Ligand-enabled γ-C–H Olefination and Carbonylation: Construction of β-Quaternary Carbon Centers

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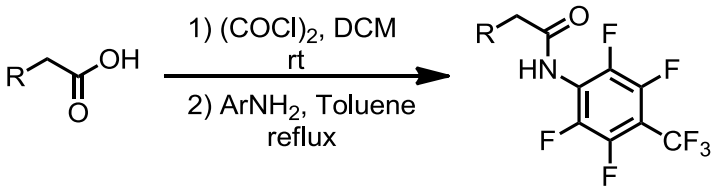
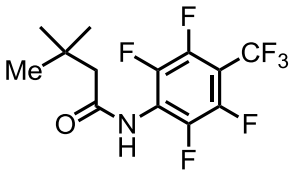
General Information: Octafluorotoluene was obtained from Oakwood Chemical. Other solvents and chemicals were from Sigma-Aldrich, Acros and Alfa Aesar and used directly without further purification. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light and Vogel's permanganate. Preparative TLC was performed on 1.0 mm silica gel (Analtech). Columns for flash chromatography (FC) contained silica gel (32–63μ, Dynamic Adsorbents, Inc.). ^{1}H NMR spectra were recorded on Bruker AV-400 instrument (400 MHz) or Varian Inova 400 (400 MHz), Bruker DRX-600 instrument (600 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, br = broad. Coupling constants, *J*, were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker DRX-600 instrument (150 MHz), and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.0 ppm of chloroform-*d*. In the ^{13}C NMR analysis, peaks that correspond to those of the polyfluoroarylamide auxiliary appeared as nearly invisible, complex sets of multiplets; they are omitted in the following spectroscopic analysis. High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

Experimental Section

2.1 Synthesis of Starting Materials





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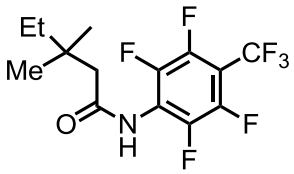

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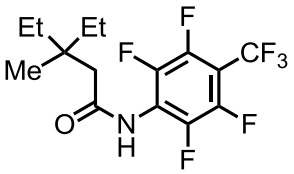

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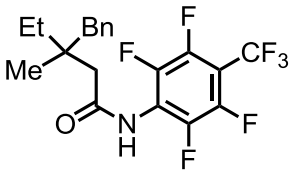

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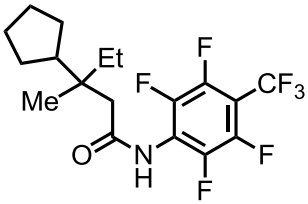

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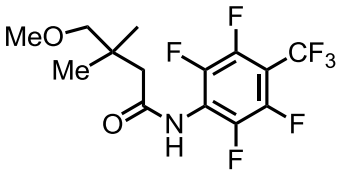

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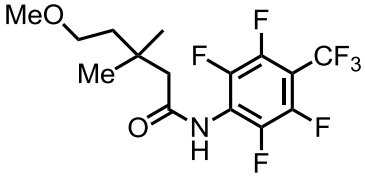
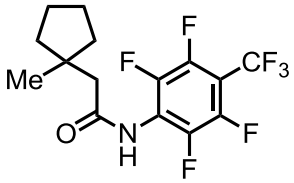


1g



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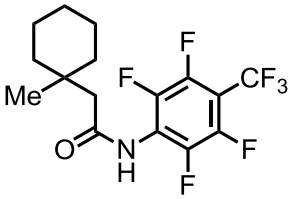

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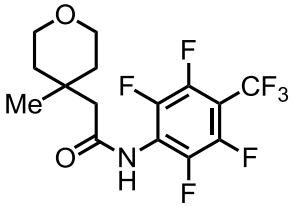
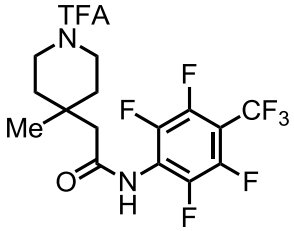


