Hexafluoroisobutylation of Enolates Through a Tandem Elimination/Allylic Shift/Hydrofluorination Reaction

Aline Delamare, Guillaume Naulet, Brice Kauffmann, Gilles Guichard,* Guillaume Compain*

Content

I. General materials and methods

All solvents and reagents were purchased from commercial suppliers and used without purification except for THF, CH_2Cl_2 and toluene, which were purified by a solvent purification system (MBRAUN MB SPS-800).
The 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane was purchased on Apollo Scientific and ABCR.
Thin layer chromatography (TLC) was performed on pre-coated aliminium plates Supelco® (TLC Silica gel 60 F_{256}) with detection by UV light (254 nm) and charring with $KMnO_4$ solution (1.5 g of $KMnO_4$, 10 g of K_2CO_3, 1.25 mL of 10% of NaOH and 200 mL of water) followed by heating.
Purification of the compounds was performed on an automatic flash column chromatography Combi-Flash® using Serlabo® or Buchi® columns.
^1H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded on Bruker Ultrashield Advance spectrometers (300 and 400 MHz). Chemical shifts are reported in parts per million (ppm) relative to the ^1H residual signal of the deuterated solvent used. ^1H NMR splitting patterns with observed first-order coupling are designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), or septet (sept), broad signal (bs), multiplet (m). Coupling constants (*J*) are reported in Hertz.
High resolution mass spectra (HRMS) were recorded on a Thermo Scientific Exactive instrument.
Melting points were recorded on Buchi Melting Point B-540.
α_D were measured using a Jasco P-2000 Digital Polarimeter.
HPLC were recorded on Thermo Scientific Dionex Ultimet 3000.
HRMS were recorded on Q Exactive Orbitrap mass spectrometer (ThermoFisher Scientific) by using an electrospray ionization (ESI), or on Accutof mass spectrometer (Jeol) using chemical ionization (CI).

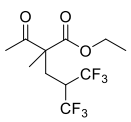
II. Synthesis procedures and analyses

II.1 General procedure for the hexafluoisobutylation reaction

In a two-neck round bottom flask flushed with argon, were introduced the solvent (to get a concentration of 33 mM of substrate) and then TBAF (10 equiv. relative to the molar quantity of the starting material). The reaction was then cooled down at -20 °C and the starting material (1.0 equiv.) was introduced. Then, 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane (1.1 equiv., unless otherwise notified in the tables) was introduced dropwise. The reaction was stirred for 1 h at -20 °C. The solvent was then evaporated and the residue was solubilized in a mixture of water and DCM. The organic layer was separated and the aqueous phase was extracted twice with DCM. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude was purified by automatic flash chromatography (combi-flash®). The solvents used for the purification and the gradient are indicated for each compounds bellow.

II.2 Characterization of compounds

Compound 1b



Compounds **1b**, **1c** and **1d** were purified using petroleum ether / DCM (100/0 to 70/30) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.24 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.13 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.08 – 2.92 (m, 1H), 2.38 (dd, *J* = 16.4, 4.3 Hz, 1H), 2.25 (dd, *J* = 16.2, 4.2 Hz, 1H), 2.16 (s, 3H), 1.36 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H).

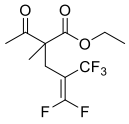
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.5 (quint, *J* = 9 Hz, 3F), -67.7 (quint, *J* = 9 Hz, 3F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 203.6, 171.7, 123.4 (q, *J* = 280 Hz), 62.3, 57.8, 43.7 (sept, *J* = 29 Hz), 27.8, 26.2, 18.8, 13.9.

HRMS (ESI+): m/z $[M+Na]^+$ 331.07348 (calcd for $C_{11}H_{14}F_6O_3Na$: 331.07393)

clear yellow oil

Compound 1c



^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.23 (dq, *J* = 11.0, 7.3 Hz, 1H), 4.15 (dq, *J* = 11.0, 7.3 Hz, 1H), 2.80 (q, *J* = 2.2 Hz, 2H), 2.14 (s, 3H), 1.32 (bs, 3H), 1.24 (t, *J* = 7.4 Hz, 3H).

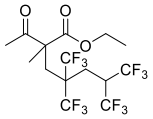
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -59.1 (dd, *J* = 19, 10 Hz, CF_3), -72.3 (quint, *J* = 17 Hz, CF), -75.8 (quint, *J* = 12 Hz).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 203.5, 171.6, 163.3 – 153.1 (ddq, *J* = 305, 293, 4 Hz), 124.4 (qdd, *J* = 271, 13, 5 Hz), 83.4, 61.9, 58.8, 27.5, 25.6, 17.8, 13.7.

HRMS (ESI+): m/z $[M+H]^+$ 289.08618 (calcd for $C_{11}H_{14}F_5O_3$: 289.08576).

clear yellow oil

Compound 1d



^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.26 (dq, *J* = 10.3, 7.3 Hz, 1H), 4.18 (dq, *J* = 11.0, 7.3 Hz, 1H), 3.49 (m, 1H), 2.68 (d, *J* = 16.3 Hz, 1H), 2.51 (d, *J* = 16.3 Hz, 1H), 2.42 – 2.27 (m, 2H), 2.19 (s, 3H), 1.48 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).

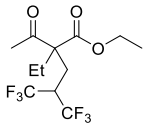
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -66.8 (m, 3F), -67.6 (m, 3F), -67.8 (m, 3F), -67.9 (m, 3F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 203.1, 171.7, 124.6 (q, *J* = 284 Hz), 123.5 (q, *J* = 281 Hz), 62.5, 58.0, 52.4 (sept, *J* = 25 Hz), 44.0 (sept, *J* = 30 Hz), 34.3, 25.5, 23.7 ,20.5, 13.8.

HRMS (ESI-): m/z $[M-H]^-$ 471.08319 (calcd for $C_{15}H_{15}F_{12}O_3$: 471.08351).

clear yellow oil

Compound 2b



Compound **2b** was purified using petroleum ether / AcOEt (100/0 to 80/20) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.25 (dq, *J* = 10.8, 7.0 Hz, 1H), 4.14 (dq, *J* = 10.8, 7.2 Hz, 1H).2.99 (m, 1H), 2.37 (dd, *J* = 16.5, 4.4 Hz, 1H), 2.28 (dd, *J* = 16.2, 4.5 Hz, 1H), 1.93 (m, , 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.76 (t, *J* = 7.6 Hz, 4H).

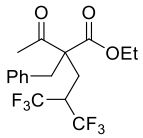
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.3 (m, 3F), -67.5 (m, 3F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 203.7, 171.5, 124.0 (q, *J* = 280 Hz), 62.1, 62.0, 43.6 (sept, *J* = 29 Hz), 26.8, 24.3, 24.0, 14.0, 7.7.

HRMS (ESI+): m/z $[M+H]^+$ 323.10646 (calcd for $C_{12}H_{17}F_6O_3$: 323.10764).

clear yellow oil

Compound 3b



Compound **3b** was purified using petroleum ether / AcOEt (100/0 to 85/15) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.32 – 7.21 (m, 3H), 7.17 – 7.05 (m, 2H), 4.18 (m, 2H), 3.27 (d, *J* = 14.1 Hz, 1H), 3.21 (m, 1H), 3.16 (d, *J* = 14.1 Hz), 2.45 (dd, *J* = 16.2, 4.3 Hz, 1H), 2.32 (dd, *J* = 16.2, 5.1 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.04 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H).

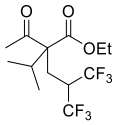
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -66.9 (m, 3F), -67.0 (m, 3F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 204.3, 171.0, 135.0, 130.1, 128.7, 127.6, 123.9 (q, *J* = 278 Hz), 62.9, 62.2, 44.2 (sept, *J* = 28 Hz), 40.1, 28.7, 27.7, 13.8.

HRMS (ESI+): m/z $[M+H]^+$ 385.12166 (calcd for $C_{17}H_{19}F_6O_3$: 385.12329).

Yellow oil

Compound 4b



Compound **4b** was purified using cyclohexane/DCM (100/0 to 50/50) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.26 (dq, *J* = 11.0, 7.5, Hz, 1H), 4.2 (da, *J* = 10.6, 6.9 Hz, 1H), 3.38 – 3.21 (m, 1H), 2.39 (dd, *J* = 16.2, 3.0 Hz, 1H), 2.26 (sept, *J* = 6.8, 1H), 2.20 (s, 3H), 2.18 (dd, *J* = 15.8, 5.8 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H).

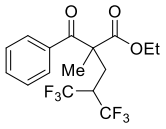
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -66.9 (quint, *J* = 10 Hz, 3F), -67.2 (quint, *J* = 10 Hz, 3F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 204.7, 171.1, 124.0 (qm, *J* = 277 Hz), 65.0, 61.8, 44.0 (p, *J* = 28 Hz), 31.9, 29.4, 24.6, 18.3 (d, *J* = 8 Hz), 14.0.

HRMS (ESI+): m/z $[M+H]^+$ 337.12182 (calcd for $C_{13}H_{19}F_6O_3$: 337.123329).

clear yellow oil

Compound 5b



Compound **5b** was purified using petroleum ether / DCM (100/0 to 80/20) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.85 – 7.77 (m, 2H), 7.60 – 7.50 (m, 1H), 7.49 – 7.39 (m, 2H), 4.15 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.02 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.12 (m, 1H), 2.58 (dd, *J* = 16.4, 3.7 Hz, 1H), 2.17 (dd, *J* = 16.5, 4.0 Hz), 1H), 1.56 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H).

^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.5 (quint, *J* = 9 Hz, 3F), -68.1 (quint, *J* = 9 Hz, 3F).

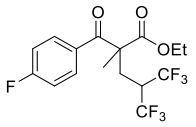
^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 196.1, 172.9, 134.9, 133.3, 128.8, 128.6, 123.9 (qm, *J* = 280 Hz), 62.2, 55.3, 43.5 (sept, *J* = 29 Hz), 29.7, 20.8, 13.5.

HRMS (CI+): m/z $[M+H]^+$ 371.10792 (calcd for $C_{16}H_{17}F_6O_3$: 371.10819).

White solid

Mp: 68-69°C

Compound 6b



Compound **6b** was purified using cyclohexane/DCM (80/20 to 50/50) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.88 – 7.80 (m, 2H), 7.11 (t, *J* = 8.6 Hz, 2H), 4.16 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.04 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.09 (m, 1H), 2.55 (dd, *J* = 16.5, 4.0 Hz, 1H), 2.46 (dd, *J* = 16.3, 4.0 Hz, 1H), 1.55 (s, 3H), 1.02 (t, *J* = 7.2 Hz, 3H).

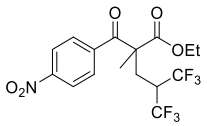
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.3 (quint, *J* = 10 Hz, 3F), -67.8 (quint, *J* = 10 Hz, 3F), -104.4.

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 194.4, 172.9, 166.9, 164.4, 131.4 (d, *J* = 9 Hz), 123.9 (qm, *J* = 281 Hz), 116.1 (d, *J* = 22 Hz), 62.4, 55.3, 43.5 (sept, *J* = 28 Hz), 29.7, 20.8, 13.6.

HRMS (CI+): m/z $[M+H]^+$ 389.09860 (calcd for $C_{16}H_{16}F_7O_3$: 389.09877).

clear yellow oil

Compound 7b



Compound **7b** was purified using cyclohexane/ DCM (100/0 to 50/50) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.30 (d, *J* = 8.9 Hz, 2H), 7.96 (d, *J* = 8.9 Hz, 2H), 4.16 (dd, *J* = 10.7, 7.0 Hz, 1H), 4.07 (dd, *J* = 10.7, 7.0 Hz, 1H), 3.11 (m, 1H), 2.60 (dd, *J* = 16.4, 3.7 Hz, 1H), 2.47 (dd, *J* = 16.2, 4.0 Hz, 1H), 1.57 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 3H).

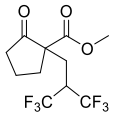
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.2 (quint, *J* = 10 Hz, 3F), -67.8 (quint, *J* = 10 Hz, 3F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 194.7, 172.2, 150.3, 139.6, 129.7, 124.0, 123.8 (q, *J* = 278 Hz), 62.7, 55.7, 43.5 (p, *J* = 29 Hz), 29.6, 20.6, 13.6.

HRMS (CI+): m/z $[M+H]^+$ 416.09315 (calcd for $C_{16}H_{16}F_6N_1O_5$: 416.09327).

clear yellow oil

Compound 8b



Compound **8b** was purified using cyclohexane/DCM (100/0 to 50/50) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.73 (s, 3H), 3.45 (m, 1H), 2.71 – 2.61 (m, 1H), 2.5 – 2.242 (m, 2H), 2. 0 (dt, *J* = 19.2, 8.5 Hz, 1H), 2.08 – 1. 92 (m, 3H), 1.85 – 1.76 (ddd, *J* = 13.1, 9.2, 7.6 Hz, 1H).

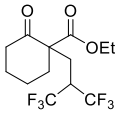
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.2 (quint, *J* = 10, 3F), -67.5 (quint, *J* = 10 Hz, 3F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 212.6, 170.2, 123.9 (q, *J* = 279 Hz), 58.6, 53.2, 44.2 (sept, *J* = 29 Hz), 37.3, 34.2, 28.0, 193.

HRMS (ESI+): m/z $[M+Na]^+$ 329.05695 (calcd for $C_{11}H_{12}F_6O_3Na$: 329.05828).

clear yellow oil

Compound 9b



Compound **9b** was purified using cyclohexane/DCM (100/0 to 50/50) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.25 (dq, *J* = 10.8, 7.3 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.3 Hz, 1H), 3.18 (m, 1H), 2.60 – 2.37 (m, 4H), 2.11 – 2.02 (m, 1H), 1.98 (dd, *J* = 16.2, 4.2 Hz, 1H), 1.88 – 1.75 (m, 1H), 1.73 – 1.53 (m, 2H), 1.41 – 1.30 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.5 (quint, *J* = 10 Hz, 3F), -68.1 (quint, *J* = 10 Hz, 3F).

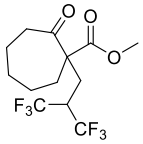
^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 206.1, 170.5, 124.0 (q, *J* = 280 Hz), 62.3, 58.6, 43.0 (sept, *J* = 29 Hz), 41.1, 35.8, 28.1, 27.4, 22.5, 13.9.

HRMS (ESI+): (m/z) $[M+H]^+$ 335.10657 (calcd for $C_{13}H_{17}F_6O_3$: 335.10764).

White solid

Mp: 63-65°C

Compound 10b



Compound **10b** was purified using petroleum ether / AcOEt (100/0 to 85/15) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.70 (s, 3H), 3.27 (m, 1H), 2.63 (m, 1H), 2.54 – 2.44 (m, 2H), 2.09 – 1.98 (m, 2H), 1.88 – 1.74 (m, 3H), 1.72 – 1.63 (m, 1H), 1.63 – 1.45 (m, 2H), 1.30 – 1.12 (m, 1H).

^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.7 (m, 3F), -67.9 (m, 3F).

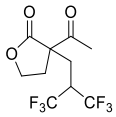
^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 207.4, 171.8, 124.0 (q, *J* = 281 Hz), 60.3, 52.9, 43.6 (sept, *J* = 28 Hz), 41.8, 31.5, 29.7, 27.0, 26.3, 23.6.

HRMS (ESI+): m/z $[M+H]^+$ 335.10635 (calcd for $C_{13}H_{16}F_6O_3$: 335.10764).

Yellow solid

Mp: 35-36°C

Compound 11b



Compound **11b** was purified using cyclohexane/AcOEt (100/0 to 50/50) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.35 (td, *J* = 8.9, 2.3 Hz, 1H), 4.11 (td, *J* = 9.6, 6.4 Hz, 1H), 3.08 – 2.88 (m, 2H), 2.66 (dd, *J* = 16.2, 4.7 Hz, 1H), 2.32 (s, 3H), 2.26 (dd, *J* = 16.3, 4.9 Hz, 1H), 2.12 (dt, *J* = 12.8, 9.2 Hz, 1H).

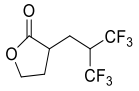
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.2 (quint, *J* = 9 Hz, 3F), -67.4 (quint, *J* = 9 Hz, 3F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 201.2, 174.6, 123.4 (q, *J* = 282 Hz), 66.2, 59.7, 44.4 (sept, *J* = 29 Hz), 30.5, 28.0, 26.1.

HRMS (CI+): m/z $[M+H]^+$ 293.06129 (calcd for $C_{10}H_{11}F_6O_3$: 293.06124).

clear yellow oil

Compound 11e



In a two-neck round bottom flask flushed with argon, were introduced the solvent (to get a concentration of 33 mM of substrate) and then TBAF (10 equiv. relative to the molar quantity of the starting material). The reaction was then cooled down at -20 °C and the starting material (1.0 equiv.) was introduced. Then, 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane (1.1 equiv., unless otherwise notified in the tables) was introduced dropwise. The reaction was stirred for 1 h at -20 °C, and then for 4 h at 0 °C. The solvent was then evaporated and the residue was solubilized in a mixture of water and DCM. The organic layer was separated and the aqueous phase was extracted twice with DCM. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude was purified by automatic flash chromatography (combi-flash®) was purified using petroleum ether / AcOEt (100/0 to 80/20) as eluent to afford compound **11e**.

.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.41 (td, *J* = 9.0, 2.1 Hz, 1H), 4.22 (ddd, *J* = 10.7, 9.4, 6.4 Hz, 1H), 3.61 (m, 1H), 2.78 (dq, *J* = 11.3, 8.3 Hz, 1H), 2.52 (dddd, *J* = 12.5, 8.4, 6.3, 2.0 Hz, 1H), 2.27 (ddd, *J* = 14.6, 8.5, 5.2 Hz, 1H), 2.06 – 1.92 (m, 2H).

^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -66.8 (quint, *J* = 9 Hz), -67.5 (quint, *J* = 9 Hz).

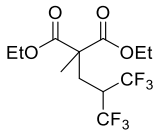
^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 177.7, 124.0 (q, *J* = 280 Hz), 123.8 (q, *J* = 280 Hz), 66.4, 45.3 (sept, *J* = 28 Hz), 36.2, 29.5, 25.0.

HRMS (CI+): m/z $[M+H]^+$ 251.05067 (calcd for $C_8H_9F_6O_2$: 251.05050).

White solid

Mp: 55-57°C

Compound 12b



Compound **12b** was purified using cyclohexane/DCM (100/0 to 50/50) as eluent.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.28 – 4.11 (m, 4H), 3.14 (m, 1H), 2.38 (d, *J* = 4.3 Hz, 2H), 1.44 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 6H).

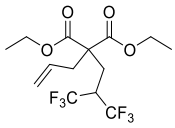
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.6 (d, *J* = 8 Hz, 6F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 171.0, 122.3 (q, *J* = 280 Hz), 62.1, 52.2, 43.9 (sept, *J* = 29 Hz), 28.8, 20.0, 14.0.

HRMS (ESI+): m/z $[M+H]^+$ 339.10116 (calcd for $C_{12}H_{17}F_6O_4$: 339.10255).

clear yellow oil

Compound 13b



Compound **13b** was purified using pentane / DCM (100/0 to 80/20) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 5.61 (ddt, *J* = 17.1, 9.7, 7.2 Hz, 1H), 5.19 – 5.14 (m, 1H), 5.13 (m, 1H), 4.25 – 4.10 (m, 4H), 3.26 (m, 1H), 2.65 (dt, *J* = 7.3, 1.3 Hz, 2H), 2.36 (d, *J* = 4.5 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 6H).

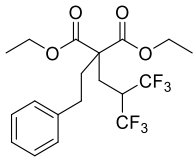
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.4 (d, *J* = 9 Hz, 6F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 170.1, 131.0, 123.9 (q, *J* = 282 Hz), 120.6, 62.0, 55.9, 44.0 (sept, *J* = 29 Hz), 37.6, 26.2, 14.0.

HRMS (CI+): m/z $[M+H]^+$ 365.11898 (calcd for $C_{14}H_{19}F_6O_4$: 365.11875).

clear colorless oil

Compound 14b



Compound **14b** was purified using pentane / DCM (100/0 to 80/20) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.32 – 7.26 (m, 2H), 7.24 – 7.18 (m, 1H), 7.17 – 7.12 (m, 2H), 4.29 – 4.12 (m, 4H), 3.20 (m 1H), 2.2 –2.44 (m, 4H), 2.22 – 2.13 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 6H).

^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.4 (d, *J* = 8 Hz, 6F).

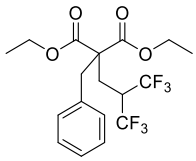
^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 170.7, 140.6, 128.7, 128.4, 126.5, 124.0 (q, *J* = 282 Hz), 62.1, 56.0, 43.9 (sept, *J* = 29 Hz), 34.5, 30.3, 26.0, 14.1.

HRMS (ESI+): m/z $[M+H]^+$ 429.14783 (calcd for $C_{19}H_{23}F_6O_4$: 429.14950).

White solid

Mp: 60-61°C

Compound 15b



Compound **15b** was purified using pentane / DCM (100/0 to 80/20) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.32 – 7.21 (m, 3H), 7.14 – 7.08 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 4H), 3.45 (m, 1H), 3.28 (s, 2H), 2.29 (d, *J* = 4.6 Hz, 2H), 1.23 (t, *J* = 7.5 Hz, 6H).

^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.1 (d, *J* = 8 Hz, 6F).

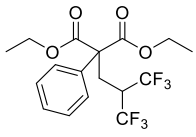
^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ δ 170.1, 135.1, 130.1, 128.6, 127.5, 123.9 (q, *J* = 281 Hz), 62.0, 57.2, 44.6 (sept, *J* = 28 Hz), 40.7, 27.8, 13.9.

HRMS (ESI+): m/z $[M+H]^+$ 415.13503 (calcd for $C_{18}H_{21}F_6O_4$: 415.13385).

White solid

Mp: 75-76°C

Compound 16b



Compound **16b** was purified using pentane / DCM (100/0 to 70/30) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.59 – 7.49 (m, 2H), 7.42 – 7.30 (m, 3H), 4.24 (qd, *J* = 7.1, 1.3 Hz, 4H), 3.05 (m, 1H), 2.80 (d, *J* = 4.7 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 6H).

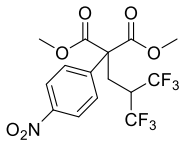
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.2 (d, *J* = 8 Hz, 6F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 169.4, 135.4, 128.9, 128.4, 127.9, 123.7 (q, *J* = 281 Hz), 62.4, 60.6, 44.2 (sept, *J* = 28 Hz), 31.4, 13.9.

HRMS (ESI+): m/z $[M+H]^+$ 401.11652 (calcd for $C_{17}H_{19}F_6O_4$: 401.11820).

clear yellow oil

Compound 17b



Compound **17b** was purified using pentane / DCM (100/0 to 30/70) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.24 (d, *J* = 9.0 Hz, 2H), 7.77 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 6H), 3.05 (m, 1H), 2.82 (d, *J* = 4.6 Hz, 2H).

^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.4 (d, *J* = 8 Hz, 6F).

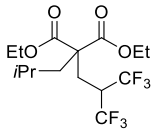
^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 169.0, 147.7, 142.1, 129.1, 123.9, 123.5 (q, *J* = 281 Hz), 60.2, 53.7, 44.0 (sept, *J* = 29 Hz), 31.3.

HRMS (CI+): m/z $[M+H]^+$ 418.07268 (calcd for $C_{15}H_{14}F_6N_1O_6$: 418.07253).

White solid

Mp: 175-178°C

Compound 18b



Compound **18b** was purified using cyclohexane/DCM (80/20 to 40/60) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.22 – 4.12 (m, 4H), 3.22 (m, 1H), 2.39 (d, *J* = 4.6 Hz, 2H), 1.87 (d, *J* = 6.3 Hz, 2H), 1.67 (sept, *J* = 6.5 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 6H), 0.88 (d, *J* = 6.6 Hz, 6H).

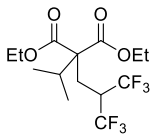
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.3 (d, *J* = 8 Hz, 6F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 170.9, 123.9 (q, *J* = 280 Hz), 61.8, 55.3, 44.2 (sept, *J* = 28 Hz), 41.8, 26.9, 24.0, 23.7, 13.9.

HRMS (ESI+): m/z $[M+H]^+$ 381.14761 (calcd for $C_{15}H_{23}F_6O_4$: 381.14950).

clear yellow oil

Compound 19b



Compound **19b** was purified using cyclohexane/DCM (80/20 to 40/60) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.28 – 4.10 (m, 4H), 3.47 (m, 1H), 2.33 (d, *J* = 4.6 Hz, 2H), 2.24 (sept, *J* = 6.8 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 6H), 1.02 (d, *J* = 6.8 Hz, 6H).

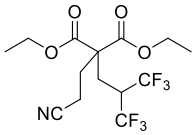
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.3 (d, *J* = 8 Hz, 6F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 170.0, 124.1 (q, *J* = 280 Hz), 61.7, 59.9, 44.2 (sept, *J* = 28 Hz), 31.9, 25.8, 18.3, 14.1.

HRMS (ESI+): m/z $[M+H]^+$ 367.13244 (calcd for $C_{14}H_{21}F_6O_4$: 367.13385).

clear yellow oil

Compound 20b



Compound **20b** was purified using pentane / DCM (100/0 to 80/20) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 4.34 – 4.15 (m, 4H), 3.14 (m, , 1H), 2.48 – 2.35 (m, 4H), 2.27 – 2.19 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 6H).

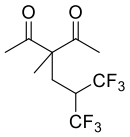
^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.5 (d, *J* = 8 Hz, 6F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 169.1, 123.6 (q, *J* = 279 Hz), 118.4, 62.8, 55.1, 43.8 (sept, *J* = 29 Hz), 29.8, 29.2, 27.0, 13.9, 13.0.

HRMS (ESI+): m/z $[M+H]^+$ 378.11209 (calcd for $C_{15}H_{18}F_6N_1O_4$: 378.11345).

clear yellow oil

Compound 21b



Compound **21b** was purified using pentane / DCM (100/0 to 50/50) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.87 (m, 1H), 2.34 (d, *J* = 4.5 Hz, 2H), 2.14 (s, 6H), 1.35 (s, 3H).

^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.2 (d, *J* = 8 Hz, 6F).

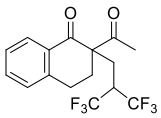
^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 205.5, 123.8 (q, *J* = 280 Hz), 64.7, 43.6 (sept, *J* = 29 Hz), 27.0, 26.9, 17.8.

HRMS (ESI-): m/z $[M-H]^-$ 277.06635 (calcd for $C_{10}H_{11}F_6O_2$: 277.06687).

White solid

Mp: 34-35°C

Compound 22b



Compound **22b** was purified using cyclohexane/DCM (100/0 to 60/40) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.08 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.52 (td, *J* = 7.5, 1.4 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 3.21 – 3.08 (m, 1H), 3.08 – 2.95 (m, 1H), 2.94 – 2.77 (m, 2H), 2.65 (dt, *J* = 13.6, 3.9 Hz, 1H), 2.10 (ddd, *J* = 16.5, 3.8, 0.9 Hz, 1H), 2.03 (s, 3H), 1.88 (td, *J* = 13.0, 5.1 Hz 1H).

^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -67.3 (quint, *J* = 9 Hz, 3F), -67.5 (quint, *J* = 9 Hz, 3F).

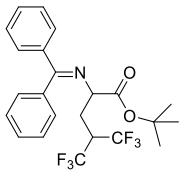
^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 204.4, 196.9, 143.5, 134.6, 131.8, 129.2, 128.2, 127.2, 123.9 (q, *J* = 285 Hz), 61.5, 42.7 (sept, *J* = 29 Hz), 29.8, 27.8, 27.6, 25.5.

HRMS (CI+): m/z $[M+H]^+$ 353.09779 (calcd for $C_{16}H_{15}F_6O_2$: 353.09762).

White solid

Mp: 84-85°C

Compound 23b



Compound **23b** was purified using cyclohexane/DCM (100/0 to 50/50) as eluent. However, this compound was found unstable on silica gel and was obtained together with benzophenone, its decomposition product (**23b**/benzophenone NMR ratio: 1/1.51).

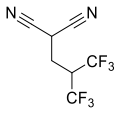
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.69 – 7.64 (m, 2H), 7.48 – 7.39 (m, 4H), 7.38 – 7.31 (m, 2H), 7.20 – 7.12 (m, 2H), 4.11 (dd, *J* = 8.6 Hz, 5.9 Hz 1H), 3.20 (m, 1H), 2.50 – 2.41 (ddd, *J* = 14.3, 7.3, 6.1 Hz, 1H), 2.39 – 2.29 (ddd, *J* = 14.3, 5.2, 4.0 Hz, 1H), 1.41 (s, 9H).

^{9}F NMR (376 MHz, $CDCl_3$, ppm): δ -66.9 (quint, *J* = 9 Hz, 3F), -67.3 (quint, *J* = 9 Hz, 3F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 196.9, 172.6, 170.0, 137.8, 136.1, 130.9, 129.0, 128.9, 128.6, 128.3, 127.7, 124.0 (q, *J* = 280 Hz) , 82.3, 62.3, 44.7 (sept, *J* = 28 Hz), 28.1, 27.8.

HRMS (CI+): m/z $[M+H]^+$ 460.17120 (calcd for $C_{23}H_{24}F_6N_1O_2$: 460.17112).

Compound 24b



Compound **24b** was purified using petroleum ether / AcOEt (100/0 to 90/10) as eluent.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.99 (t, *J* = 8.4 Hz, 1H), 3.25 (dhept, *J* = 7.0, 7.0 Hz, 1H), 2.60 (dd, *J* = 8.4, 6.5 Hz, 2H).

^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ -66.7 (d, *J* = 7 Hz, 6F).

^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 122.8 (q, *J* = 281 Hz), 110.7, 45.9 (sept, *J* = 29 Hz), 25.6, 21.2.

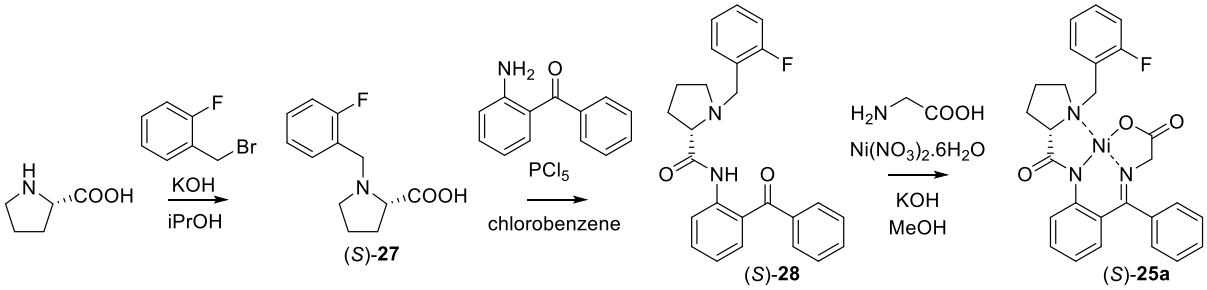
HRMS (ESI-): m/z $[M-H]^-$ 229.02017 (calcd for $C_7H_3F_6N_2$: 229.01949).

White solid

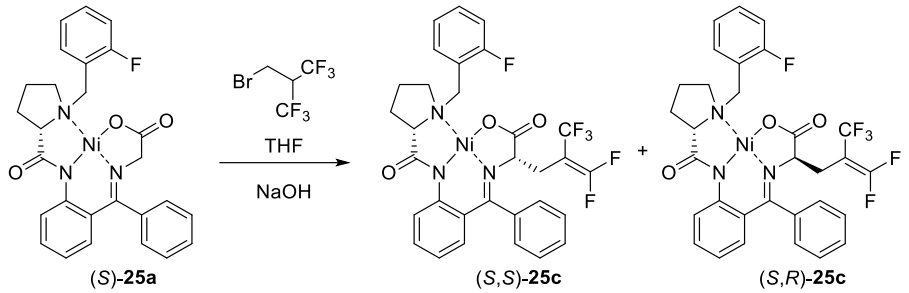
Mp: 104-105°C

II.3 Synthesis of nickel (II) complex (*S*)-25a

The synthesis was adapted from the literature[1–3] using the synthesis pathway depicted on the following scheme.



II.4 Synthesis of (*S*,*S*)-25c



(*S*)-**25a** (*S*,*S*)-**25c** (*S*,*R*)-**25c**

In a double neck round bottom flask, under argon, nickel complex (*S*)-**25a** (100 mg, 516.20 g mol^{-1}, 0.19 mmol) was dissolved in anhydrous THF (8 mL). The solution was cooled to -20 °C and sodium hydroxyde (31 mg, 112.21 g mol^{-1}, 0.77 mmol) was introduced. The reaction mixture was stirred for 10 minutes at -20 °C and 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane was added dropwise (72 µL, 130 mg, 244.96 g mol^{-1}, 0.54 mmol, 1.83 g mL^{-1}). The mixture was stirred at -20 °C for 1 h and at 20 °C for 3 h. The reaction mixture was concentrated under high vacuum. The crude product was then purified by flash column chromatography on silica gel in Et_2O/MeOH: 98/2 to afford compound **25b** (8 mg, 680.25 g mol^{-1}, 0.012 mmol, 6 %), followed by a mixture of (*S*,*S*)-**25c** and (*S*,*R*)-**25c** (70 mg, 660.24 g mol^{-1}, 0.11 mmol, 56%) as a red solid and compound (*S*)-**25a** (20 mg, 0.04 mmol, 20%). Monocrystals of (*S*,*S*)-**25c** for X-ray analysis were obtained in a mixture of CH_2Cl_2/hexane.

^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 8.31 (td, 1H, *J* =7.8 ; 1.8 Hz), 8.14 (d, 1H, *J* = 8.5 Hz), 7.55-7.44 (m, 3H), 7.28-7.24 (m, 1H), 7.23-7.14 (m, 3H), 7.05 (td, 1H, *J* = 8.3 ; 1.3 Hz), 6.93 (d, 2H, *J* = 7.2 Hz), 6.73-6.66 (m, 2H), 4.38 (d, 1H, *J* = 13.4 Hz), 3.93 (dd, 1H, *J* = 10.3 ; 5.4 Hz), 3.83 (d, 1H, *J* = 13.4 Hz), 3.70-3.56 (m, 1H), 3.51-3.44 (m, 2H), 3.33-3.26 (m, 1H), 2.85-2.79 (m, 1H), 2.66-2.56 (m, 1H), 2.53-2.44 (m, 1H), 2.28-2.19 (m, 1H), 2.12-2.03 (m, 1H).

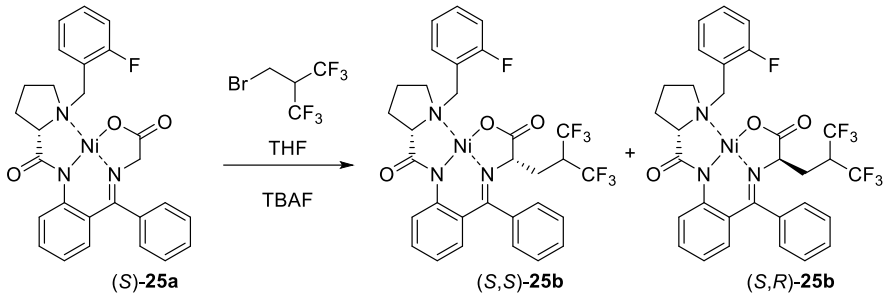
^{19}F NMR (282 MHz, $CDCl_3$, ppm): δ = -61.11 (dd, 3F, $^3J_{F\text{-}F}$ = 20.9 Hz, $^3J_{F\text{-}F}$ = 10.3 Hz), -73.10 (qdd, 1F, $^3J_{F\text{-}F}$ = 22.0 Hz, $^2J_{F\text{-}F}$ = 13.3 Hz, $^4J_{F\text{-}H}$ = 4.1 Hz), -77.11 (dq, 1F, $^2J_{F\text{-}F}$ = 10.2 Hz, $^3J_{F\text{-}F}$ = 10.2 Hz), -114.12 (m, 1F).

^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 180.2, 176.8, 171.7, 163.0 and 160.5 (d, $^1J_{C\text{-}F}$ = 248 Hz, CF_{ar}), 160.3 and 157.3 and 154.4 (ddm, $^1J_{C\text{-}F}$ = 292 Hz, $^1J_{C\text{-}F}$ = 305 Hz, CF_2), 142.7, 134.2 (d, $^4J_{C\text{-}F}$ = 3 Hz), 133.7, 133.1, 132.8, 131.4 (d, $^3J_{C\text{-}F}$ = 9 Hz), 130.3, 129.3, 129.2, 127.4, 127.4, 126.4, 124.7 (d, $^4J_{C\text{-}F}$ = 3 Hz), 123.9, 121.0, 120.5 (d, $^2J_{C\text{-}F}$ = 14 Hz), 116.2 (d, $^2J_{C\text{-}F}$ = 23 Hz), 81.9-81.1 (qdd, $^2J_{C\text{-}F}$ = 35 Hz, $^2J_{C\text{-}F}$ = 28 Hz, $^2J_{C\text{-}F}$ = 11 Hz), 70.6, 67.9, 57.2, 55.9, 30.8, 29.6, 23.9.

In ^{1}H ^{19}F NMR and ^{13}C NMR, most of the peaks are duplicated due to the presence of the two diastereoisomers. Only the main diastereoisomer (*S*,*S*)-**25c** is described. The CF_3 signal on carbon NMR is not visible probably due to an overlap with C_{ar}.

HRMS (ESI+): m/z $[M+H]^+$ 660.12265 (calcd for $C_{31}H_{26}F_6N_3NiO_3$: 660.12264).

II.5 Multi-gram scale synthesis of (*S*,*S*)-25b and (*S*,*R*)-25b



In a double neck round bottom flask, under argon, nickel complex (*S*)-**25a** (8.10 g, 516.20 g mol^{-1}, 15.69 mmol) was dissolved in anhydrous THF (122 mL). The solution was cooled to -20 °C and TBAF (41.02 g, 261.46 g mol^{-1}, 156.9 mmol) was added. The reaction mixture was stirred for 10 minutes at -20 °C. Then, the 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane was introduced dropwise (10.0 g, 244.96 g mol^{-1}, 40.8 mmol, 1.83 g mL^{-1}) over a period of . The mixture was stirred under argon at -20 °C for 1 h and at 20 °C for 3 h. The reaction mixture was diluted with CH_2Cl_2 to change the solution to a one neck round bottom flask and concentrated under reduced pressure. The residue was solubilized in DCM, and the solution was washed three times with water. The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel with Et_2O first as eluent, and then with Et_2O/MeOH: 98/2. Compound (*S*,*S*)-**25b** eluted first (5.51 g, 680.25 g mol^{-1}, 8.1 mmol, 56 %) followed by (*S*,*R*)-**25b** (0.54 g, 680.25 g mol^{-1}, 0.79 mmol, 5 %). Both (*S*,*S*)-**25b** and (*S*,*R*)-**25b** were obtained as a red solid. Monocrystals of (*S*,*S*)-**25b** and of (*S*,*R*)-**25b** for X-ray analysis were obtained in a mixture of CH_2Cl_2/hexane.

Analyses of (*S*,*S*)-**25b**:

^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 8.26 (td, 1H, *J* =7.4 ; 1.8 Hz), 8.10 (d, 1H, *J* = 8.5 Hz), 7.55-7.45 (m, 3H), 7.27-7.21 (m, 2H), 7.20-7.14 (m, 2H), 7.05 (td, 1H, *J* = 9.7, 1.2 Hz), 6.94 (m, 1H), 6.72-6.65 (m, 2H), 4.37 (d, 1H, *J* = 12.9 Hz), 3.92 (dd, 1H, *J* = 12.4 ; 4.8 Hz), 3.80 (d, 1H, *J* = 13.3 Hz), 3.72 (q, 1H, *J* = 8.2 Hz), 3.65-3.53 (m, 1H), 3.53-3.39 (m, 2H), 2.95 (t, 1H, *J* = 13.6 Hz), 2.90-2.77 (m, 1H), 2.69-2.51 (m, 1H), 2.33-2.19 (m, 1H), 2.14-1.94 (m, 2H).

^{19}F NMR (282 MHz, $CDCl_3$, ppm): δ = -68.49 (m, 6F), -113.95 (m, 1F).

^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 180.1, 177.5, 172.0, 163.4 and 160.1 (d, $^1J_{C\text{-}F}$ = 248 Hz), 142.5, 134.1 and 134.1 (d, $^4J_{C\text{-}F}$ = 3 Hz), 133.6, 132.9, 132.8, 131.5 and 131.4 (d, $^3J_{C\text{-}F}$ = 9 Hz), 130.3, 129.4, 129.3, 127.1, 127.1, 126.4, 124.7 and 124.7 (d, $^3J_{C\text{-}F}$ = 3 Hz), 129.2 and 125.4 and 121.7 and 118.0 (qm, $^1J_{C\text{-}F}$ = 280 Hz, 1CF_3), 124.0, 128.9 and 125.1 and 121.4 and 117.7 (qm, $^1J_{C\text{-}F}$ = 281 Hz, 1CF_3), 121.1, 120.5 and 120.3 (d, $^2J_{C\text{-}F}$ = 14 Hz), 116.4 and 116.1 (d, $^2J_{C\text{-}F}$ = 22 Hz), 70.5, 66.9, 57.3, 55.9, 43.5 (sept, $^2J_{C\text{-}F}$ = 29 Hz), 30.7, 29.6, 24.0.

HRMS (ESI+): m/z $[M+H]^+$ 680.12906 (calcd for $C_{31}H_{27}F_7N_3NiO_3$: 680.12886).

Mp: 283-285 °C

$[\alpha]_D^{24}$ = +2901 (c = 0.206; $CHCl_3$).

Analyses of (*S*,*R*)-**25b**:

^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 8.53 (td, 1H, *J* = 7.5, 1.7 Hz), 8.48 (dd, 1h, *J* = 8.5 Hz, 0.8 Hz), 7.56-7.43 (m, 4H), 7.38 (td, 1H, *J* = 7.5, 1.1 Hz), 7.32-7.27 (m, 1H), 7.25-7.16 (m, 2H), 7.04 (m.1H), 6.80-6.69 (m, 2H), 4.33-4.20 (m, 2H), 3.95 (dd, 1H, *J* = 12.5, 4.6 Hz), 3.77 (q, 1H, *J* = 8.4 Hz), 3.68 (d, 1H, *J* = 13.2 Hz), 3.59 (dd, 1H, *J* = 7.4, 6.3 Hz), 2.78-2.67 (m, 1H), 2.67-2.47 (m, 2H), 2.37-2.26 (m, 2H), 2.09-1.91 (m, 2H).

^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -67.96 (m, 6F), -114.12 (s, 1F).

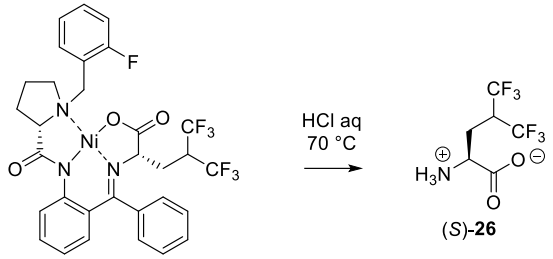
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 182.0, 178.2, 173.2, 163.2 and 160.8 (d, $^{1}J_{C\text{-}F}$ = 248 Hz), 143.2, 134.1, 133.6 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 133.4, 133.2, 131.8 and 131.7 (d, $^{3}J_{C\text{-}F}$ = 9 Hz), 130.2, 129.6, 129.3, 127.7, 126.8, 125.5, 125.0 (d, $^{3}J_{C\text{-}F}$ = 3 Hz), 124.1, 127.9 and 125.1 and 122.3 and 119.5 (qm, $^{1}J_{C\text{-}F}$ = 180 Hz, CF_3), 122.0 (qm, $^{1}J_{C\text{-}F}$ = 179 Hz, CF_3), 121.3 and 121.1 (d, $^{2}J_{C\text{-}F}$ = 15 Hz), 121.1, 116.6 and 116.4 (d, $^{2}J_{C\text{-}F}$ = 23 Hz), 69.4, 66.8, 59.3, 54.5, 43.3 (sept, $^{2}J_{C\text{-}F}$ = 29 Hz), 30.3, 28.8, 23.3.

HRMS (ESI+): m/z $[M+H]^+$ 680.12921 (calcd for $C_{31}H_{27}F_7N_3NiO_3$: 680.12886).

Mp: 279-284 °C

$[\alpha]_D^{24}$ = -1152 (c = 0.21; $CHCl_3$).

II.6 Synthesis of (*S*)-5,5,5,5',5',5'-hexafluoroleucine (*S*)-26



(*S*,*S*)-**25b** (*S*)-**26**

Compound (*S*,*S*)-**25b** (600 mg, 680.25 g mol^{-1}, 0.88 mmol) was dissolved in methanol (18 mL) and an aqueous solution of HCl 3 M was introduced (3.60 mL, 10.8 mmol). The reaction mixture was heated under reflux for 30 minutes. The initially red reaction mixture turned pale green. Then, the mixture was cooled down to room temperature, and concentrated under reduced pressure. mQ water was added to the solid residue and the resulting solution was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Ligand (*S*)-**28** was obtained pure (354 mg, 402.47 g mol^{-1}, 0.88 mmol, quantitative yield). The aqueous phase was concentrated under reduced pressure to dryness. The residue was solubilized with a minimum amount of mQ water for purification on a Dowex 50WX2 200 H^+ resin column activated with 200 mL of mQ water, 80 mL of EtOH, 200 mL of mQ water, 200 mL of HCl 1 M, 200 mL of mQ water. 400 mL of mQ water was eluted first to remove nickel (II) salts, and then a 2% NH_4OH aqueous solution (400 mL) was eluted to obtain, after concentration under vacuum, pure amino acid (*S*)-**26** as a white powder (201 mg, 239.12 g mol^{-1}, 841 µmol, 99%).

