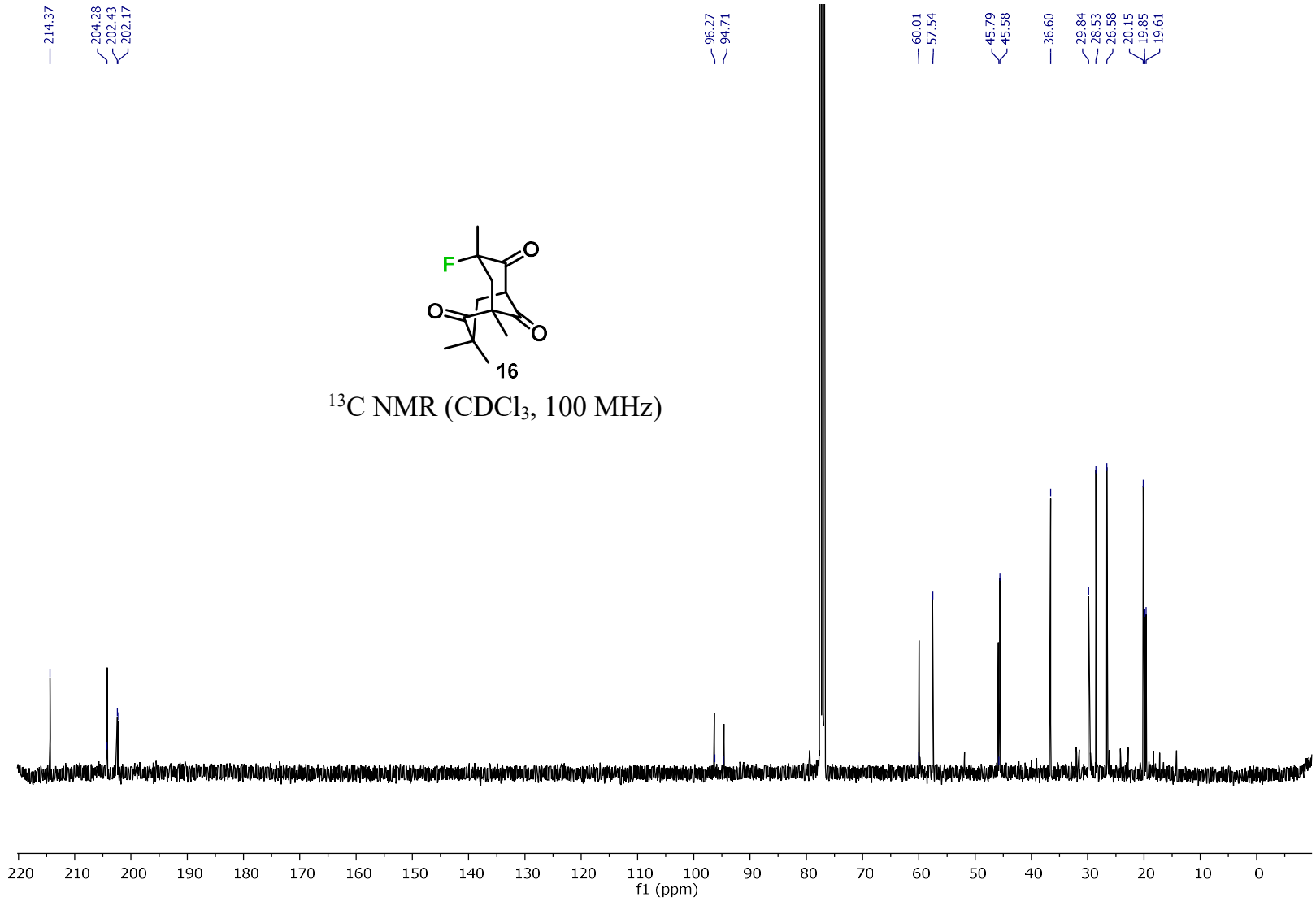
13

^{19}F NMR ($CDCl_3$, 376 MHz)