1k



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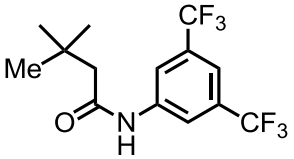

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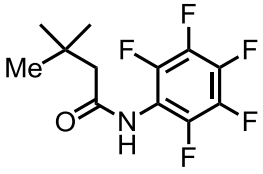

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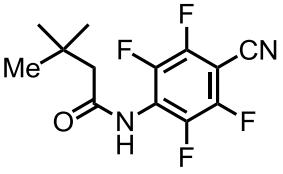
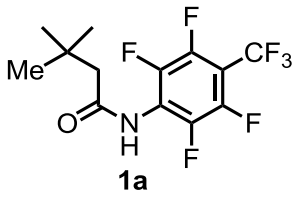


1o

General Procedure for the Preparation of Amide Substrates:

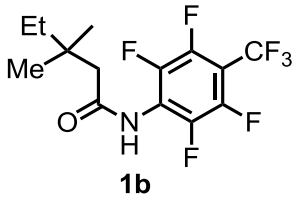
An acid chloride (10 mmol), prepared from the corresponding carboxylic acid and oxalyl chloride, was added to a solution of 2,3,5,6-tetrafluoro-4-(trifluoromethlyl)aniline (10 mmol) in toluene (10 mL). The reaction mixture was stirred for 12 h under reflux. After cooling to room temperature, the product mixture was concentrated in vacuum and was recrystallized from ethyl acetate/hexane to give the amide.



1a

3,3-dimethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide

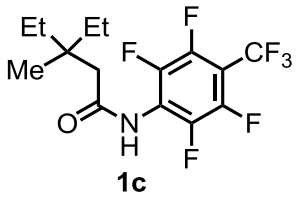
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (br s, 1 H), 2.35 (s, 2 H), 1.13 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 50.1, 31.3, 29.6; HRMS (ESI-TOF) Calcd for $C_{13}H_{13}F_7NO$ $[M-H]^-$: 330.0729; found: 330.0740.



1b

3,3-dimethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pentanamide

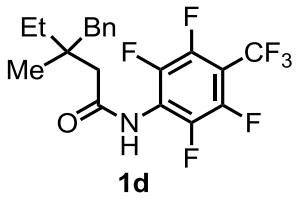
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (br s, 1 H), 2.33 (s, 2 H), 1.44 (q, J = 7.6 Hz, 2 H), 1.07 (s, 6 H), 0.91 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 47.8, 34.8, 33.9, 26.5, 8.4; HRMS (ESI-TOF) Calcd for $C_{14}H_{15}F_7NO$ $[M+H]^+$: 346.1042; found: 346.1037.



1c

3-ethyl-3-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pentanamide

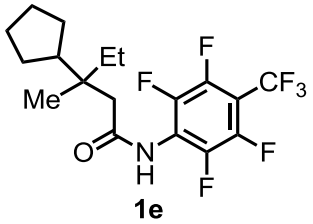
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (br s, 1 H), 2.33 (s, 2 H), 1.44 (q, *J* = 7.5 Hz, 4 H), 1.03 (s, 3 H), 0.88 (t, *J* = 7.4 Hz, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 45.4, 36.6, 31.1, 24.0, 8.1; HRMS (ESI-TOF) Calcd for $C_{15}H_{17}F_7NO$ $[M+H]^+$: 360.1198; found: 360.1189.