^{1}H NMR (400 MHz, CD_3OD, ppm): δ = 4.31-4.14 (septdd, 1H, *J* = 8.2, 8.2, 3.9 Hz), 3.67 (dd, 1H, *J* = 9.7, 5.8 Hz), 2.33 (ddd, 1H, *J* = 14.6, 10.0, 3.6 Hz), 2.20 (ddd, 1H, *J* = 15.0, 7.6, 5.9 Hz).

^{19}F NMR (282 MHz, CD_3OD, ppm): δ = -68.97 (qd, 3F, $^4J_{F\text{-}F}$ = 9.1 Hz, $^3J_{F\text{-}H}$ = 9.1 Hz), -69.66 (qd, 3F, $^4J_{F\text{-}F}$ = 9.1 Hz, $^3J_{F\text{-}H}$ = 9.1 Hz).

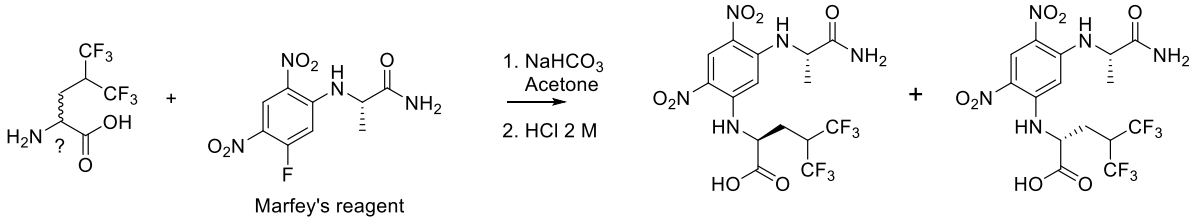
^{13}C NMR (100 MHz, CD_3OD, ppm): δ = 172.3, 129.7 and 126.9 and 224.1 and 121.4 (q, *J* = 279 Hz, CF_3), 129.4 and 126.7 and 124.9 and 121.1 (q, *J* = 279 Hz, CF_3), 52.9, 45.8 (sept, *J* = 28 Hz), 25.7.

HRMS (ESI+): m/z $[M+H]^+$ 240.04595 (calcd for $C_6H_8F_6NO_2$: 240.04592).

Mp: 239-241 °C

$[\alpha]_D^{24}$ = +9.6 (c = 0.202; MeOH).

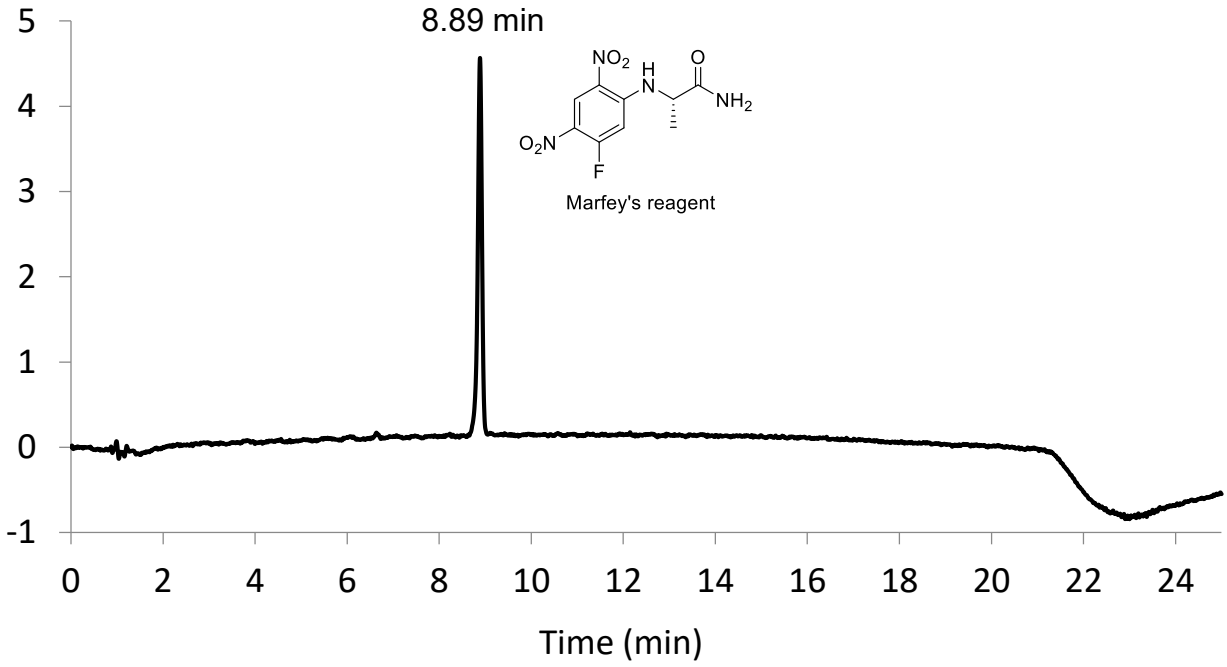
II.7 Determination of the enantiomeric excess of (*S*)-5,5,5,5',5',5'-hexafluoroleucine (Marfey's derivatization method)



Procedure: In a vial were introduced the amino acid (1.2 mg, 5 µmol), then 200 µL of a solution Marfey's reagent (3 mg, 272.19 g mol^{-1}, 11 µmol) dissolved in acetone (300 µL) and 40 µL of an aqueous solution of $NaHCO_3$ 1 M. The reaction mixture was heated at 40 °C during 1 h. An aqueous solution of HCl 2 M was added (20 µL) and the mixture was filtered and diluted with water. Then, the solution was analyzed by reversed phase HPLC with a 25 minutes run using a gradient of 15 to 60% MeCN in water.

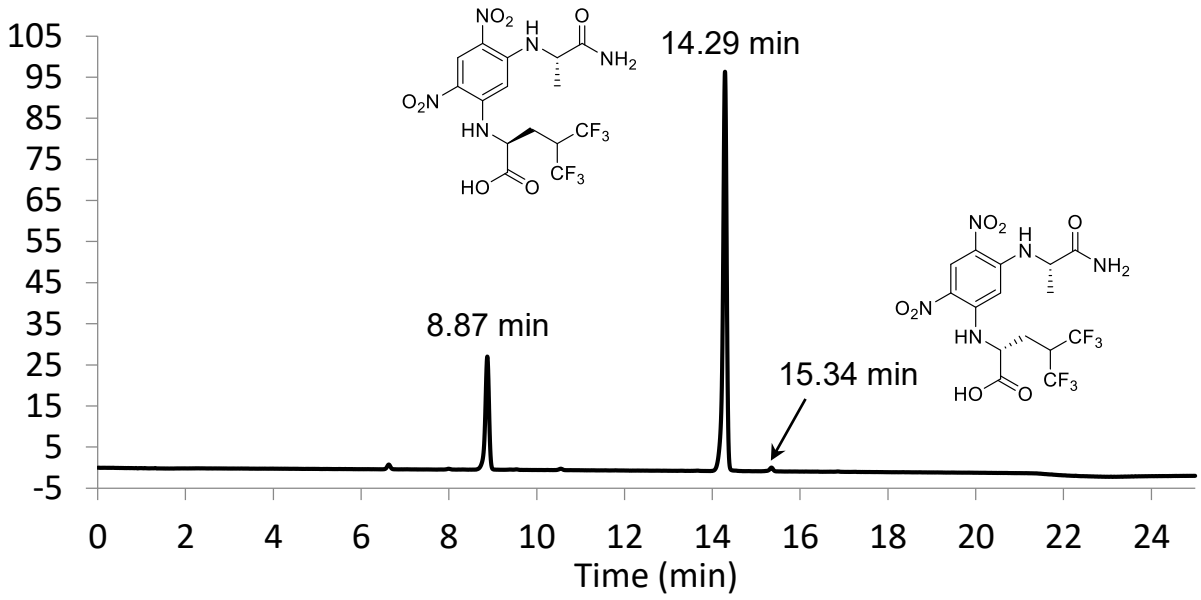
Reference [4]

- Chromatogram of the Marfey's reagent



- Determination of the enantiomeric excess of (*S*)-**26**

Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		14.290	9.456	97.132	99.13	99.09	n.a.
2		15.347	0.083	0.895	0.87	0.91	n.a.
Total:			**9.539**	**98.027**	**100.00**	**100.00**	



e.r.

((*S*)-**26**) > 99%

III. Mechanistic study

III.1 Figure S1: *In situ* ^{1}H NMR experiments of the reaction of 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane with TBAF

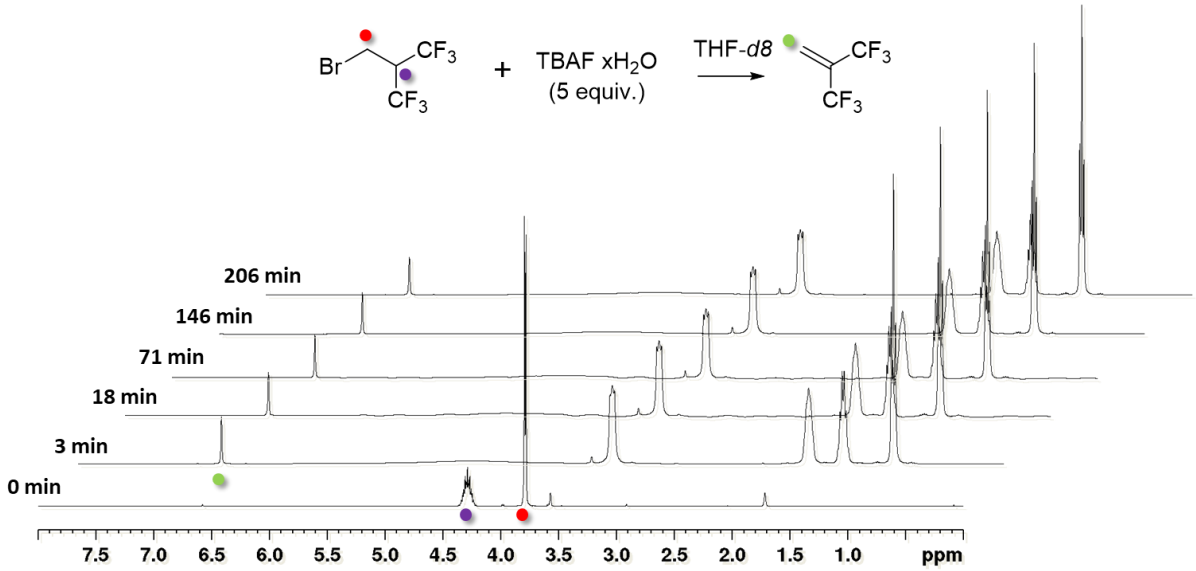


Figure S1: *In situ* ^{1}H NMR (400 MHz) experiments of the reaction of 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane with 5 equiv. of TBAF in THF-*d8* monitored at -20 °C.

III.2 Figure S2: TLC monitoring of the reaction mixture with (*S*)-25a

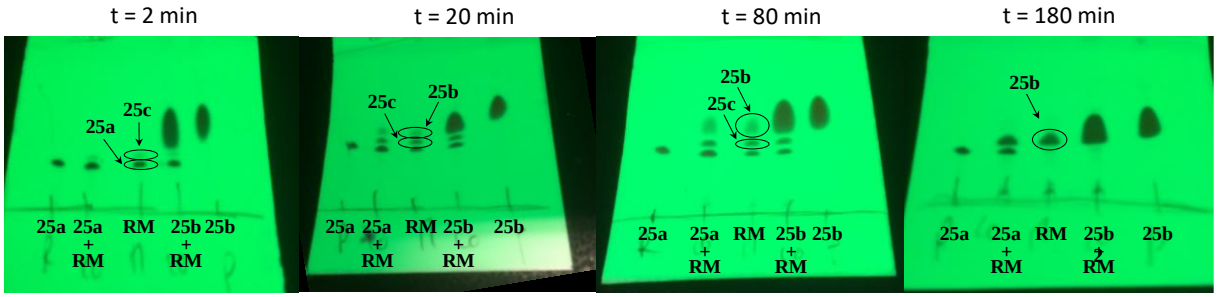


Figure S2: TLC monitoring of the reaction of (*S*)-**25a**, TBAF (10 equiv.), 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane (2.8 equiv.) in THF (1.5 mL); TLC eluent: CH_2Cl_2/MeOH: 95/5; RM: reaction mixture.

III.3 Figure S3: Experiments with compounds 25b and 25c.

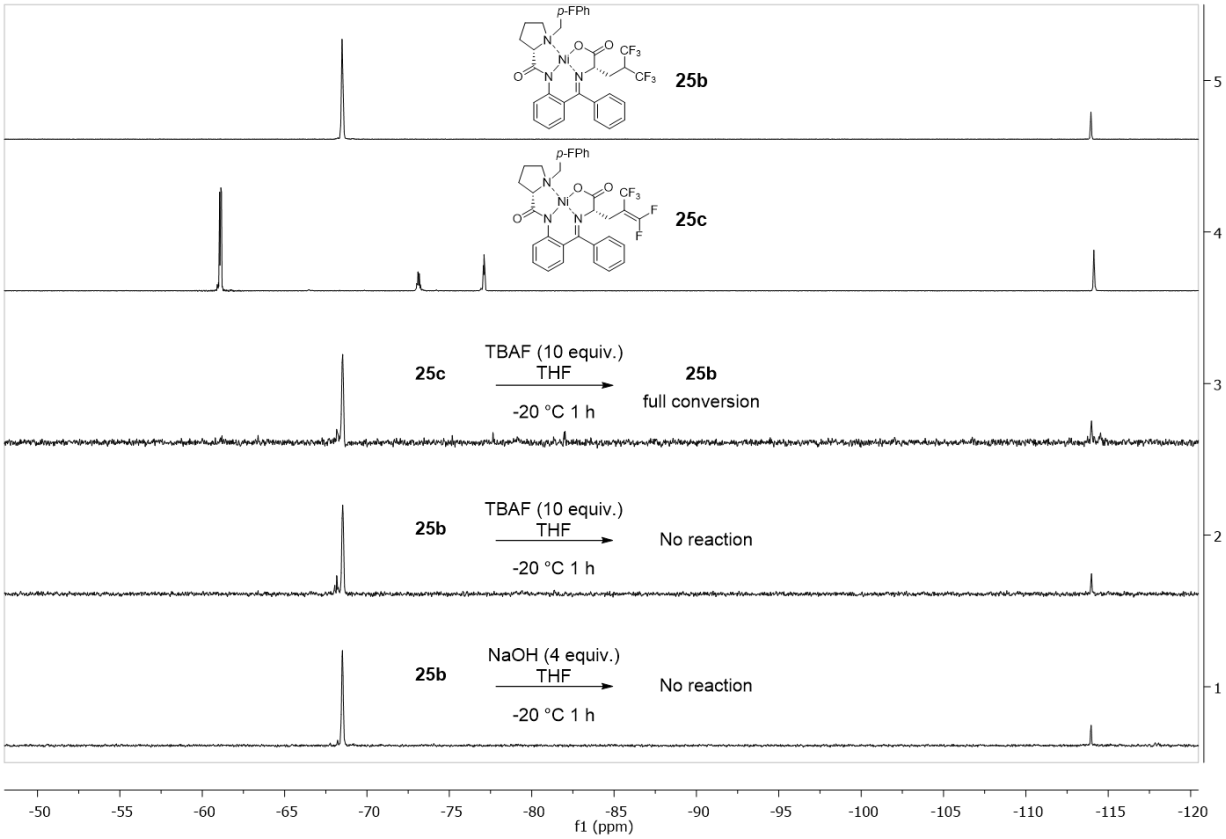
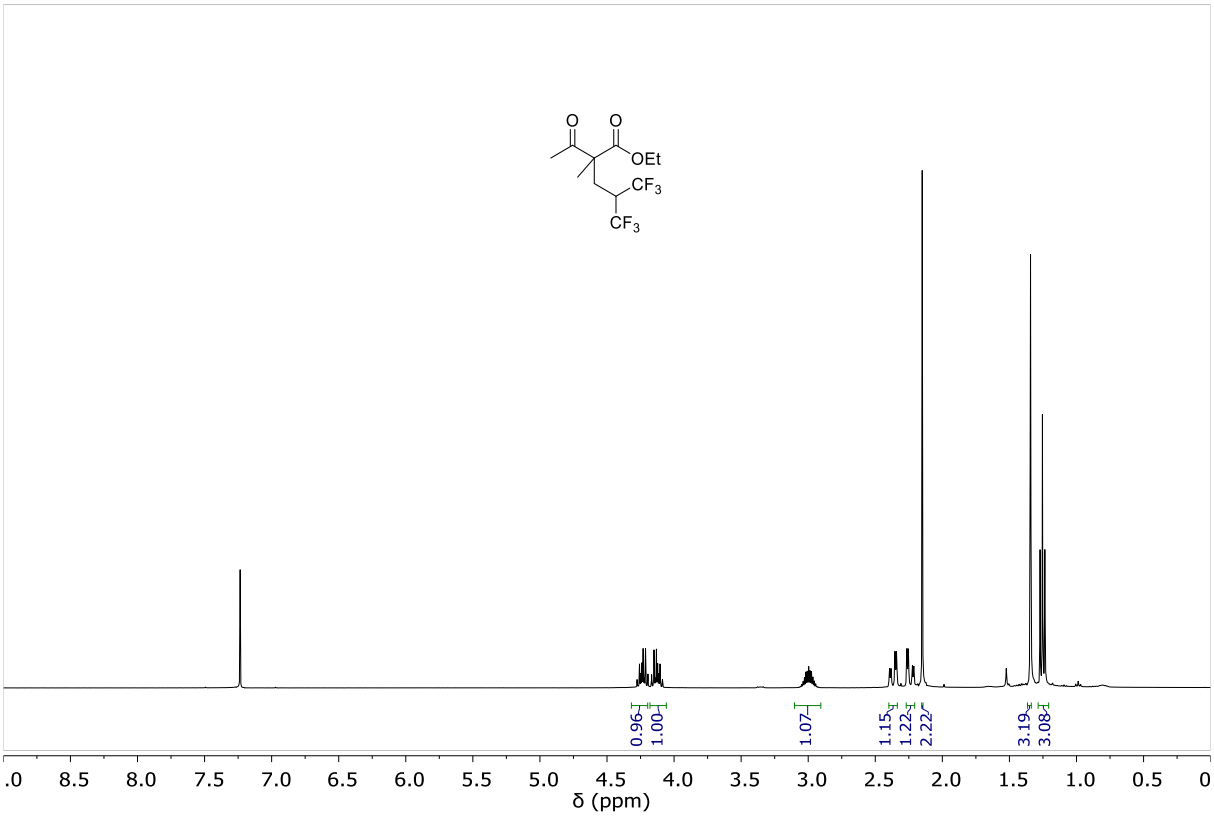


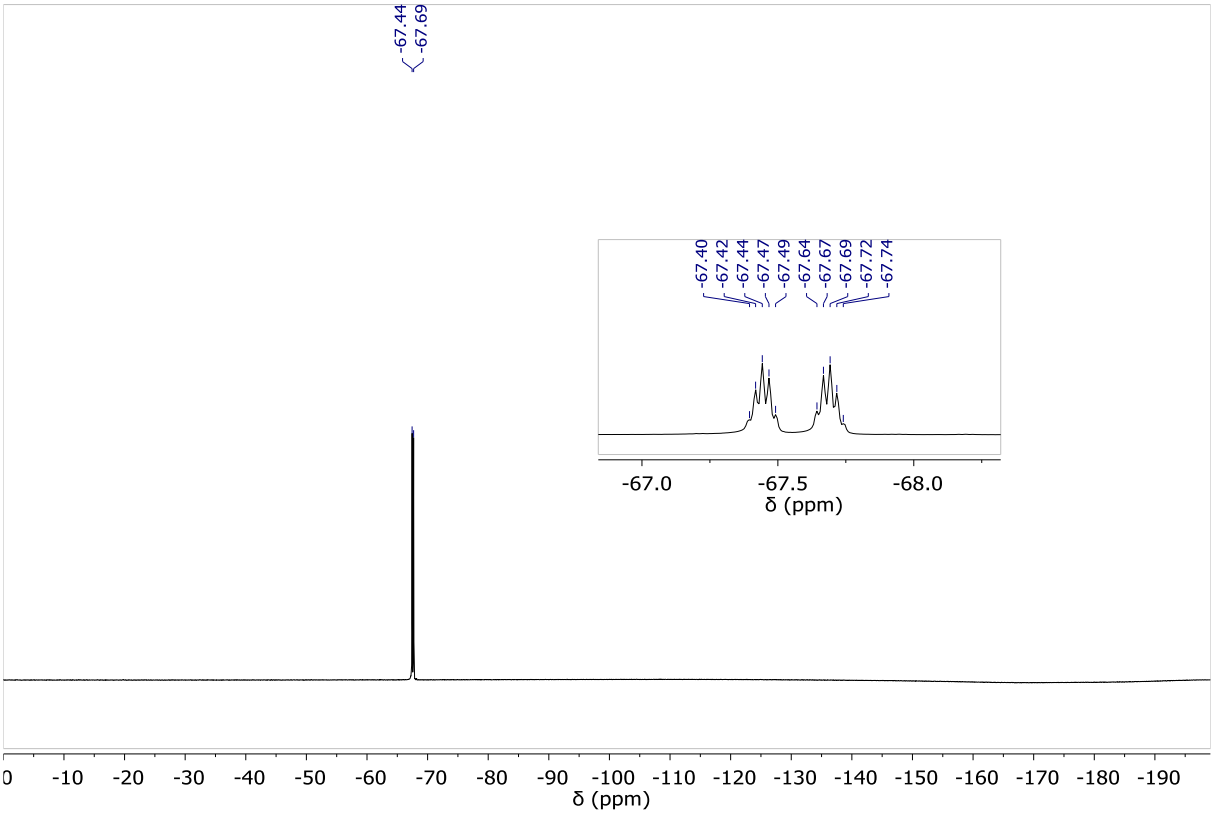
Figure S3: ^{19}F NMR of the crude in $CDCl_3$ (282 MHz)

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

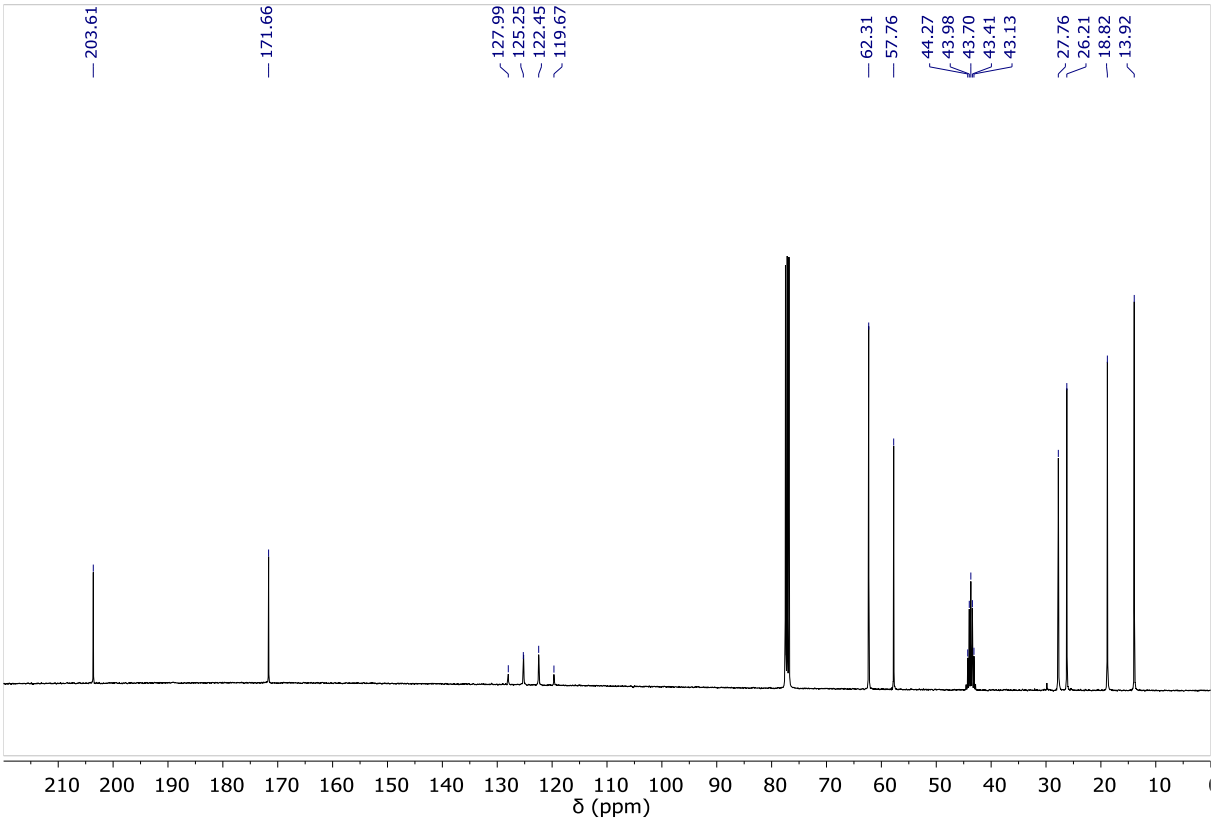
Compound 1b



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

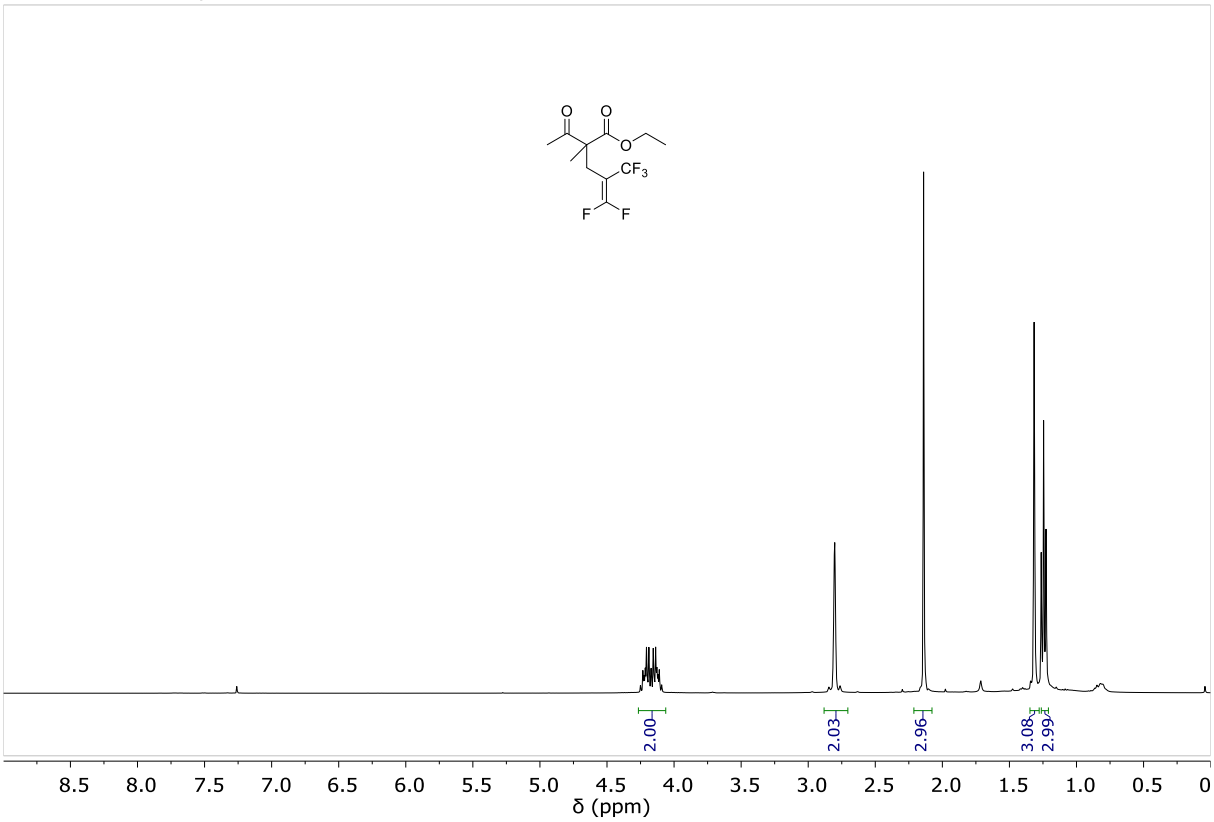


^{19}F NMR ($CDCl_3$, 376 MHz)

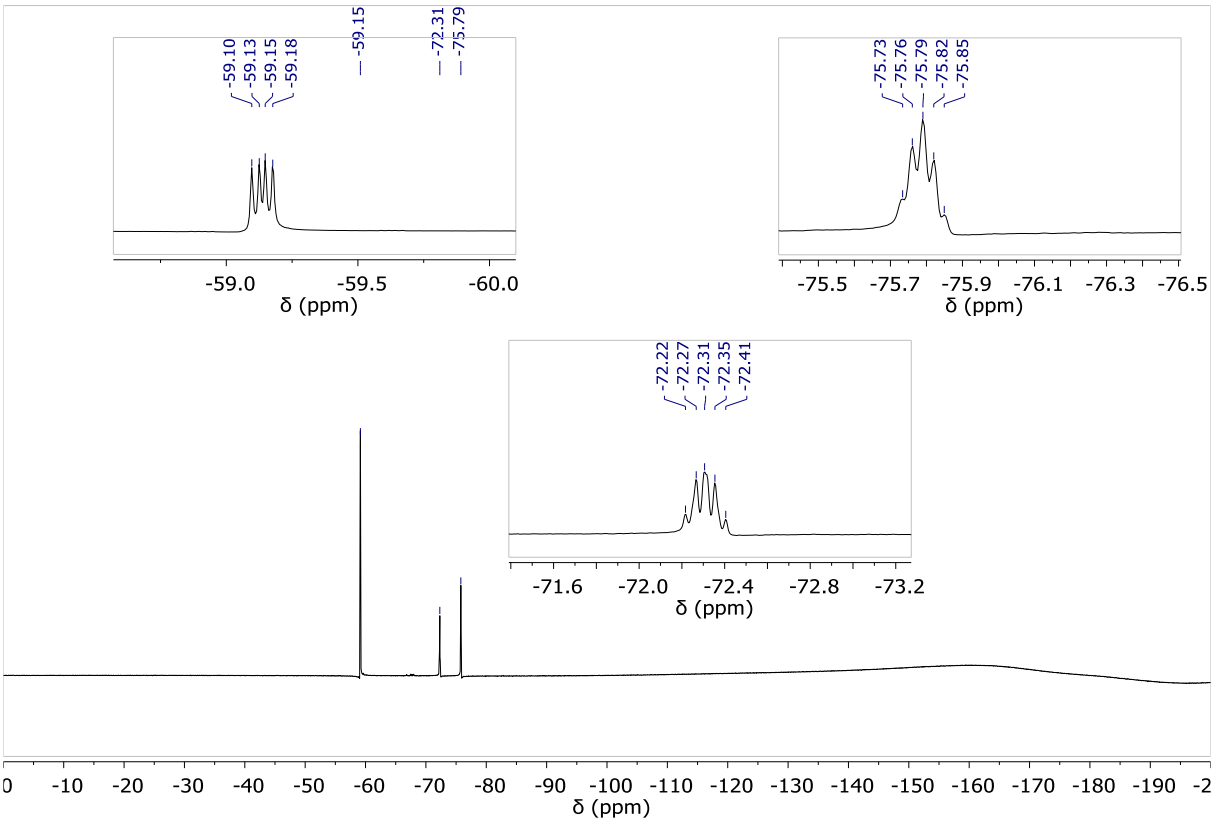


^{13}C NMR ($CDCl_3$, 101 MHz)

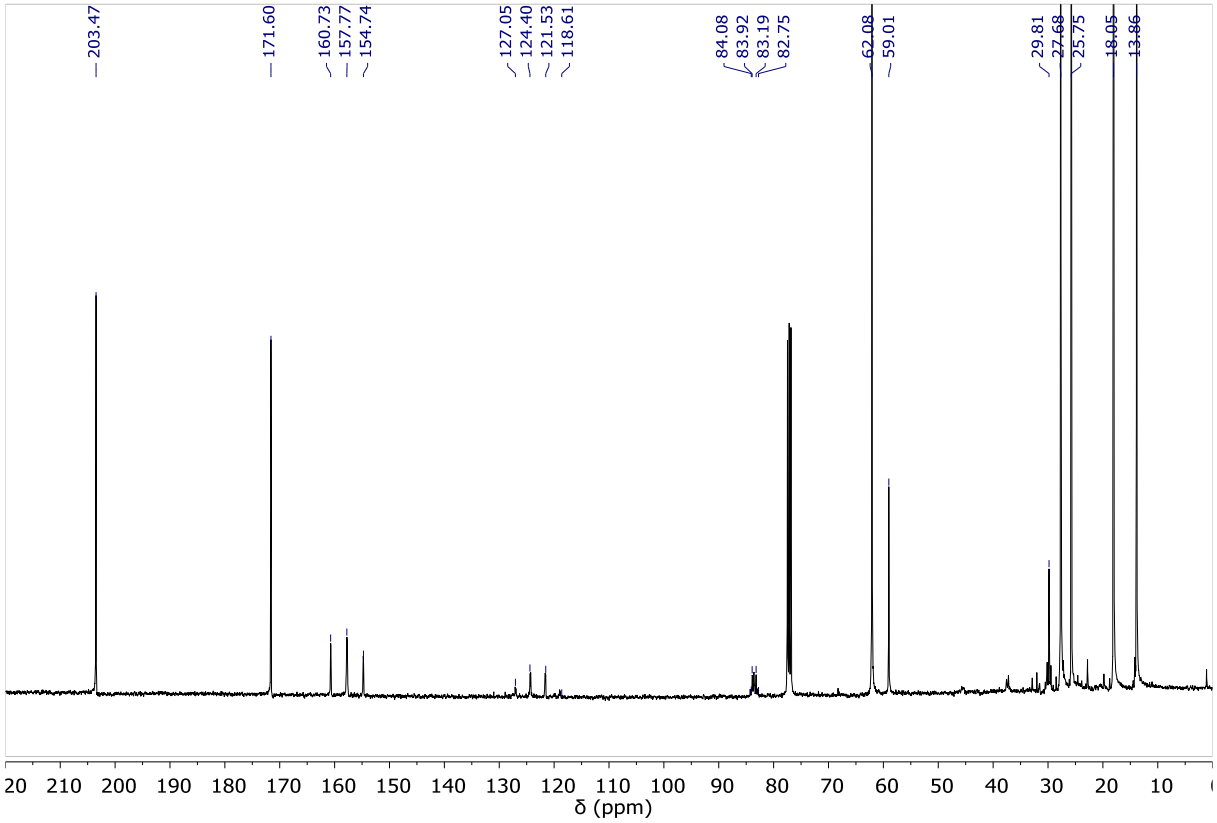
Compound 1c



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

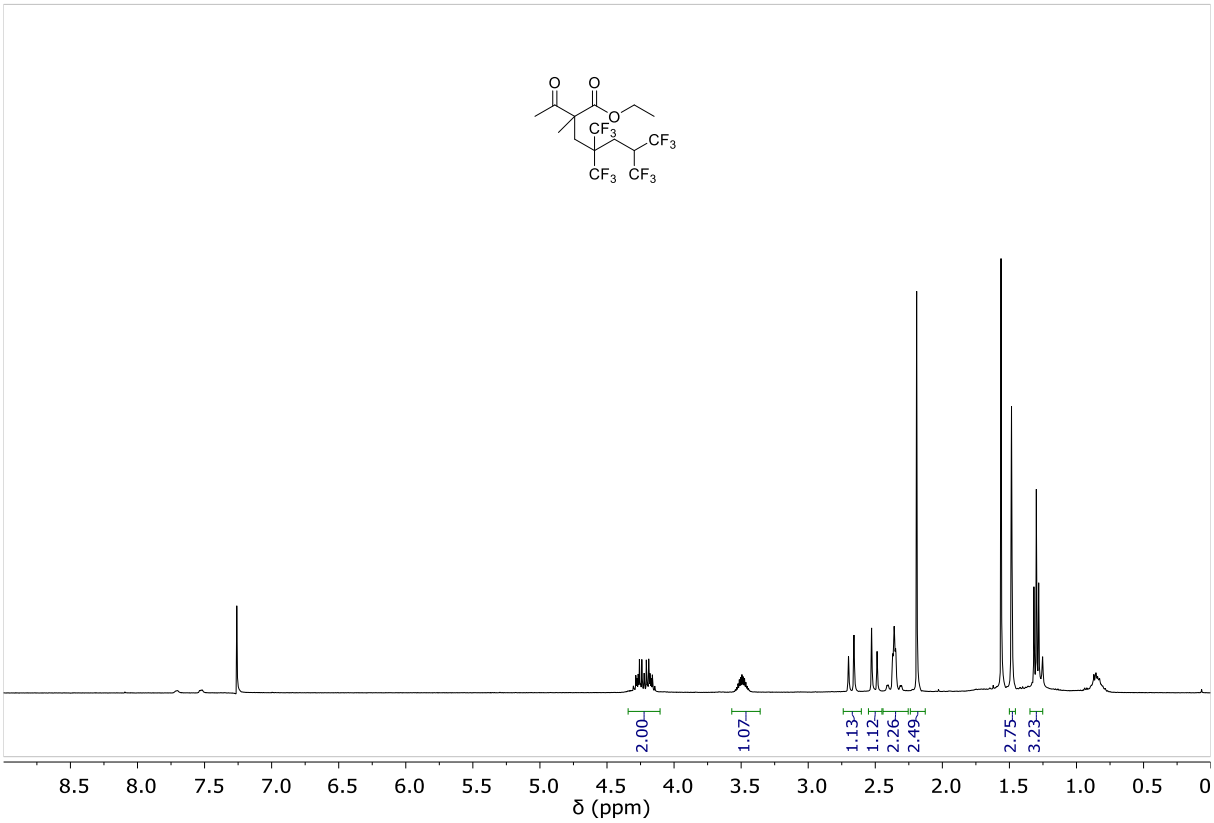


^{19}F NMR ($CDCl_3$, 376 MHz)

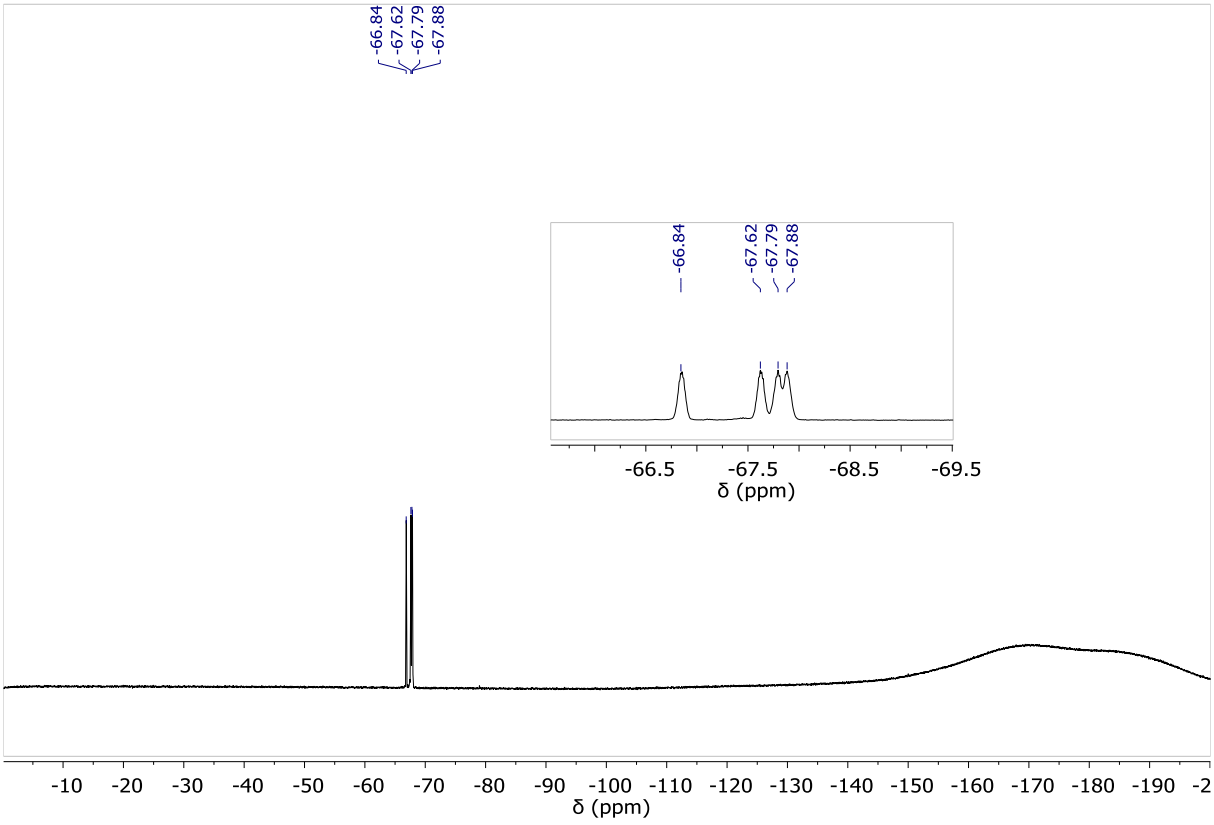


^{13}C NMR ($CDCl_3$, 101 MHz)

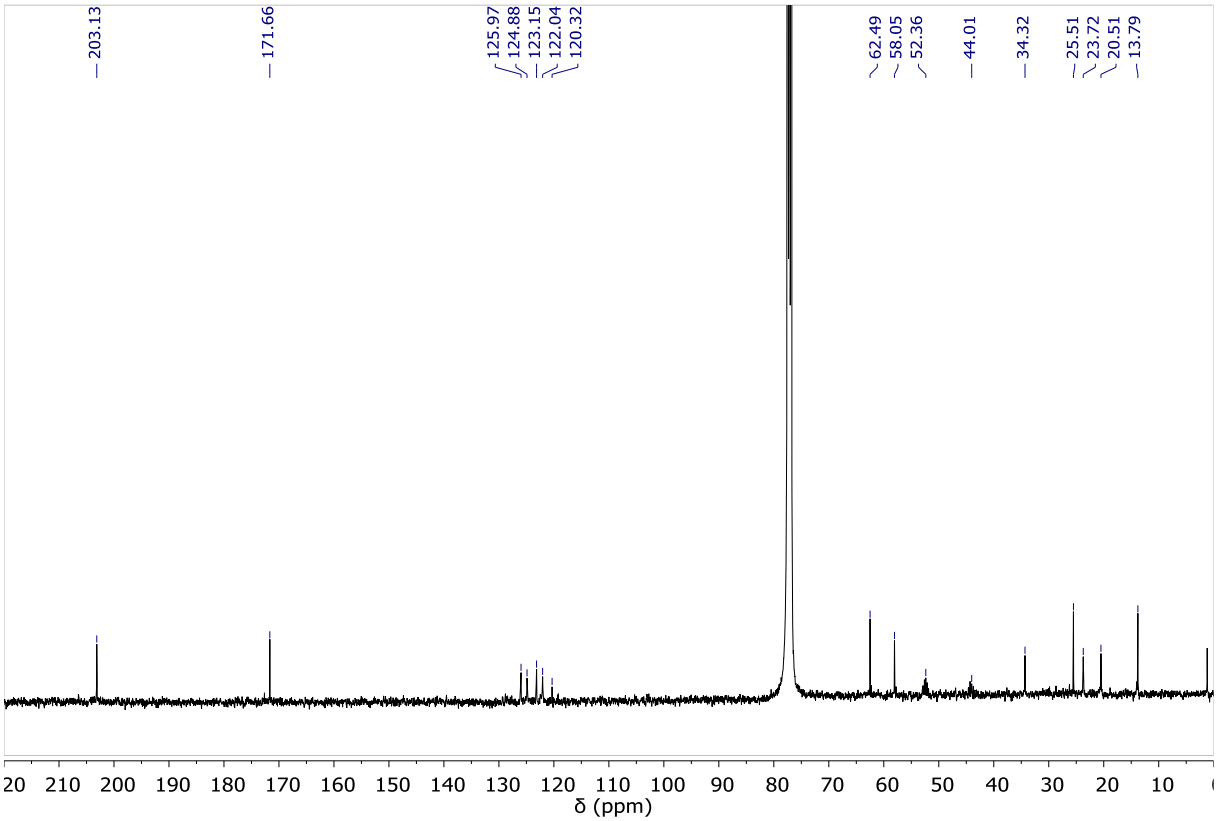
Compound 1d



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

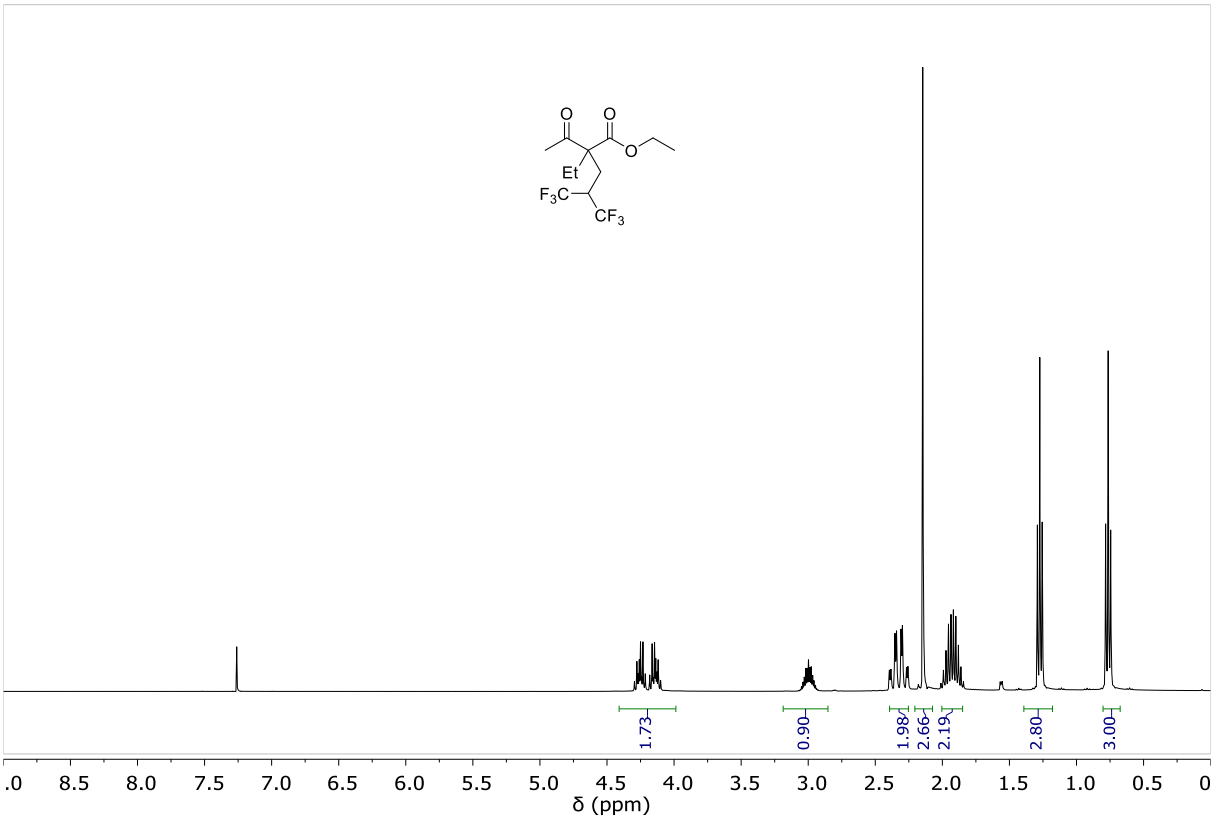


^{19}F NMR ($CDCl_3$, 376 MHz)