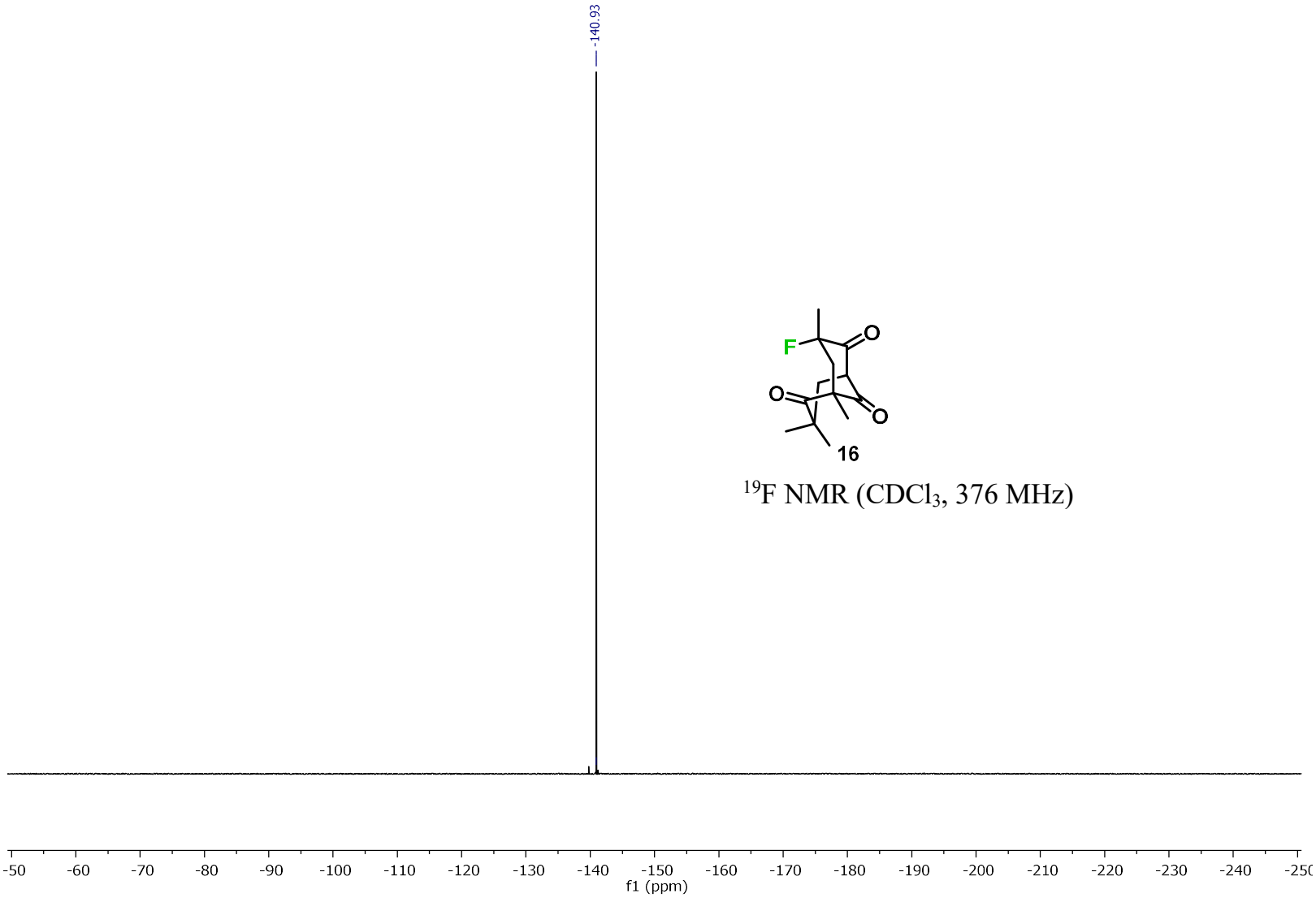


16

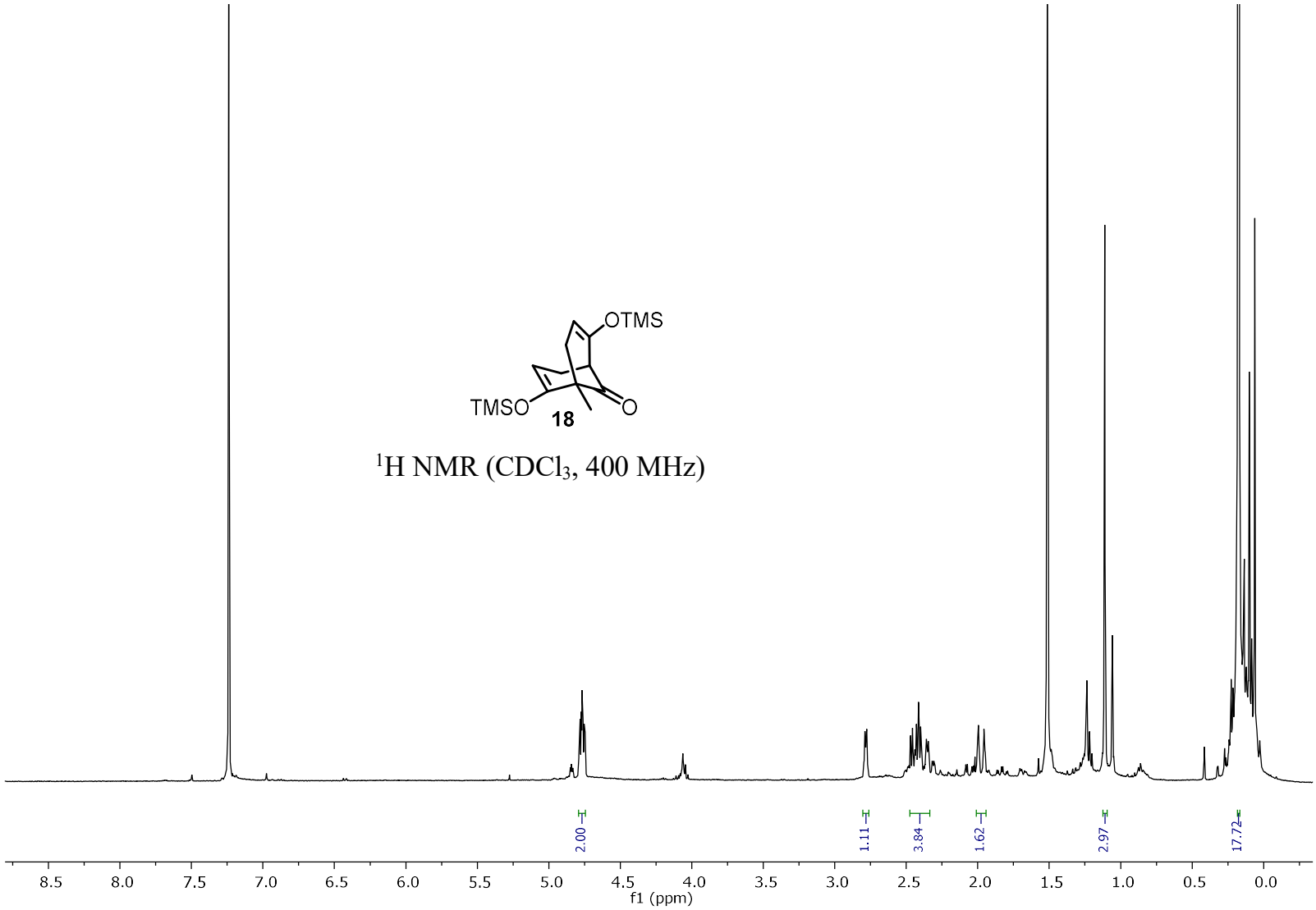
^{1}H NMR ($CDCl_3$, 400 MHz)



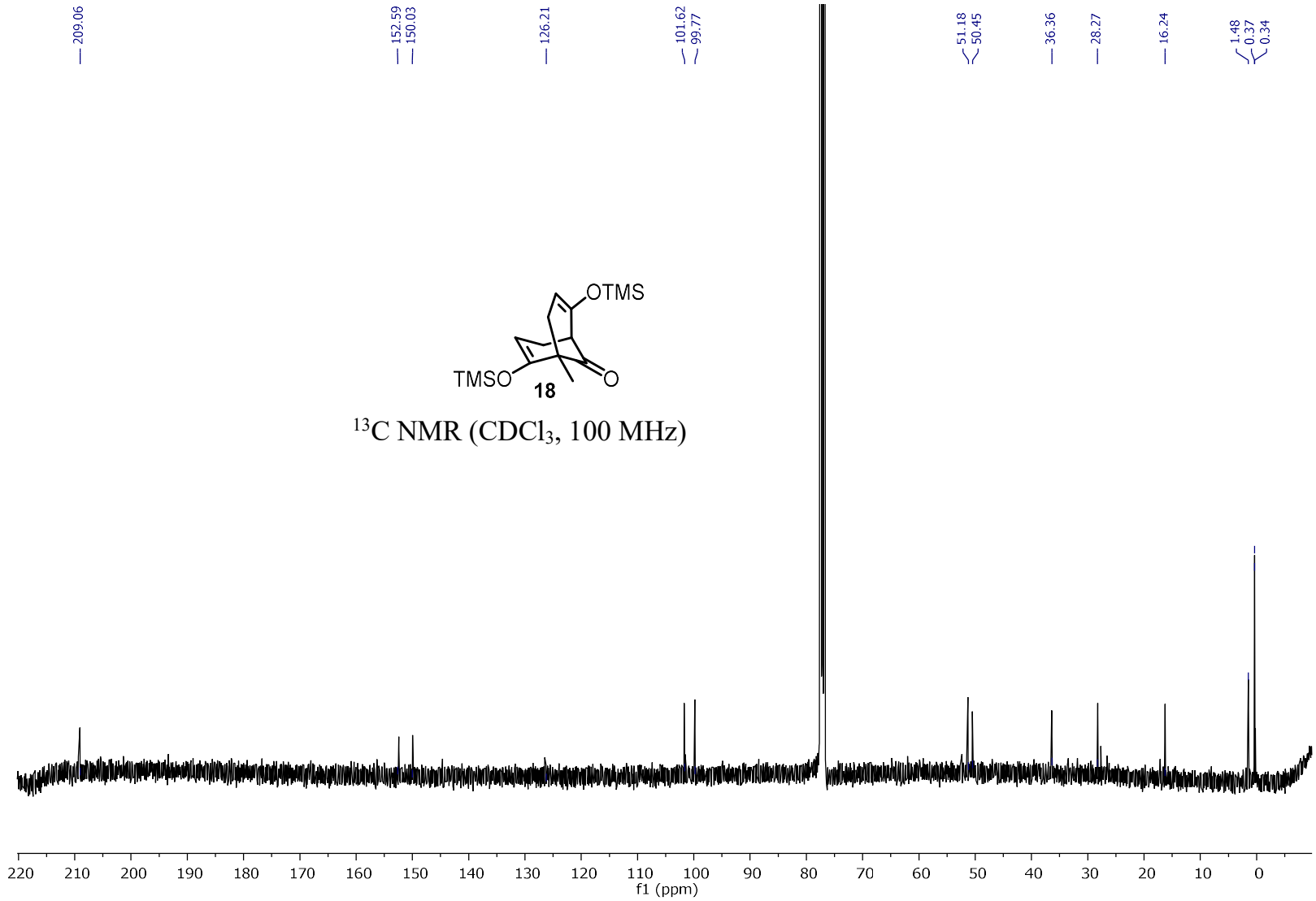
^{13}C NMR ($CDCl_3$, 100 MHz)