1d

3-benzyl-3-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pentanamide

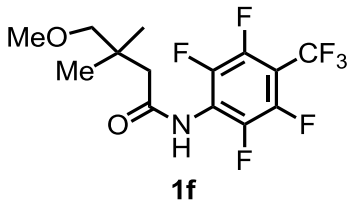
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.15 (m, 5 H), 7.01 (br s, 1 H), 2.79 (d, *J* = 13.2 Hz, 1 H), 2.70 (d, *J* = 13.2 Hz, 1 H), 2.32 (d, *J* = 14.4 Hz, 1 H), 2.25 (d, *J* = 14.4 Hz, 1 H), 1.58-1.41 (m, 2 H), 1.04 (s, 3 H), 0.98 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 138.1, 130.7, 128.0, 126.2, 44.9, 44.3, 37.6, 31.7, 24.2, 8.4; HRMS (ESI-TOF) Calcd for $C_{20}H_{19}F_7NO$ $[M+H]^+$: 422.1355; found: 422.1351.



1e

3-cyclopentyl-3-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pentanamide

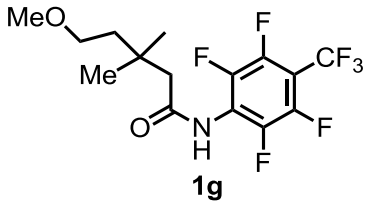
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (br s, 1 H), 2.38 (s, 2 H), 2.09-1.97 (m, 1 H), 1.70-1.49 (m, 9 H), 1.40-1.25 (m, 2 H), 1.03 (s, 3 H), 0.95 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 47.1, 44.0, 38.4, 30.4, 26.8, 26.5, 25.7, 21.2, 8.3; HRMS (ESI-TOF) Calcd for $C_{18}H_{21}F_7NO$ $[M+H]^+$: 400.1511; found: 400.1500.



1f

4-methoxy-3,3-dimethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide

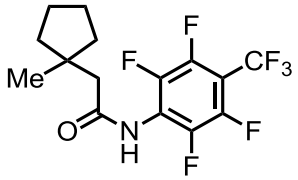
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (br s, 1 H), 3.46 (s, 3 H), 3.28 (s, 2 H), 2.49 (s, 2 H), 1.07 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 81.2, 59.3, 46.4, 34.8, 25.7; HRMS (ESI-TOF) Calcd for $C_{14}H_{15}F_7NO_2$ $[M+H]^+$: 362.0991; found: 362.0991.



1g

5-methoxy-3,3-dimethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pentanamide

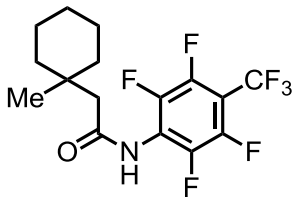
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (br s, 1 H), 3.65 (t, *J* = 5.0 Hz, 2 H), 3.45 (s, 3 H), 2.48 (s, 2 H), 1.76 (t, *J* = 5.2 Hz, 2 H), 1.09 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 70.2, 58.9, 47.7, 39.4, 33.0, 29.1; HRMS (ESI-TOF) Calcd for $C_{15}H_{17}F_7NO$ $[M+H]^+$: 376.1148; found: 376.1145.



1i

2-(1-methylcyclopentyl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide

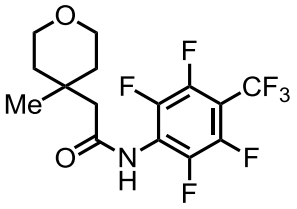
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (br s, 1 H), 2.46 (s, 2 H), 1.76-1.48 (m, 8 H), 1.15 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 48.1, 41.9, 39.5, 25.7, 23.9; HRMS (ESI-TOF) Calcd for $C_{15}H_{15}F_7NO$ $[M+H]^+$: 358.1042; found: 358.1039.



1j

2-(1-methylcyclohexyl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide

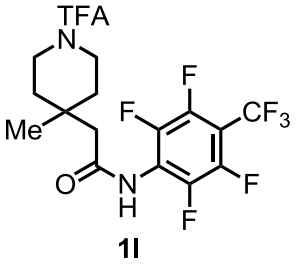
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (br s, 1 H), 2.37 (s, 2 H), 1.56-1.34 (m, 10 H), 1.11 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.1, 48.6, 37.9, 33.9, 26.0, 25.1, 22.0; HRMS (ESI-TOF) Calcd for $C_{16}H_{17}F_7NO$ $[M+H]^+$: 372.1198; found: 372.1185.