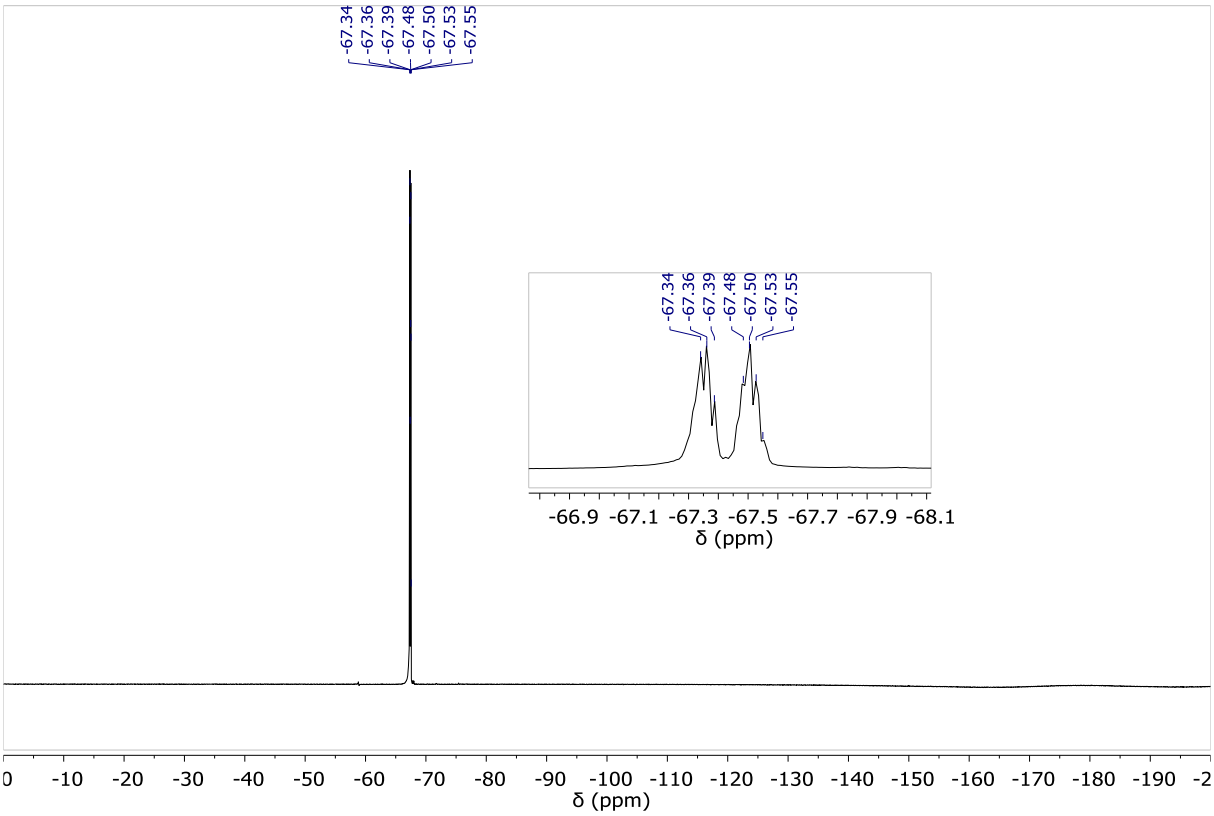


^{13}C NMR ($CDCl_3$, 101 MHz)

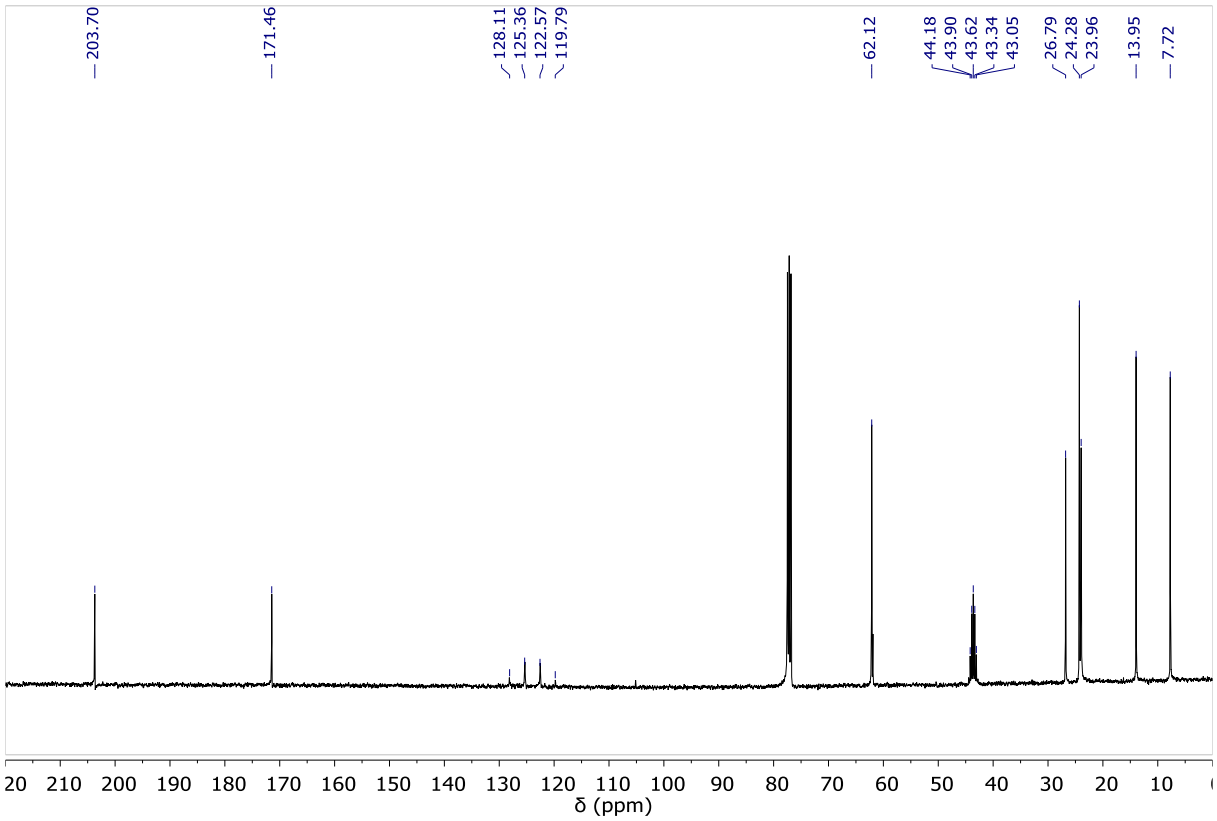
Compound 2b



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

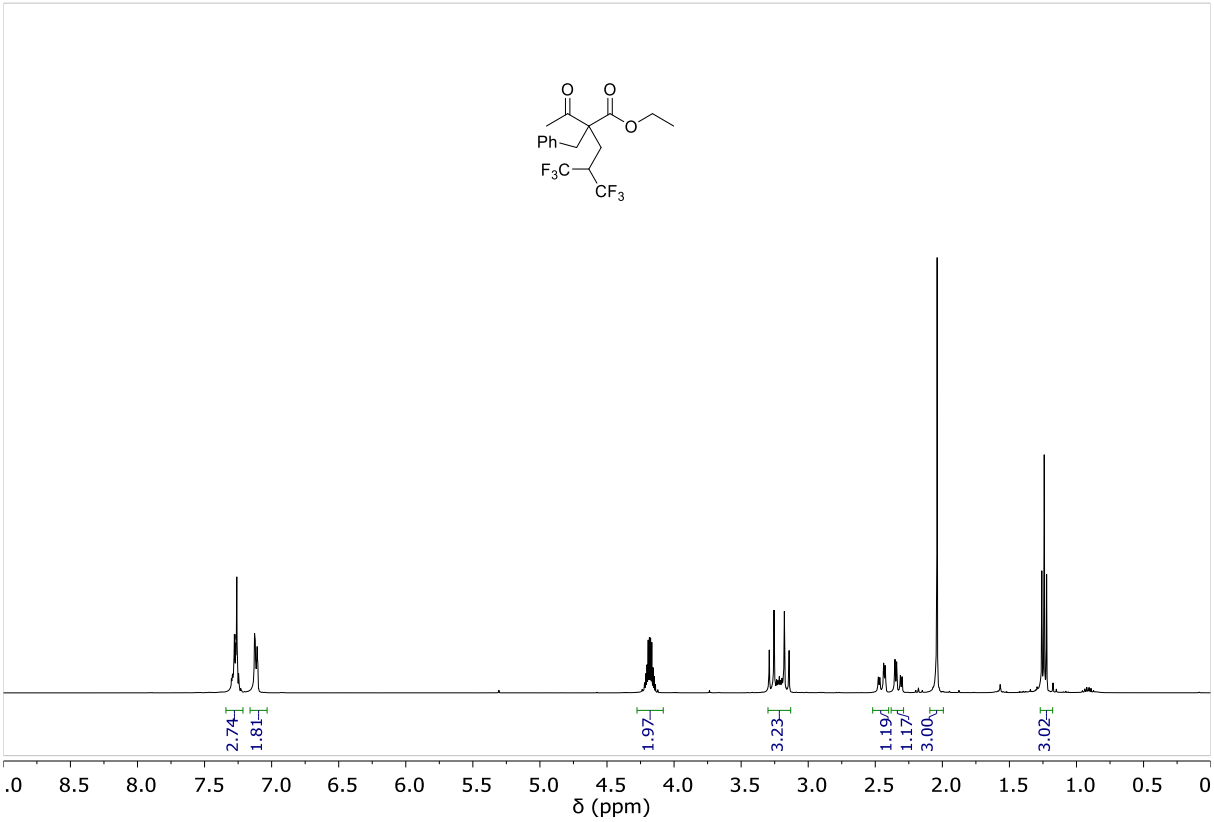


^{19}F NMR ($CDCl_3$, 376 MHz)

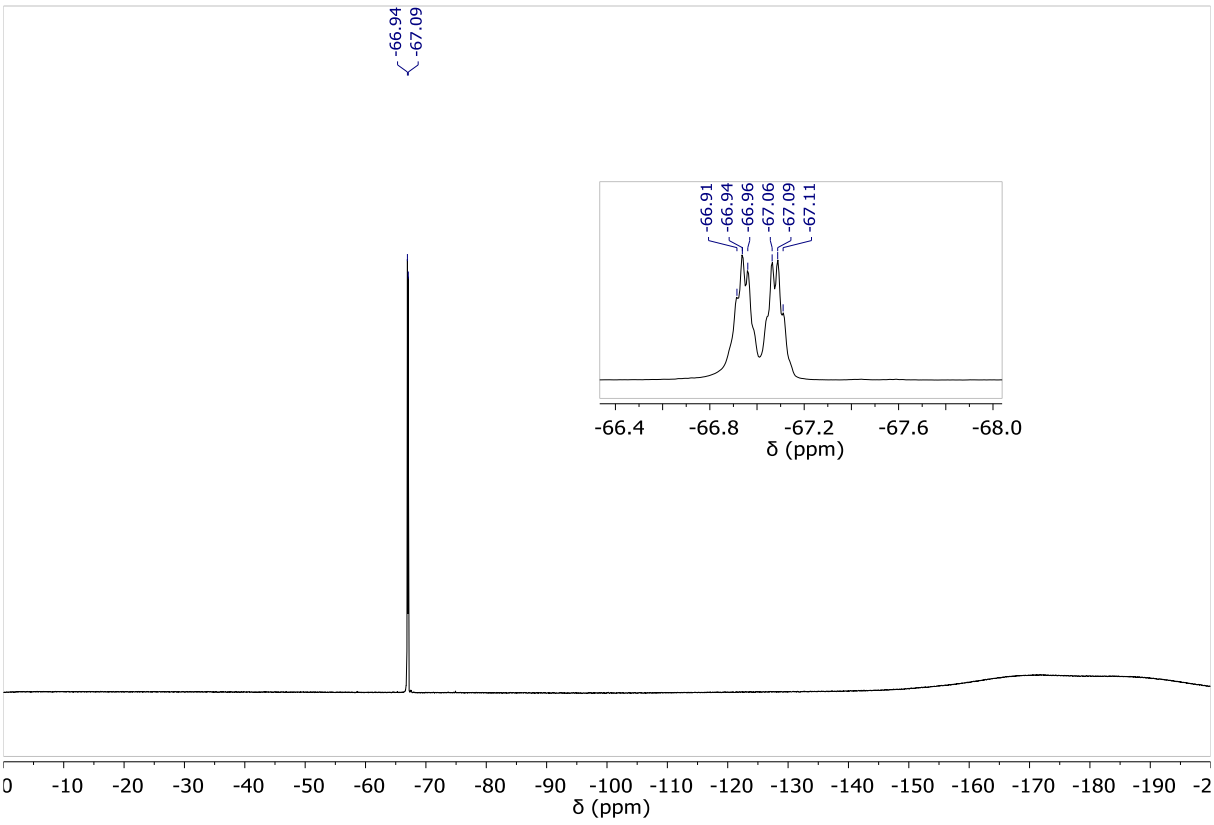


^{13}C NMR ($CDCl_3$, 101 MHz)

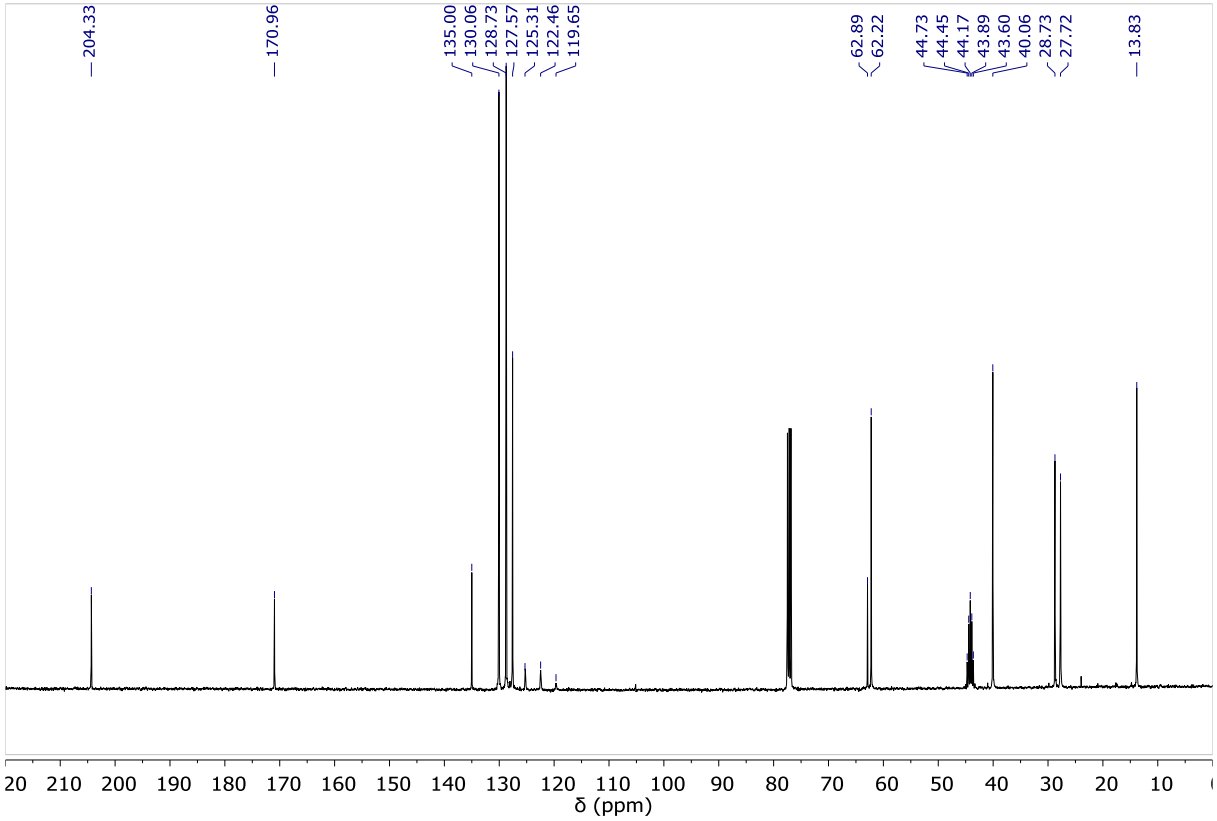
Compound 3b



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

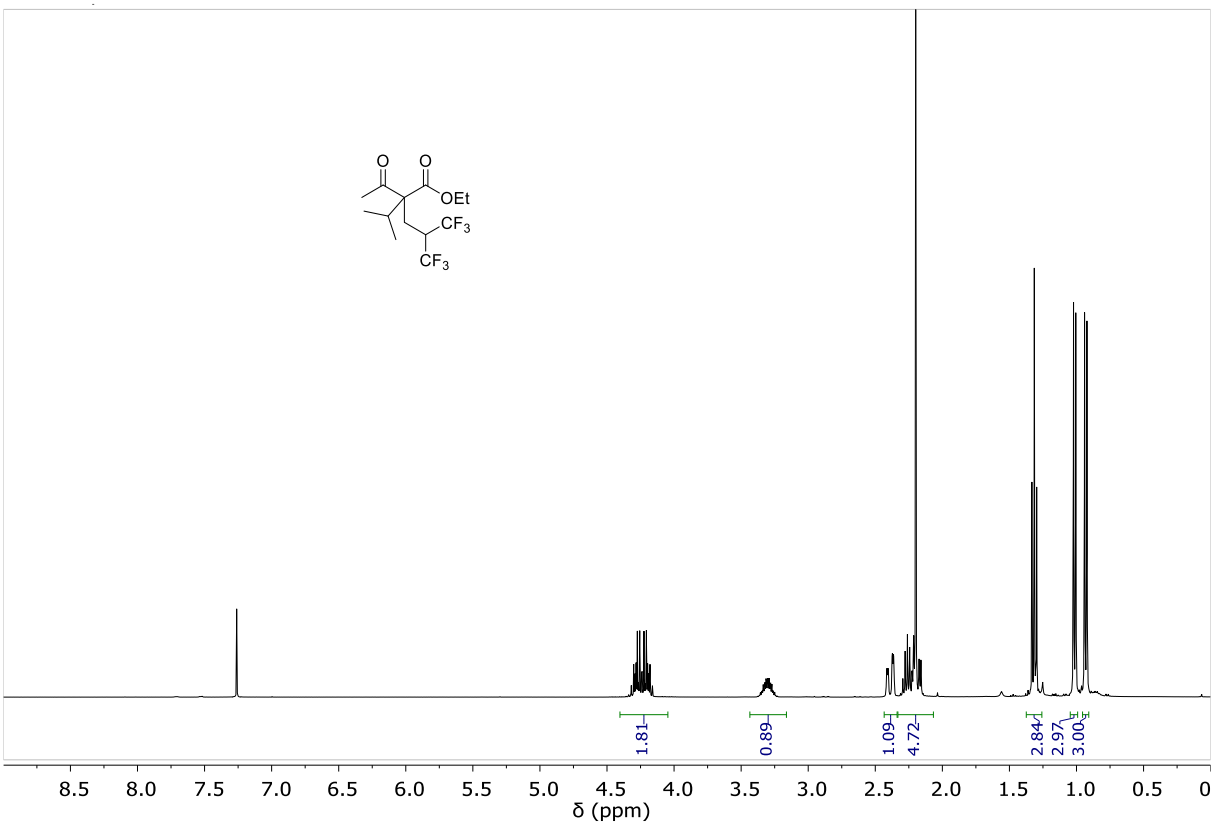


^{19}F NMR ($CDCl_3$, 376 MHz)

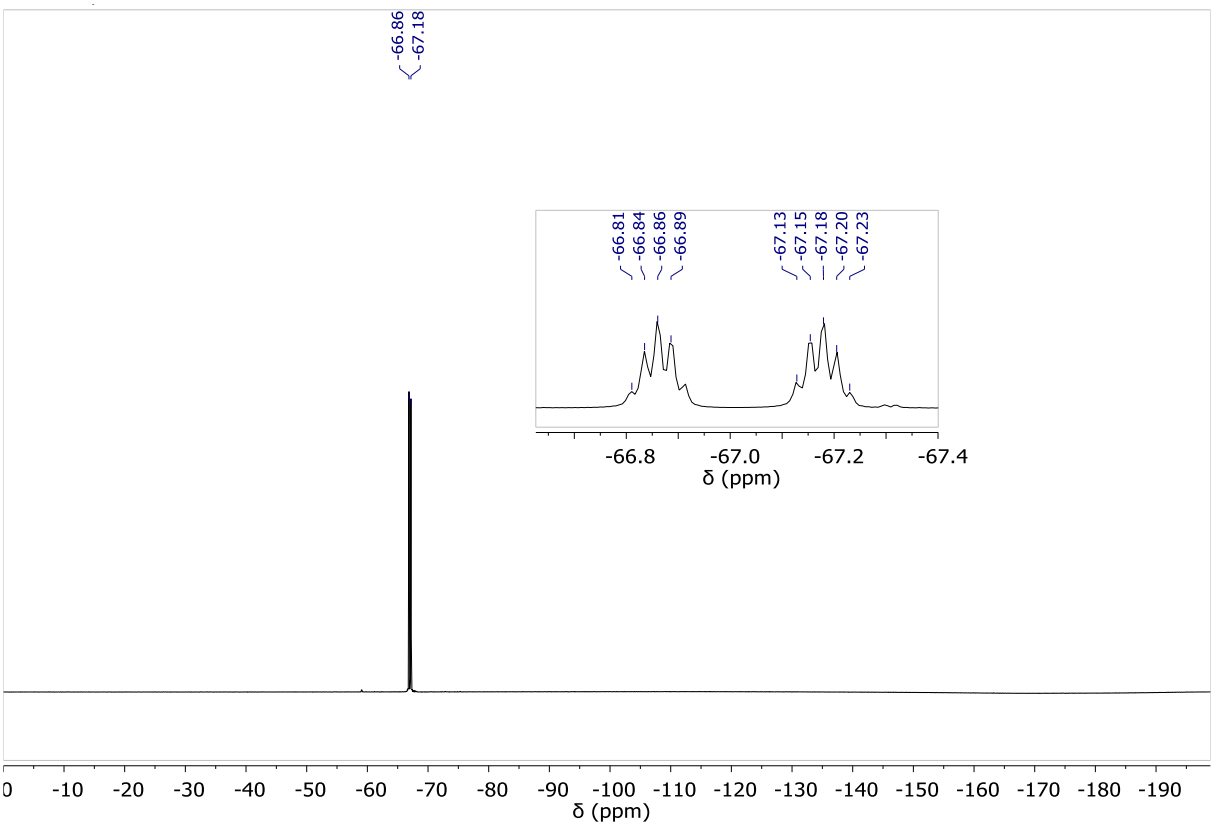


^{13}C NMR ($CDCl_3$, 101 MHz)

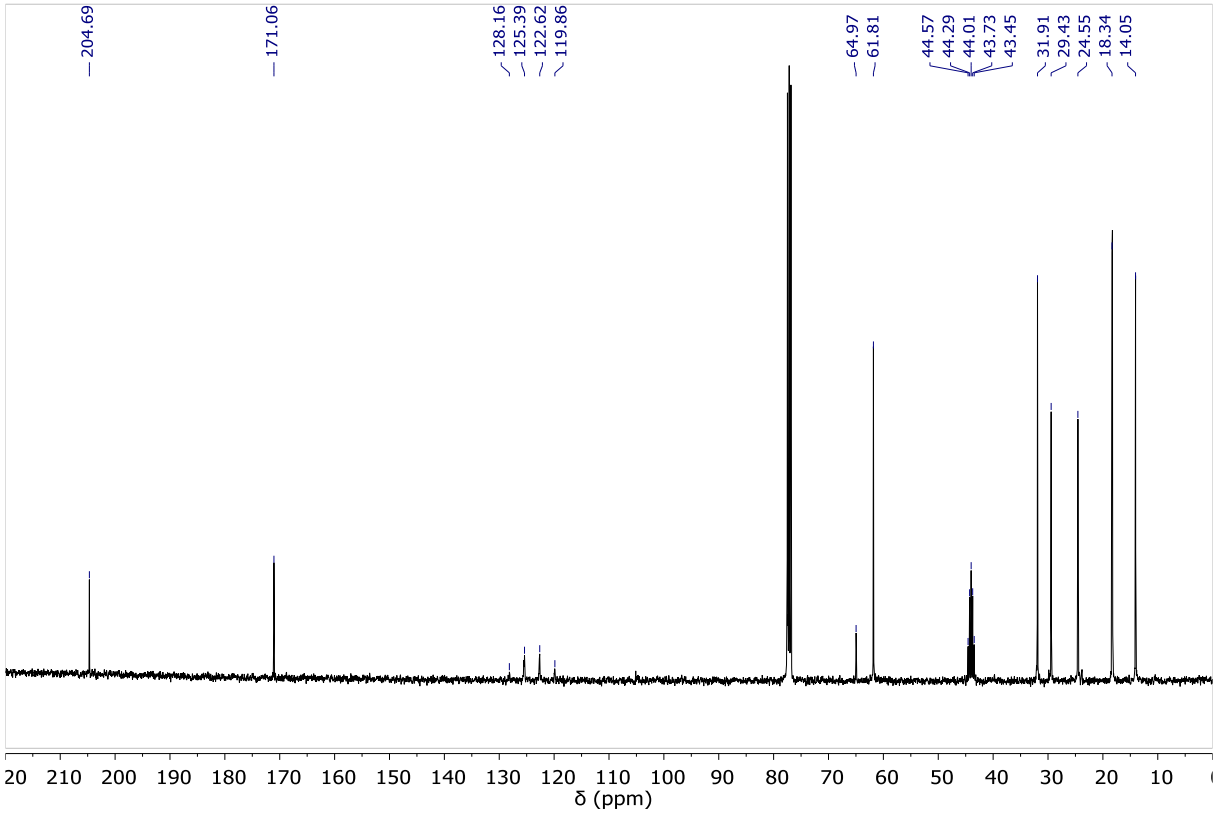
Compound 4b



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

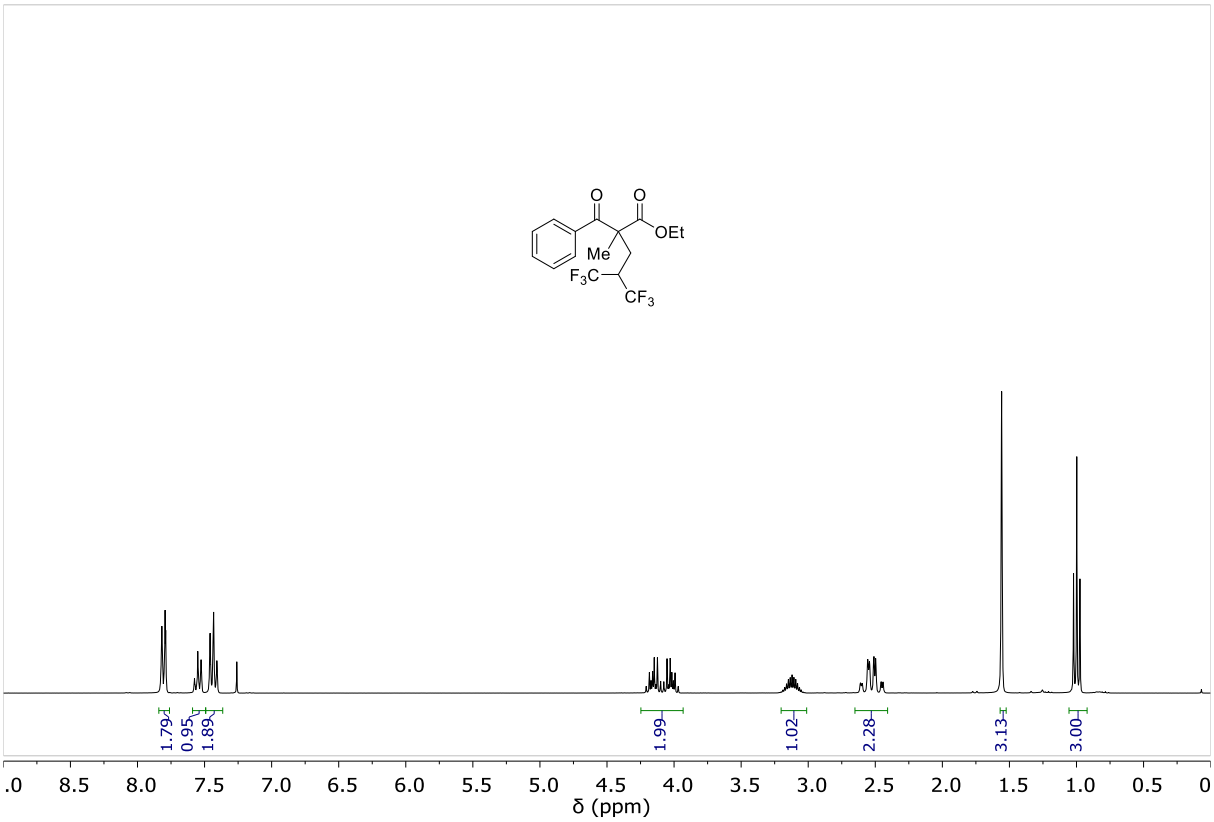


^{19}F NMR ($CDCl_3$, 376 MHz)

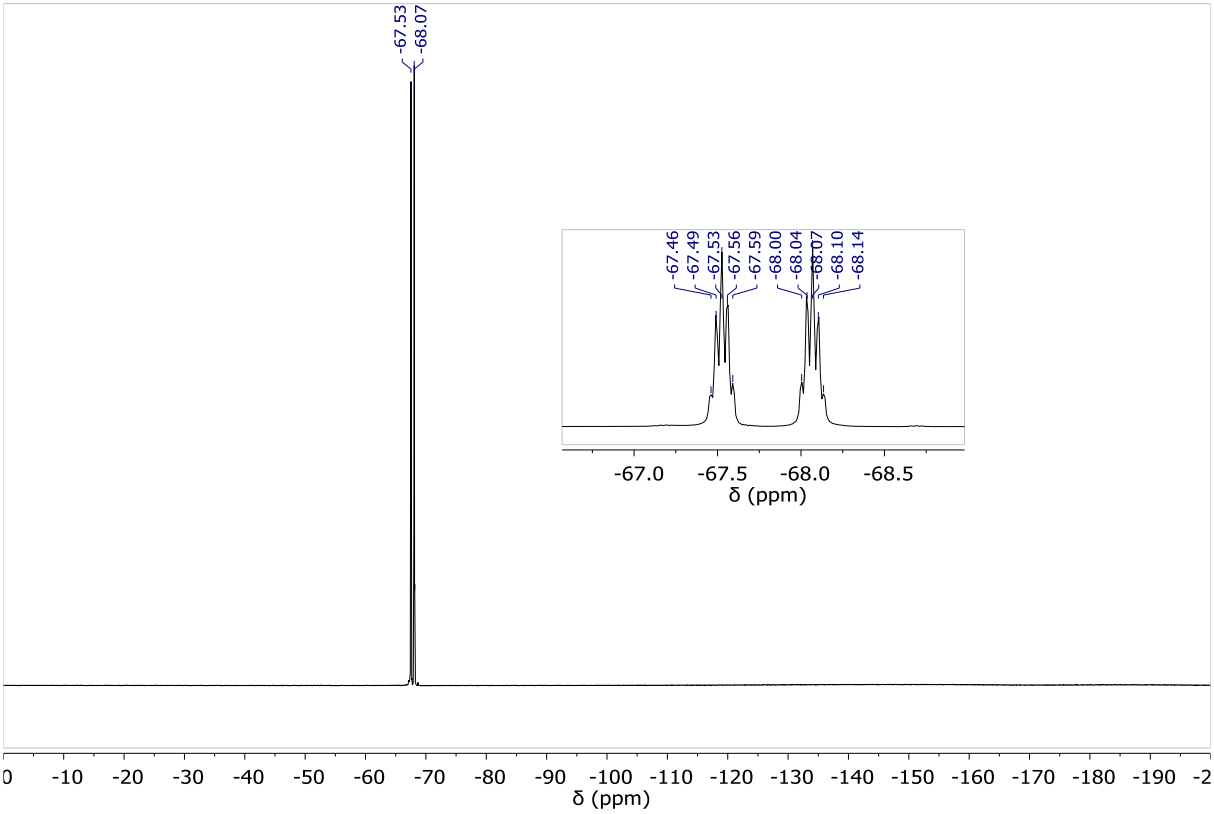


^{13}C NMR ($CDCl_3$, 101 MHz)

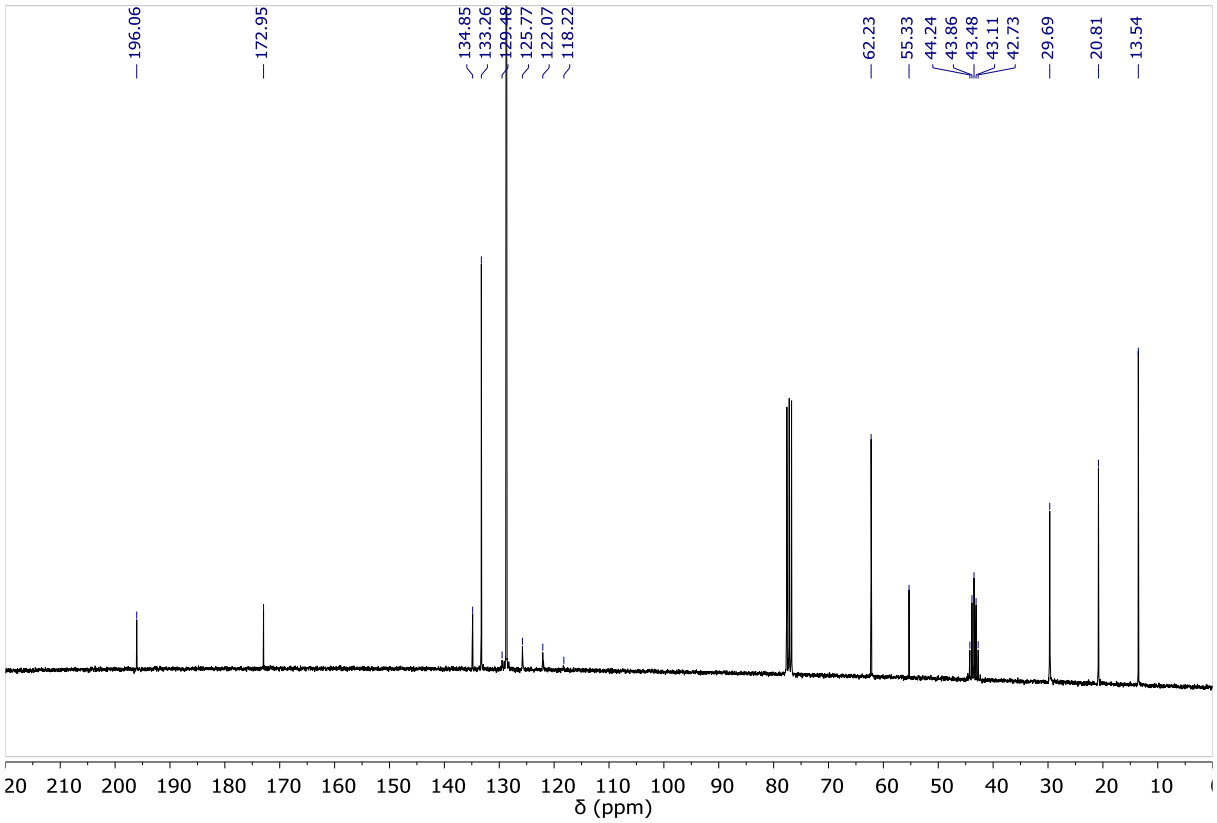
Compound 5b



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

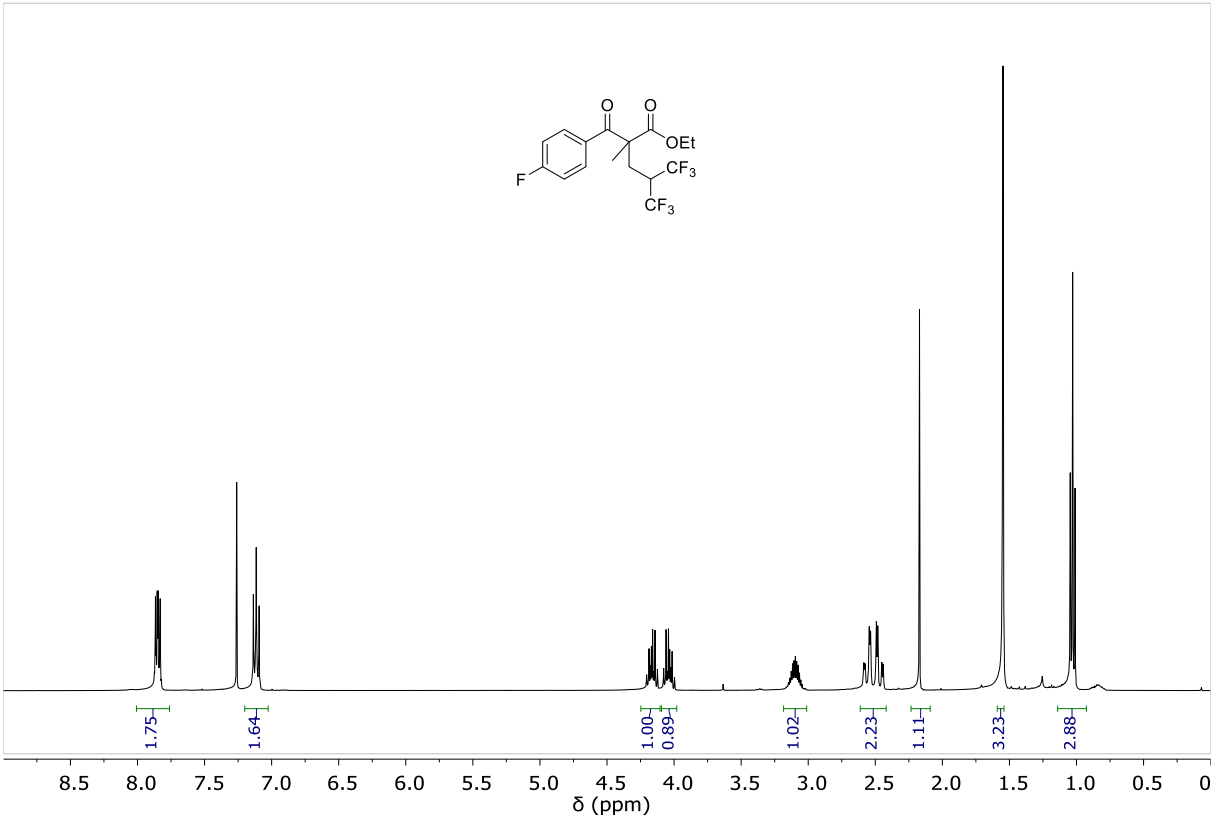


^{19}F NMR ($CDCl_3$, 376 MHz)

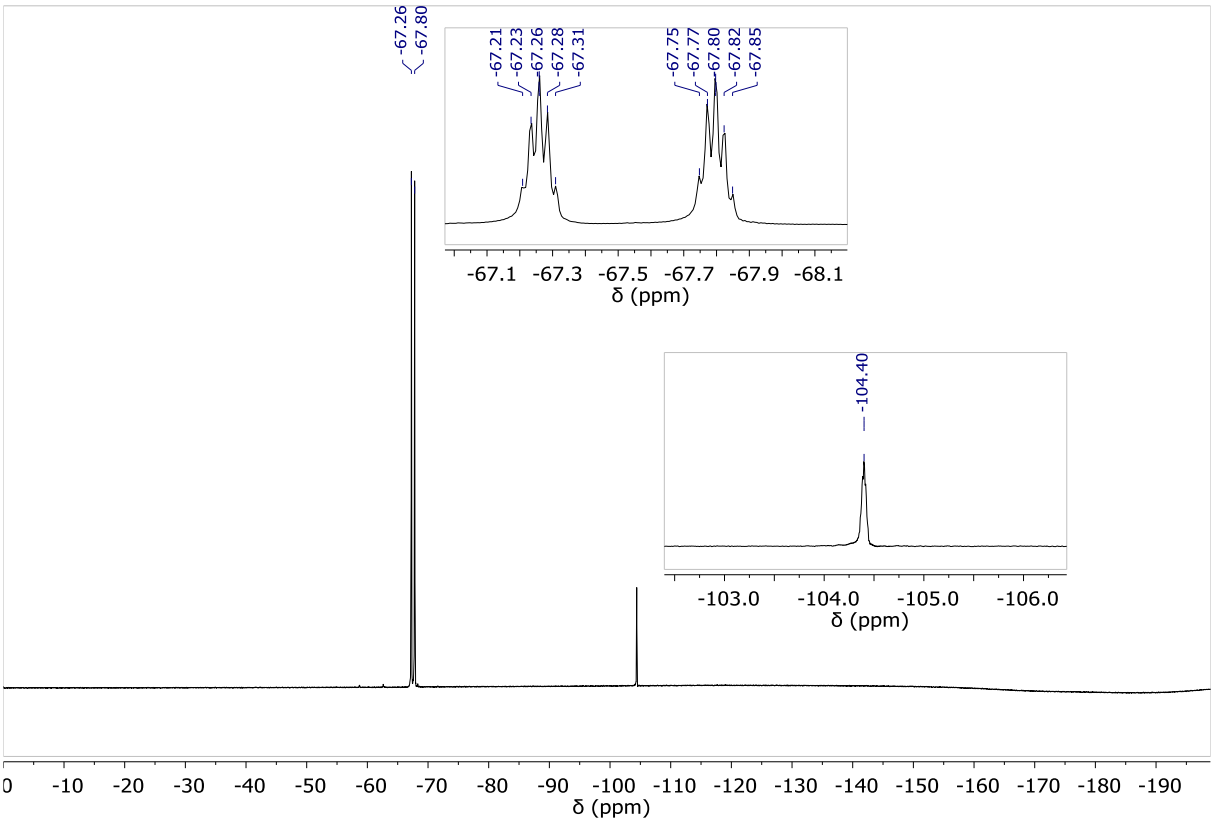


^{13}C NMR ($CDCl_3$, 101 MHz)