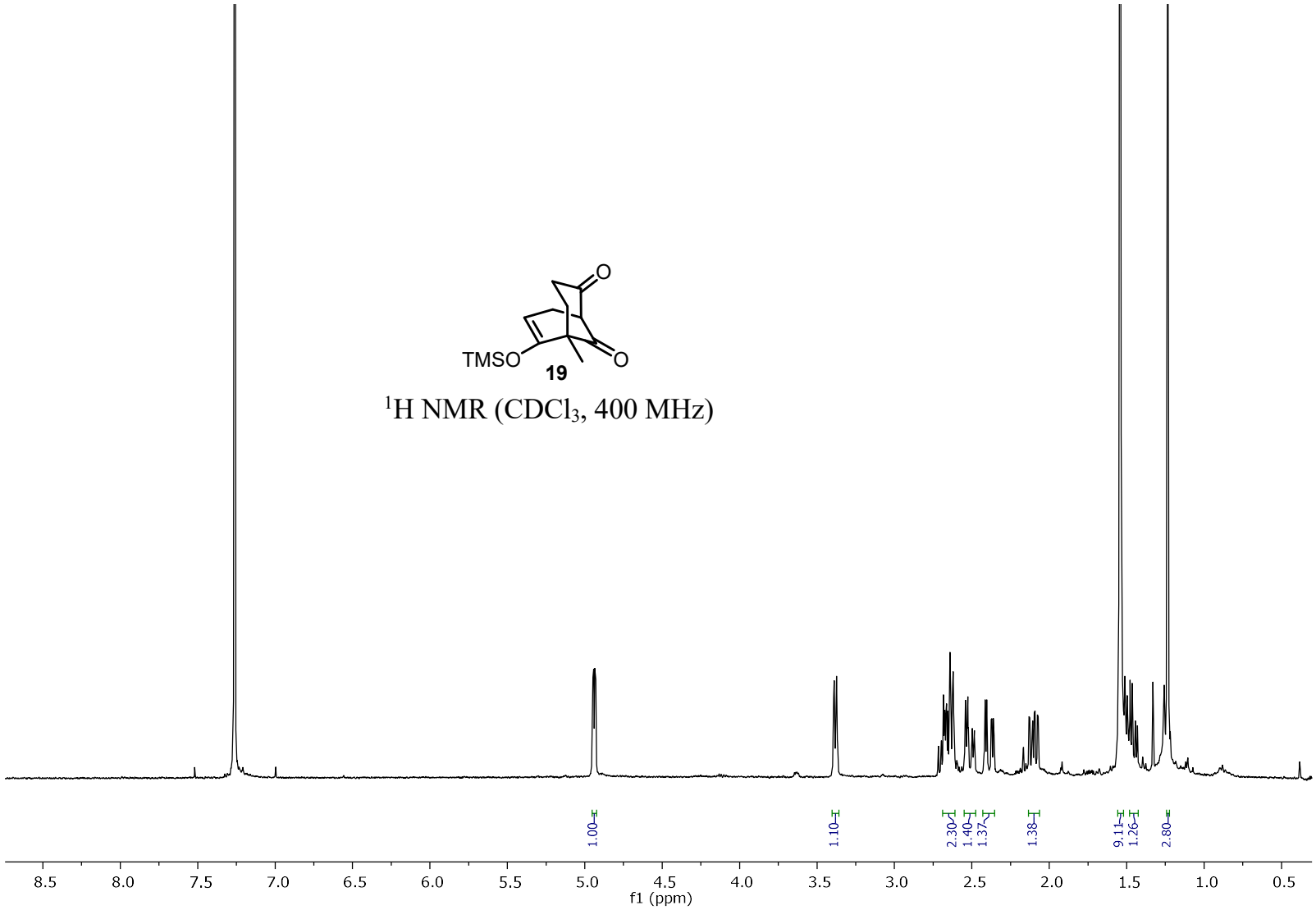
^{19}F NMR ($CDCl_3$, 376 MHz)