1k

2-(1-methylcyclohexyl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide

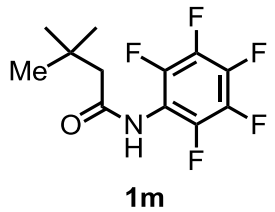
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (br s, 1 H), 3.81-3.64 (m, 4 H), 2.44 (s, 2 H), 1.76-1.66 (m, 2 H), 1.58-1.49 (m, 2 H), 1.24 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4, 63.7, 48.6, 37.6, 31.6, 23.7; HRMS (ESI-TOF) Calcd for $C_{15}H_{15}F_7NO$ $[M+H]^+$: 374.0991; found: 374.0991.



1l

2-(4-methyl-1-(2,2,2-trifluoroacetyl)piperidin-4-yl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)acetamide

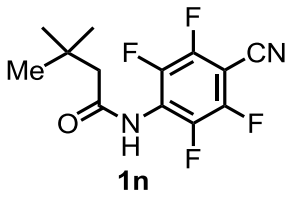
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (br s, 1 H), 4.02-3.92 (m, 1 H), 3.80-3.68 (m, 1 H), 3.56-3.37 (m, 2 H), 2.48 (d, *J* = 13.6 Hz, 1 H), 2.43 (d, *J* = 13.6 Hz, 1 H), 1.78-1.60 (m, 4 H), 1.27 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1, 155.5 (q, *J* = 35.6 Hz), 116.5 (q, *J* = 286.1 Hz), 47.6, 42.1 (q, *J* = 3.3 Hz), 39.8, 37.1, 36.5, 32.5, 23.2; HRMS (ESI-TOF) Calcd for $C_{17}H_{15}F_{10}N_2O_2$ $[M+H]^+$: 469.0974; found: 469.0968.



1m

3,3-dimethyl-*N*-(perfluorophenyl)butanamide

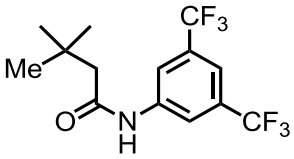
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (br s, 1 H), 2.31 (s, 2 H), 1.12 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 50.1, 31.2, 29.7; HRMS (ESI-TOF) Calcd for $C_{12}H_{13}F_5NO$ $[M+H]^+$: 282.0917; found: 282.0910.



1n

***N*-(4-cyano-2,3,5,6-tetrafluorophenyl)-3,3-dimethylbutanamide**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (br s, 1 H), 2.35 (s, 2 H), 1.12 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 147.4 (ddt, J_1 = 259.8 Hz, J_2 = 15.0 Hz, J_3 = 4.4 Hz), 141.7 (ddt, J_1 = 251.6 Hz, J_2 = 12.6 Hz, J_3 = 4.3 Hz), 122.7 (t, J = 14.2 Hz), 107.3 (t, J = 3.4 Hz), 91.1 (t, J = 2.2 Hz), 50.0, 31.3, 29.6; HRMS (ESI-TOF) Calcd for $C_{13}H_{13}F_4N_2O$ $[M+H]^+$: 289.0964; found: 289.0969.