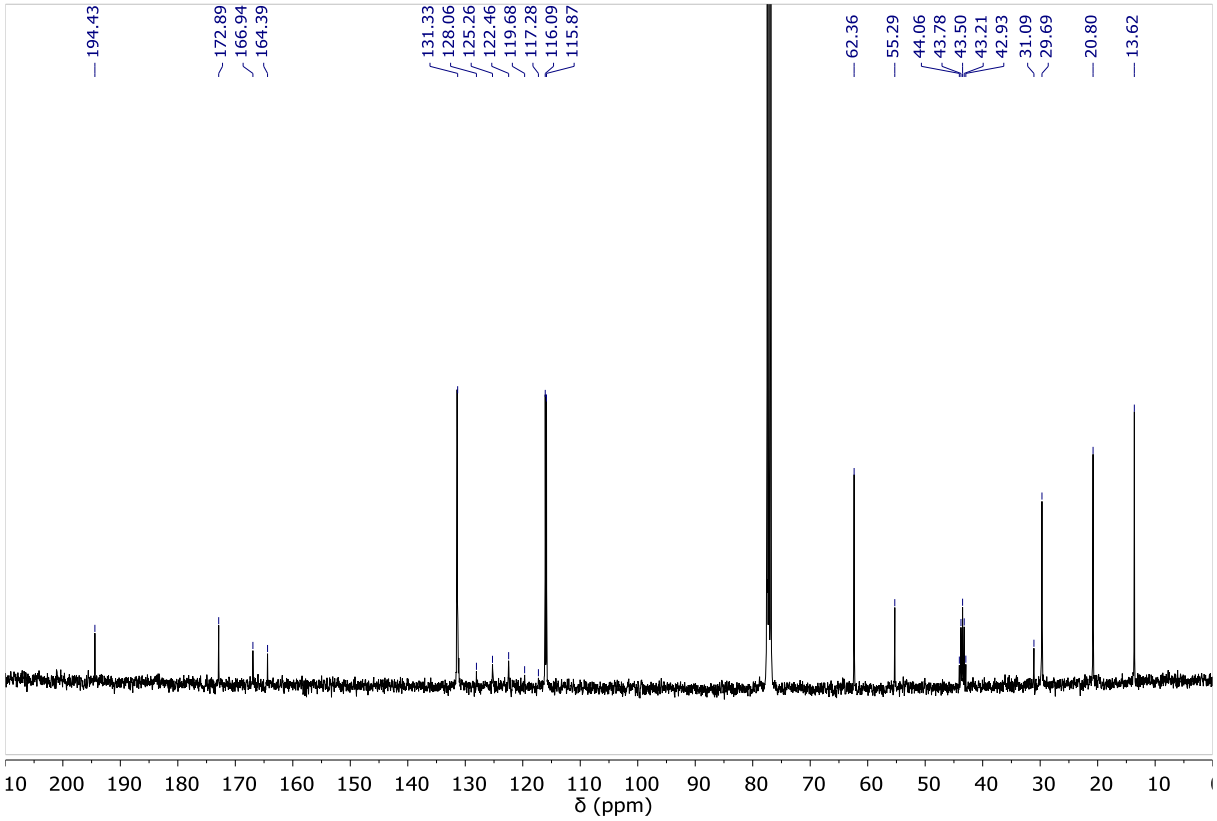
Compound 6b



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

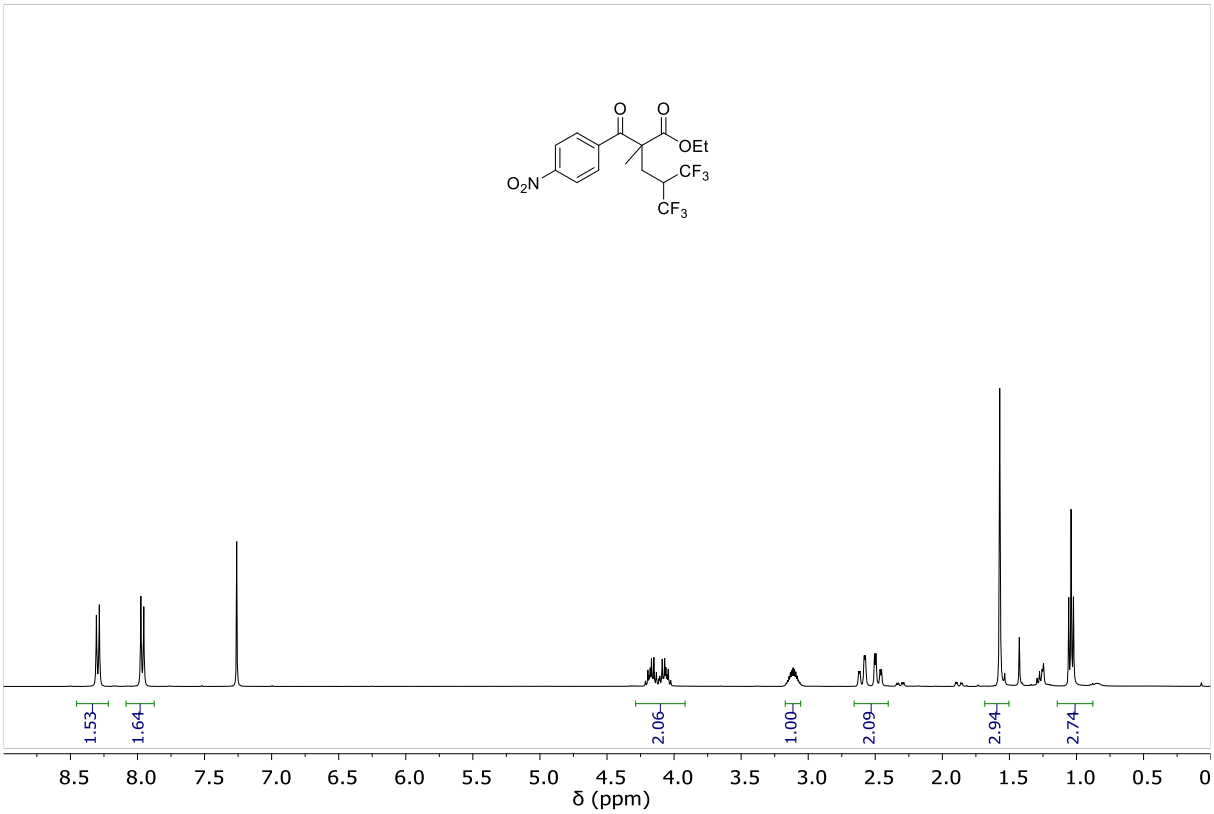


^{19}F NMR ($CDCl_3$, 376 MHz)

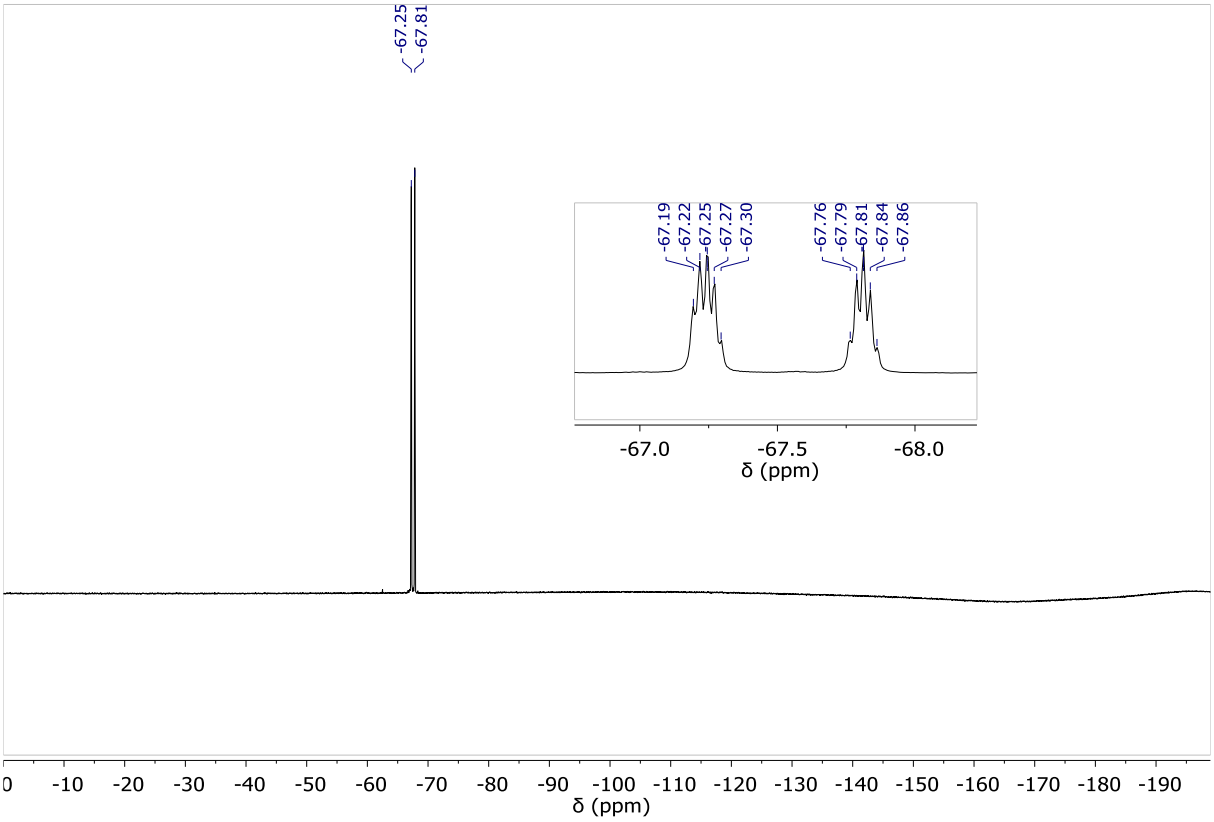


^{13}C NMR ($CDCl_3$, 101 MHz)

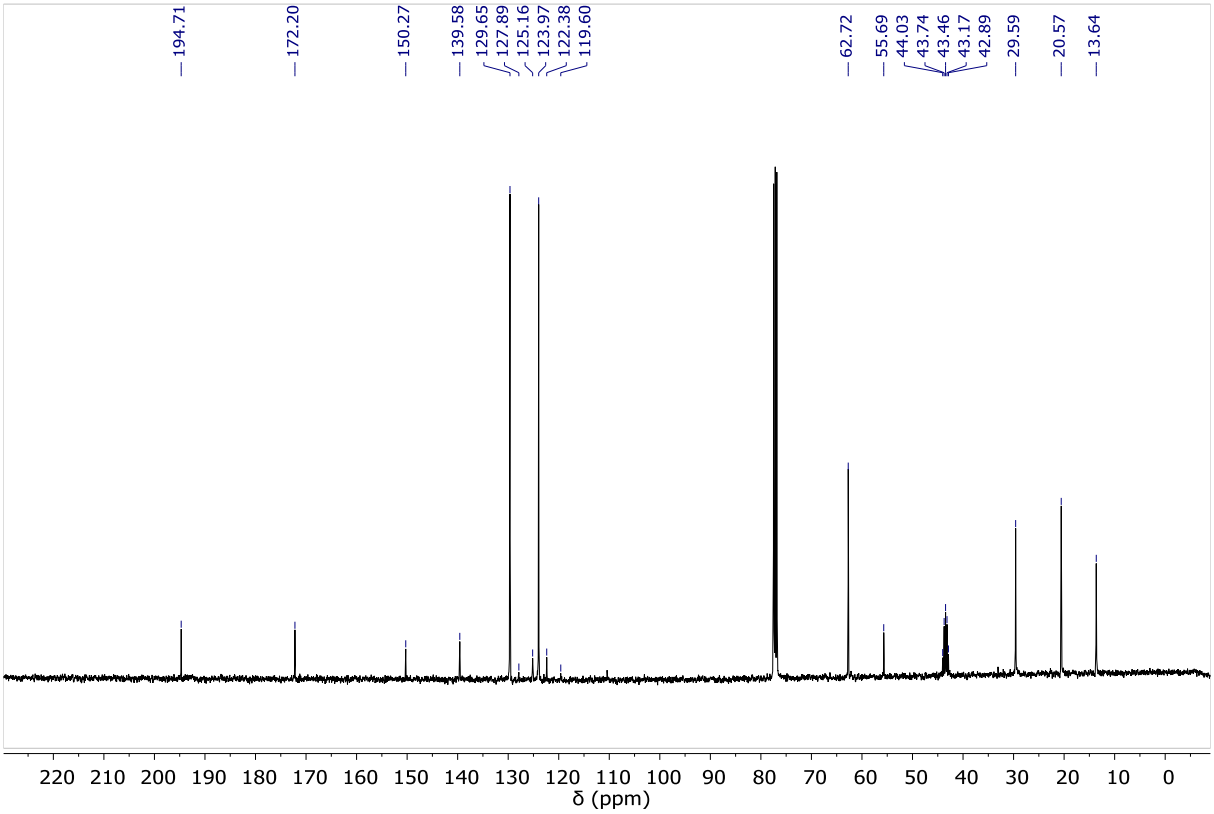
Compound 7b



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

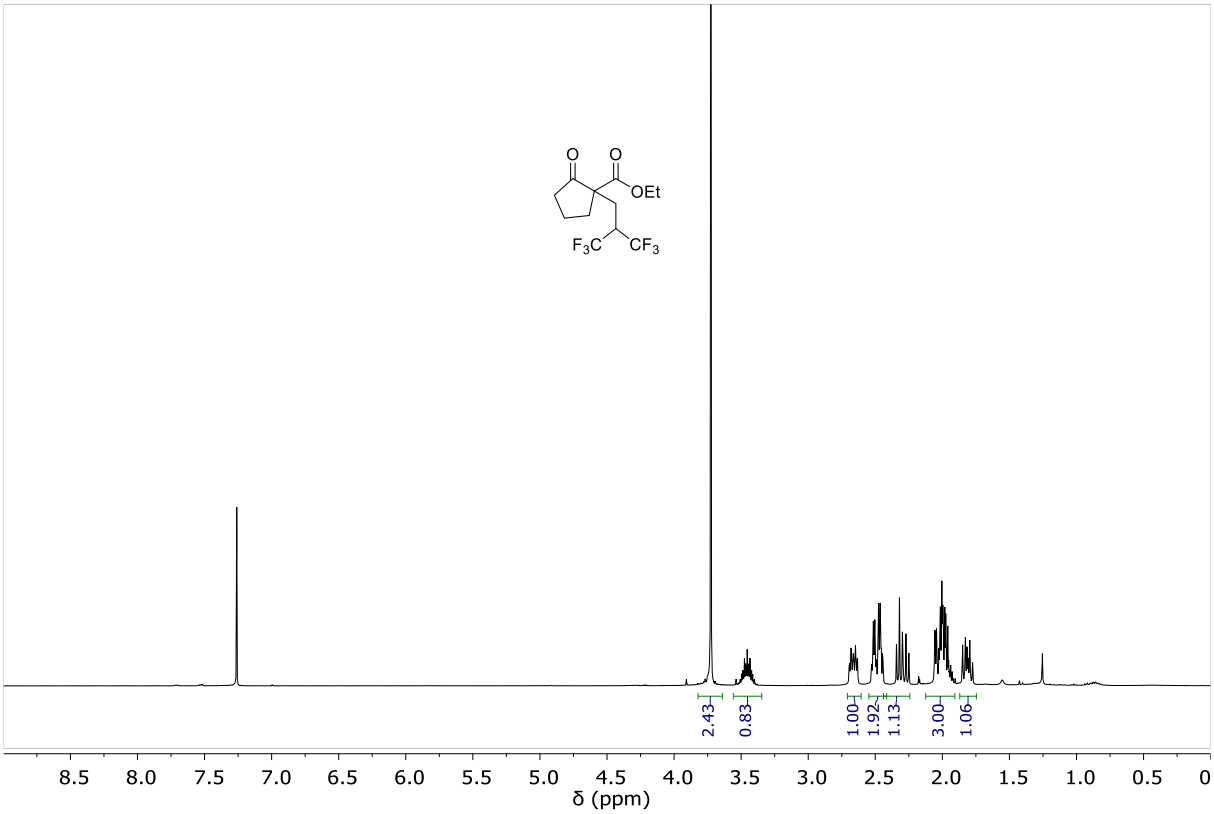


^{19}F NMR ($CDCl_3$, 376 MHz)

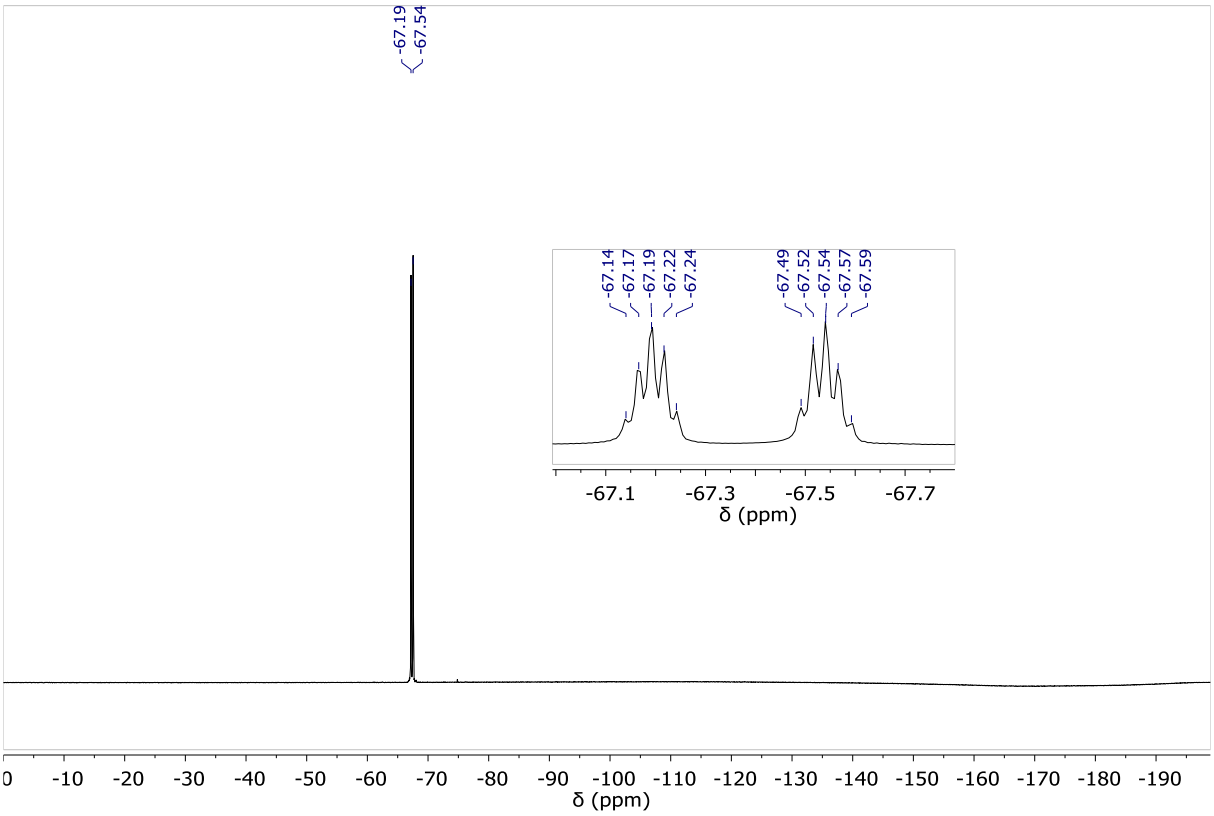


^{13}C NMR ($CDCl_3$, 101 MHz)

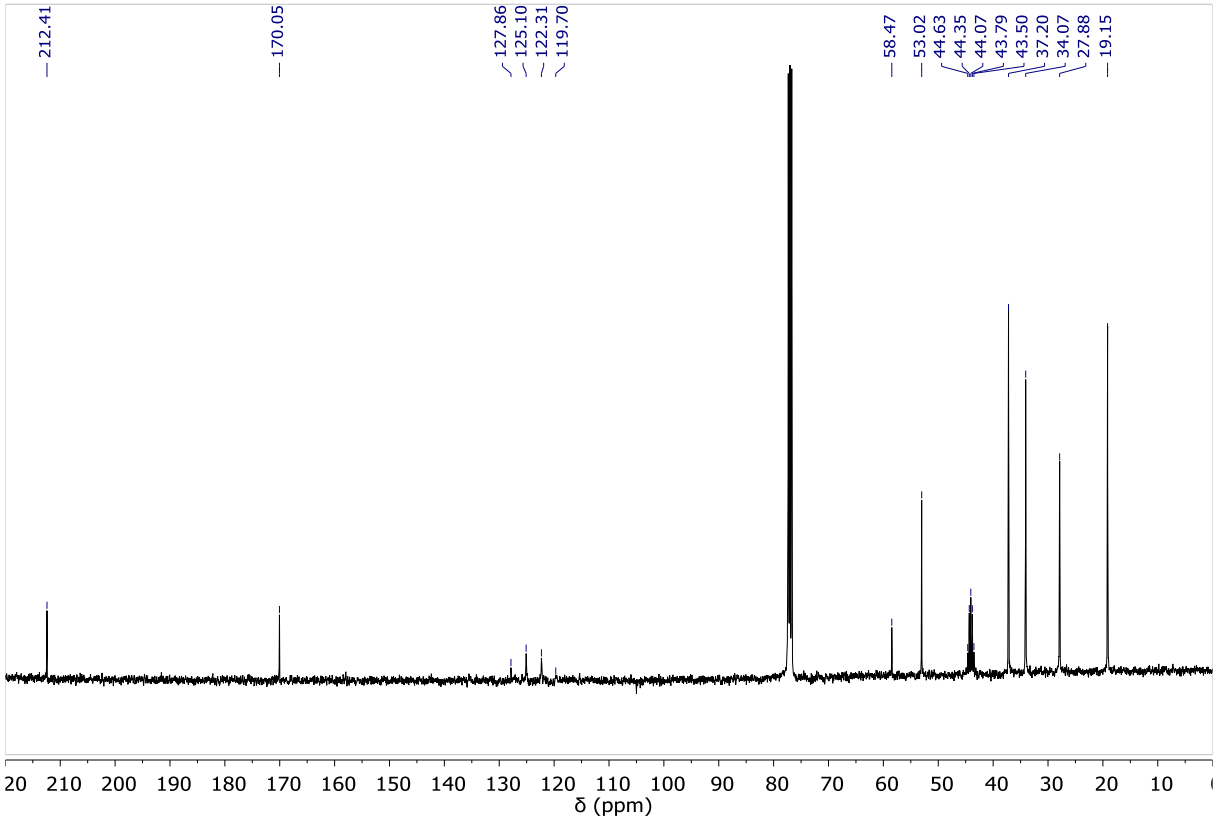
Compound 8b



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

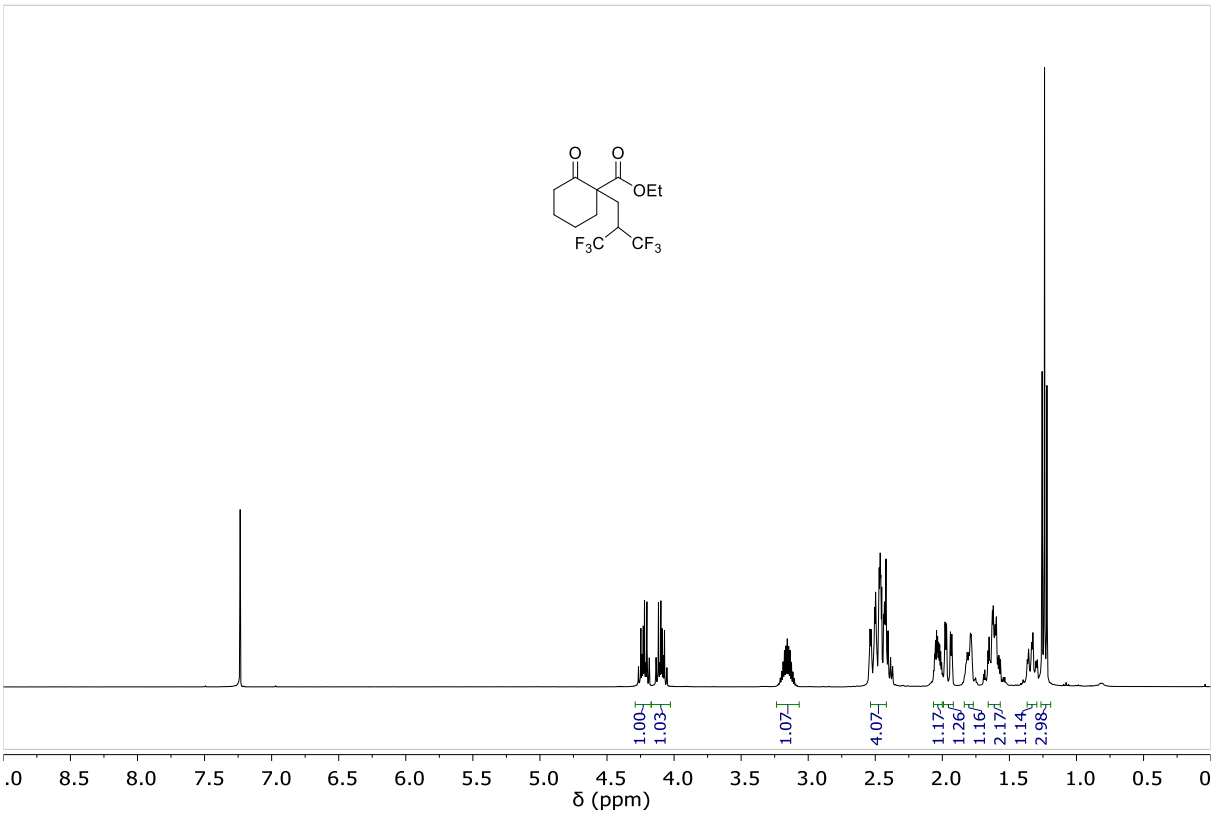


^{19}F NMR ($CDCl_3$, 376 MHz)

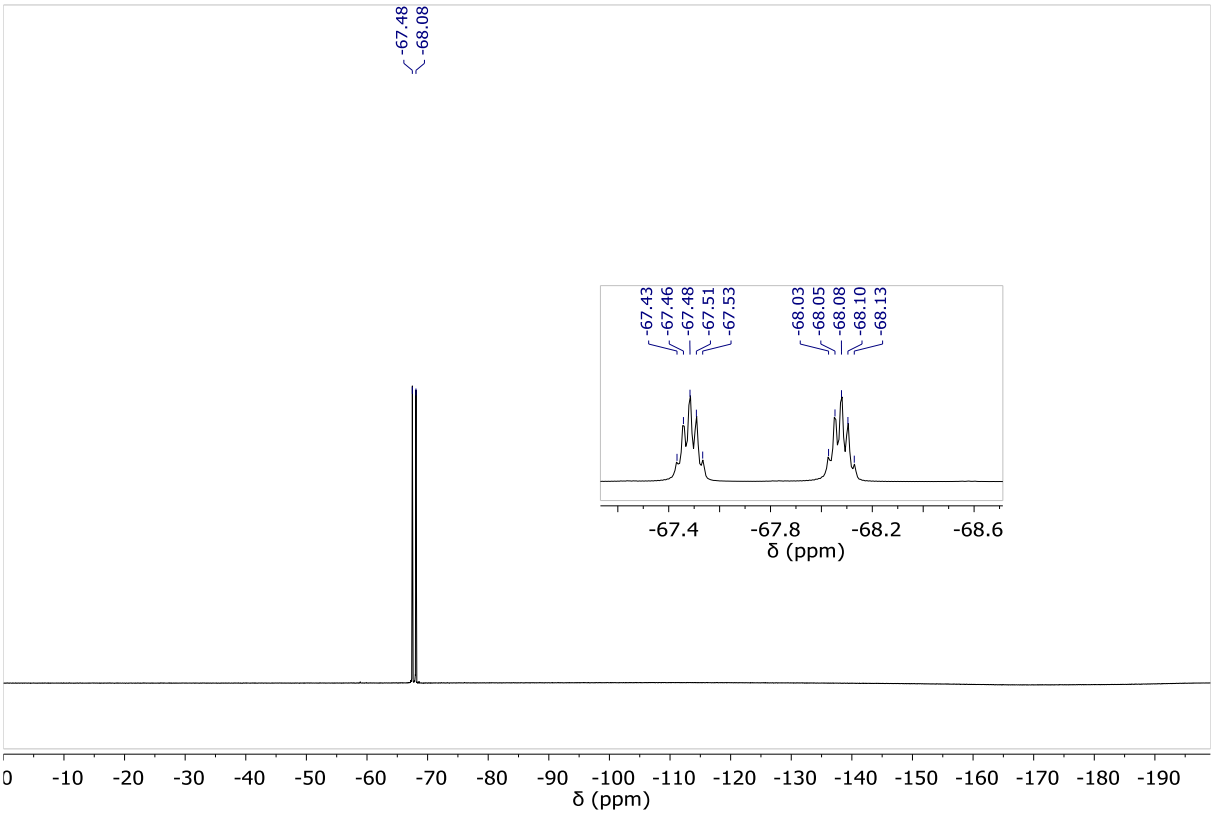

212.41
170.05
127.86
125.10
122.31
119.70
58.47
53.02
44.63
44.35
44.07
43.79
43.50
37.20
34.07
27.88
19.15
δ (ppm)

^{13}C NMR ($CDCl_3$, 101 MHz)

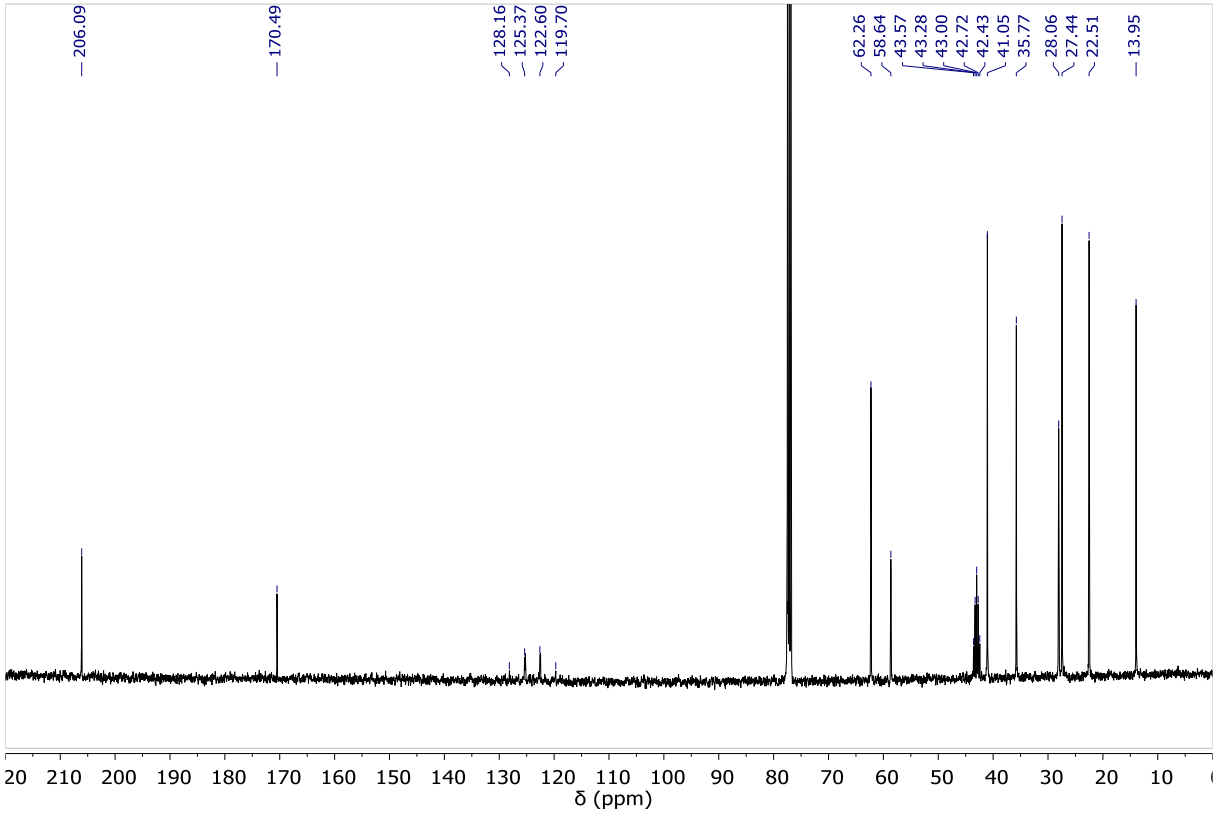
Compound 9b



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

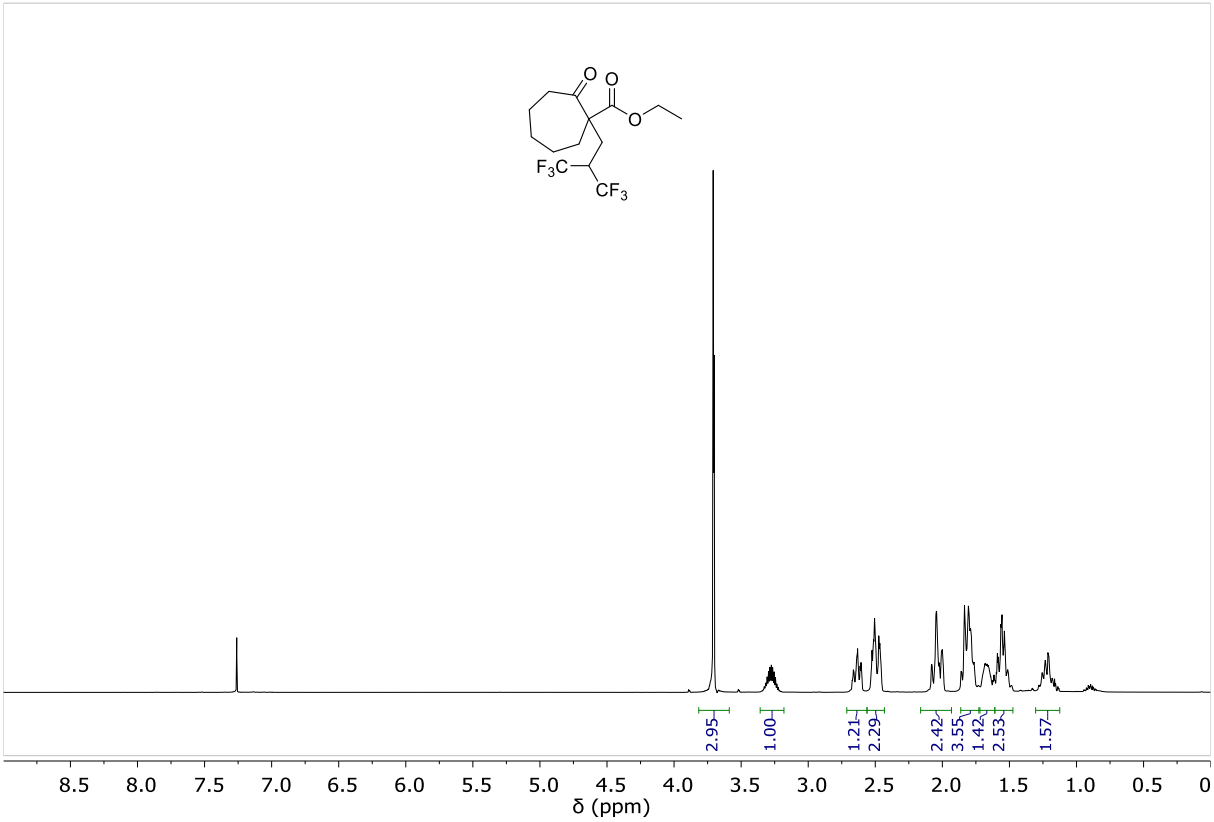


^{19}F NMR ($CDCl_3$, 376 MHz)

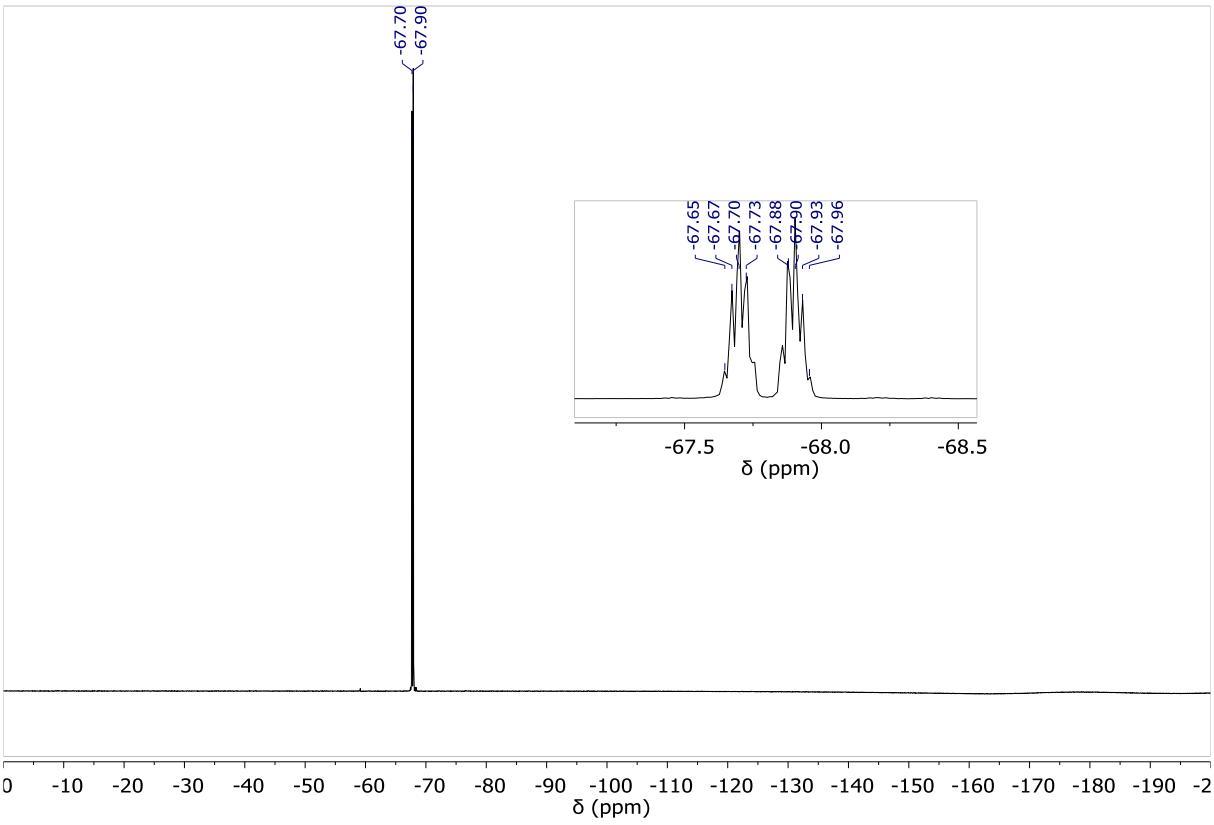


^{13}C NMR ($CDCl_3$, 101 MHz)

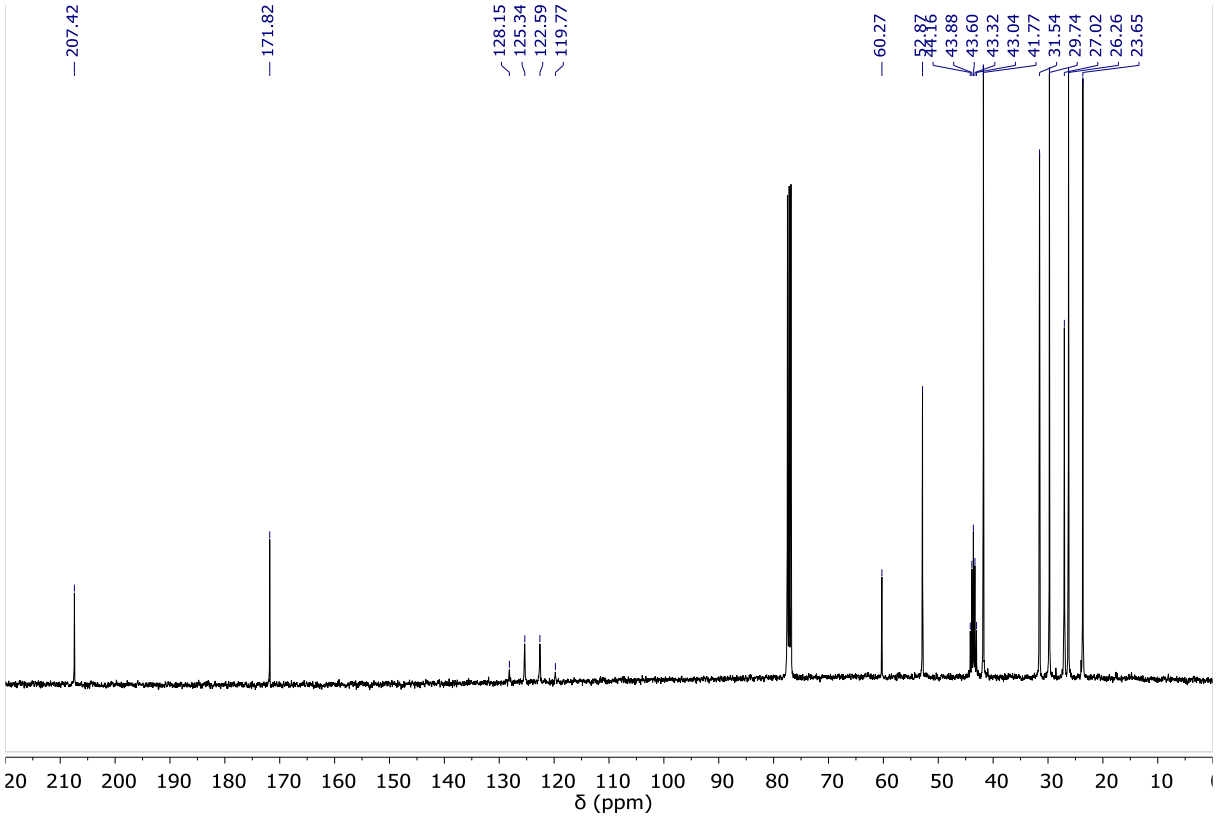
Compound 10b



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

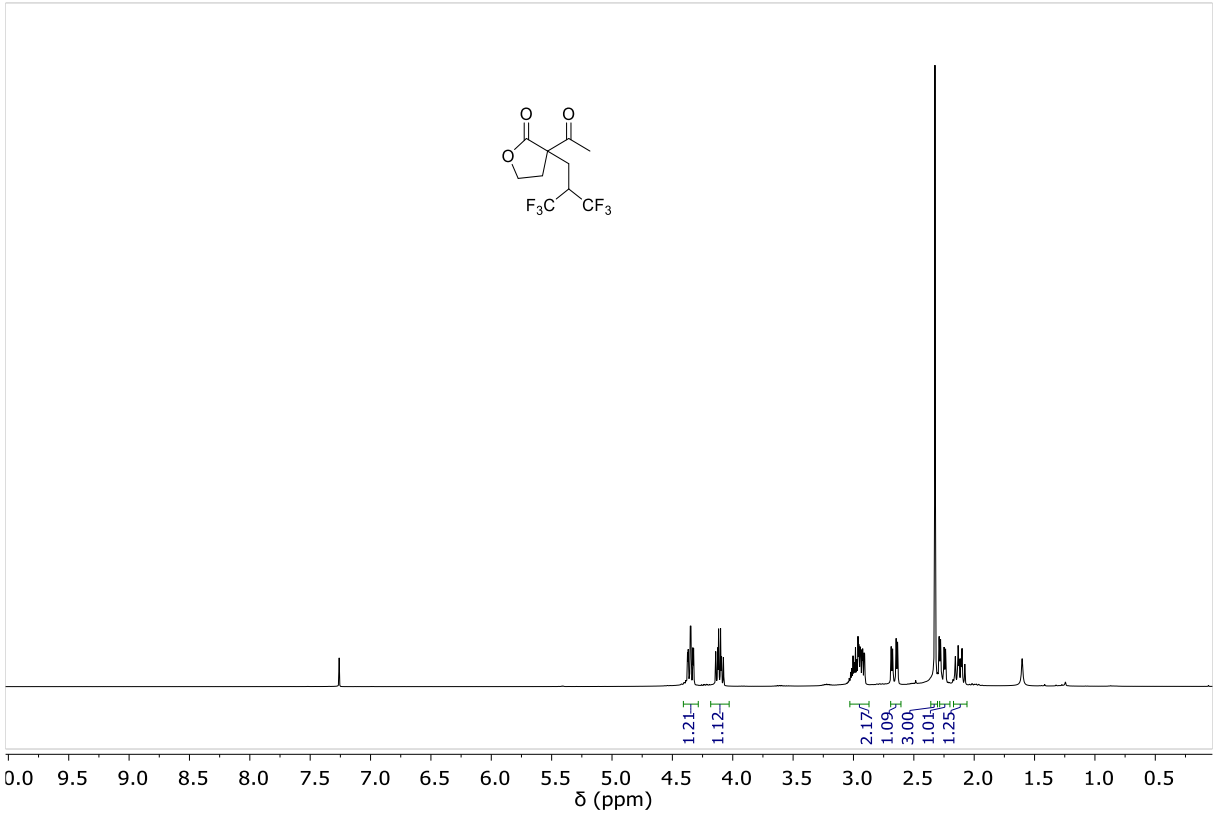


^{19}F NMR ($CDCl_3$, 376 MHz)