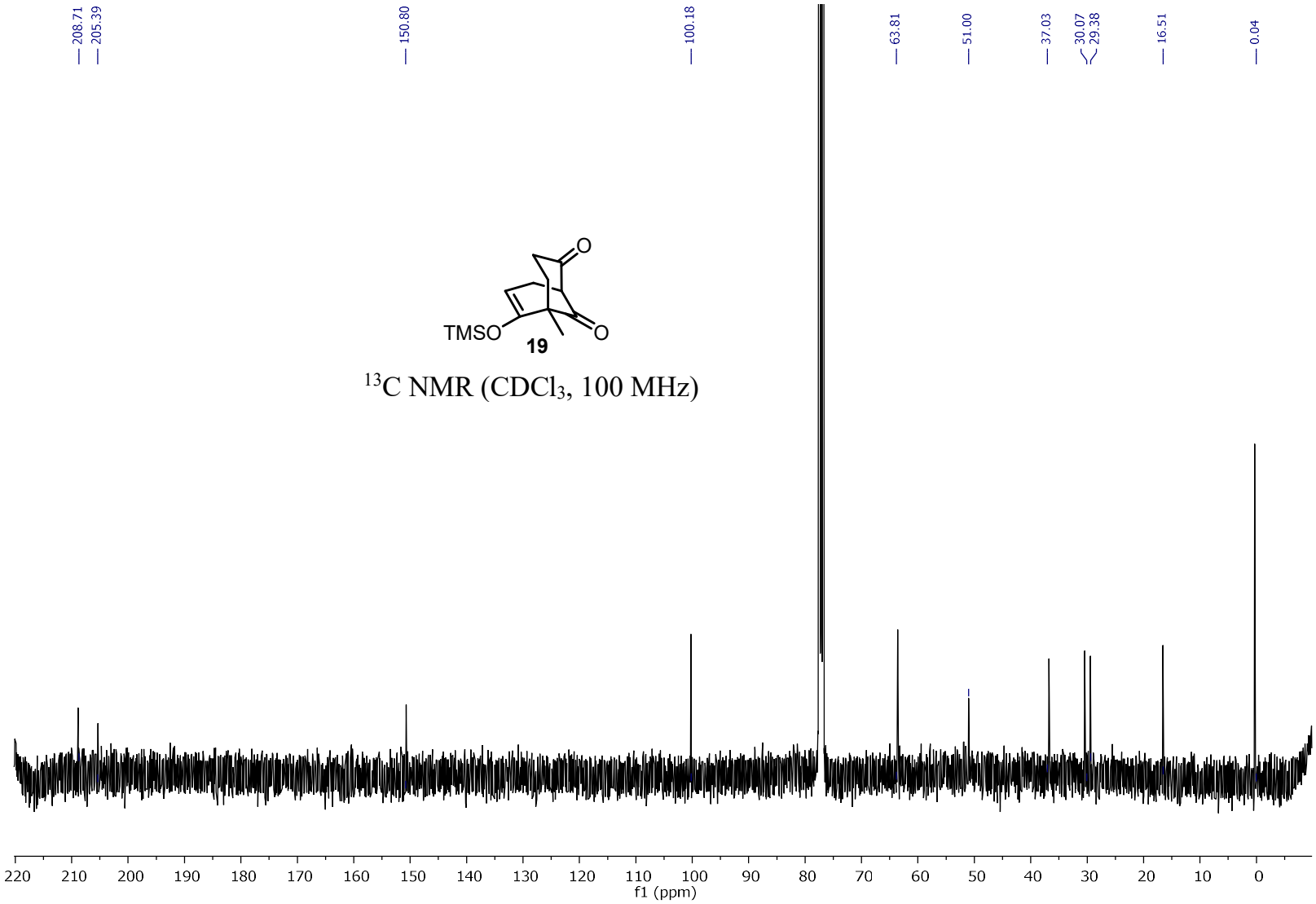
^{1}H NMR ($CDCl_3$, 400 MHz)



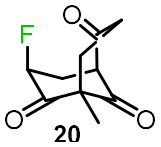
^{13}C NMR ($CDCl_3$, 100 MHz)



^{1}H NMR ($CDCl_3$, 400 MHz)

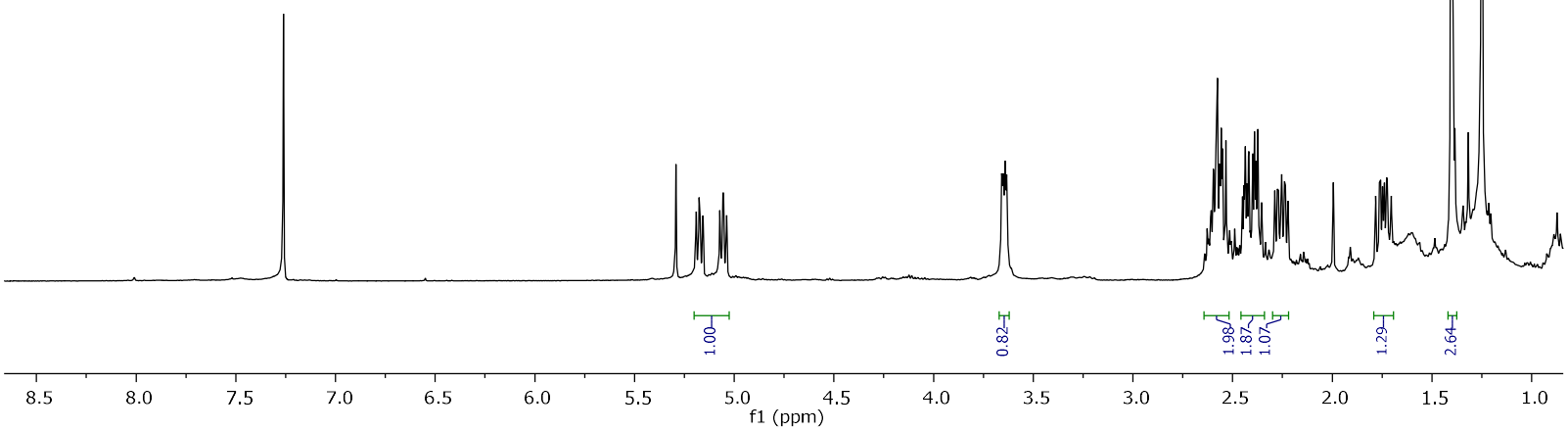


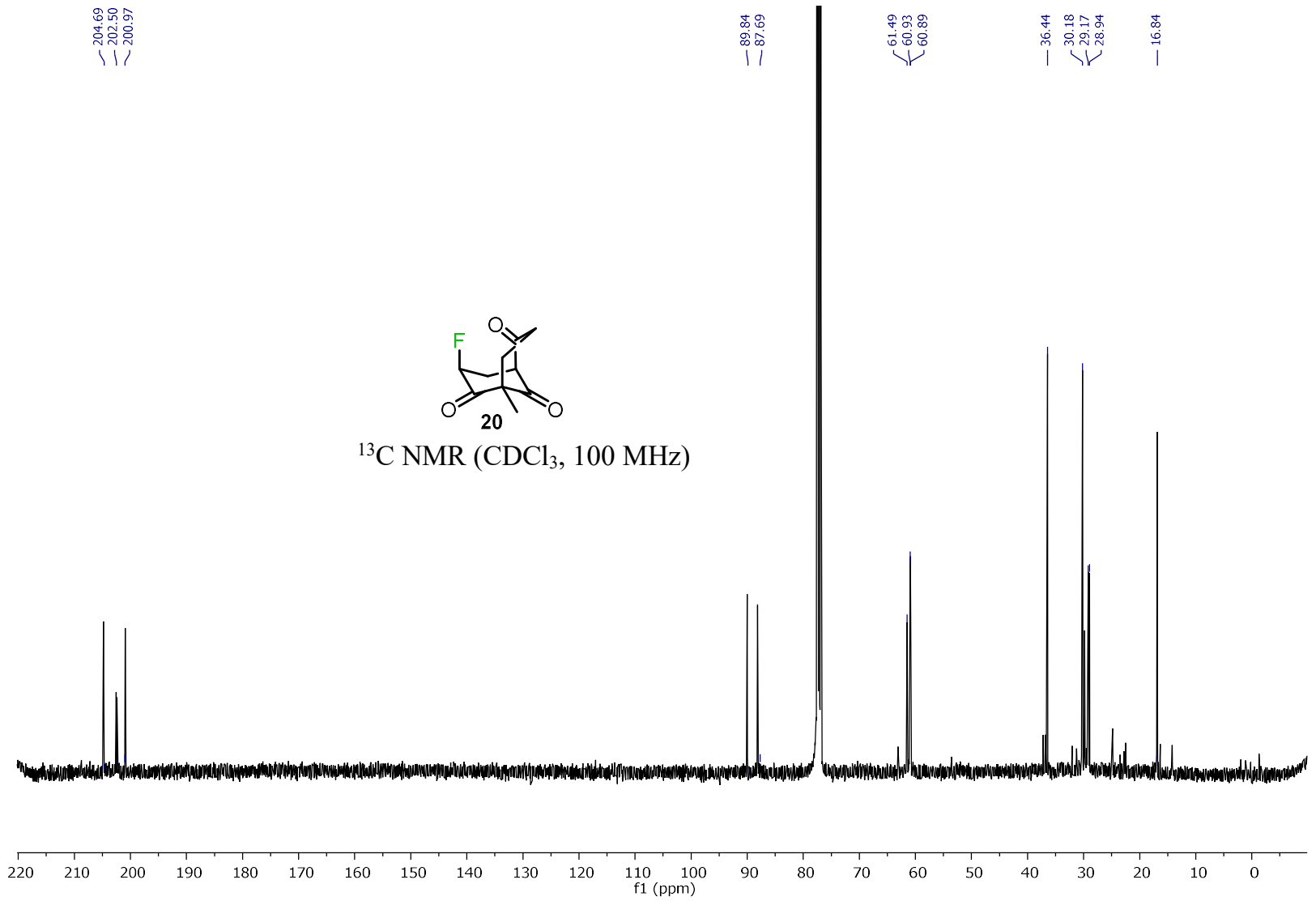
^{13}C NMR ($CDCl_3$, 100 MHz)