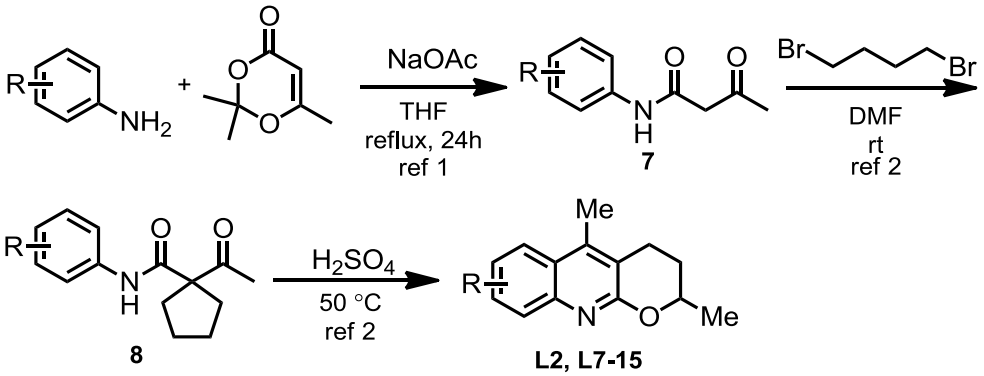
1o

***N*-(3,5-bis(trifluoromethyl)phenyl)-3,3-dimethylbutanamide**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1 H), 7.59 (s, 1 H), 7.44 (s, 1 H), 2.27 (s, 2 H), 1.12 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 139.2, 132.3 (q, J = 33.3 Hz), 123.0 (q, J = 271.1 Hz), 119.4, 117.5 (quint, J = 3.8 Hz), 51.5, 31.4, 29.7; HRMS (ESI-TOF) Calcd for $C_{14}H_{16}F_6NO$ $[M+H]^+$: 328.1136; found: 328.1132.

2.2 Synthesis of Quinoline Ligands

The ligand **L2**, **L7 ~ 15** were prepared according to the literature with small modifications.



1. Synthesis of **7**[1]

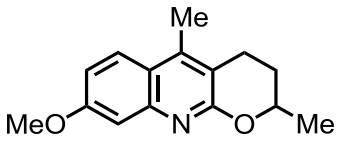
A mixture of aniline (30 mmol), dioxinone (42 mmol), and NaOAc (30 mmol) in THF (6 mL) were heated under reflux for 24 h. After cooled to room temperature, the mixture was diluted with AcOEt, washed with H_2O and brine. The organic phase was dried with anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography (silica gel, hexane/EtOAc 5/1 to 2/1).

2. Synthesis of **8**[2]

To a 250 mL of round bottle flask were added **7** (20 mmol) and K_2CO_3 (46 mmol) and DMF (50 mL). After stirring for 1 h, 1,4-dibromobutane (22 mmol) was added. The reaction was stirred for additional 12 h (monitored by TLC) before it was poured into water (150 mL). The mixture was extracted with EtOAc (40 mL × 3). The combined organic layers was washed with HCl (3 M, 40 mL × 2) and brine, dried with Na_2SO_4, filtrated and concentrated under vacuum affording the crude product which could be used without further purification.

3. Synthesis of **L2, L7-15**[2]

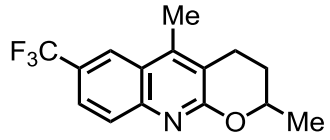
To a 100 mL of round bottle were added **8** (~ 20 mmol) and 15 mL of H_2SO_4. The mixture was stirred at 50 ºC until full conversion of **8** (about 1.5 hours). The reaction mixture was carefully poured into ammonia/ice (ammonia: 28%, 50 mL; ice: ~ 100 mL). The mixture was extracted with EtOAc (60 mL × 3). The combined organic layers was washed with brine, dried with $MgSO_4$, filtrated and concentrated affording the crude product which was purified by flash column chromatography (silica gel, hexane/EtOAc 4/1 to 1/1).



L9

8-methoxy-2,5-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (L9)

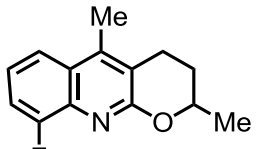
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, J = 9.6 Hz, 1 H), 7.18 (d, J = 2.4 Hz, 1 H), 7.00 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1 H), 4.38-4.31 (m, 1 H), 3.89 (s, 3 H), 2.93 (ddd, J_1 = 16.4 Hz, J_2 = 3.9 Hz, J_3 = 2.6 Hz, 1 H), 2.85-2.76 (m, 1 H), 2.48 (s, 3 H), 2.15-2.08 (m, 1 H), 1.82-1.73 (m, 1 H), 1.50 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.4, 160.2, 147.4, 144.1, 124.4, 120.0, 116.0, 113.4, 106.5, 73.0, 55.3, 29.0, 23.2, 21.3, 13.9; HRMS (ESI-TOF) Calcd for $C_{15}H_{18}NO_2$ $[M+H]^+$: 244.1338; found: 244.1340.