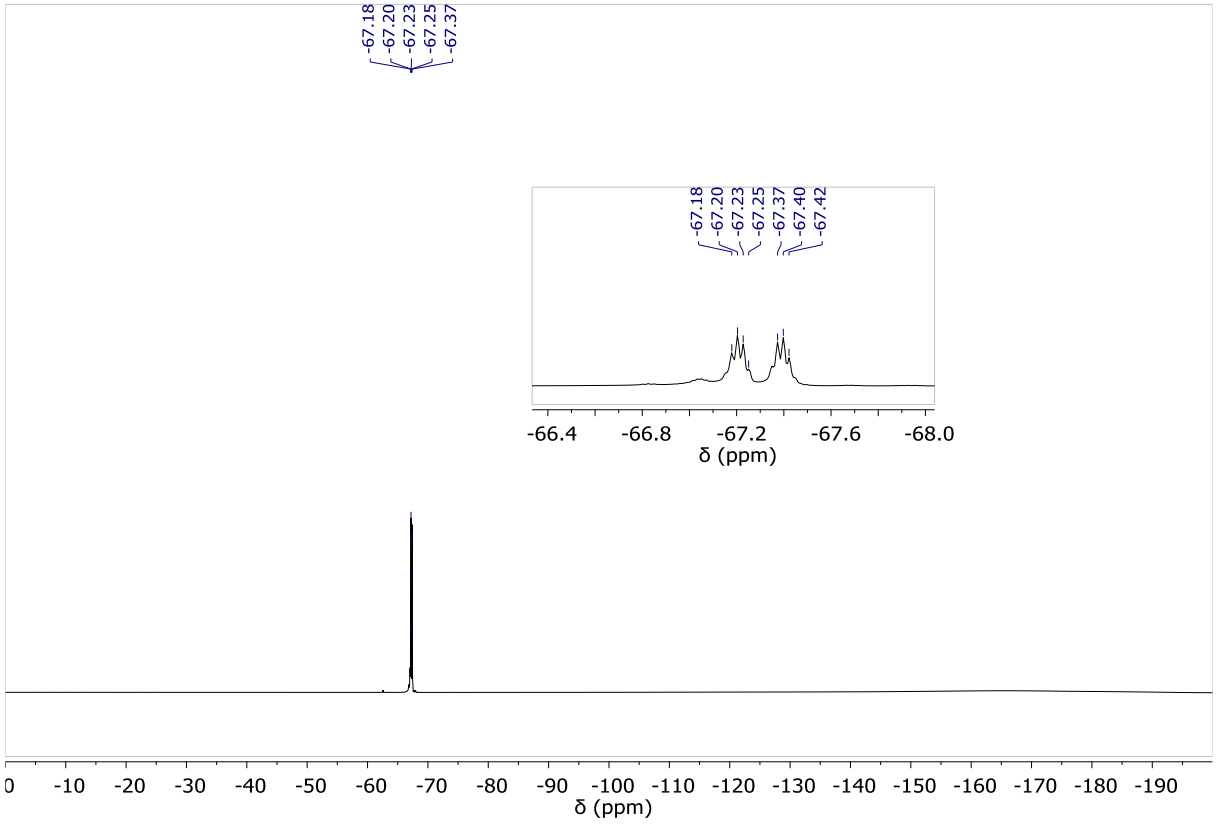


^{13}C NMR ($CDCl_3$, 101 MHz)

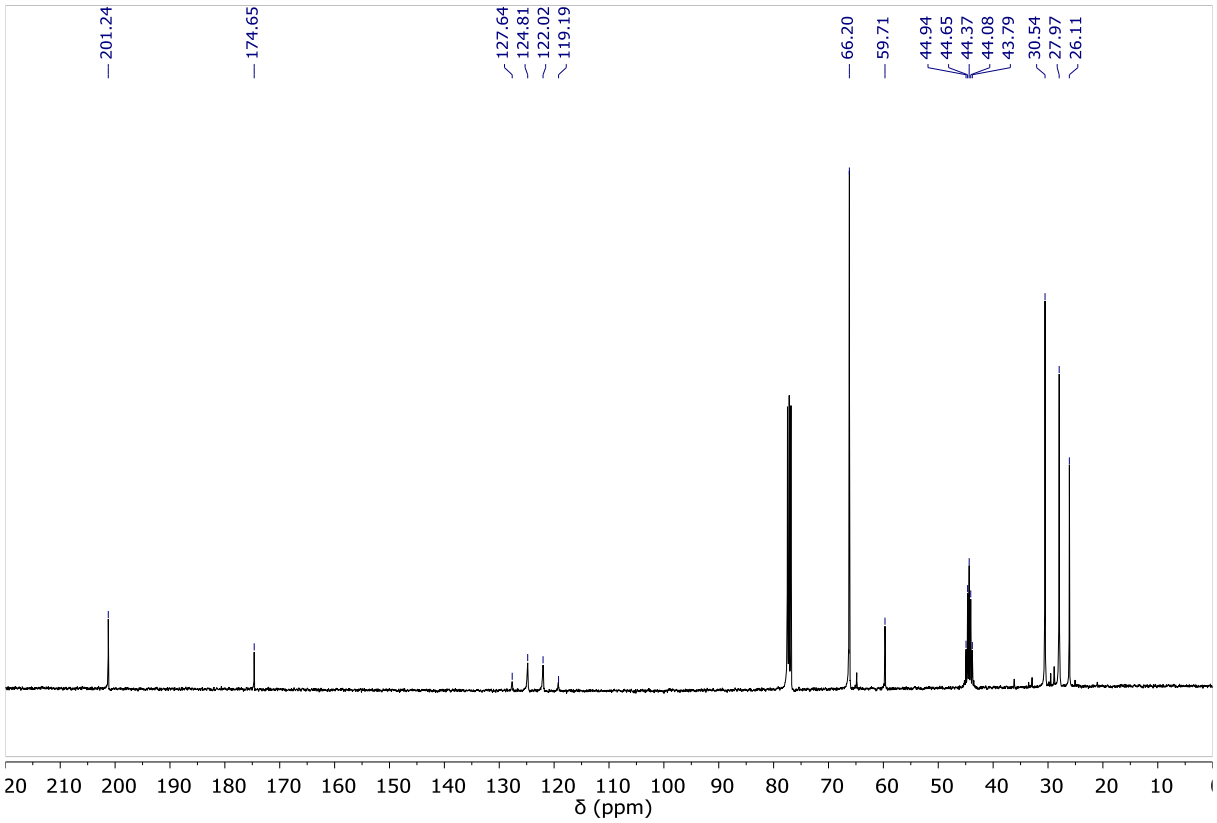
Compound 11b



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

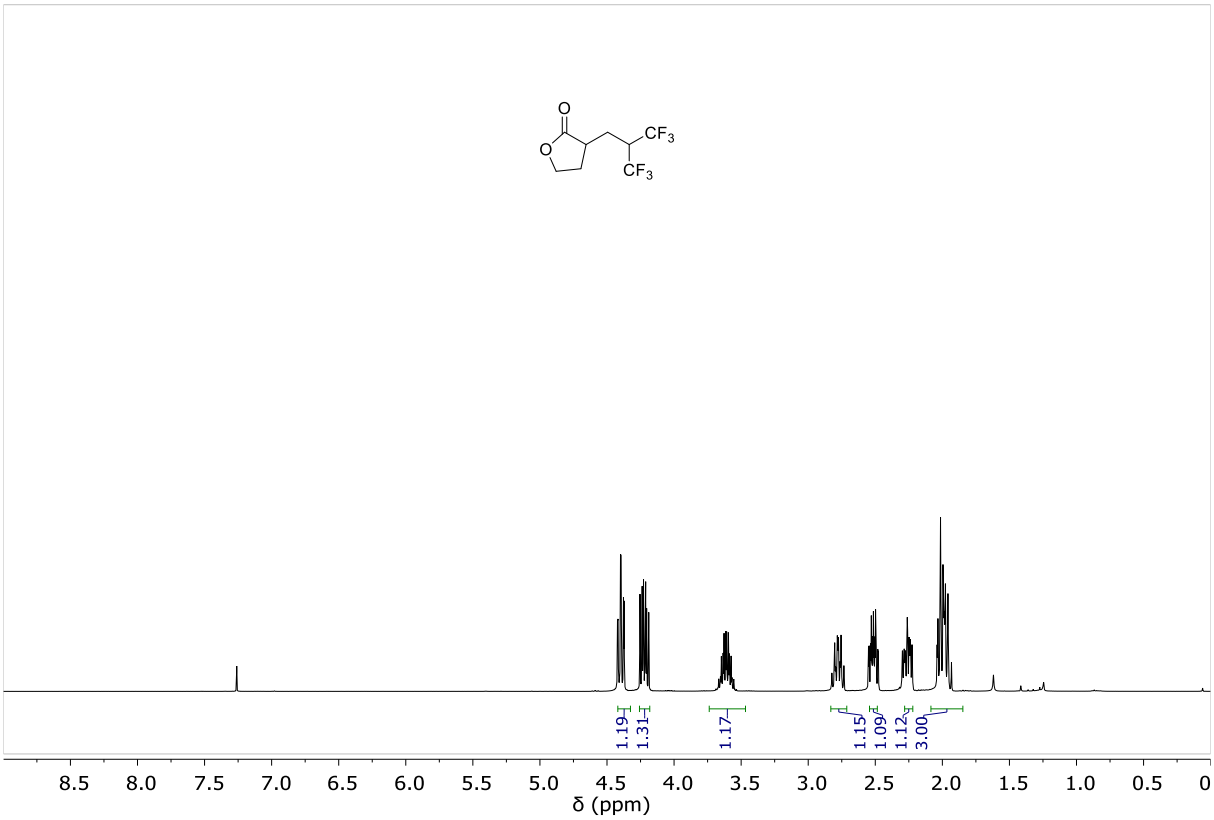


^{19}F NMR ($CDCl_3$, 376 MHz)

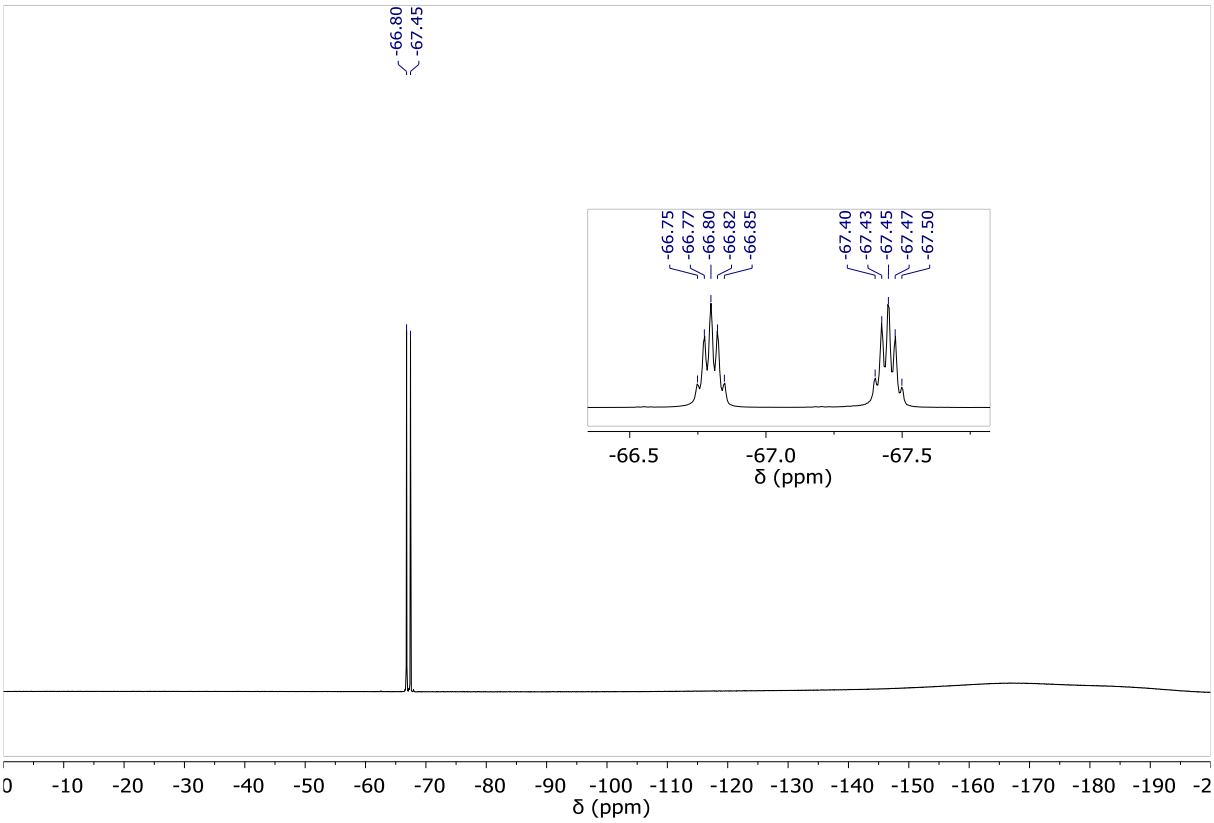


^{13}C NMR ($CDCl_3$, 101 MHz)

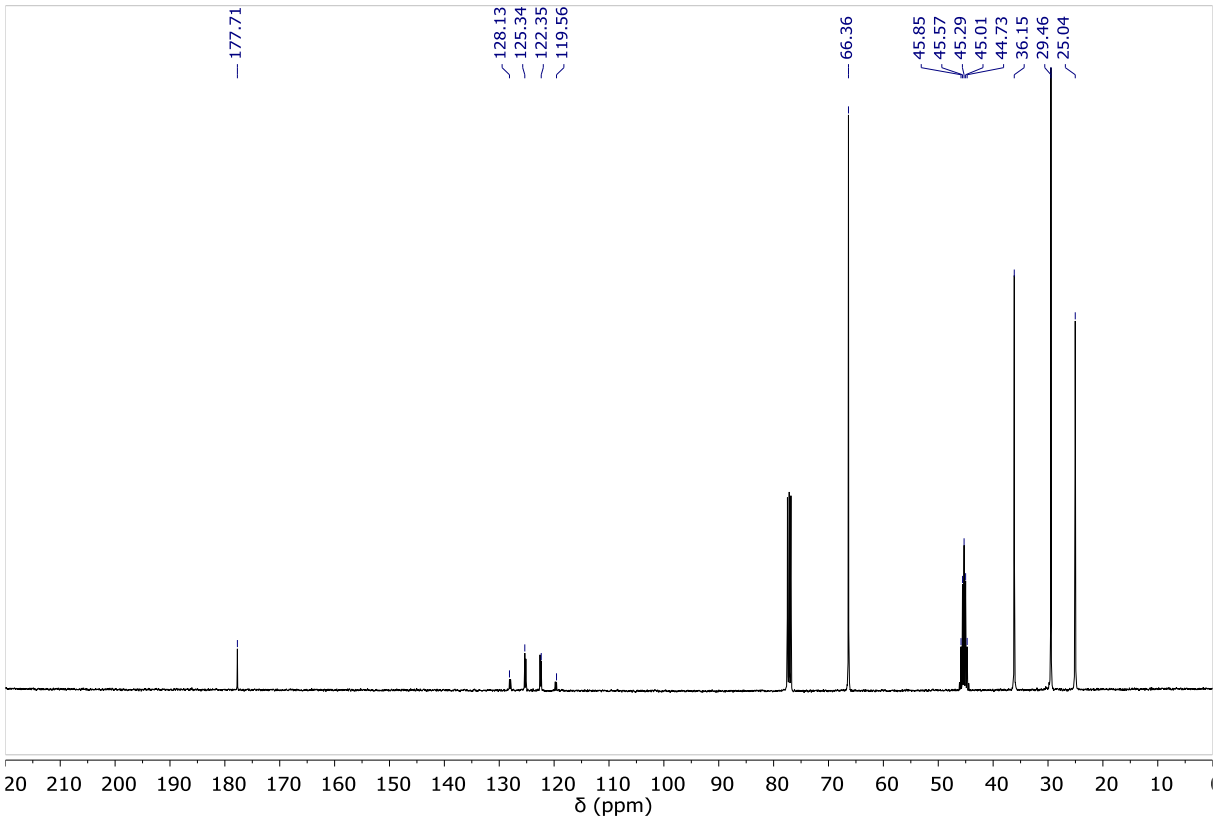
Compound 11e



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

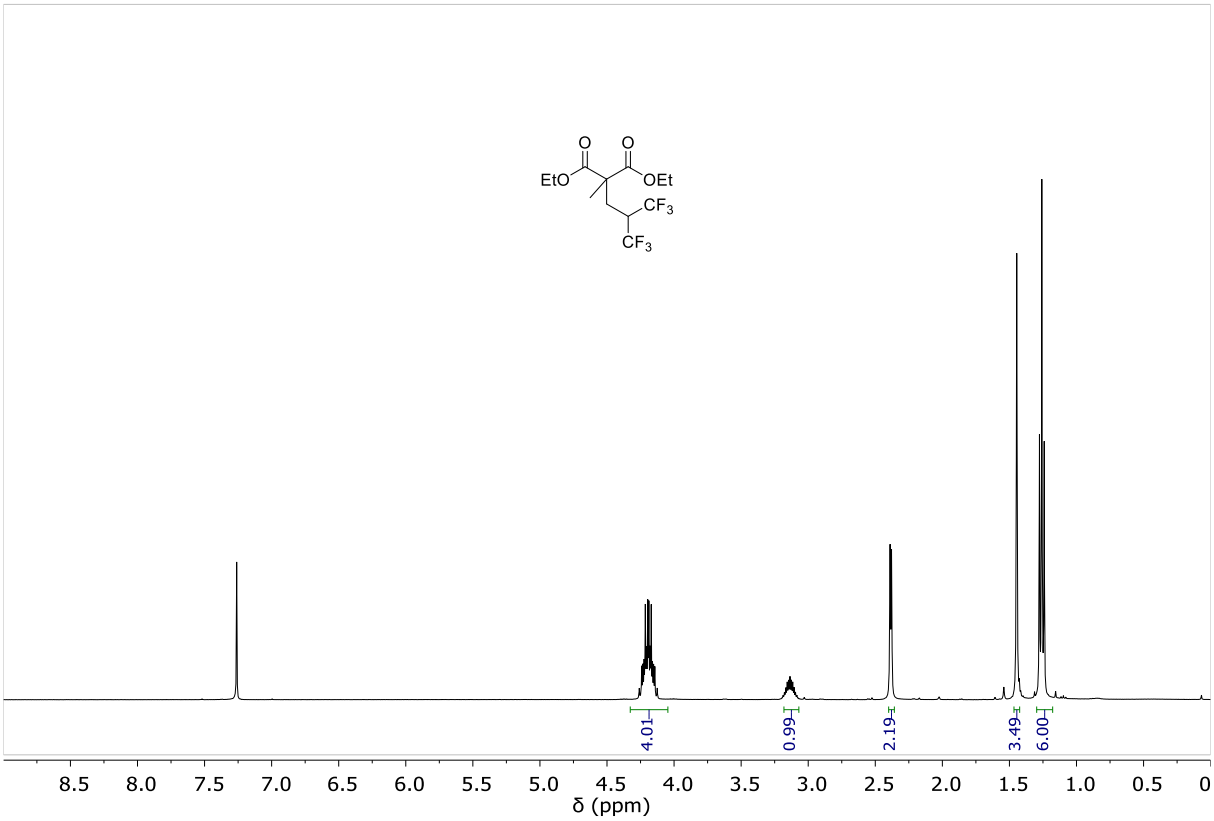


^{19}F NMR ($CDCl_3$, 376 MHz)

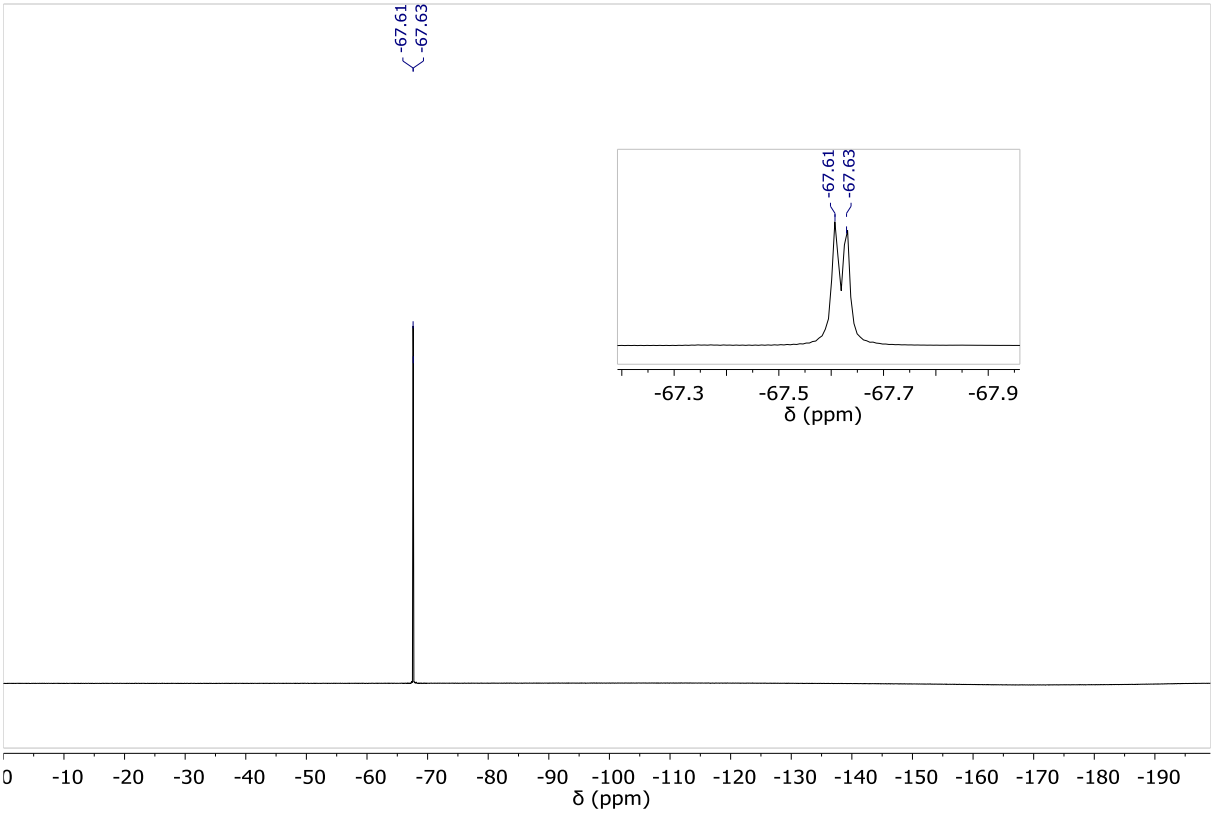


^{13}C NMR ($CDCl_3$, 101 MHz)

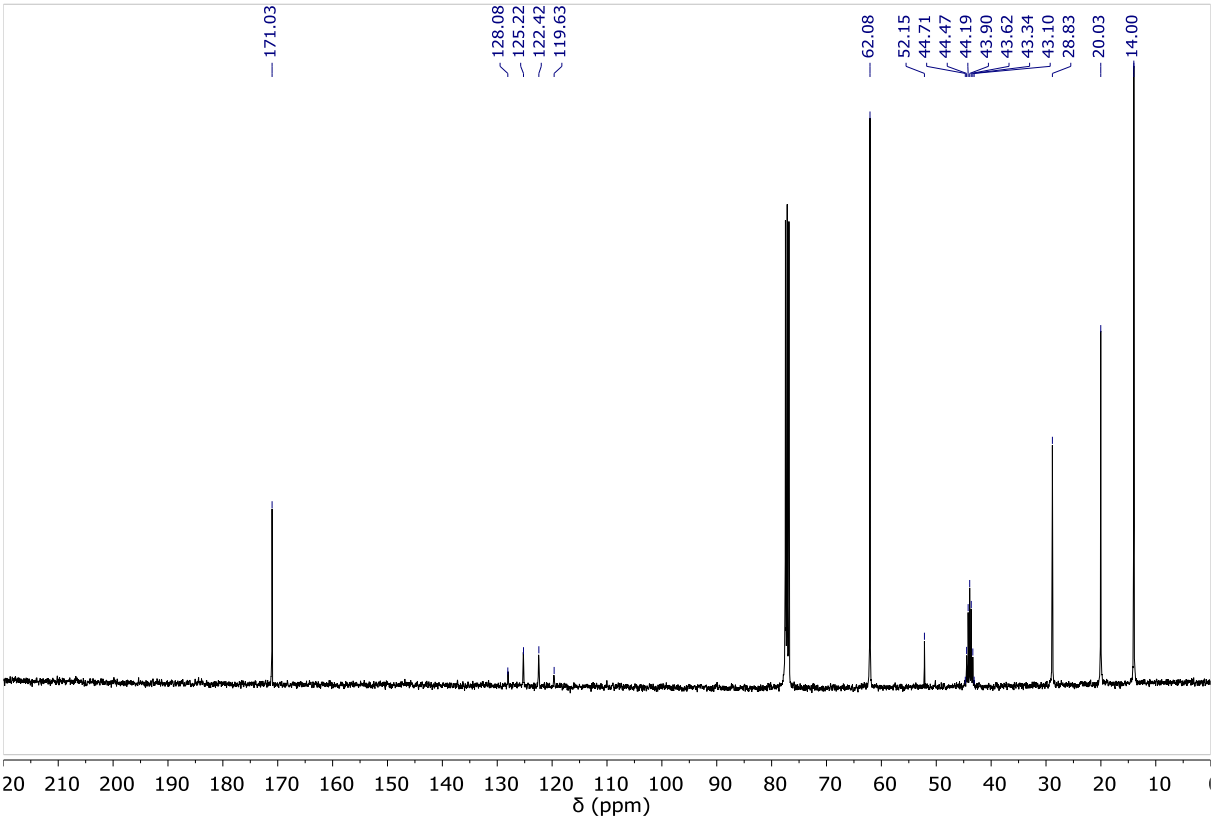
Compound 12b



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

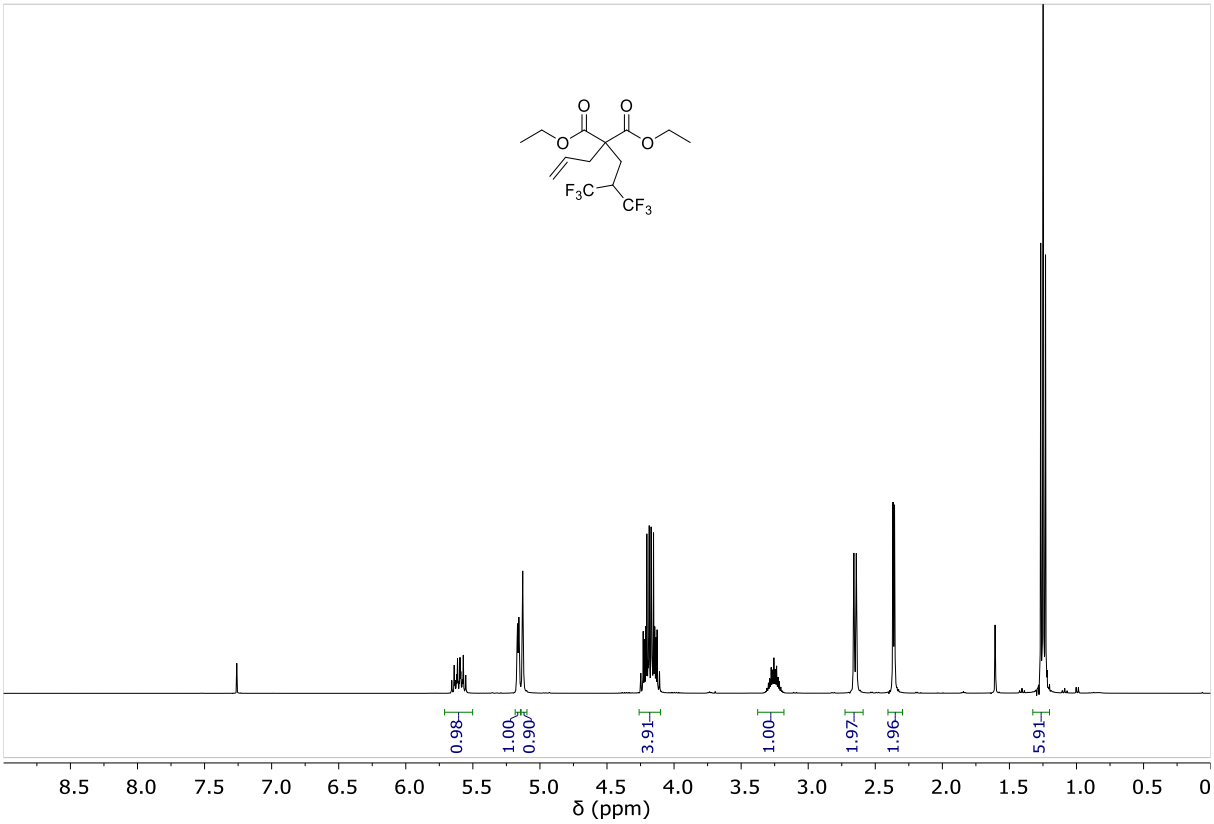


^{19}F NMR ($CDCl_3$, 376 MHz)

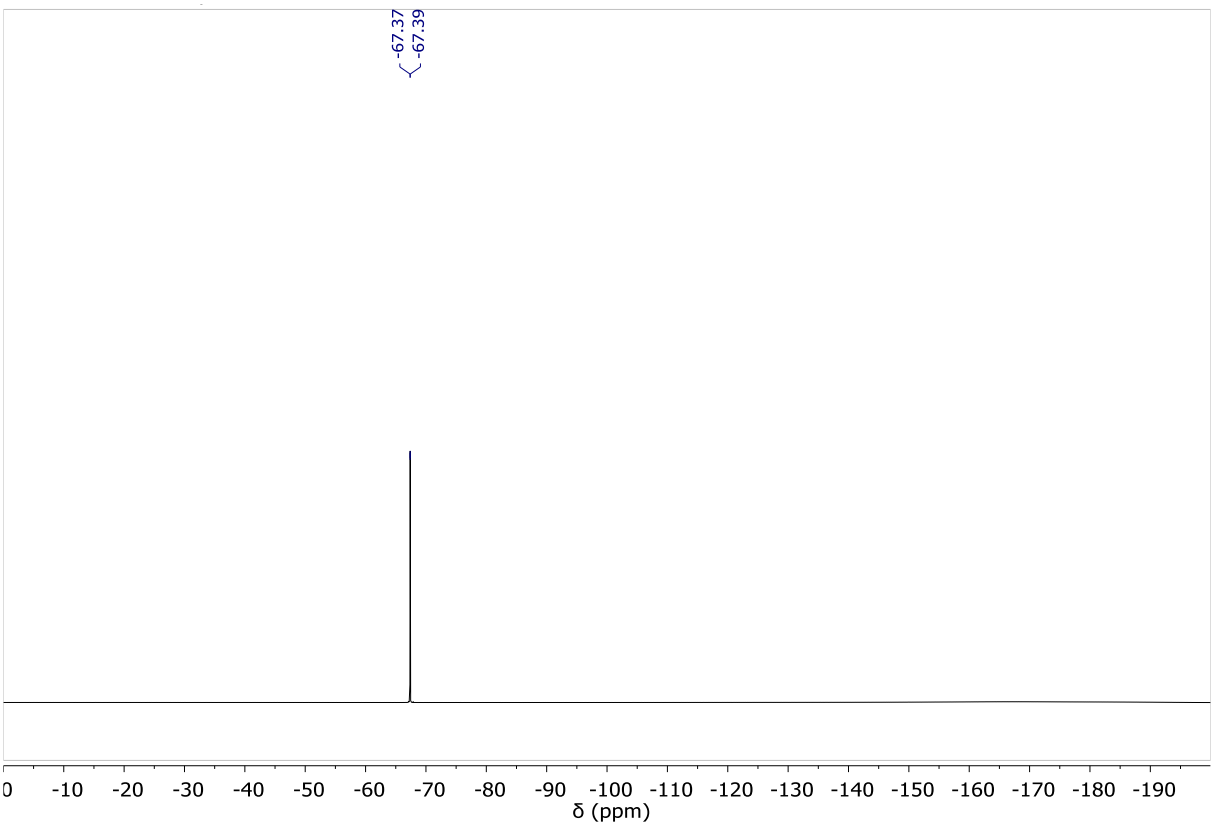


^{13}C NMR ($CDCl_3$, 101 MHz)

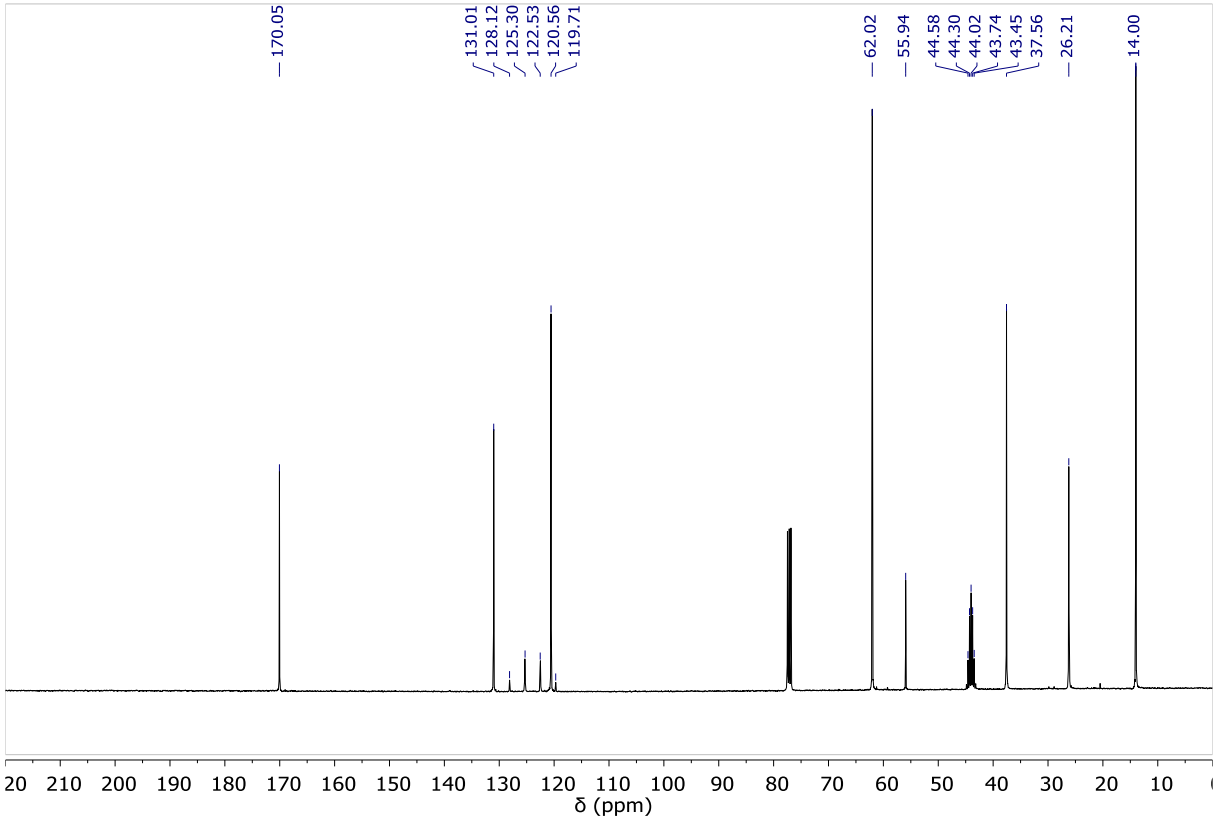
Compound 13b



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

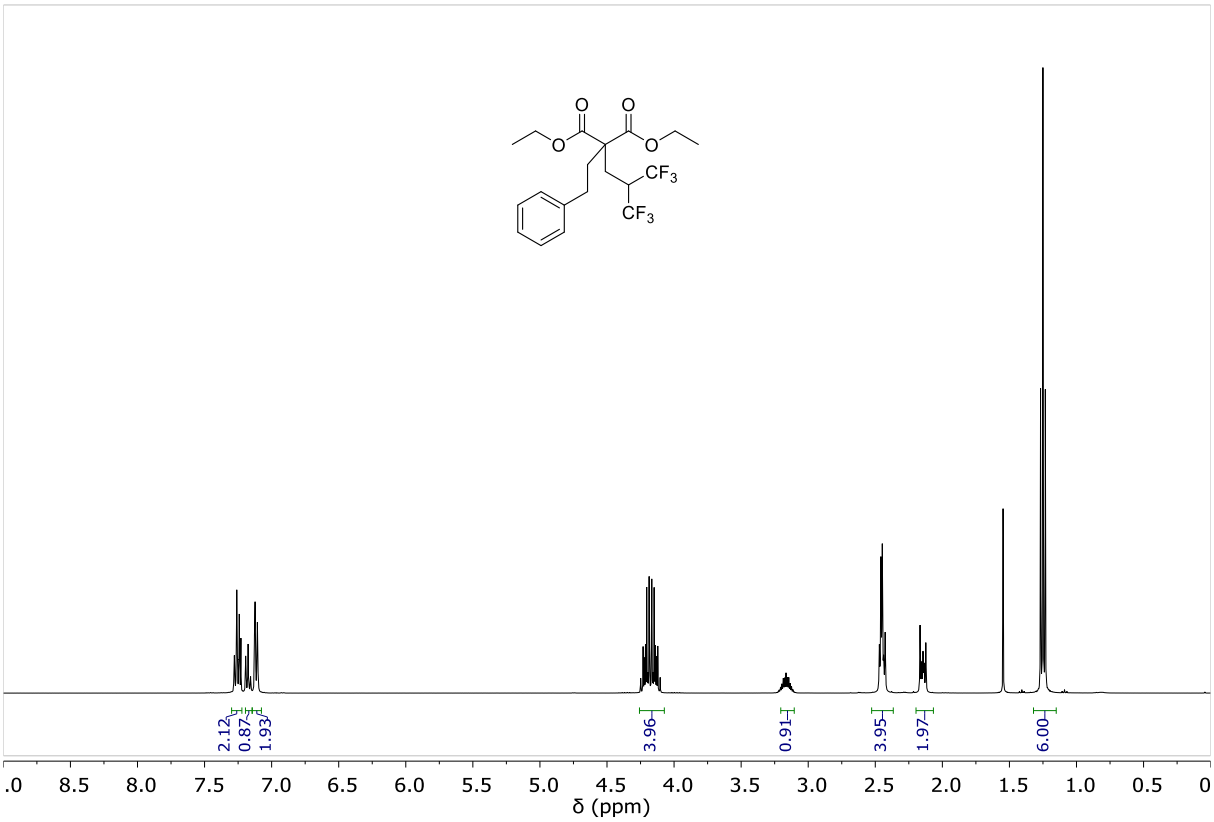


^{19}F NMR ($CDCl_3$, 376 MHz)

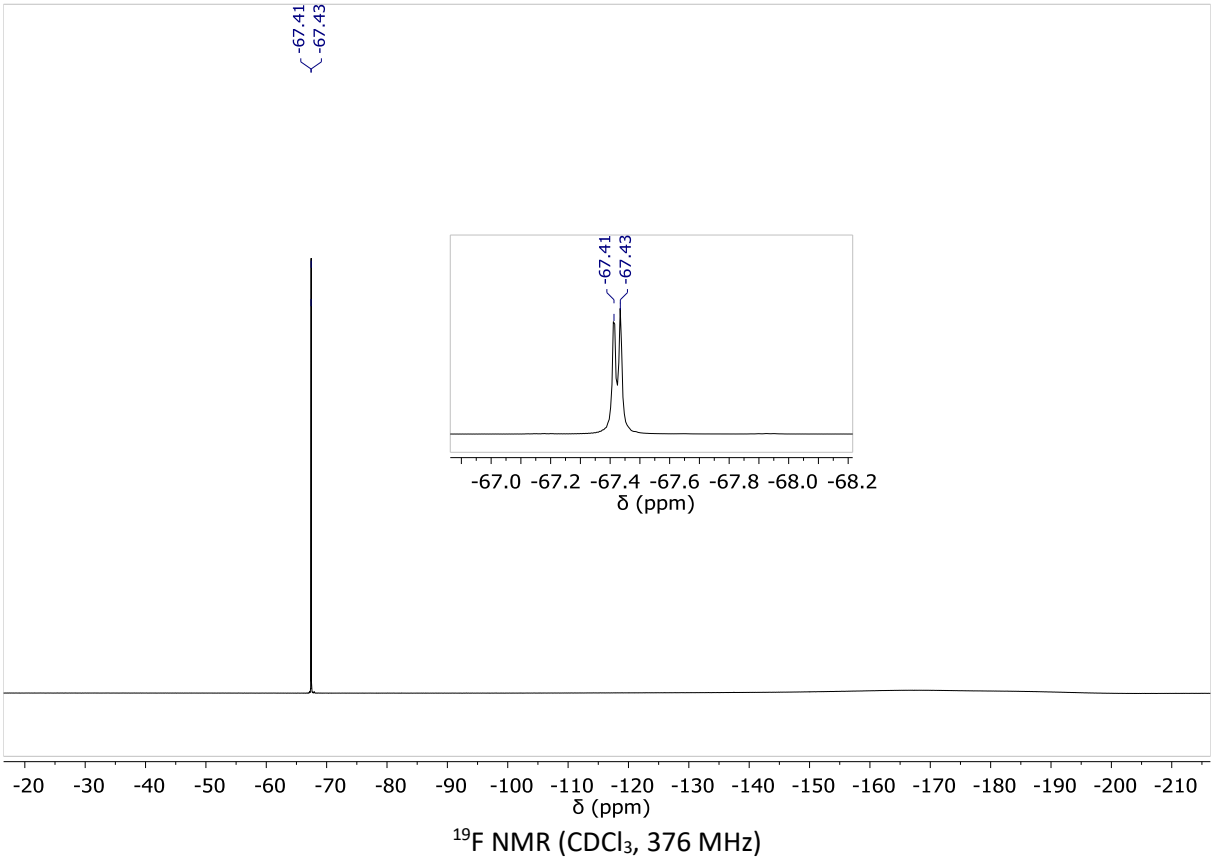


^{13}C NMR ($CDCl_3$, 101 MHz)

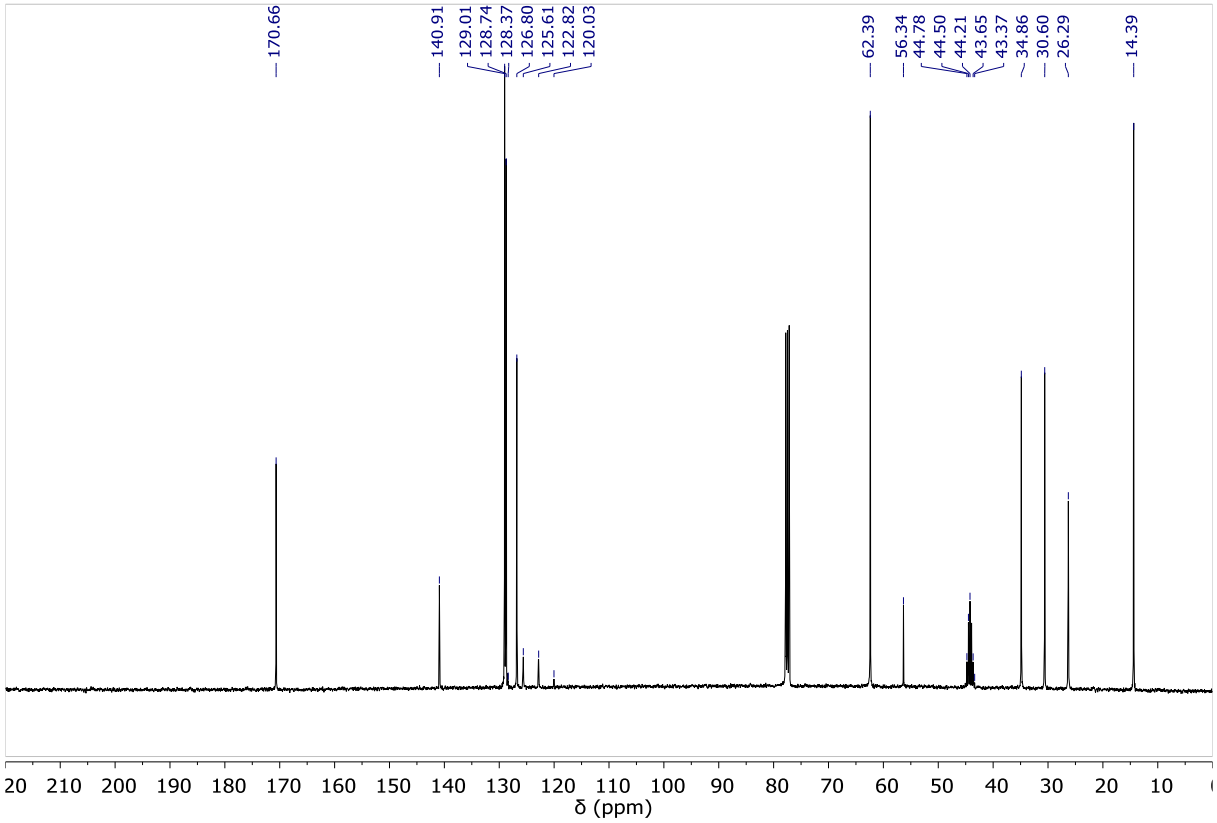
Compound 14b



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

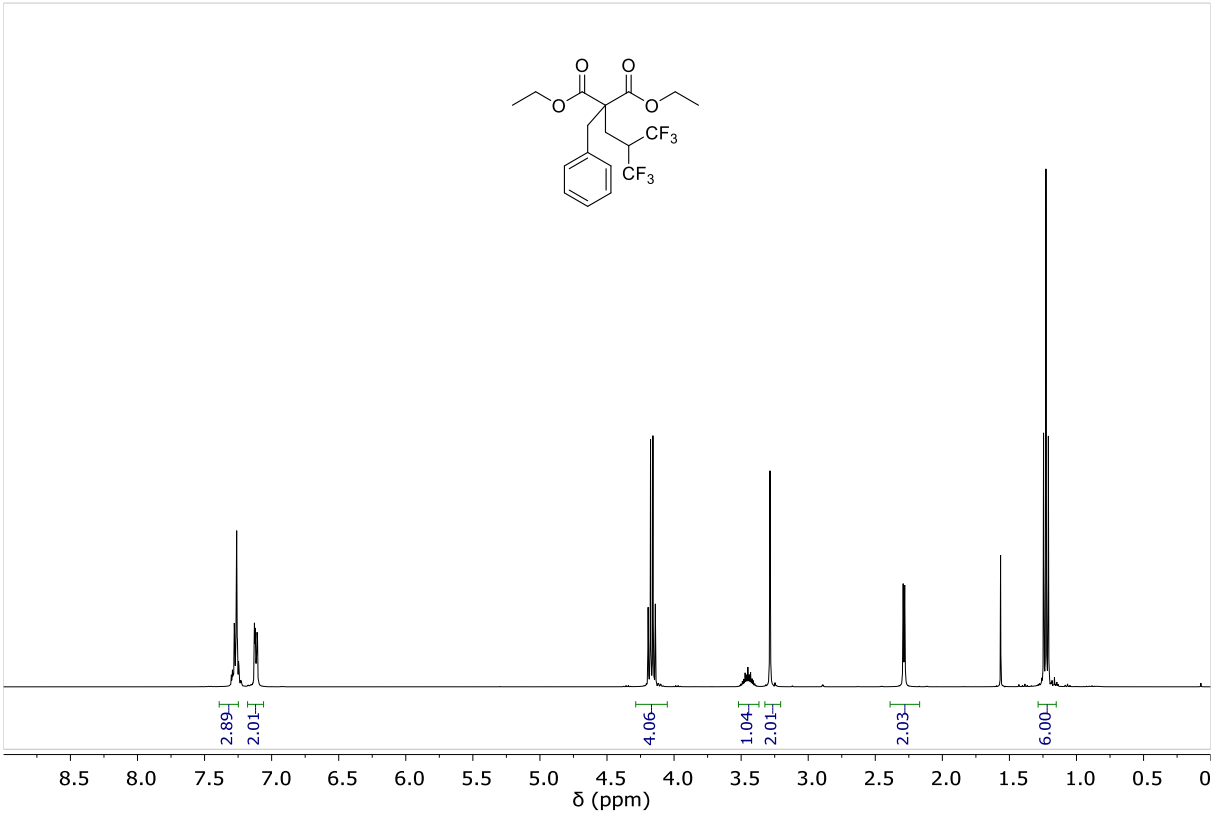


^{19}F NMR ($CDCl_3$, 376 MHz)