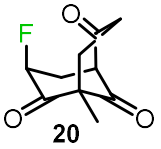
20

^{1}H NMR ($CDCl_3$, 400 MHz)



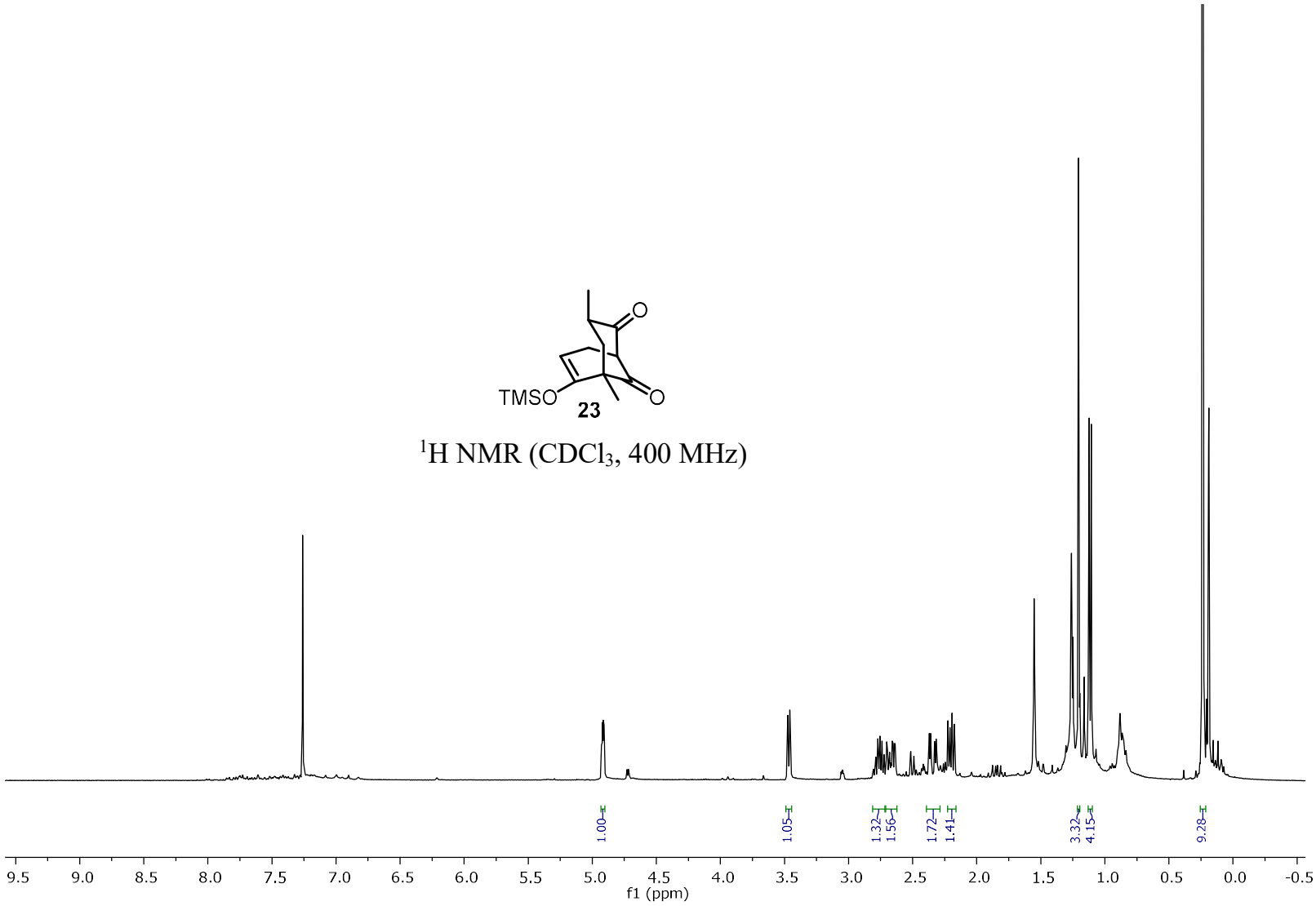


^{13}C NMR ($CDCl_3$, 100 MHz)