L10

2,5-dimethyl-7-(trifluoromethyl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolone (L10)

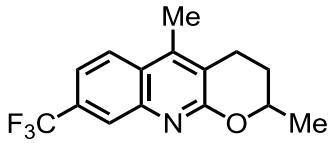
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1 H), 7.91 (d, *J* = 8.8 Hz, 1 H), 7.74 (d, *J* = 8.8 Hz, 1 H), 4.48-4.37 (m, 1 H), 3.08-2.82 (m, 2 H), 2.60 (s, 3 H), 2.23-2.13 (m, 1 H), 1.90-1.76 (m, 1 H), 1.54 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.4, 147.2, 145.0, 128.9, 125.5 (q, *J* = 32.1 Hz), 124.6 (q, *J* = 3.0 Hz), 124.5 (q, *J* = 270.3 Hz), 124.1, 121.3 (q, *J* = 4.4 Hz), 117.7, 73.6, 28.7, 23.5, 21.3, 14.0; HRMS (ESI-TOF) Calcd for $C_{15}H_{15}F_3NO$ $[M+H]^+$: 282.1106; found: 282.1113.



L11

9-fluoro-2,5-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolone (L11)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.62 (m, 1 H), 7.30-7.25 (m, 2 H), 4.45-4.35 (m, 1 H), 3.01 (ddd, J_1 = 16.9 Hz, J_2 = 5.3 Hz, J_3 = 2.9 Hz, 1 H), 2.94-2.83 (m, 1 H), 2.56 (s, 3 H), 2.20-2.12 (m, 1 H), 1.88-1.76 (m, 1 H), 1.52 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.1, 157.0 (d, *J* = 252.6 Hz), 144.3 (d, *J* = 2.7 Hz), 135.9 (d, *J* = 11.4 Hz), 126.9 (d, *J* = 2.6 Hz), 123.0 (d, *J* = 7.7 Hz), 118.8 (d, *J* = 4.5 Hz), 117.3, 112.9 (d, *J* = 18.5 Hz), 73.3, 28.7, 23.6, 21.3, 14.2; HRMS (ESI-TOF) Calcd for $C_{14}H_{15}FNO$ $[M+H]^+$: 232.1138; found: 232.1140.

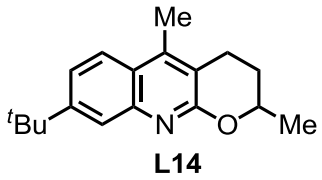


L12

2,5-dimethyl-8-(trifluoromethyl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolone (L12)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 7.97 (d, *J* = 8.8 Hz, 1 H), 7.53 (d, *J* = 8.8 Hz, 1 H), 4.48-4.34 (m, 1 H), 3.10-2.80 (m, 2 H), 2.56 (s, 3 H), 2.24-2.10 (m, 1 H), 1.90-1.76 (m, 1 H), 1.53 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.8, 144.9, 144.1, 130.5 (q, *J* = 32.3 Hz), 126.7, 125.5 (q, *J* = 4.2

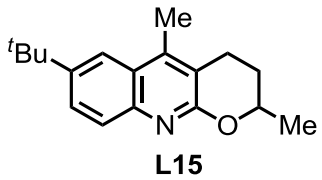
Hz), 124.4, 124.1 (q, J = 270.6 Hz), 119.3 (q, J = 2.9 Hz), 118.5, 73.5, 28.6, 23.6, 21.3, 14.0; Calcd for $C_{15}H_{15}F_3NO$ $[M+H]^+$: 282.1106; found: 282.1105.