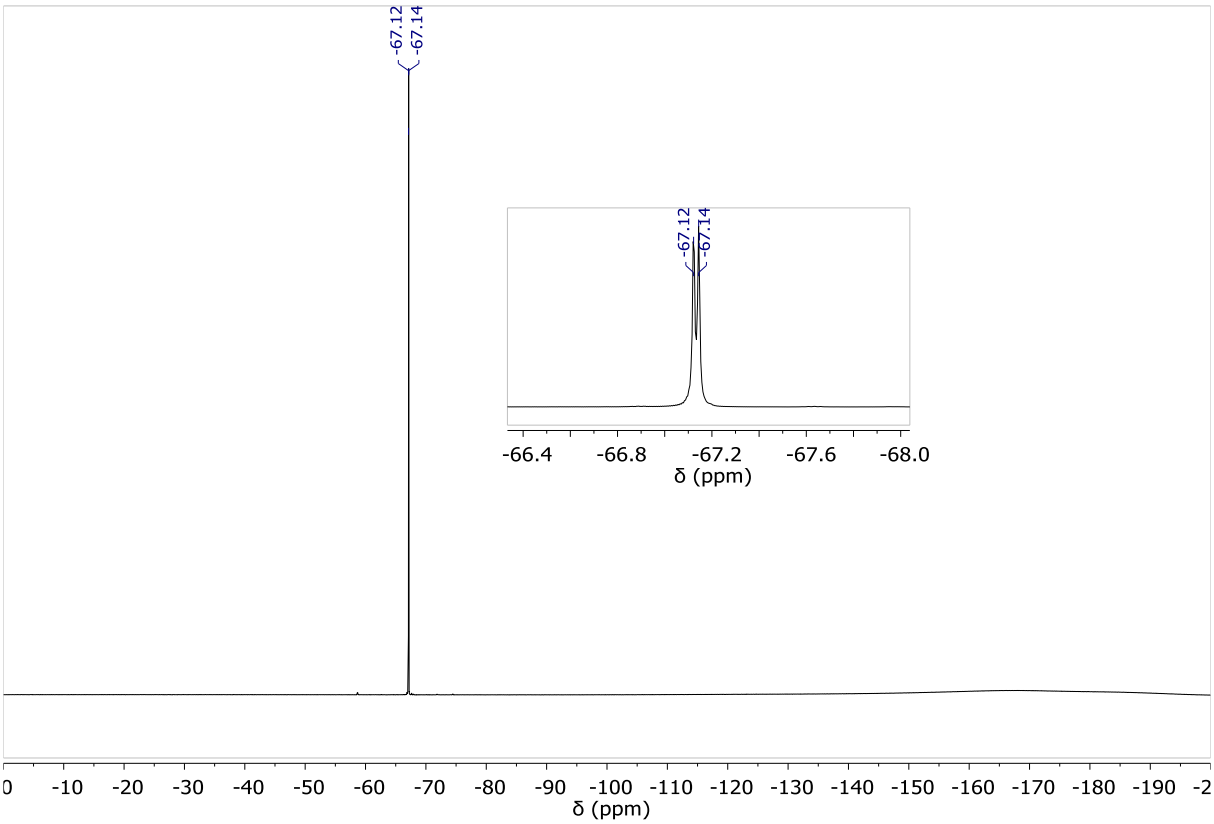


^{13}C NMR ($CDCl_3$, 101 MHz)

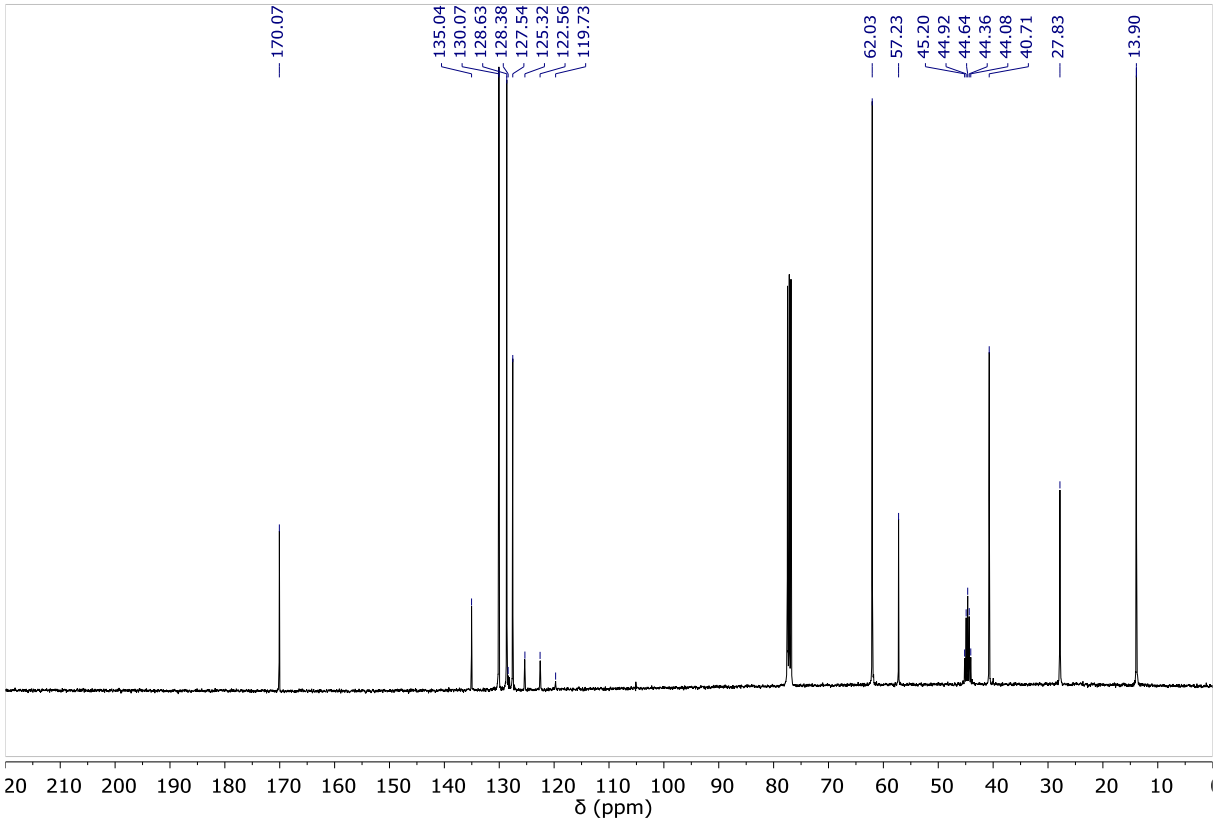
Compound 15b



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

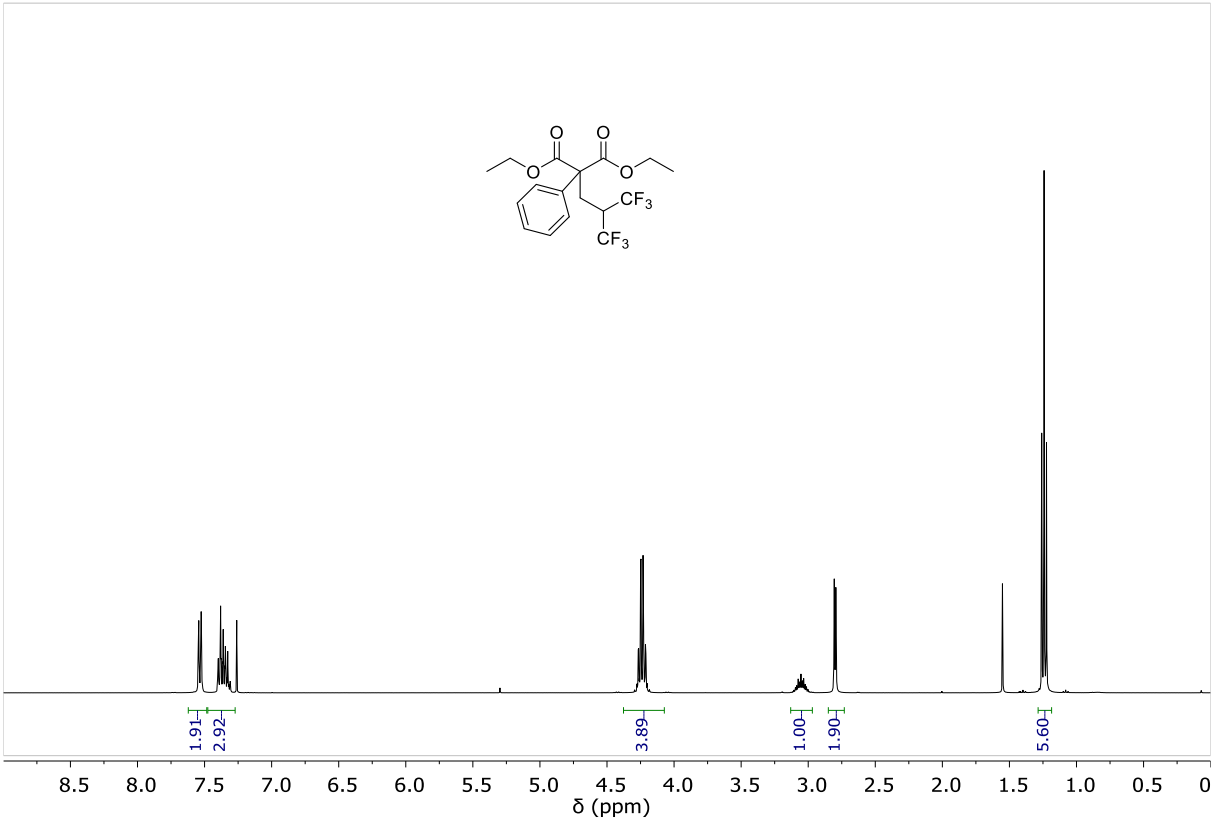


^{19}F NMR ($CDCl_3$, 376 MHz)

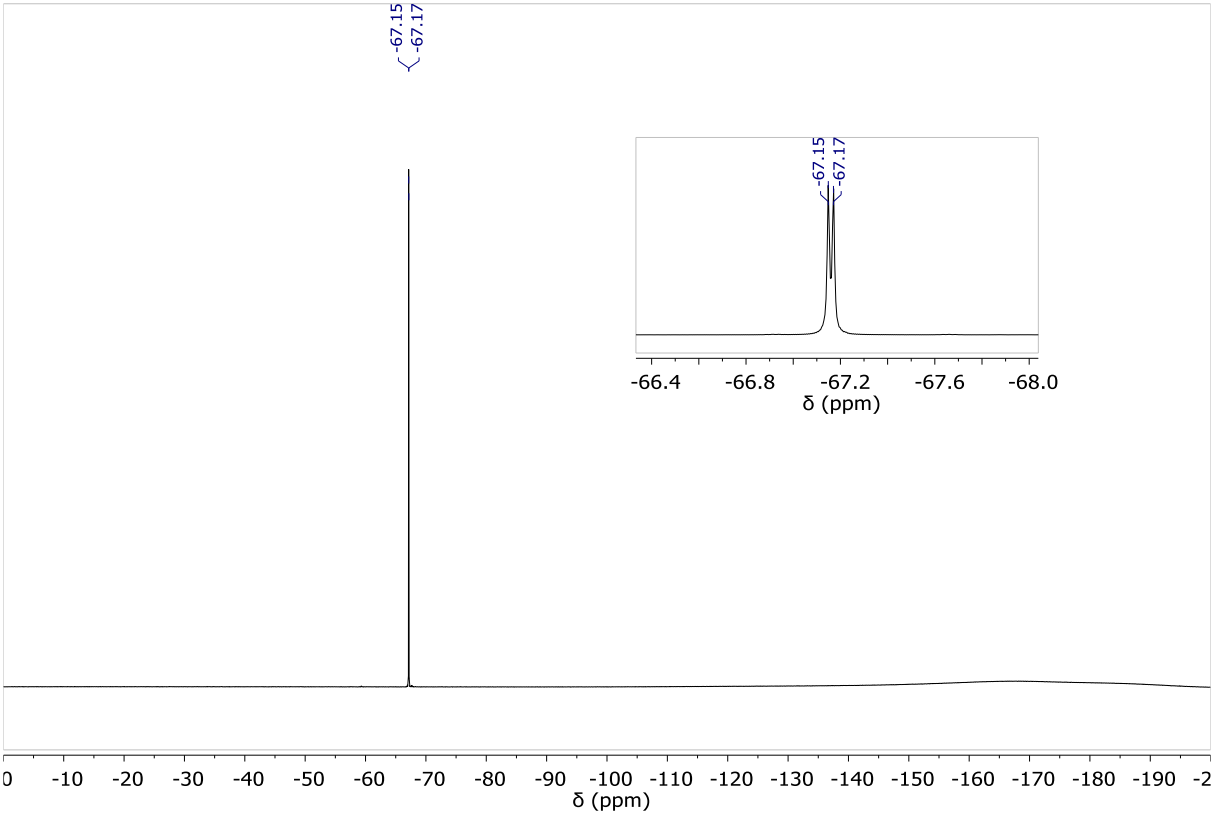


^{13}C NMR ($CDCl_3$, 101 MHz)

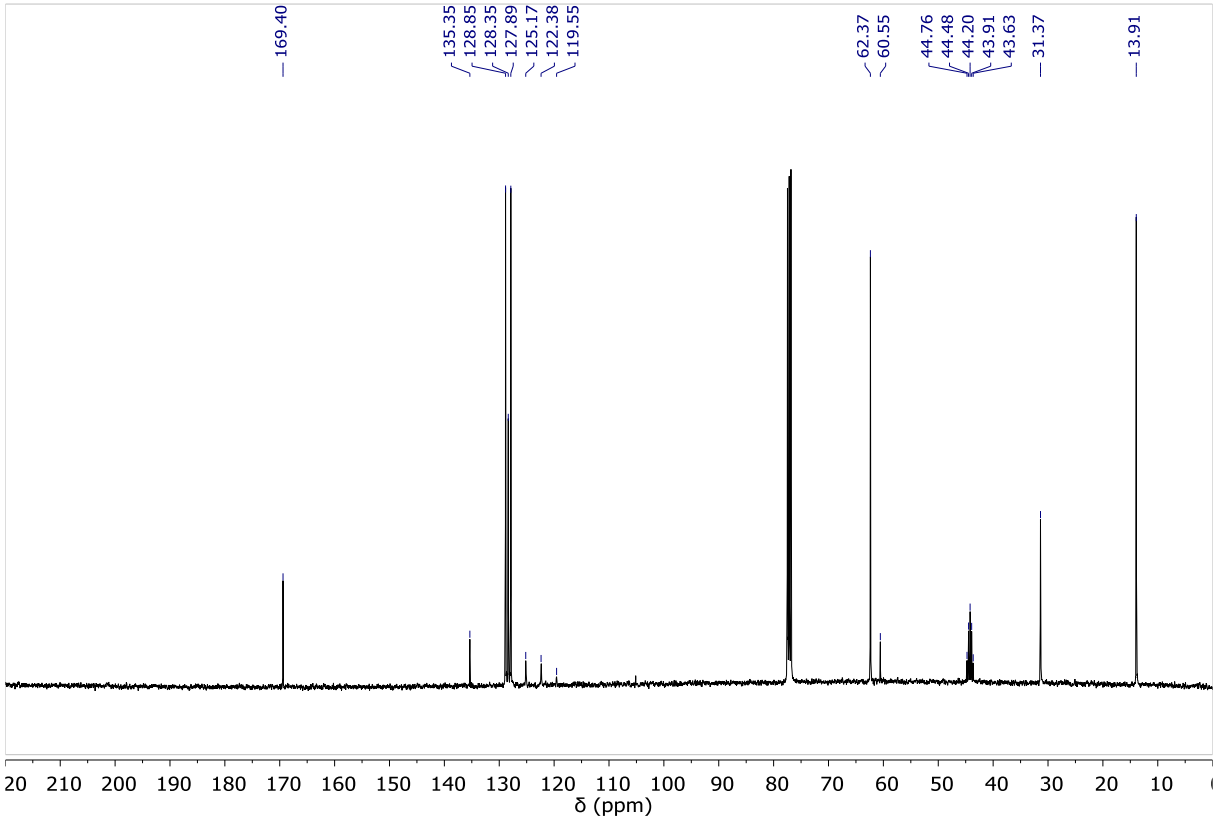
Compound 16b



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

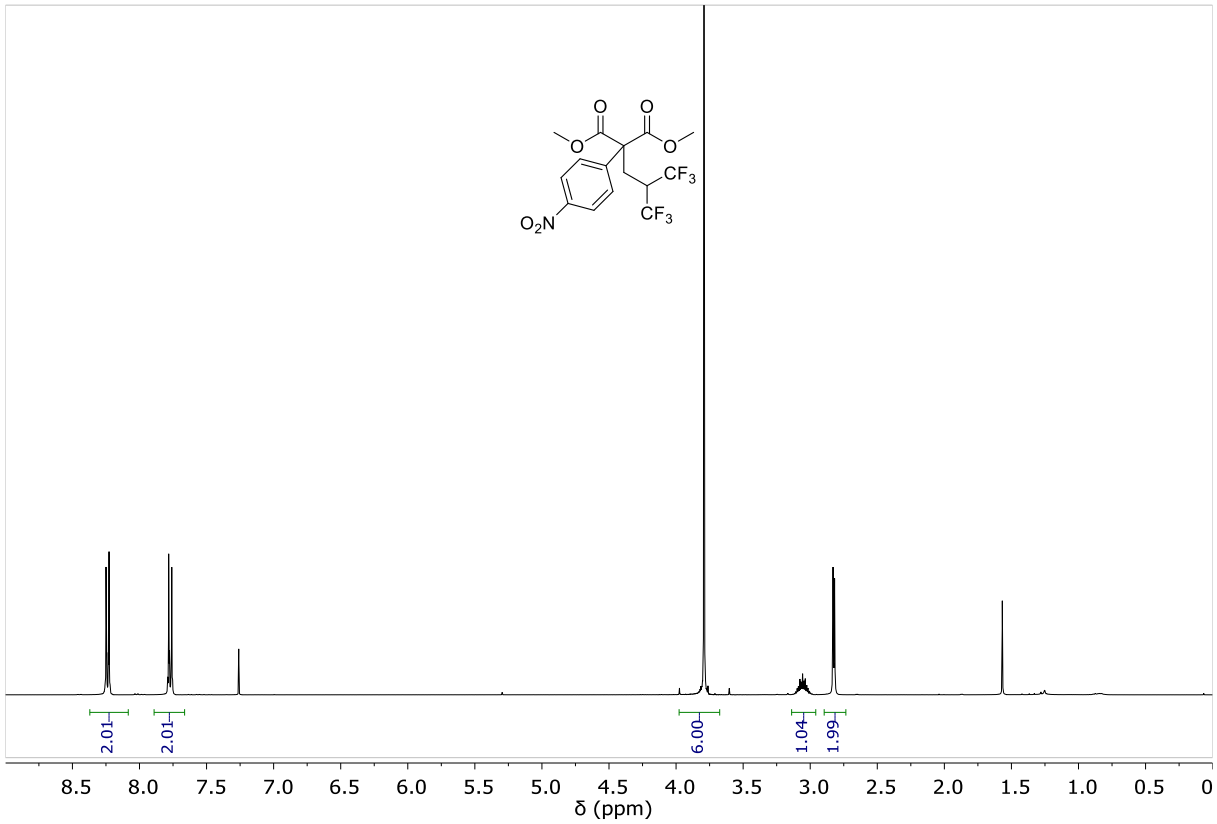


^{19}F NMR ($CDCl_3$, 376 MHz)

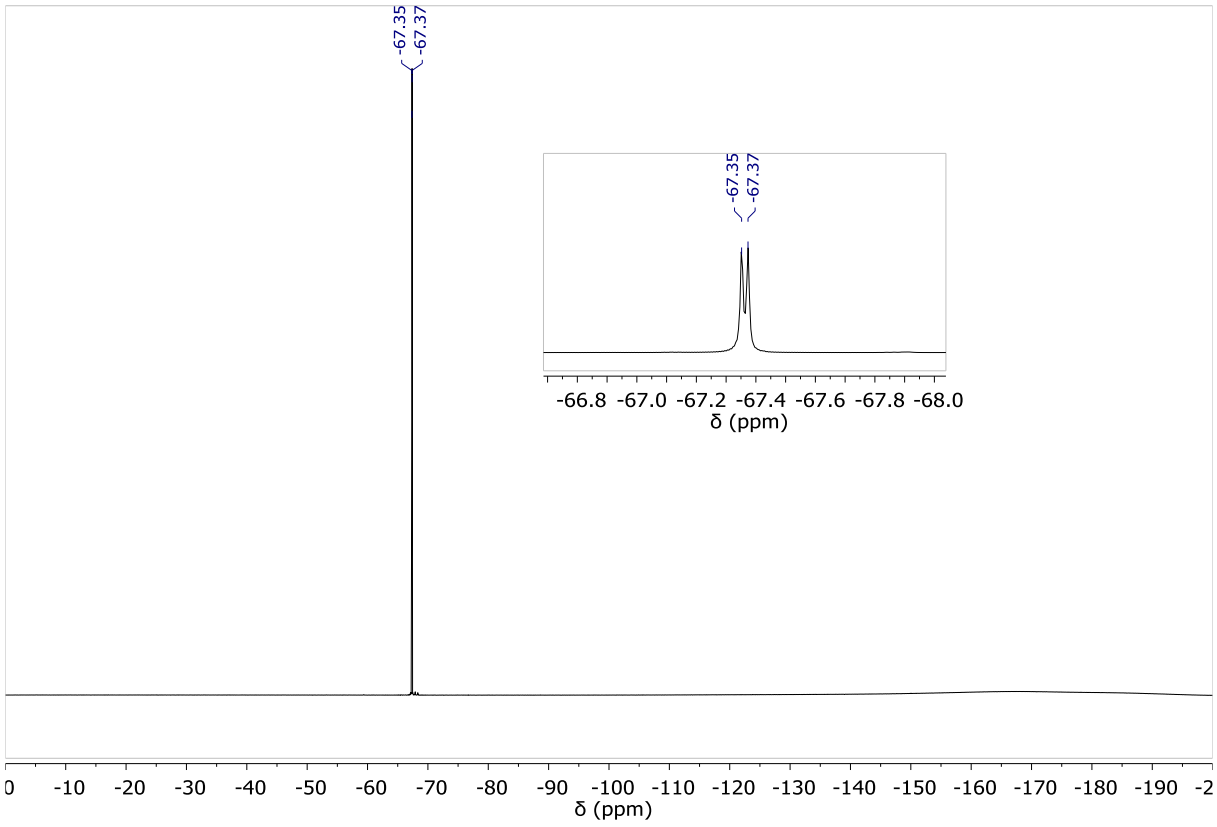


^{13}C NMR ($CDCl_3$, 101 MHz)

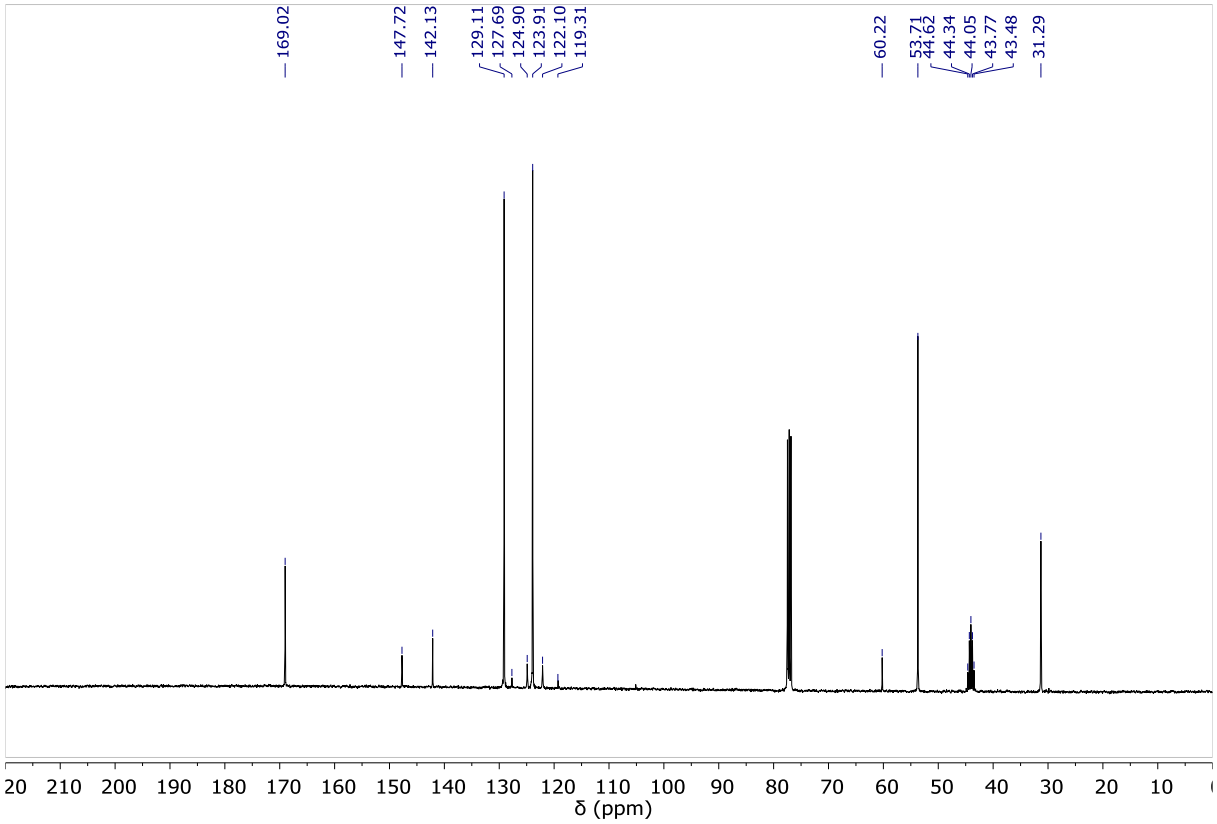
Compound 17b



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

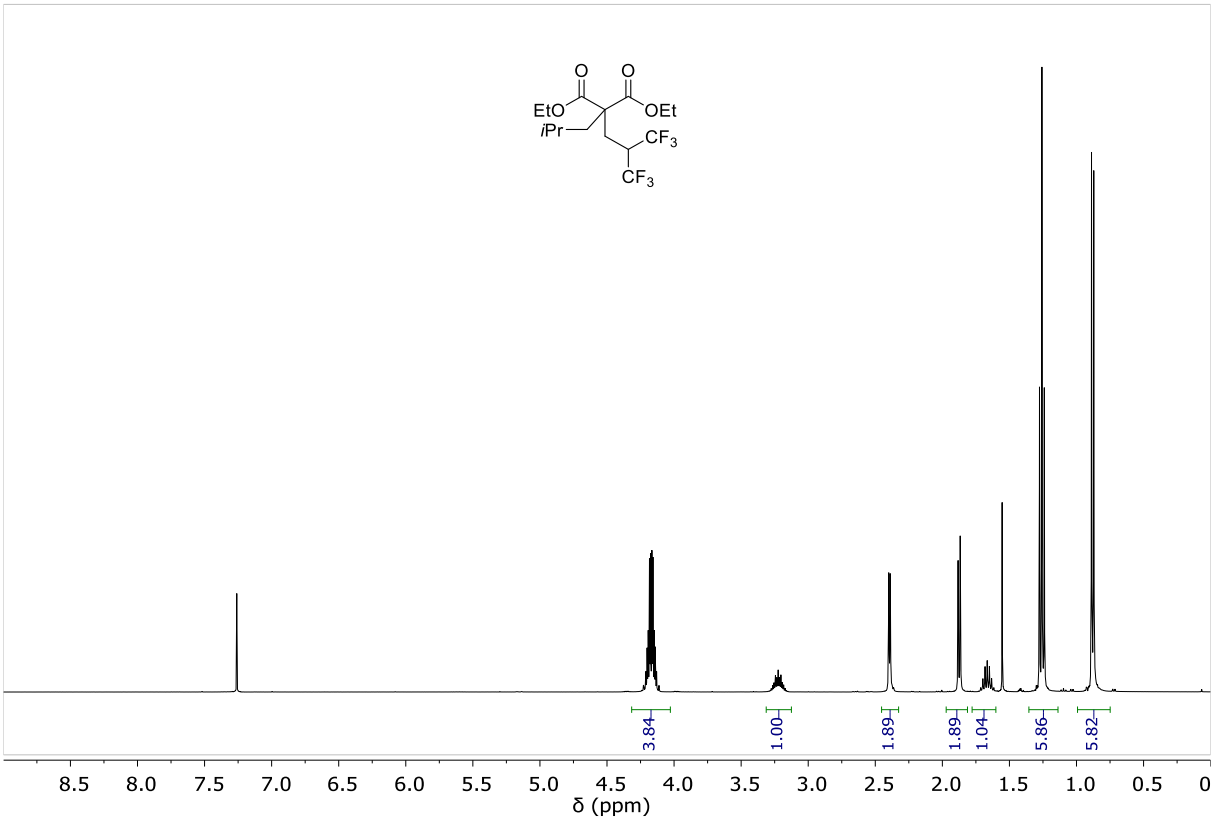


^{19}F NMR ($CDCl_3$, 376 MHz)

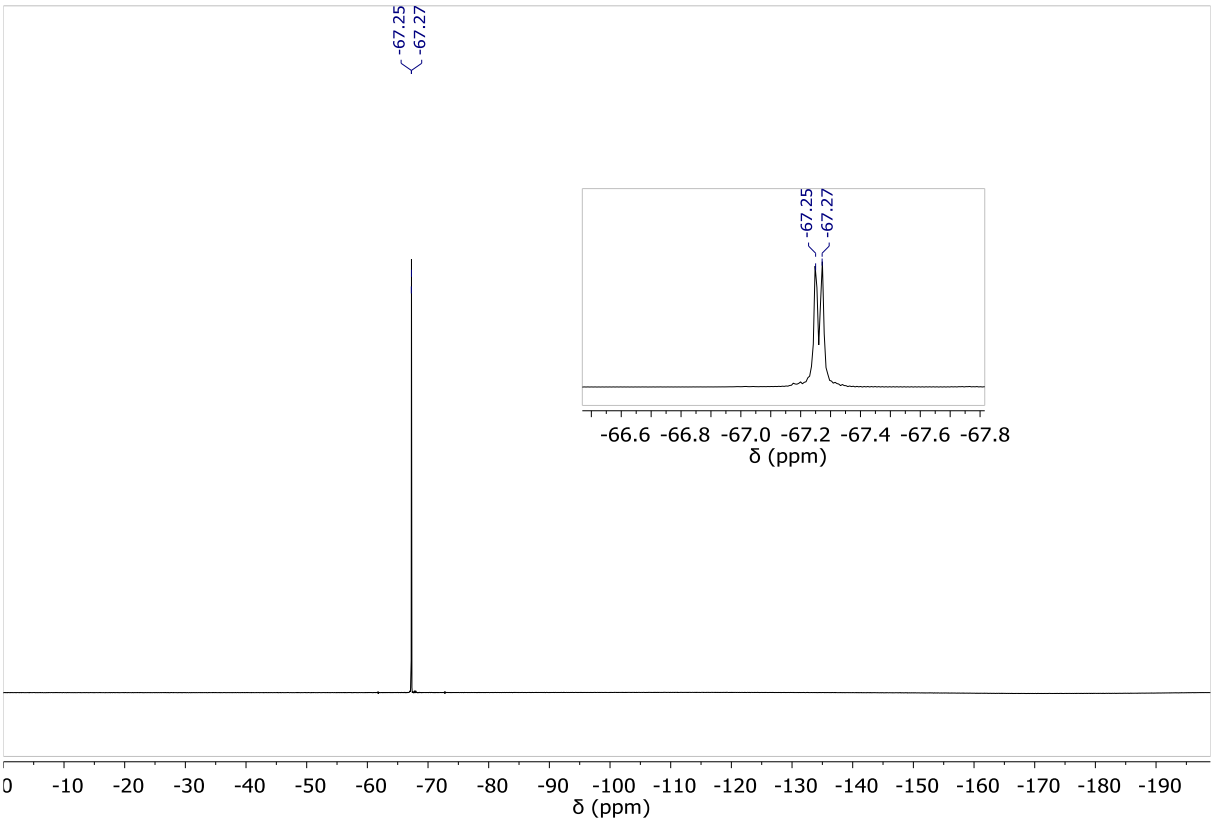


^{13}C NMR ($CDCl_3$, 101 MHz)

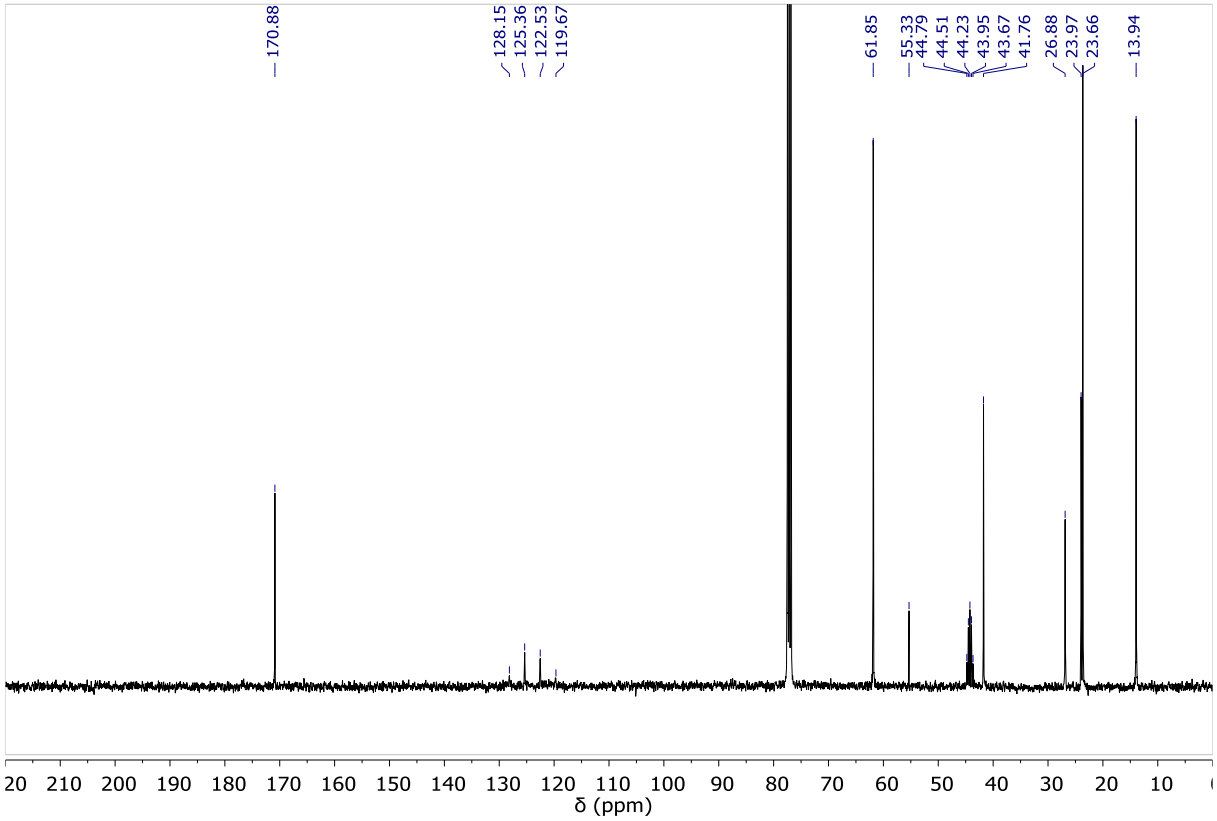
Compound 18b



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

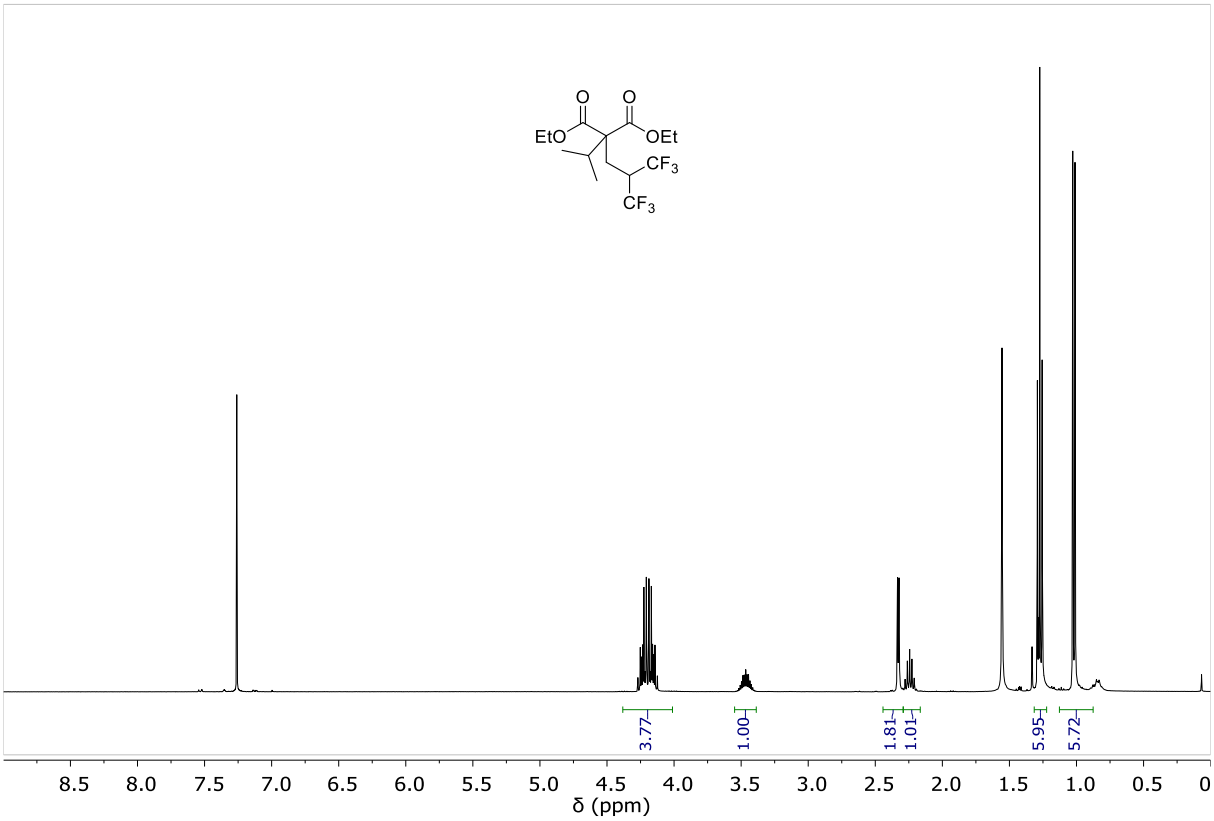


^{19}F NMR ($CDCl_3$, 376 MHz)

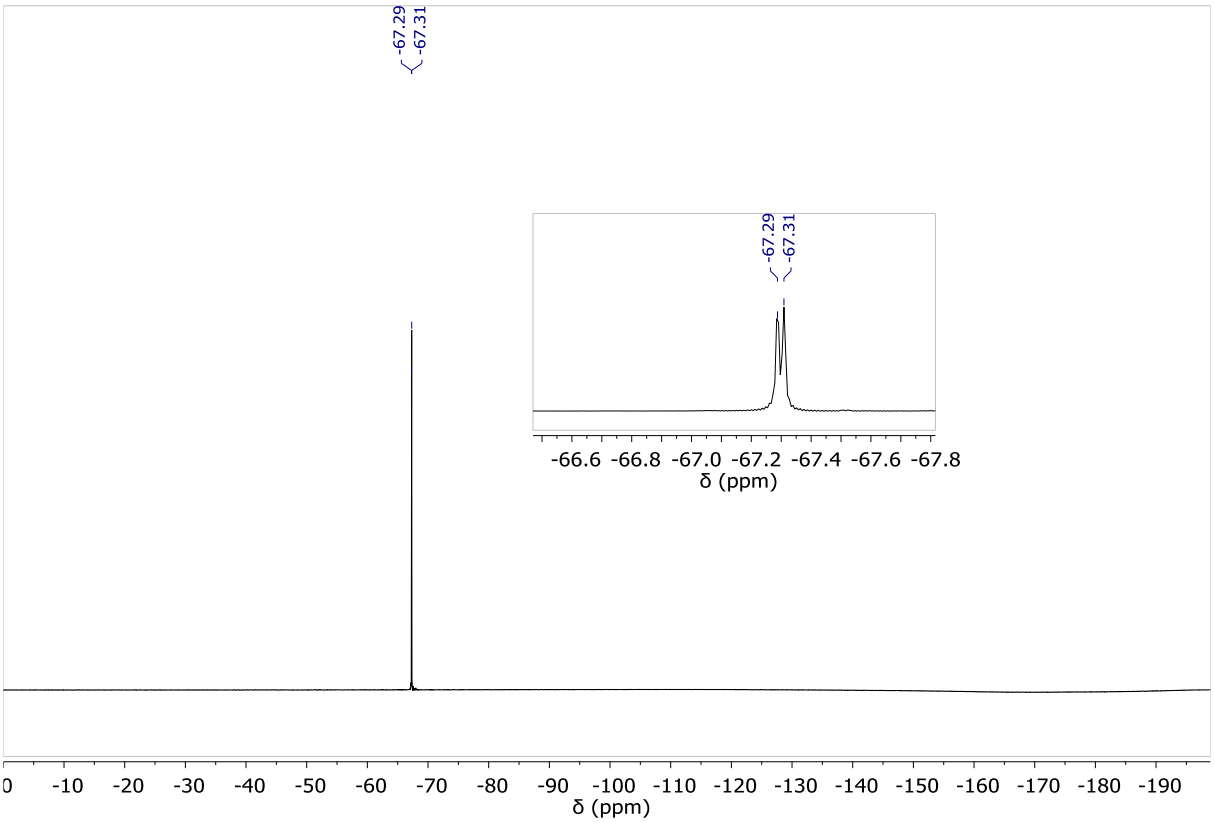


^{13}C NMR ($CDCl_3$, 101 MHz)