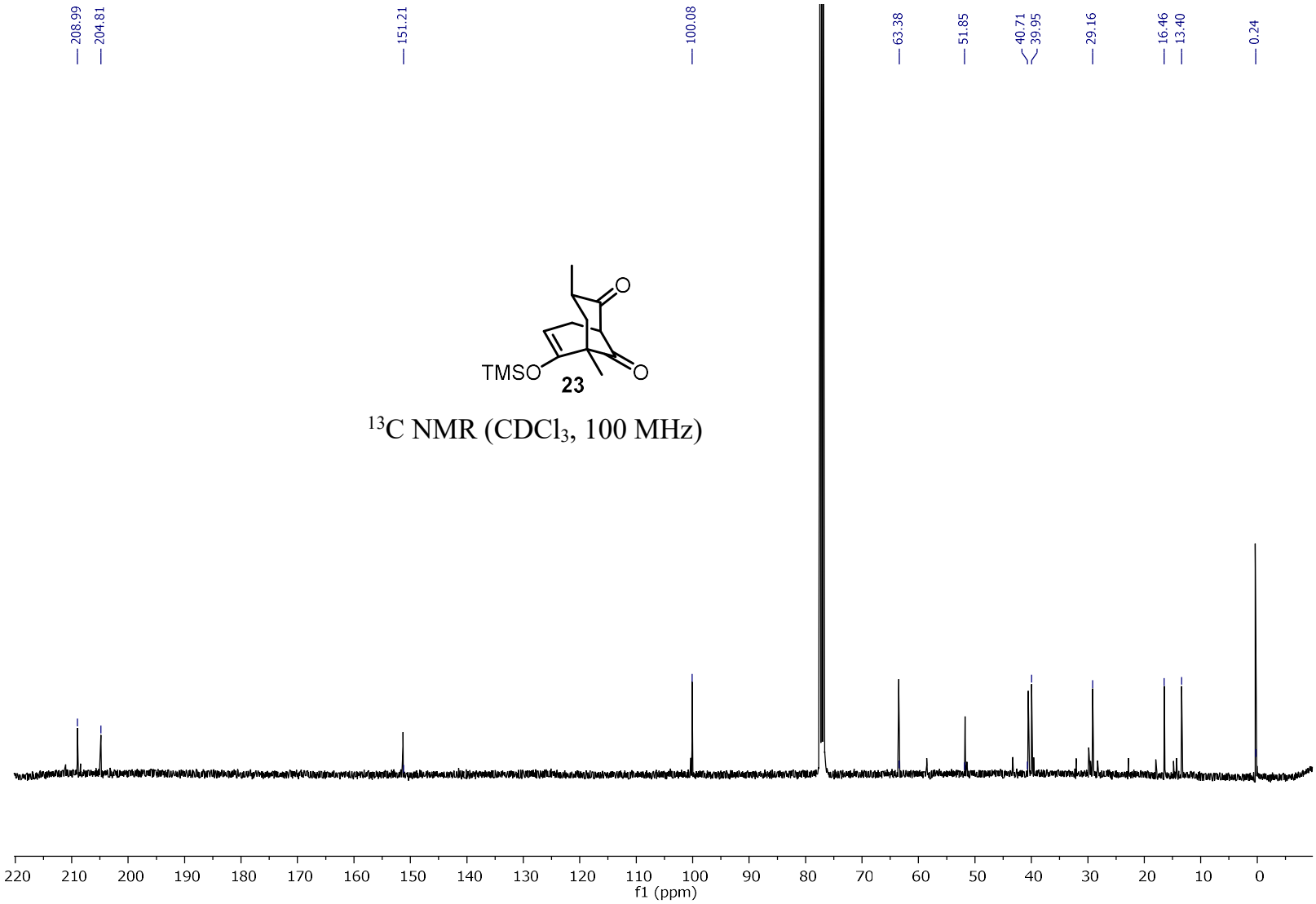


20

^{19}F NMR ($CDCl_3$, 376 MHz)