L14

8-(*tert*-butyl)-2,5-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolone (L14)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.77 (m, 2 H), 7.45 (dd, J_1 = 9.0 Hz, J_2 = 1.8 Hz, 1 H), 4.42-4.28 (m, 1 H), 2.96 (ddd, J_1 = 16.8 Hz, J_2 = 5.6 Hz, J_3 = 2.8 Hz, 1 H), 2.90-2.78 (m, 1 H), 2.51 (s, 3 H), 2.16-2.07 (m, 1 H), 1.86-1.72 (m, 1 H), 1.50 (d, J = 6.0 Hz, 3 H), 1.39 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.0, 151.9, 145.7, 143.7, 123.5, 123.0, 122.7, 122.3, 115.3, 73.0, 34.8, 31.1, 29.0, 23.3, 21.3, 13.7; HRMS (ESI-TOF) Calcd for $C_{18}H_{24}NO$ $[M+H]^+$: 270.1858; found: 270.1861.



L15

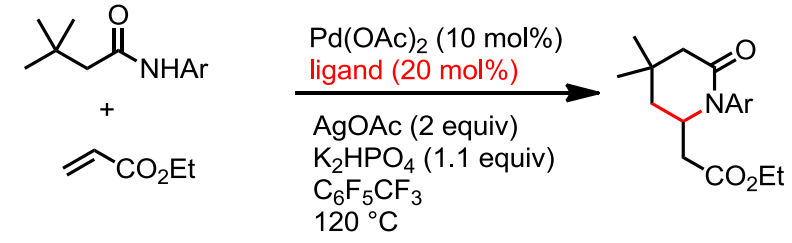
7-(*tert*-butyl)-2,5-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (L15)

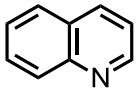
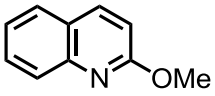
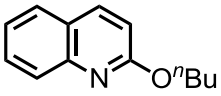
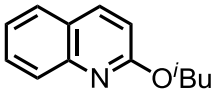
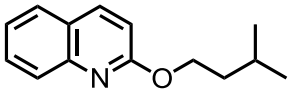
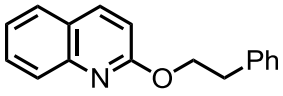
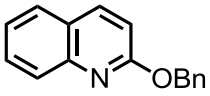
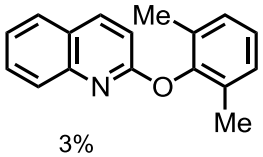
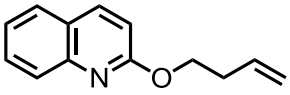
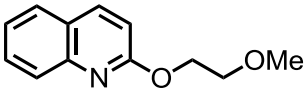
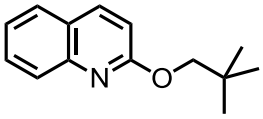
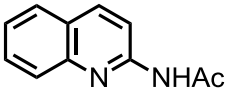
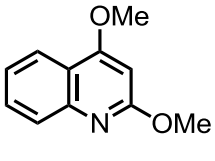
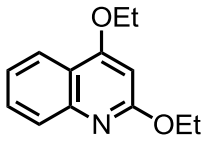
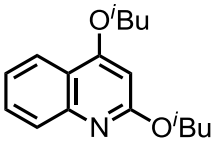
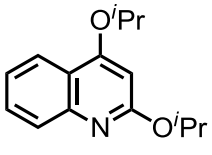
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 2.4 Hz, 1 H), 7.77 (d, J = 8.8 Hz, 1 H), 7.66 (dd, J_1 = 9.0 Hz, J_2 = 1.8 Hz, 1 H), 4.41-4.31 (m, 1 H), 2.99 (ddd, J_1 = 16.8 Hz, J_2 = 5.6 Hz, J_3 = 2.8 Hz, 1 H), 2.92-2.80 (m, 1 H), 2.56 (s, 3 H), 2.18-2.09 (m, 1 H), 1.87-1.74 (m, 1 H), 1.51 (d, J = 6.4 Hz, 3 H), 1.41 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.6, 146.3, 143.97, 143.95, 127.5, 124.5, 118.1, 115.9, 73.0, 34.9, 31.4, 29.0, 23.6, 21.4, 13.8; HRMS (ESI-TOF) Calcd for $C_{18}H_{24}NO$ $[M+H]^+$: 270.1858; found: 270.1856.