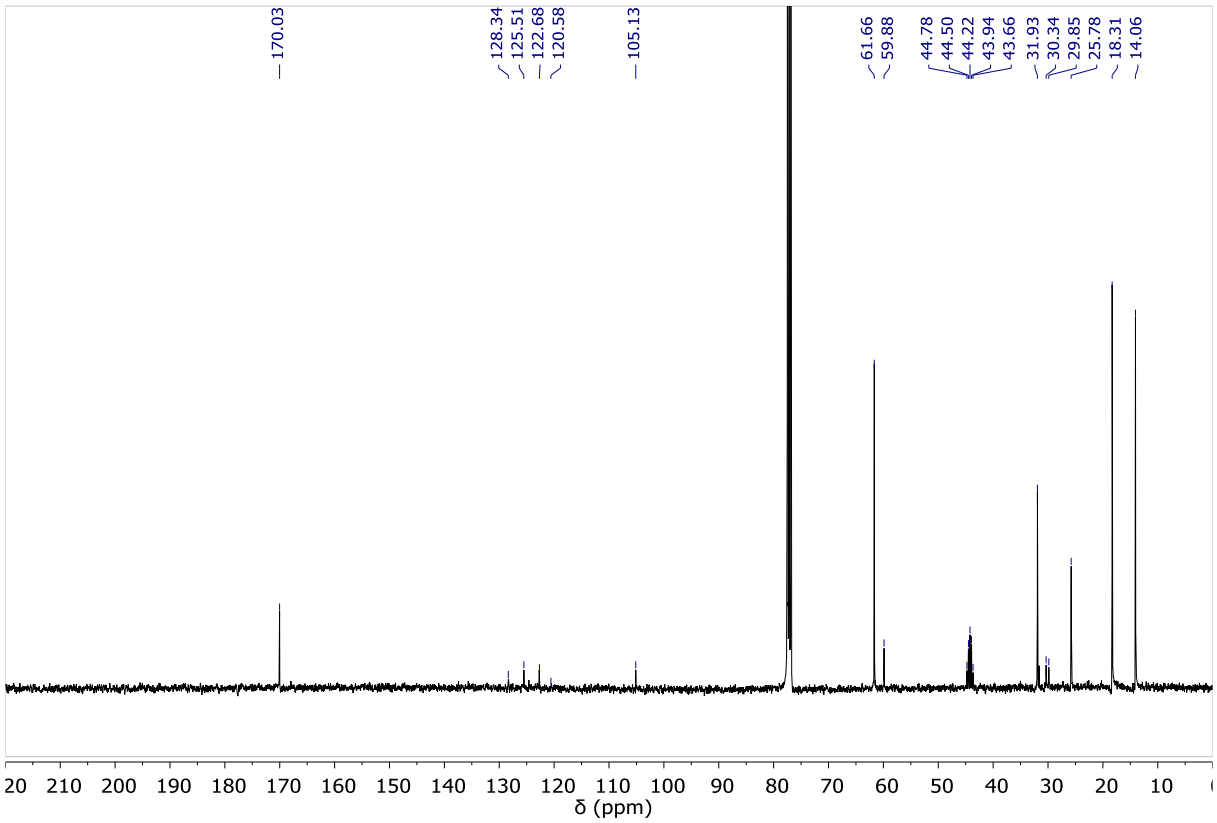
Compound 19b



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

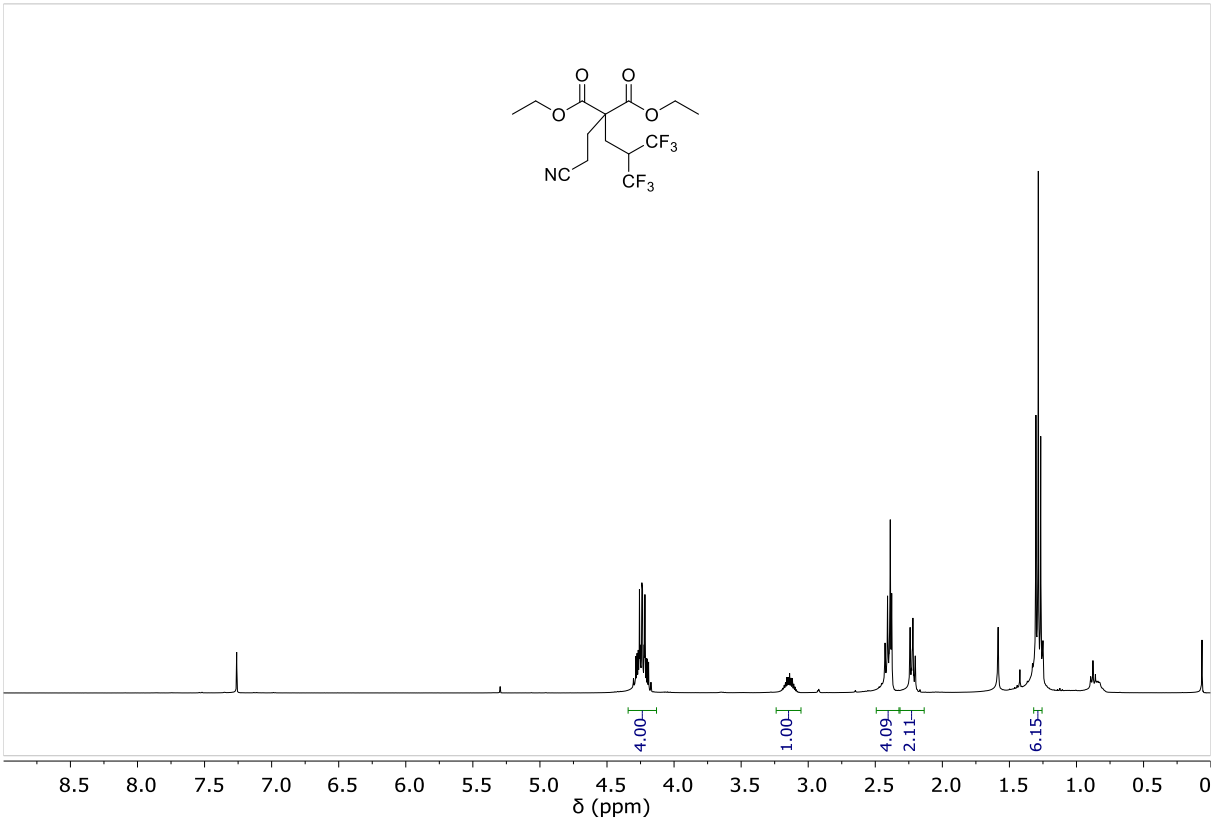


^{19}F NMR ($CDCl_3$, 376 MHz)

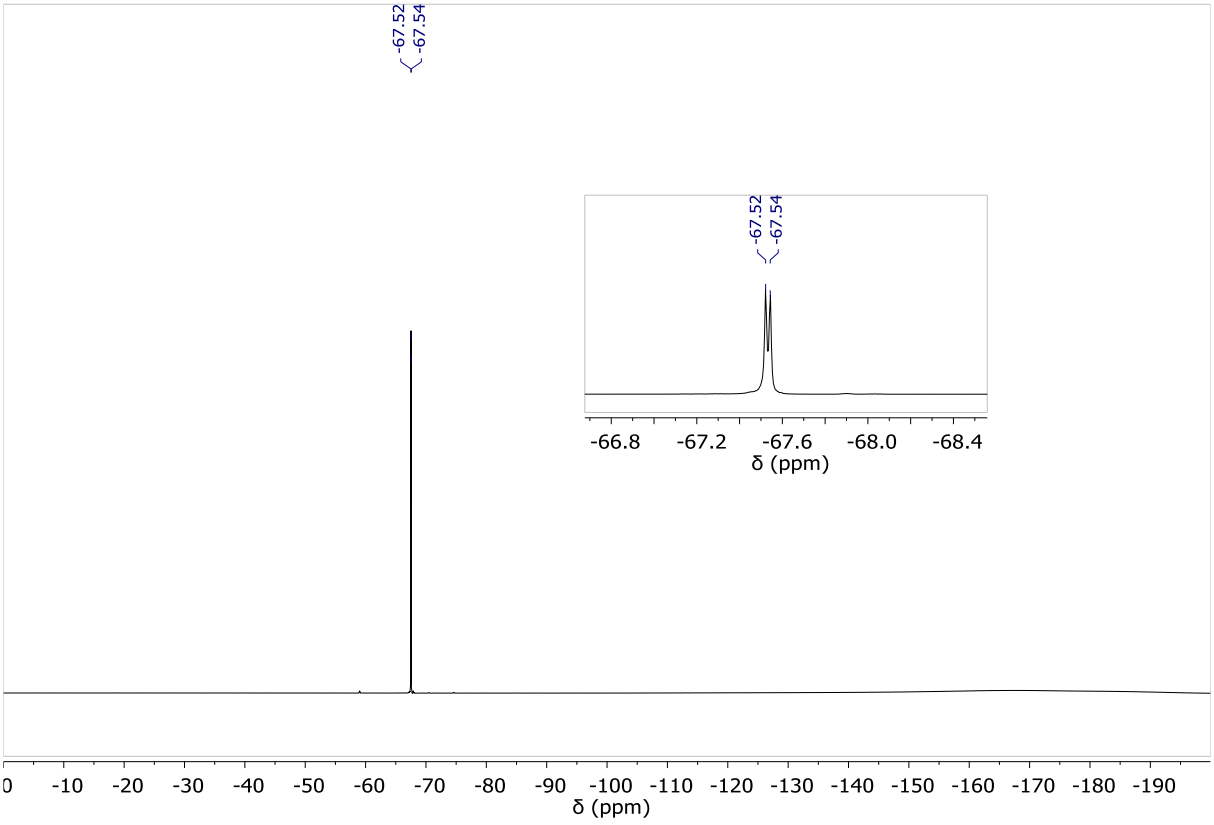


^{13}C NMR ($CDCl_3$, 101 MHz)

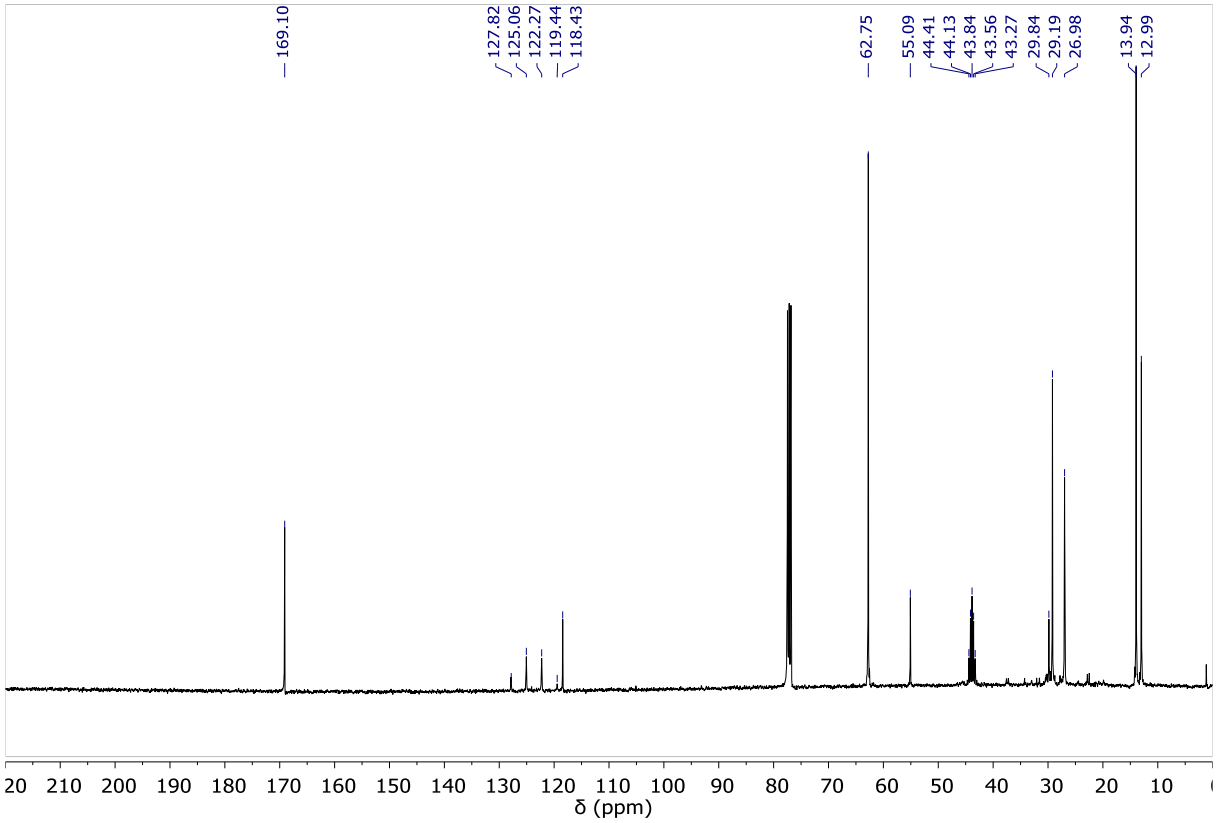
Compound 22b



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

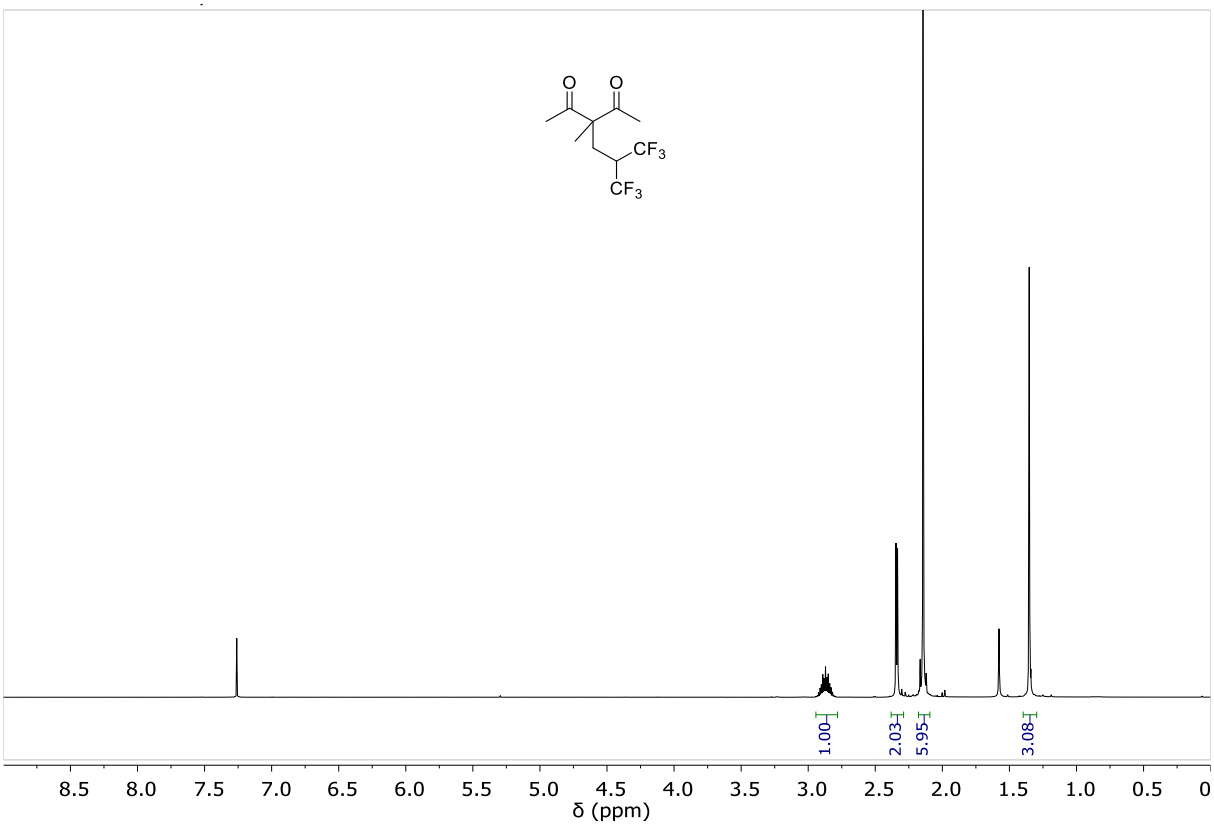


^{19}F NMR ($CDCl_3$, 376 MHz)

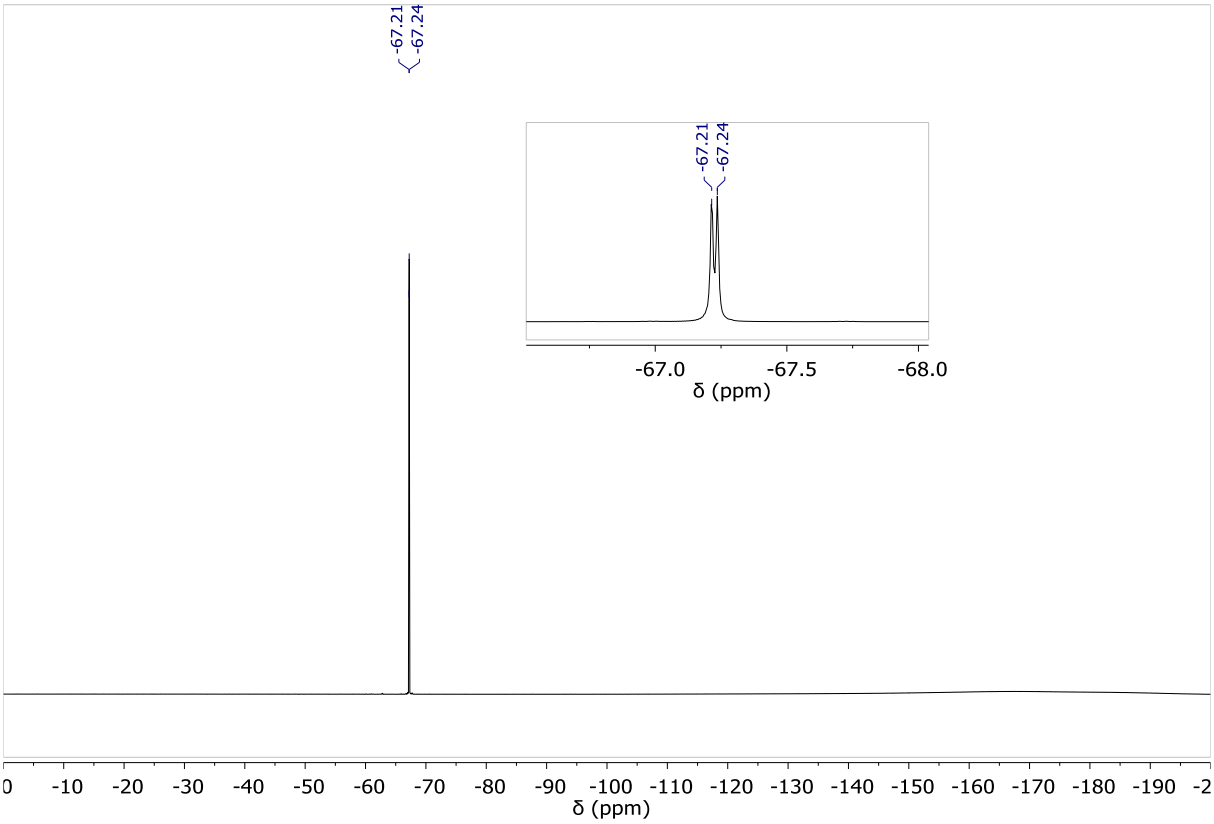


^{13}C NMR ($CDCl_3$, 101 MHz)

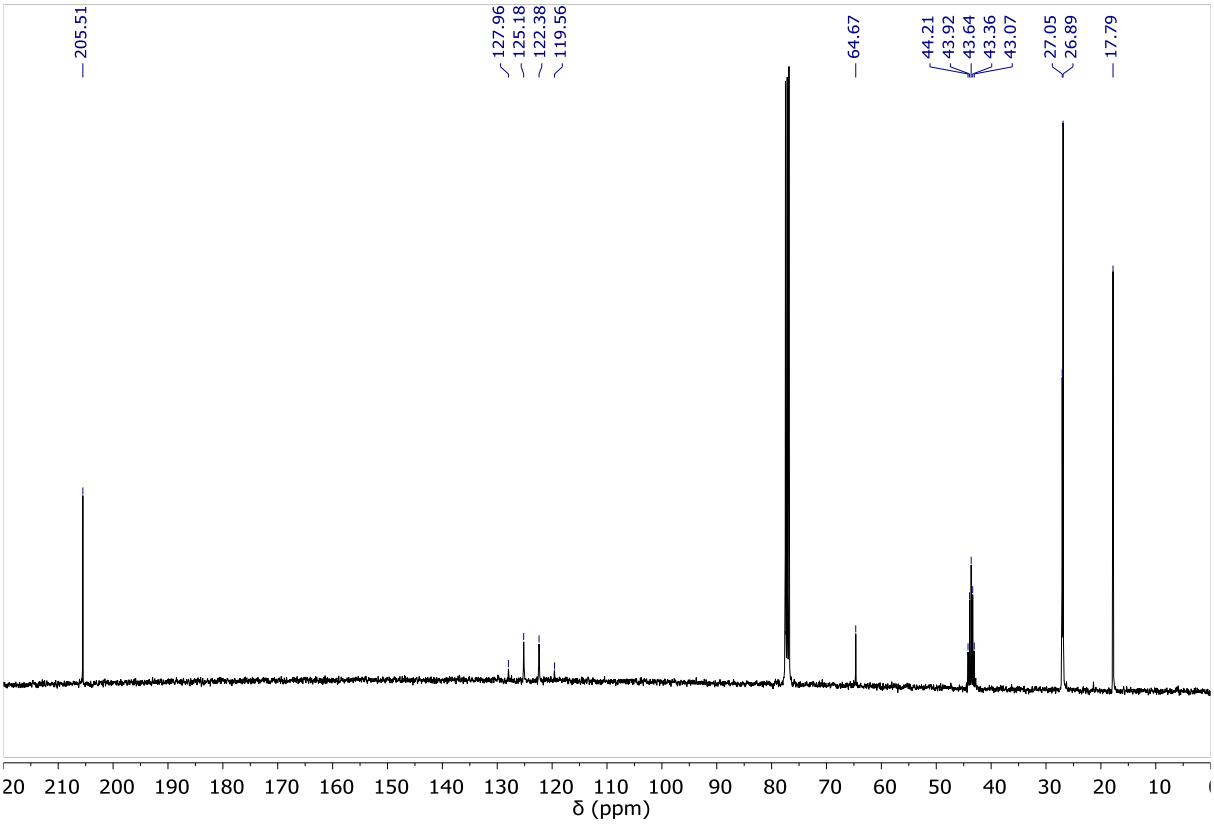
Compound 21b



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

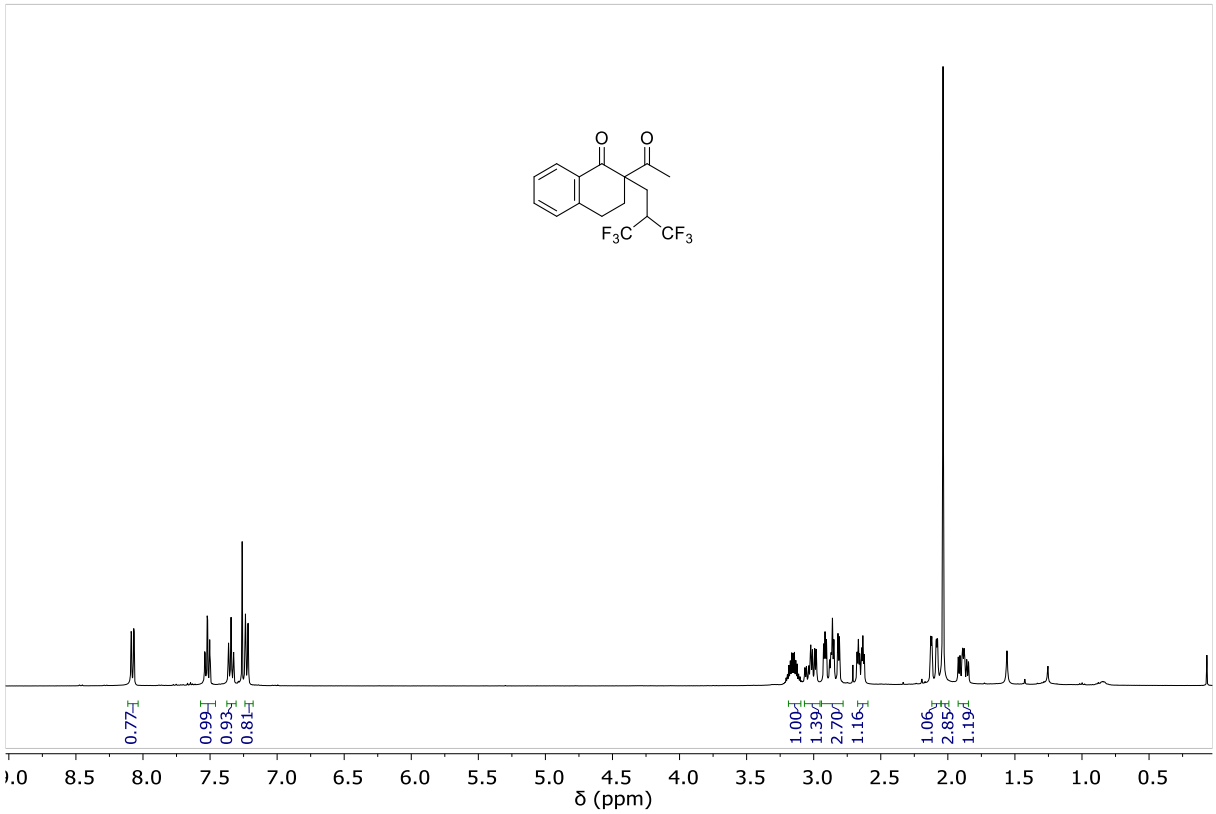


^{19}F NMR ($CDCl_3$, 376 MHz)

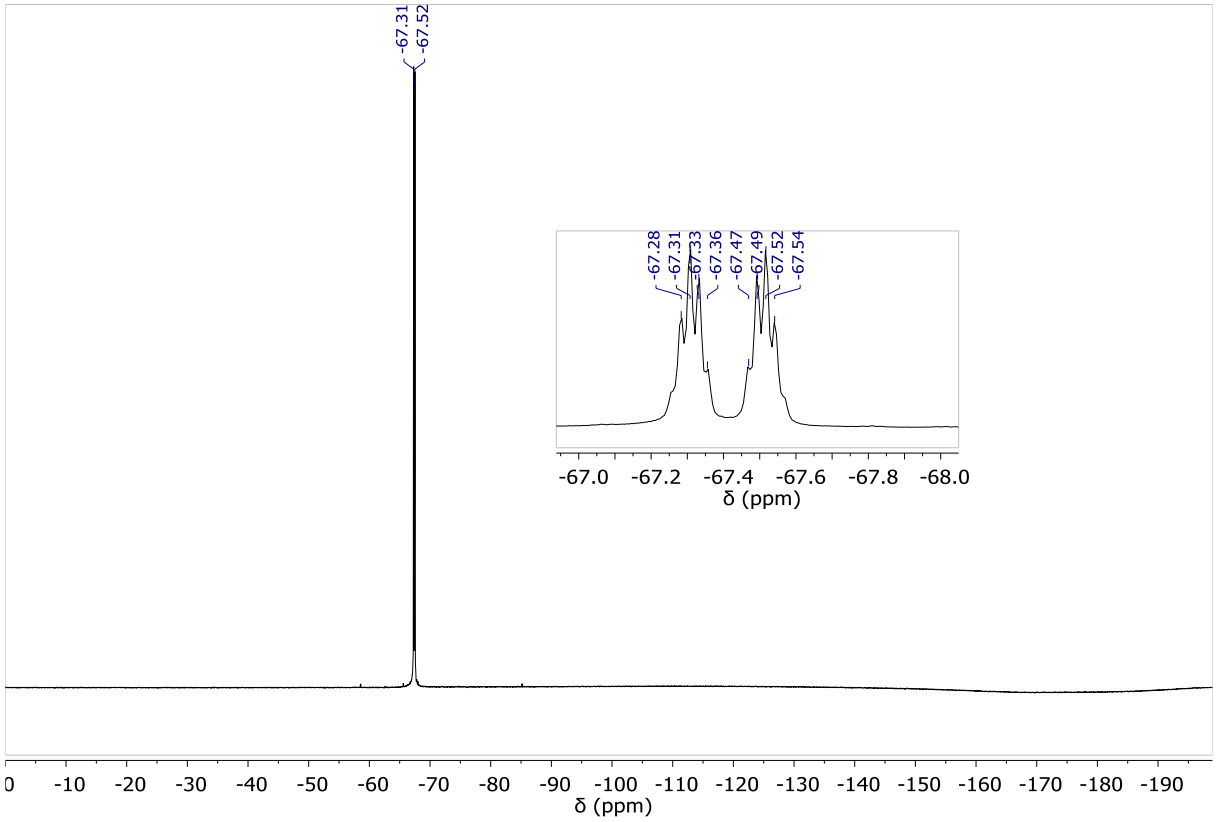


^{13}C NMR ($CDCl_3$, 101 MHz)

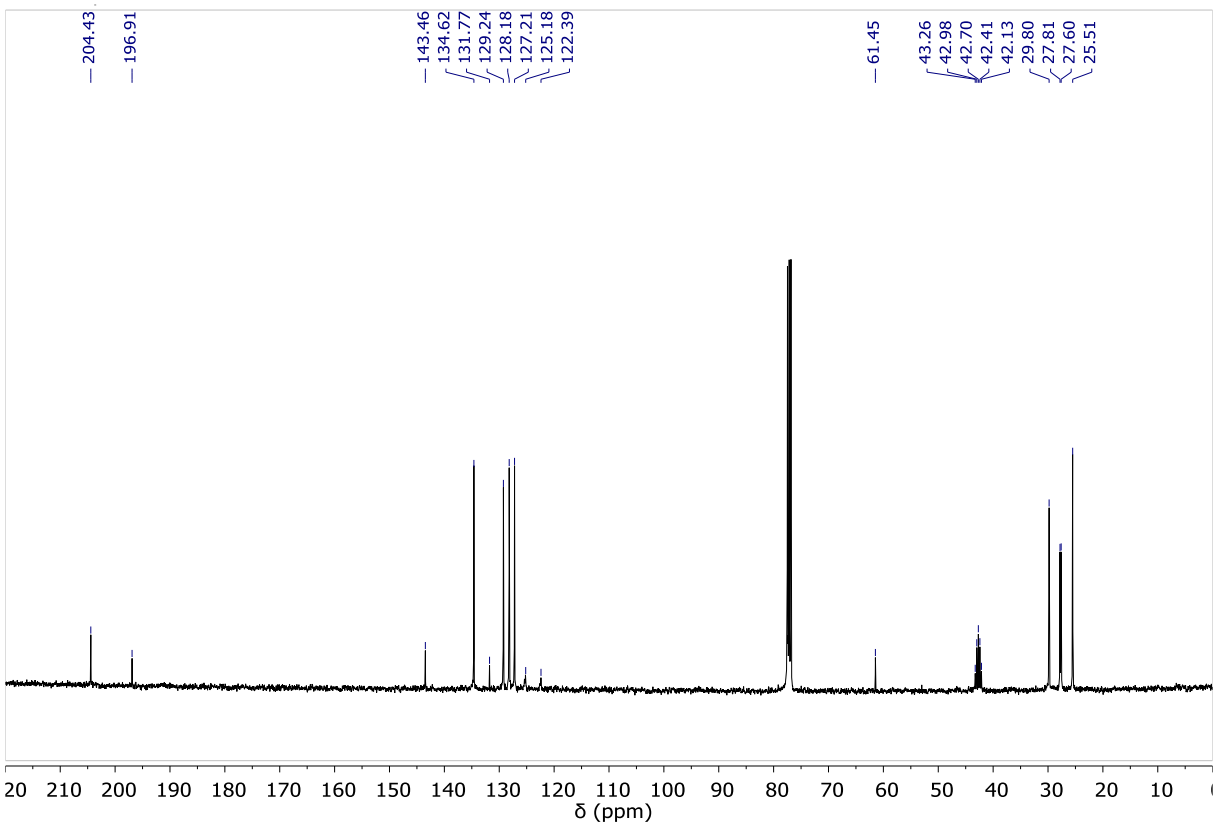
Compound 22b



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

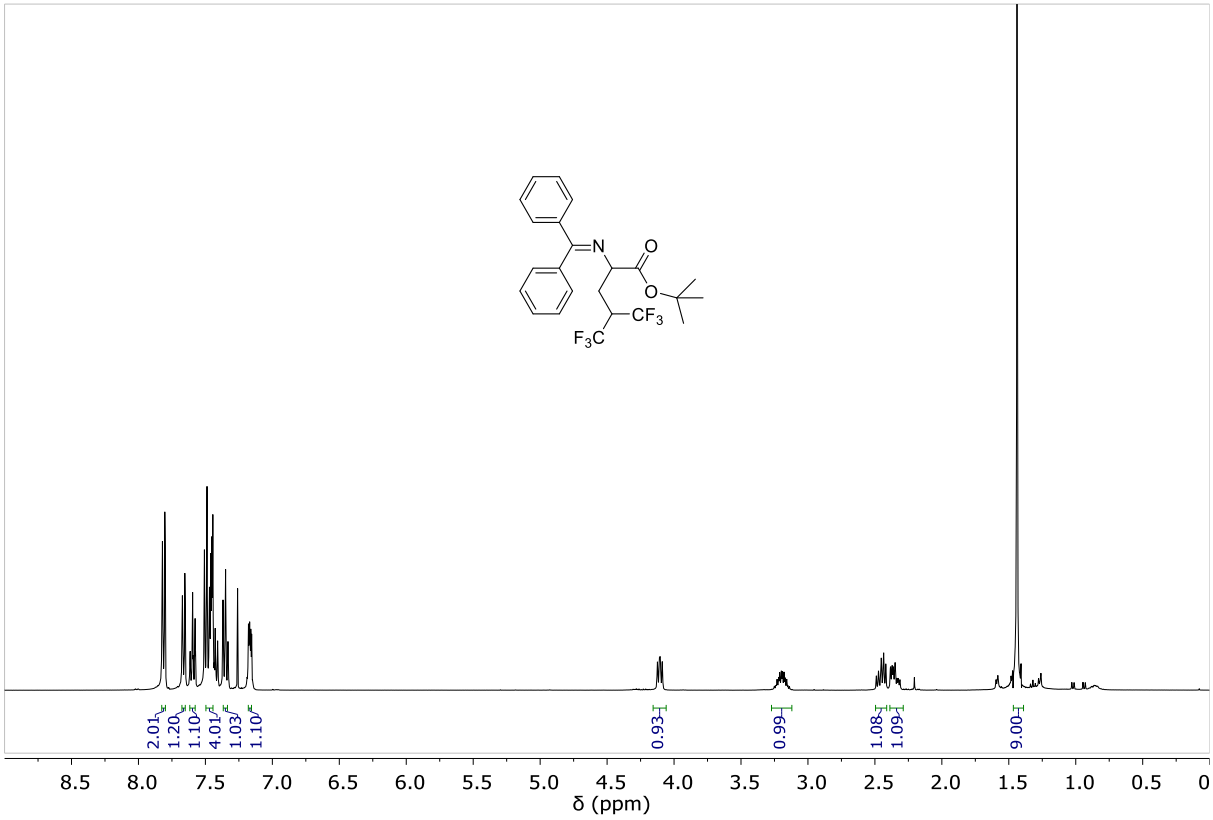


^{19}F NMR ($CDCl_3$, 376 MHz)

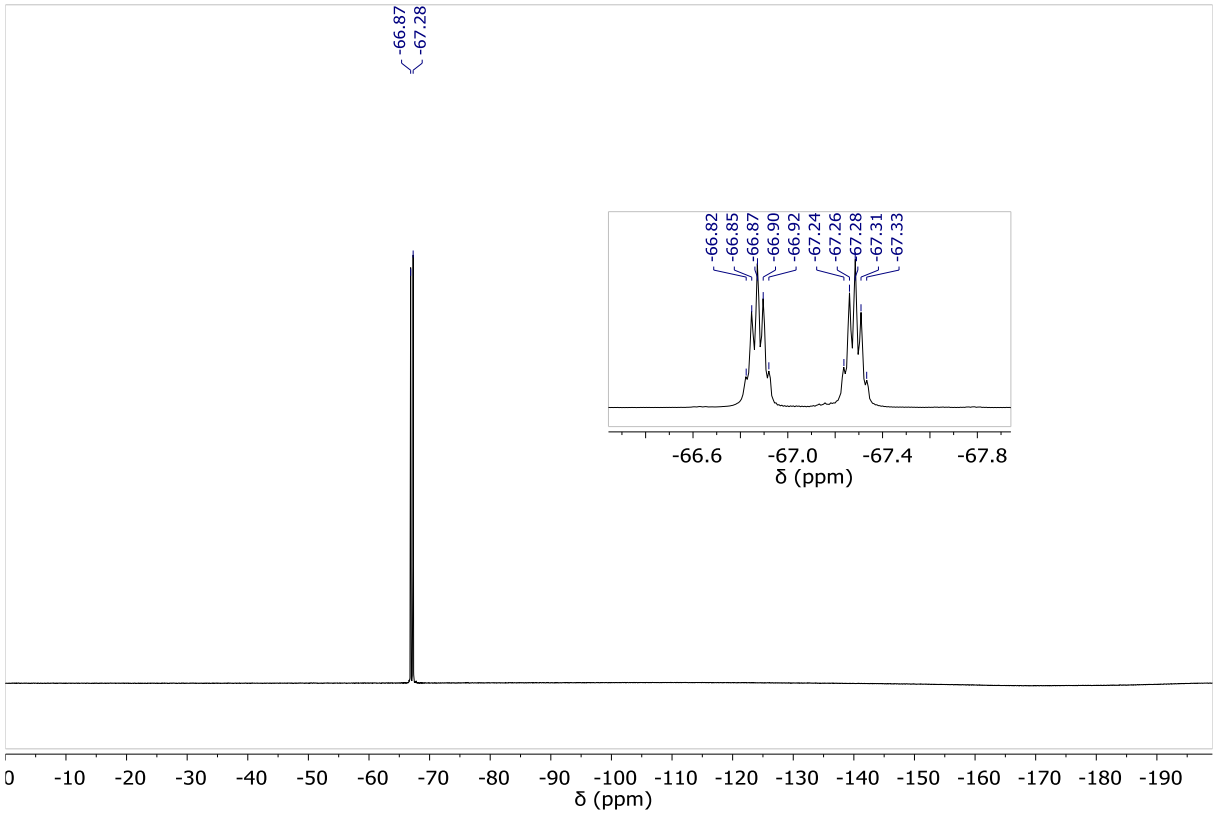


^{13}C NMR ($CDCl_3$, 101 MHz)

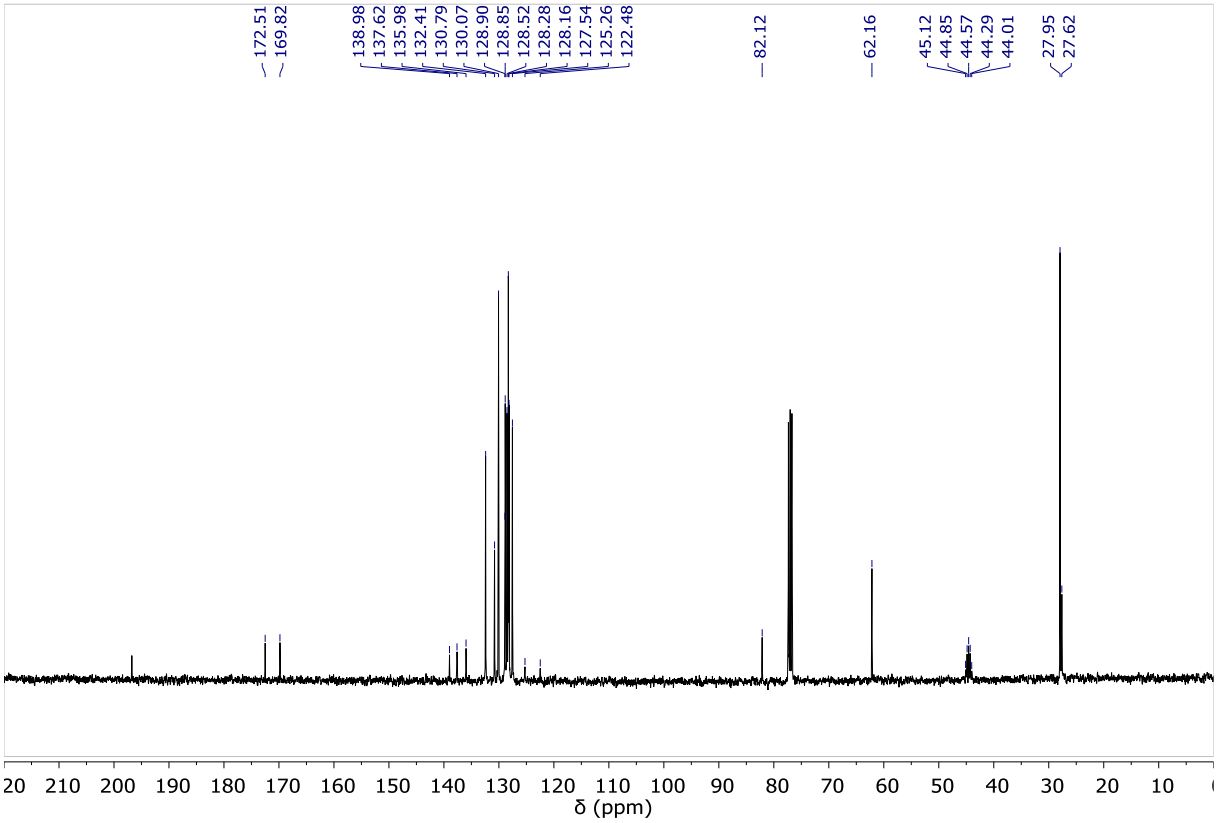
Compound 23b



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

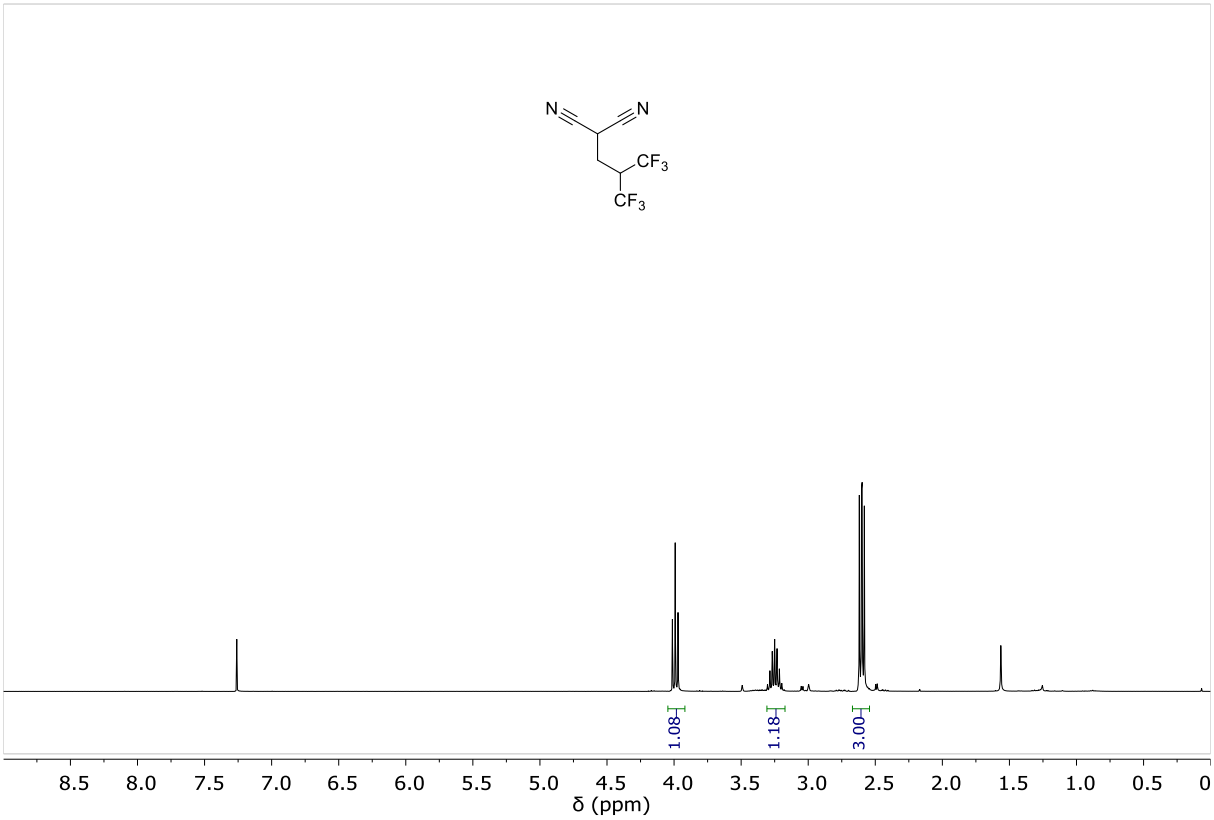


^{19}F NMR ($CDCl_3$, 376 MHz)