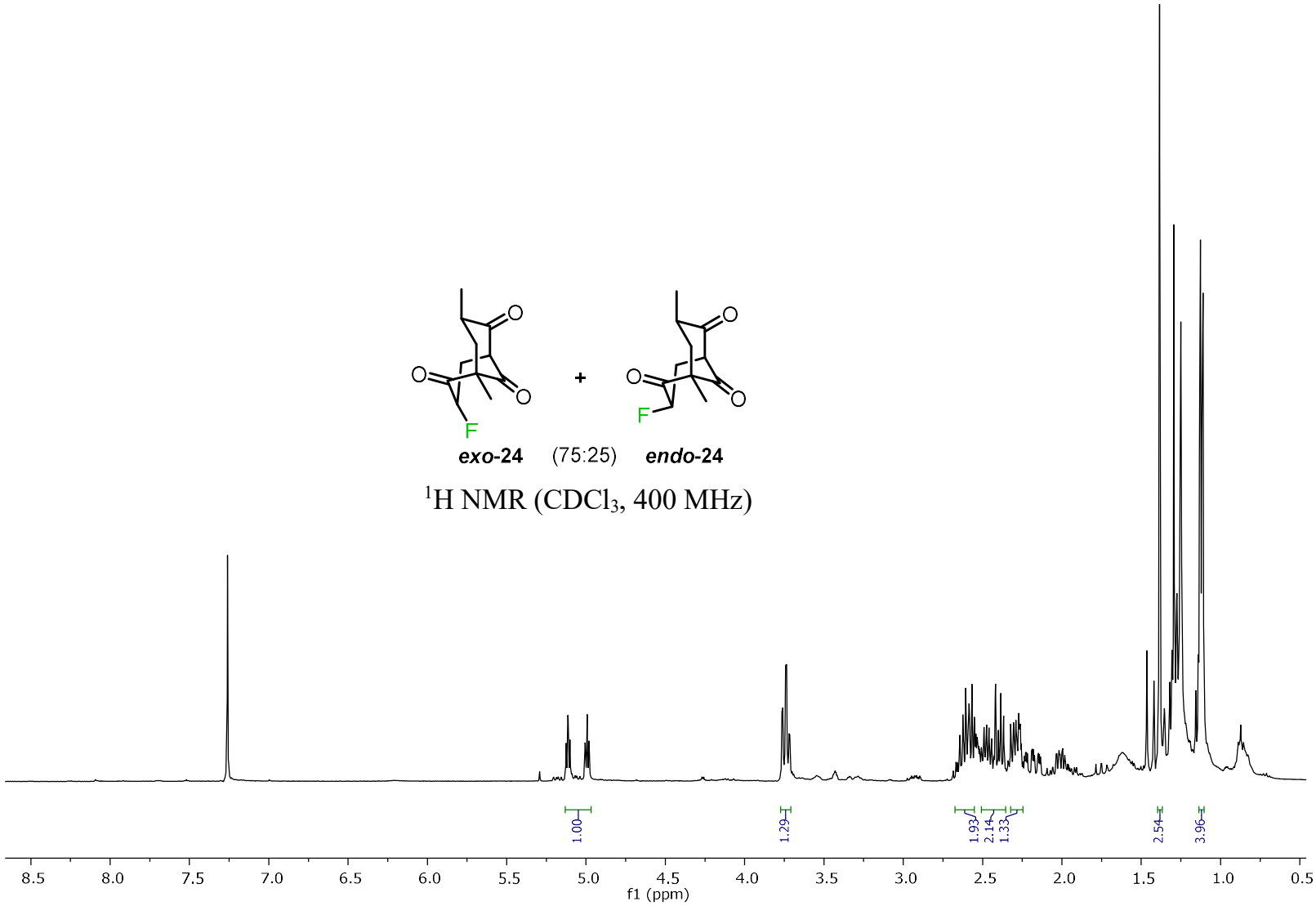


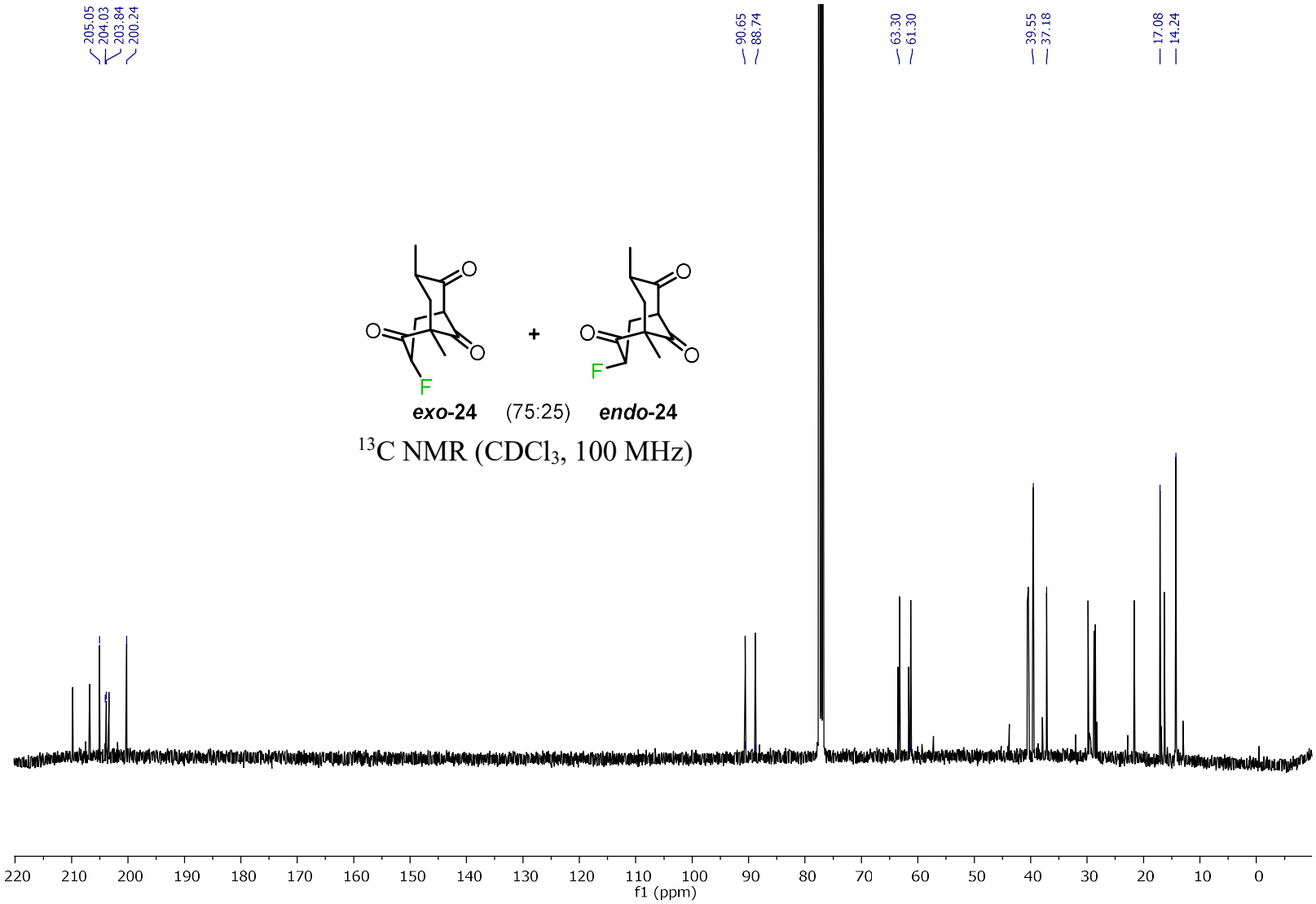
^{1}H NMR ($CDCl_3$, 400 MHz)



23

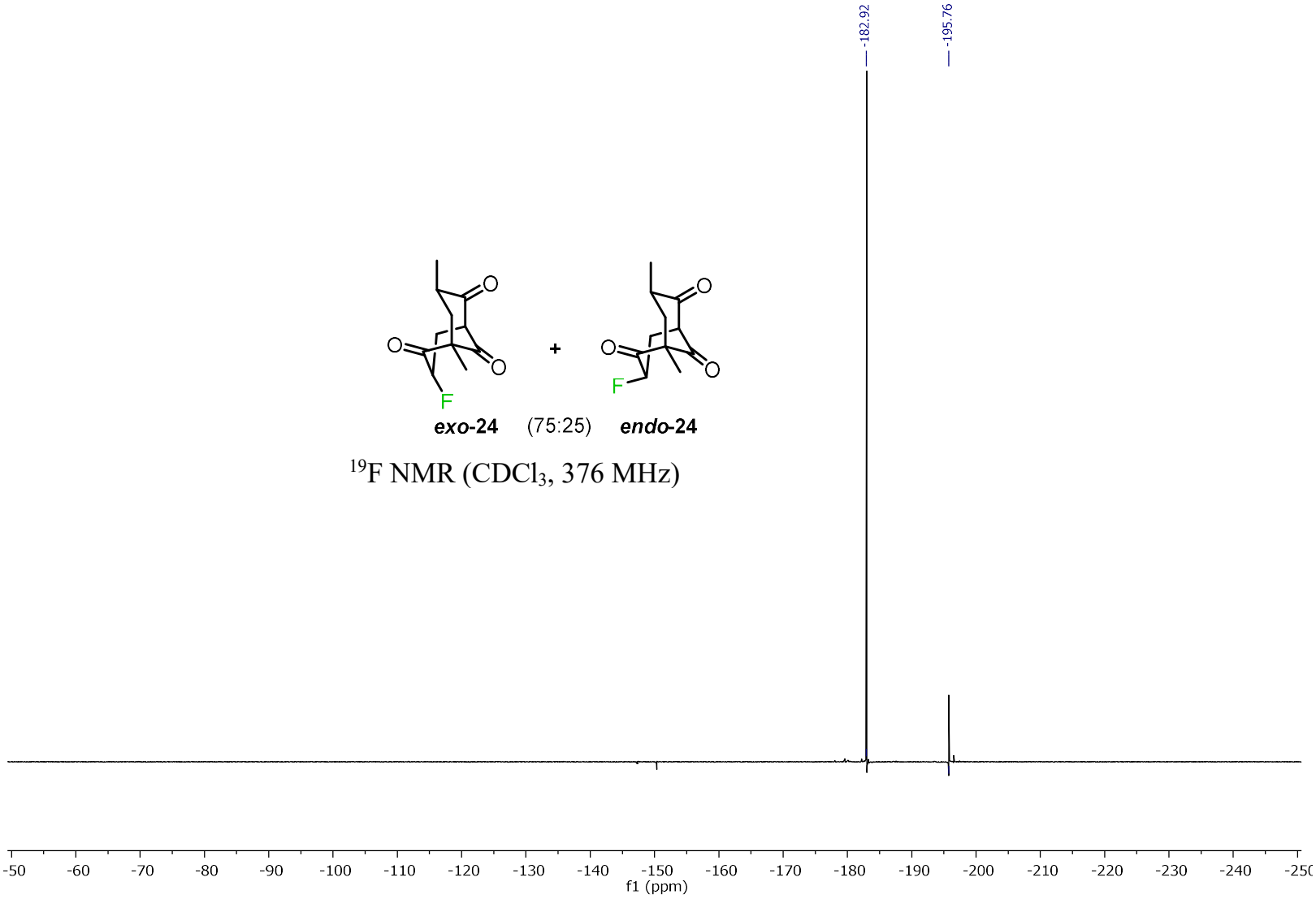
^{13}C NMR ($CDCl_3$, 100 MHz)


F
+
F
exo-24 (75:25) endo-24
1H NMR (CDCl3, 400 MHz)
1.00
1.29
1.93
2.14
1.33
2.54
3.96
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)



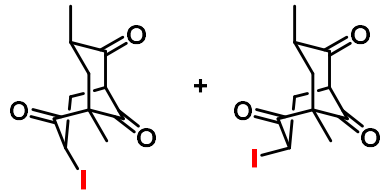
***exo*-24** (75:25) ***endo*-24**

^{13}C NMR ($CDCl_3$, 100 MHz)



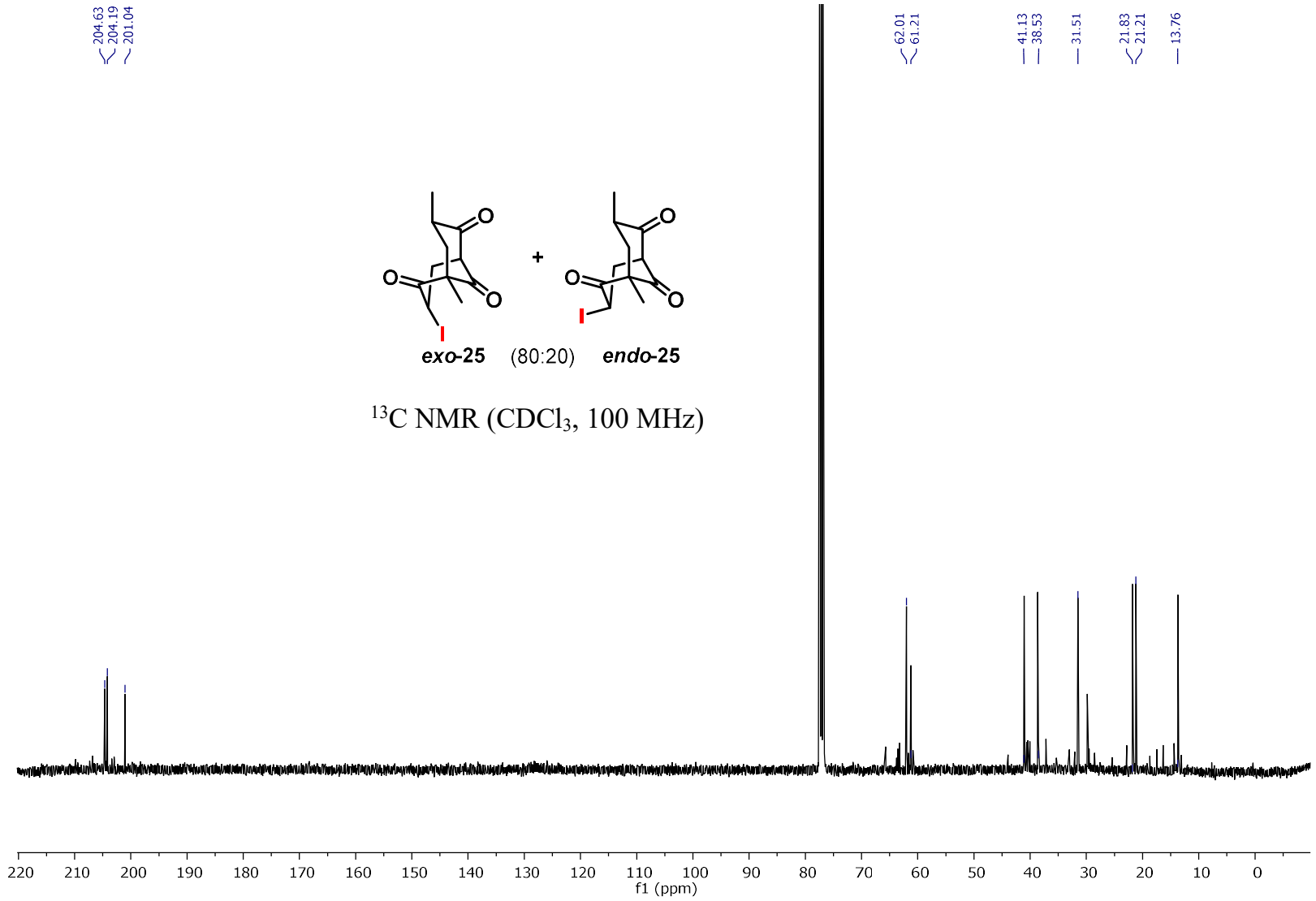
***exo*-24** (75:25) ***endo*-24**

^{19}F NMR ($CDCl_3$, 376 MHz)



***exo*-25** (80:20) ***endo*-25**

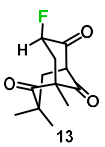
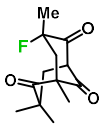
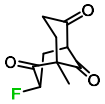
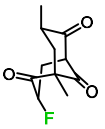
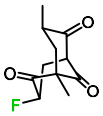
^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 100 MHz)

DFT calculations

Computational experiments were performed using the Spartan 16 software package. Initial molecular mechanics minimization and conformational analyses were performed with the Merck Molecular Force Field (MMFF). Then, the results obtained were further refined with DFT calculations in the gas phase using the M06-2X 6-31+G* hybrid functional.

	 **13**	 **16**	 **20b**	 ***exo*-24**	 ***endo*-24**
Chair (F), boat[c]	**0 (83)**	**0 (99.6)**	2.0 (29)	9.8 (2)	6.2 (7)
Boat (F), chair[c]	10.7	16.3	**0 (64)**	**0 (95)**	**0 (89)**
Twist-boat, twist-boat	4.1 (16)	15.4	11.5	—[d]	—[d]
Twist-boat, twist-boat 2	—[d]	18.6	—[d]	—[d]	—[d]
Twist-chair, twist-chair	—[d]	—[d]	5.66 (7)	8.9 (3)	7.5 (4)

[a] Energies quoted are relative to the most stable conformation whose energy is assigned to zero.

[b] Value in parenthesis refer to the Boltzmann Weights (*i.e.*, the percentage that the conformer contributes to the total distribution).

[c] (F) refers to the position of fluorine atom.

[d] Not found during the conformationa search.

Table 1. M06-2X 6-31+G* gas phase relative conformational energies (kJ mol^{-1}) of fluorobicyclo compounds **13**, **16**, **20** and **24**.