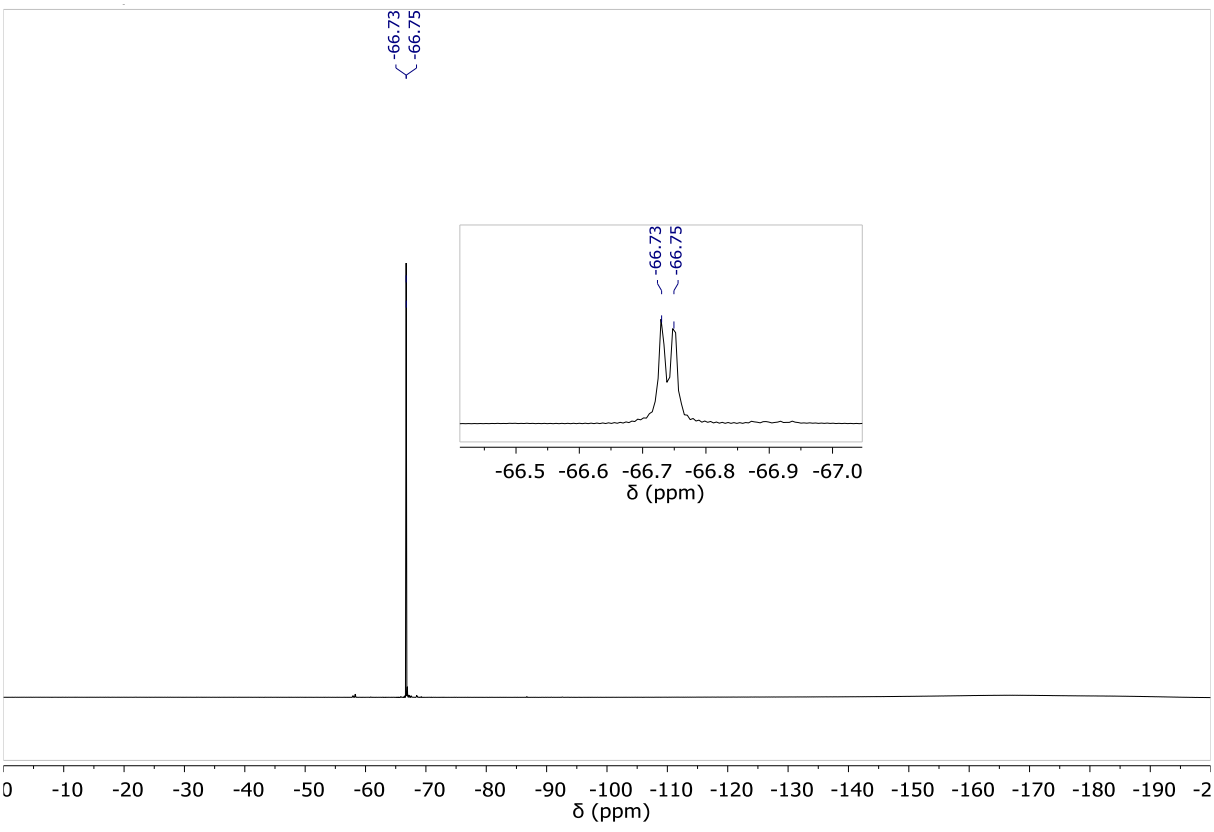


^{13}C NMR ($CDCl_3$, 101 MHz)

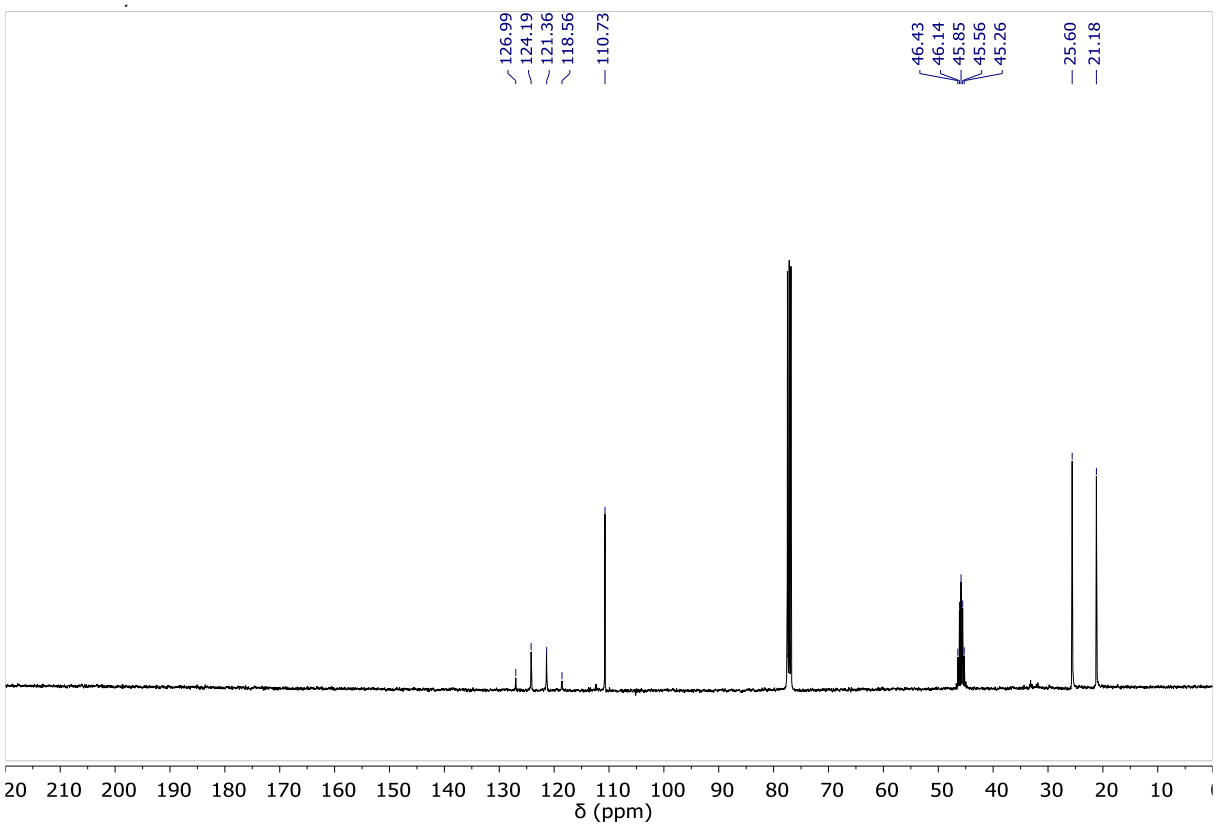
Compound 24b



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

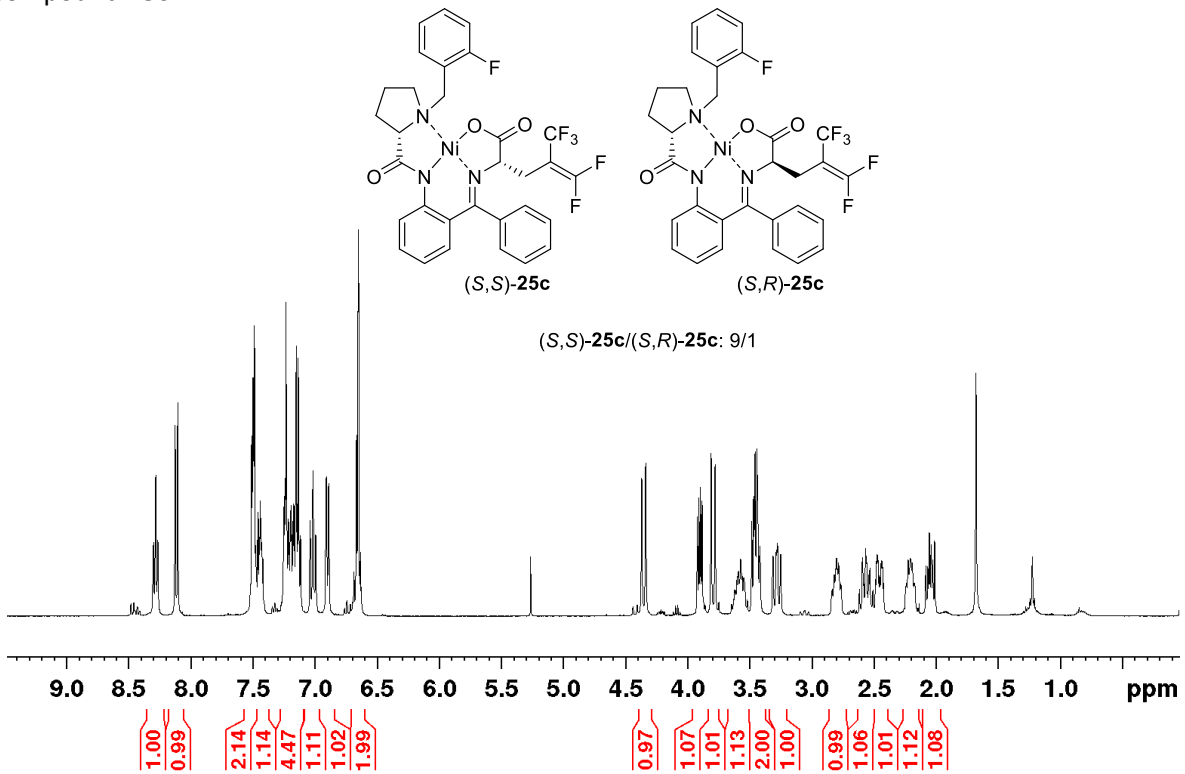


^{19}F NMR ($CDCl_3$, 376 MHz)

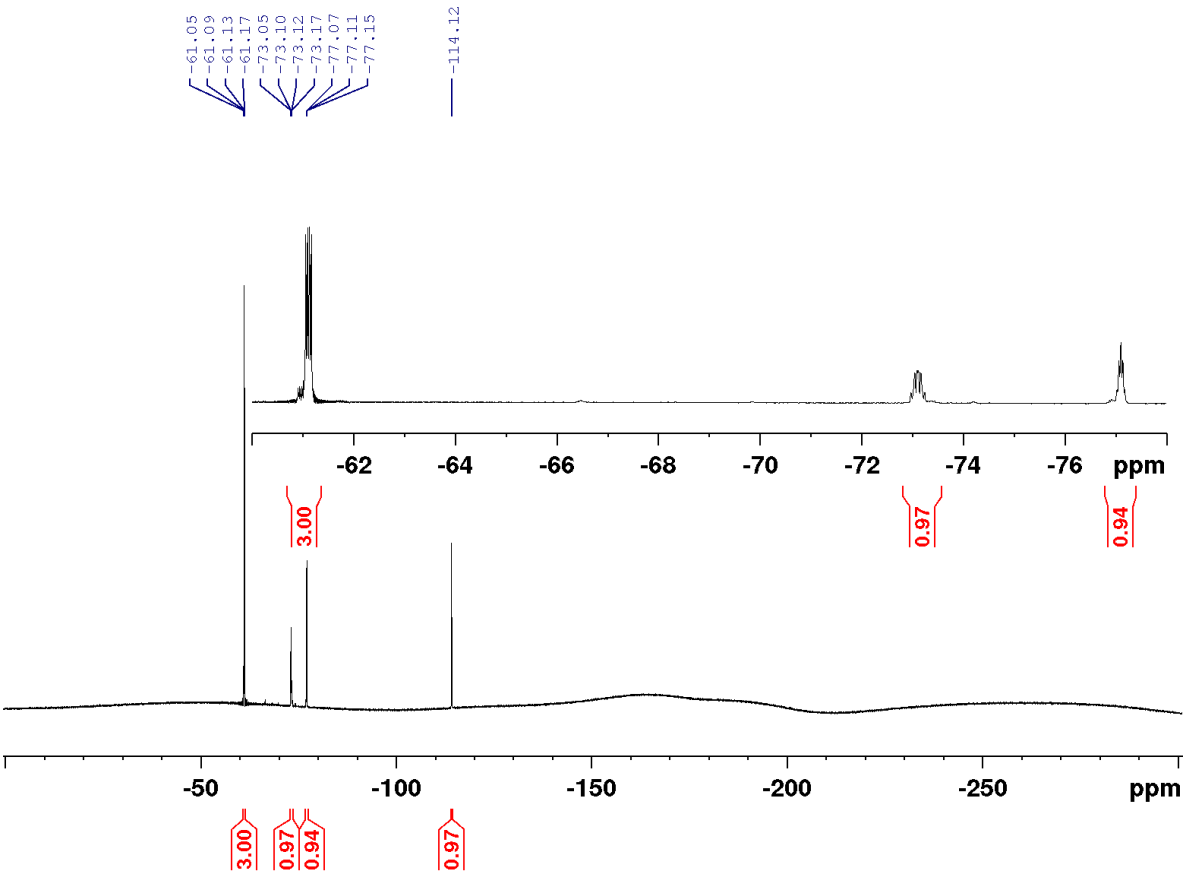


^{13}C NMR ($CDCl_3$, 101 MHz)

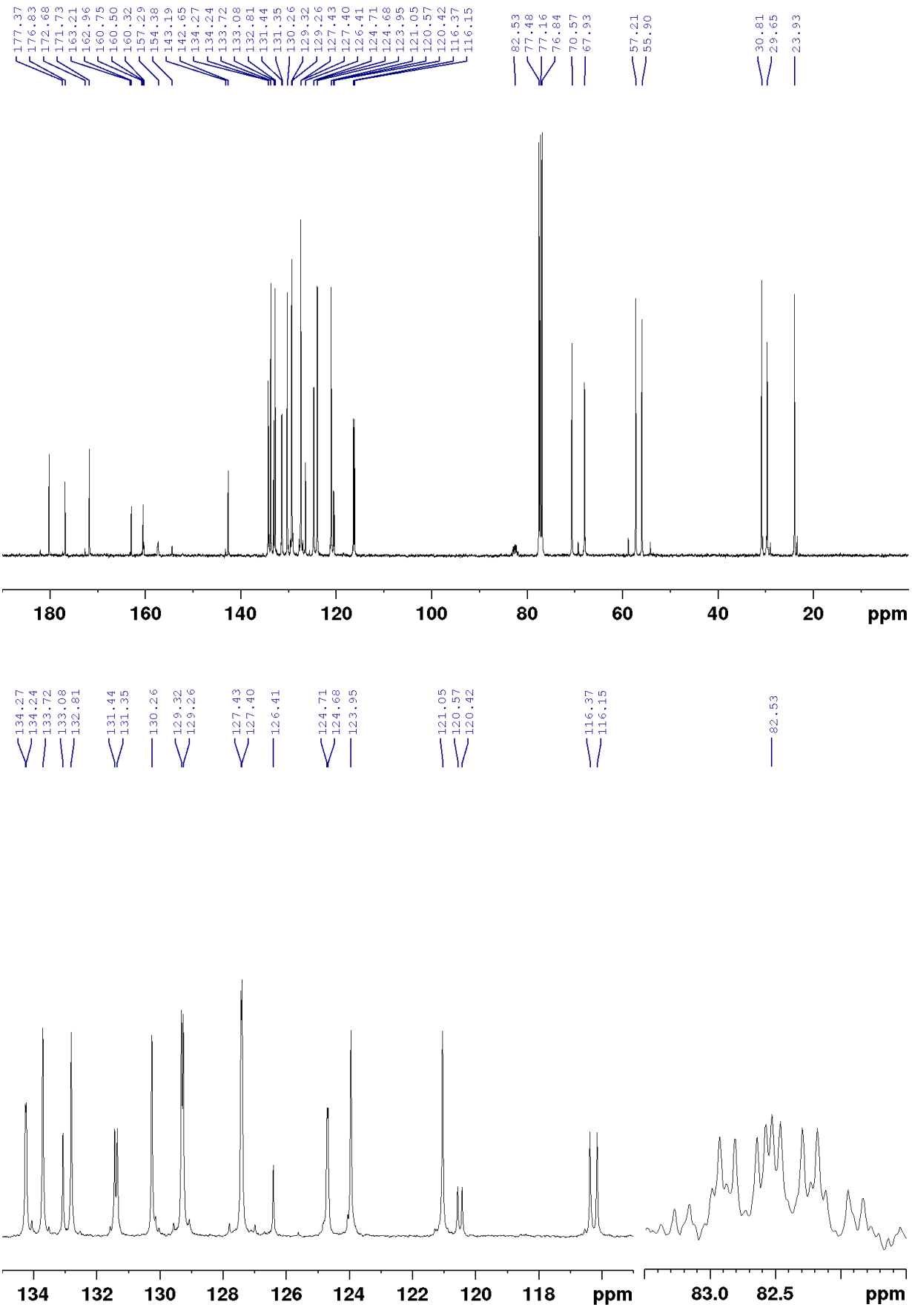
Compound **25c**



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

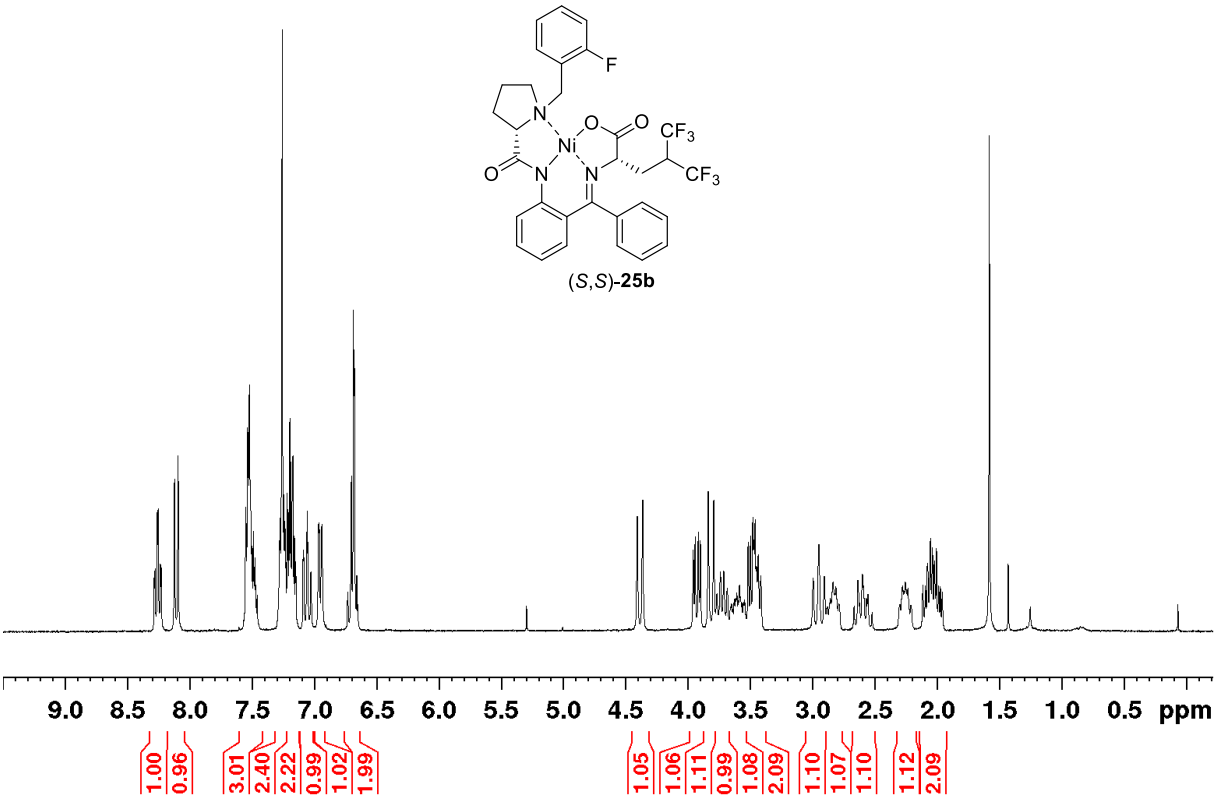


^{19}F NMR ($CDCl_3$, 282 MHz)

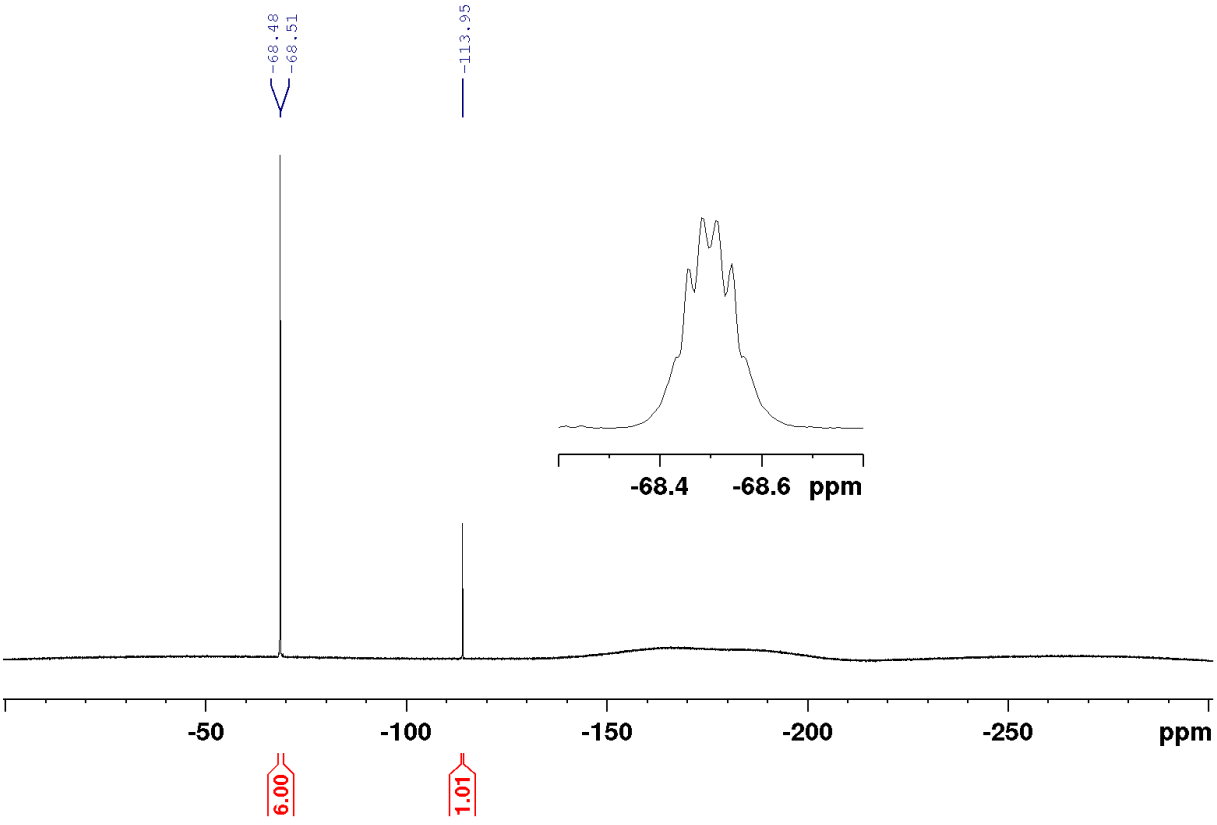


^{13}C NMR ($CDCl_3$, 100 MHz)

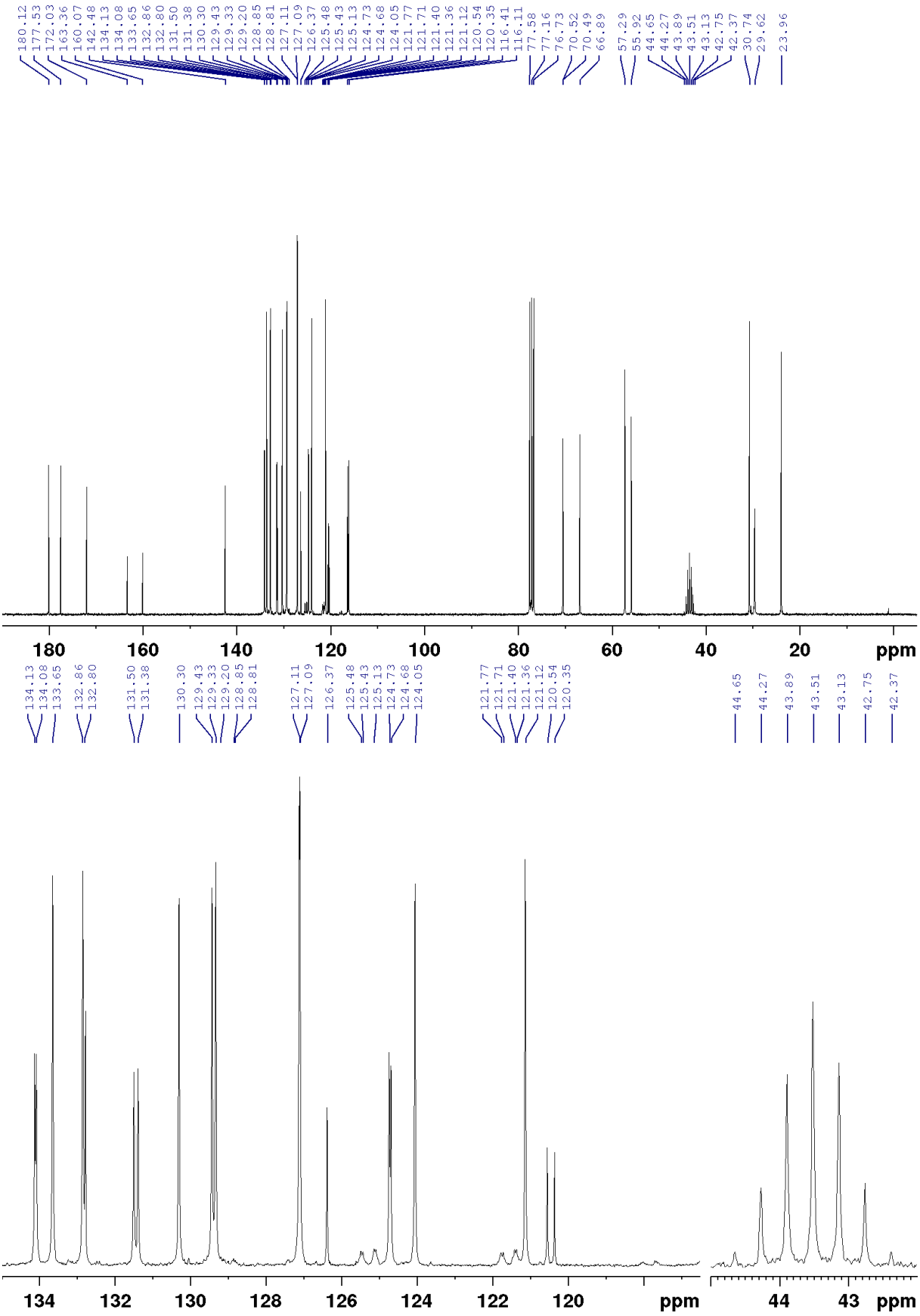
Compound (*S*,*S*)-**25b**



^{1}H NMR ($CDCl_3$, 300 MHz)

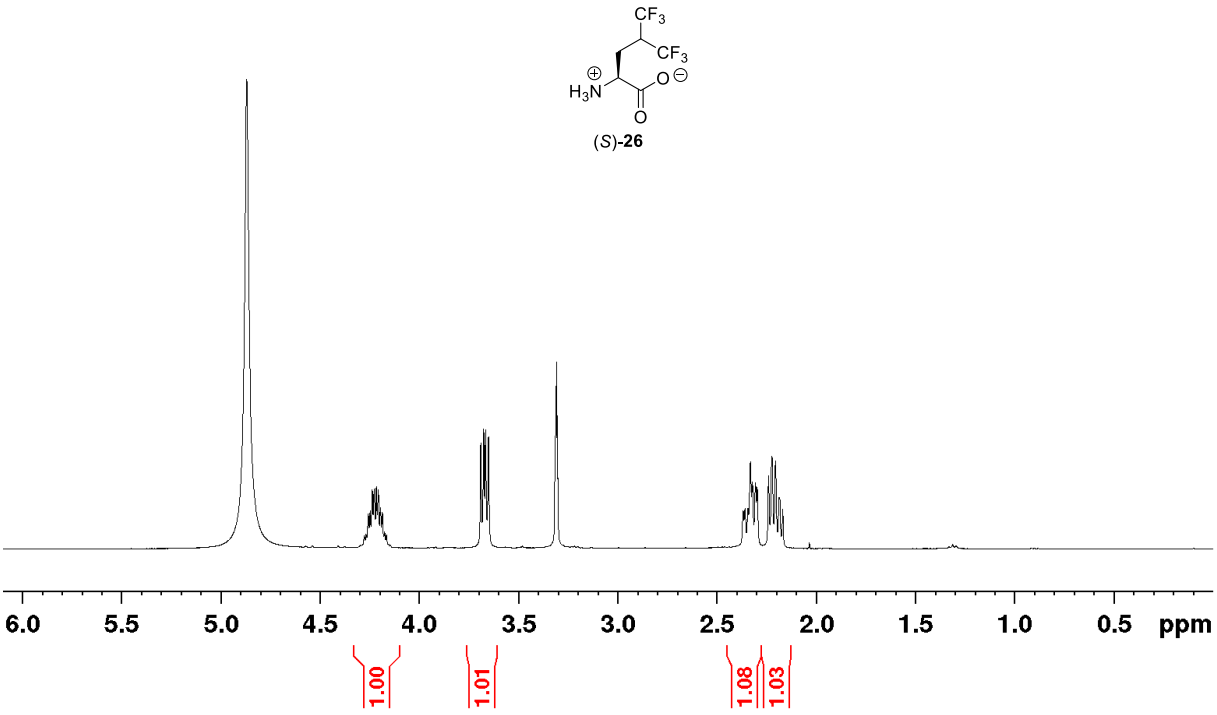


^{19}F NMR ($CDCl_3$, 282 MHz)

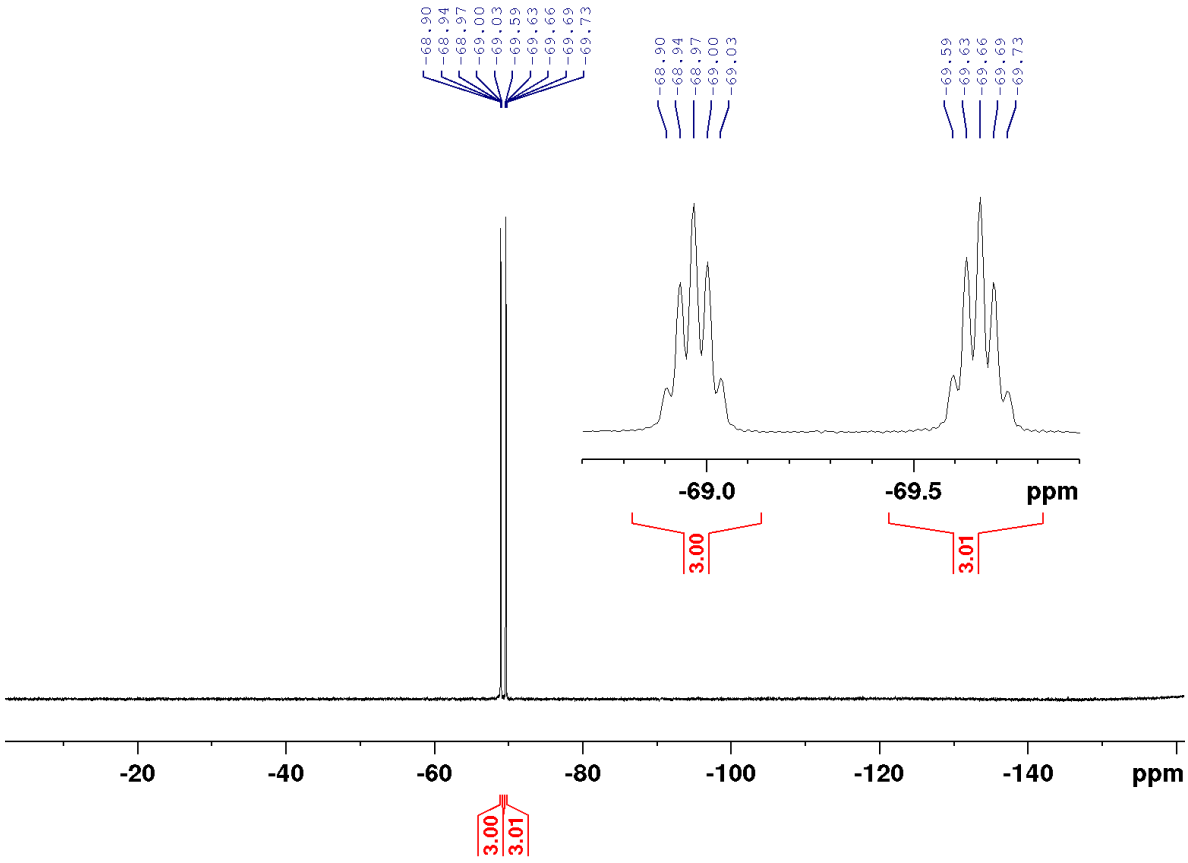


^{13}C NMR ($CDCl_3$, 75 MHz)

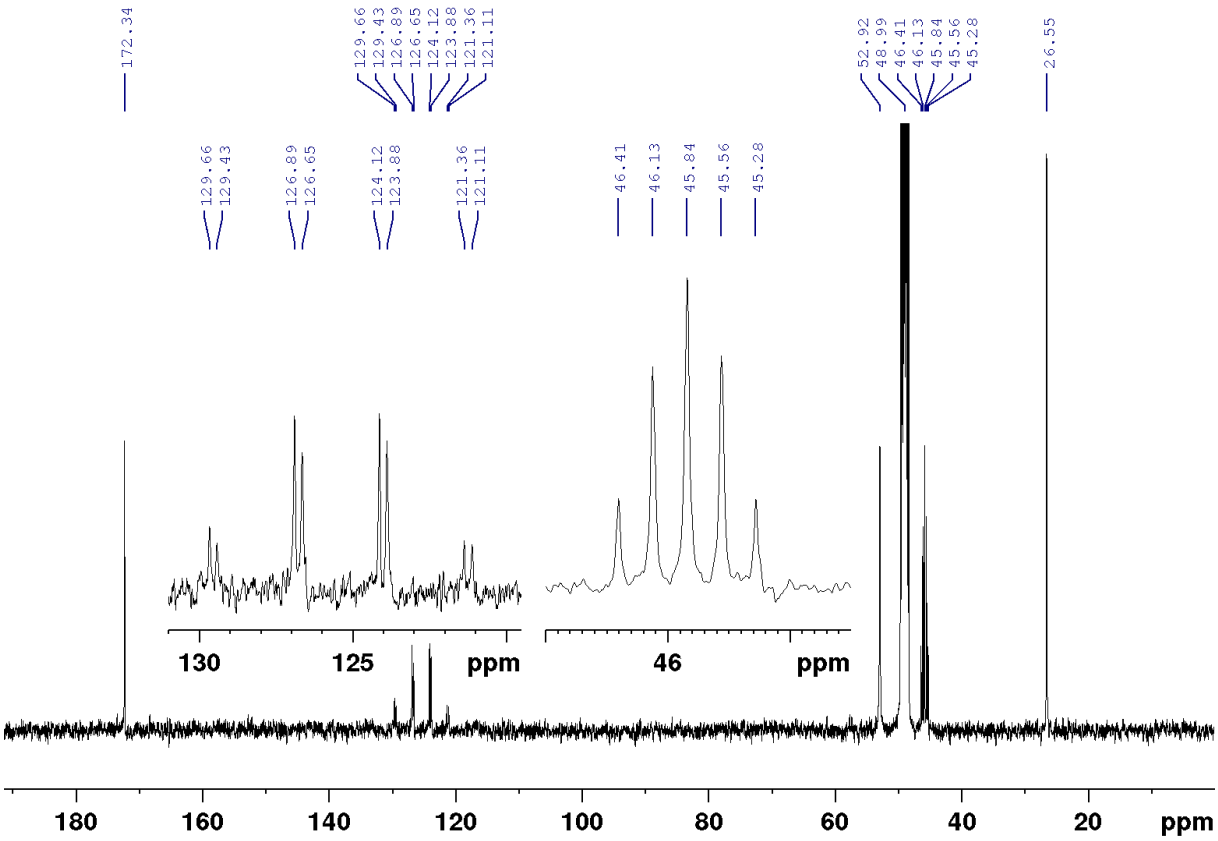
Compound (*S*)-**26**



^{1}H NMR (CD_3OD, 400 MHz)



^{19}F NMR (CD_3OD, 282 MHz)



^{13}C NMR (CD_3OD, 100 MHz)

V. X-ray diffraction analysis

The diffraction data for compounds **11e**, **24b**, (*S*,*S*)-**25b** and (*S*,*S*)-**25c** were collected at the IECB X-ray facility (CNRS UMS 3033 – INSERM US001, University of Bordeaux) with a Rigaku FRX rotating anode (2.9 kW) diffractometer using CuKα wavelength with a partial chi goniometer. The X-ray source is equipped with high flux Osmic Varimax mirrors and a Dectris Pilatus 200K detector. Data were processed with the Rigaku Oxford Diffraction CrysalisPro software (version1.171.40.69a).[6]

Structures were solved with Shelxt and refined by full-matrix least-squares method on F[7] with Shelxl-2014[7] within Olex2.[8] Further details of the data collection and structure refinement are given in the cif files.

CCDC numbers:

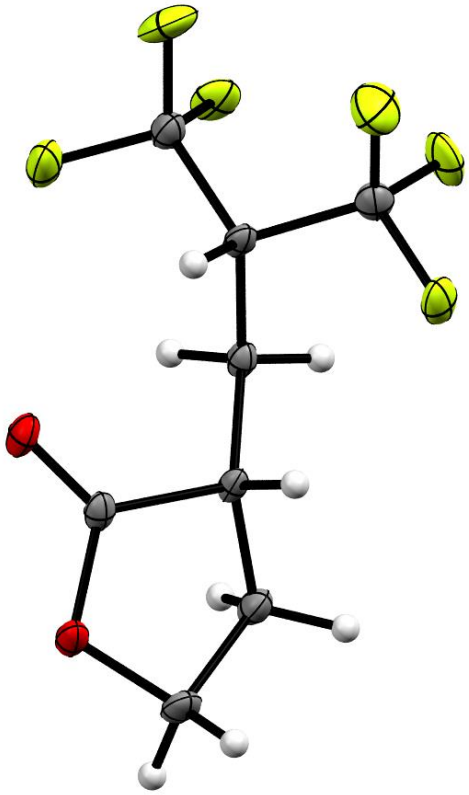
11e: 2144790

24b: 2144789

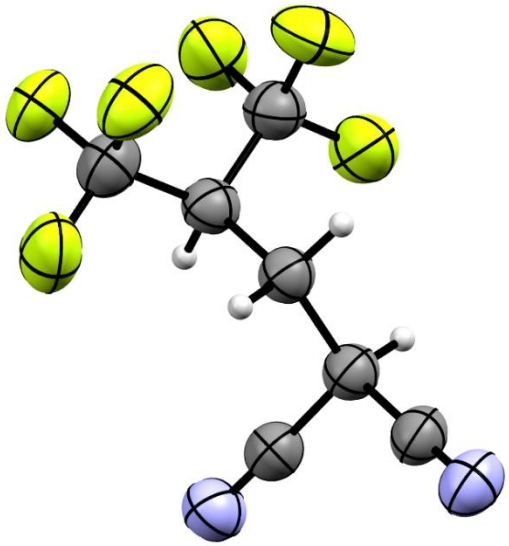
(*S*,*S*)-**25b**: 1998317

(*S*,*S*)-**25c**: 1998318

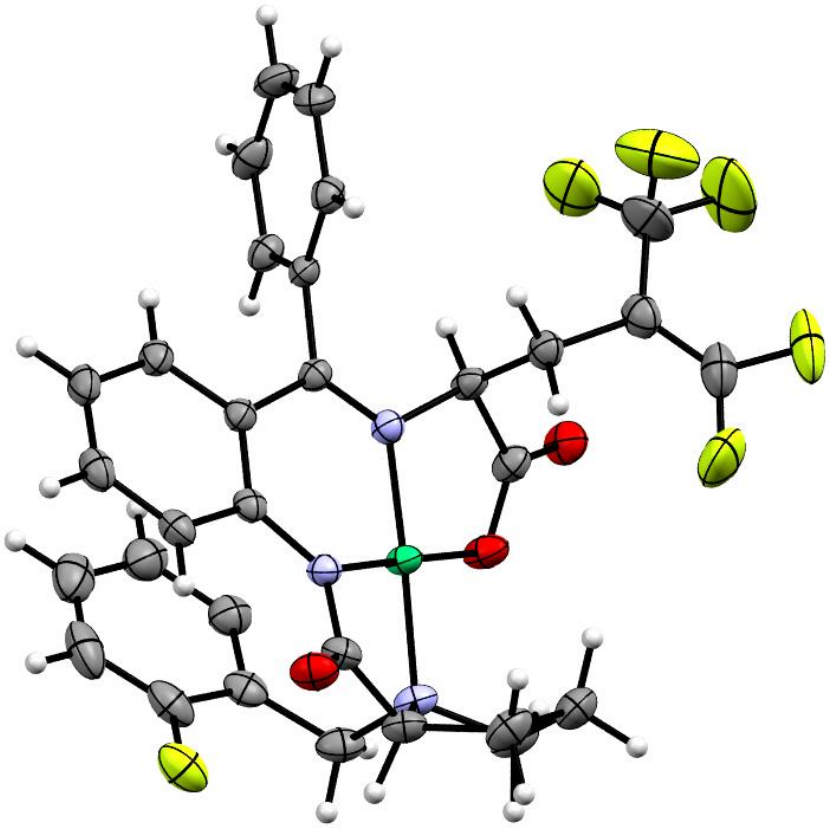
ORTEP plot of compound **11e** drawn at 50% probability level



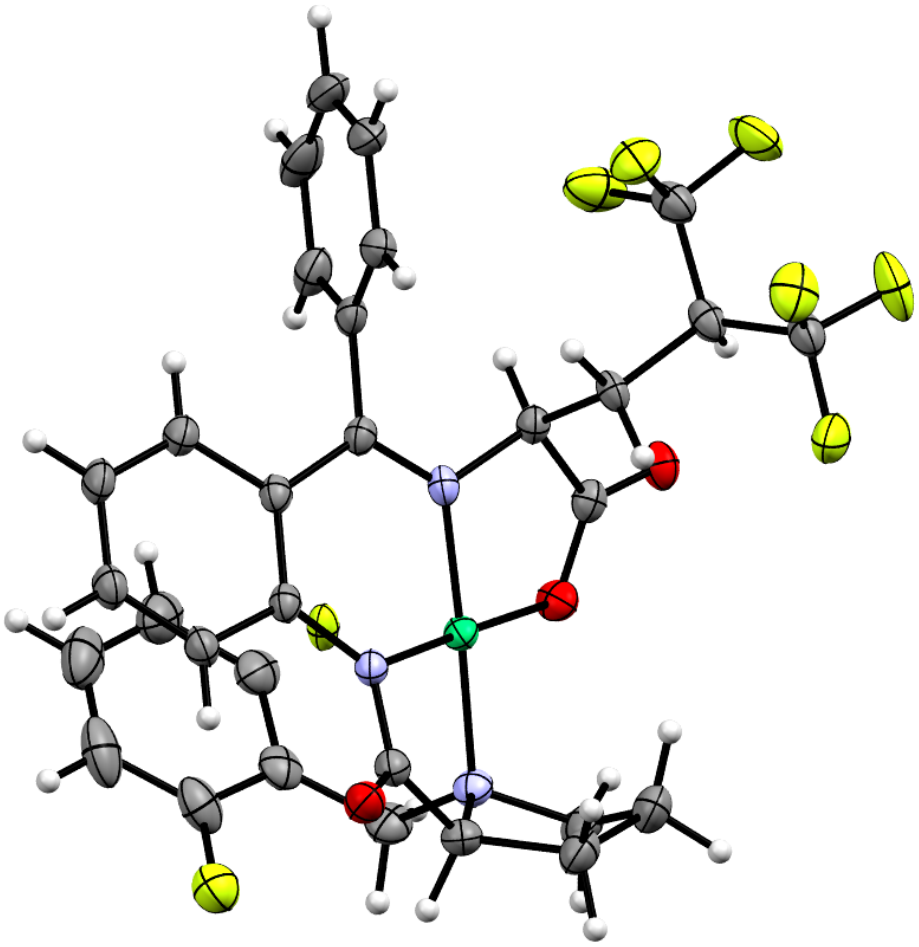
ORTEP plot of compound **24b** drawn at 50% probability level



ORTEP plot of compound (*S*,*S*)-**25c** drawn at 50% probability level



ORTEP plot of compound (*S*,*S*)-**25b** drawn at 50% probability level



VI. References

[1] B. Aillard, N. S. Robertson, A. R. Baldwin, S. Robins, A. G. Jamieson, *Org Biomol Chem* **2014**, *12*, 8775–8782.

[2] J. Spiegel, P. M. Cromm, A. Itzen, R. S. Goody, T. N. Grossmann, H. Waldmann, *Angew. Chem. Int. Ed.* **2014**, *53*, 2498–2503.

[3] T. T. Romoff, A. B. Palmer, N. Mansour, C. J. Creighton, T. Miwa, Y. Ejima, H. Moriwaki, V. A. Soloshonok, *Org. Process Res. Dev.* **2017**, *21*, 732–739.

[4] R. Bhushan, H. Brückner, *Amino Acids* **2004**, *27*, 231–247.

[5] N. Aoyagi, Y. Furusho, T. Endo, *Tetrahedron* **2019**, *75*, 130781.

[6] *CrysalisPro (Rigaku Oxford Diffraction)*, **2020**.

[7] G. M. Sheldrick, *Acta Cryst* **2015**, *71*, 3–8.

[8] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J Appl Cryst* **2009**, *42*, 339–341.