2.3 Optimization of Reaction Conditions

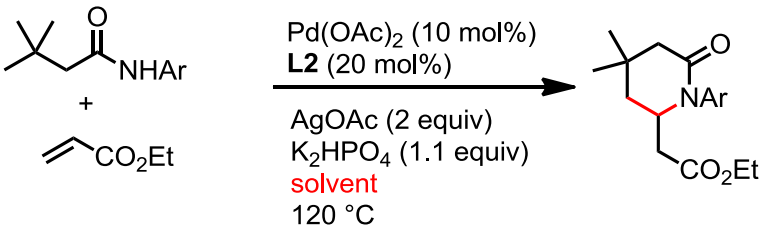
General: The reactions were conducted using 0.1 mmol of substrate **1a** in the indicated conditions in 1 mL of solvent. The temperature is the oil bath temperature. All yields were determined by ^{1}H NMR using CH_2Br_2 as internal standard.

Ligand Screening



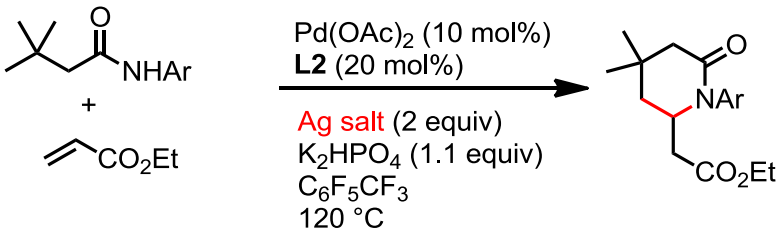
 Trace	 Trace	 Trace	 Trace
 Trace	 Trace	 Trace	
 3%	 2%	 3%	
 3%	 2%	 5%	
 trace	 trace	 7%	

Solvent Screening:



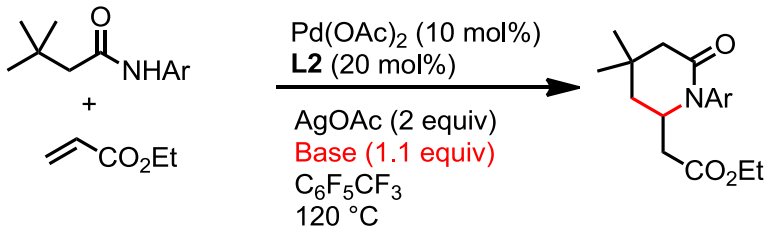
Entry	Solvent	NMR Yield (%)
1	$C_6F_5CF_3$	45
2	$PhCF_3$	16
3	C_6F_6	30
4	Hex	33
5	Toluene	37
6	DCE	28
7	*t*-AmylOH	32
8	*t*-BuOH	35
9	DMF	Trace
10	DMSO	0
11	EA	19
12	Hexafluoro-2-propanol	Trace
13	THF	16
14	Dioxane	27

Ag Salt Screening:



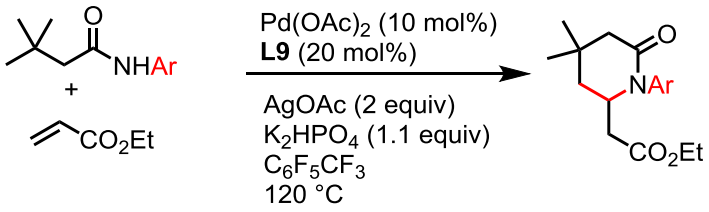
Entry	Ag	NMR yield (%)
1	AgOAc	45
2	Ag_3PO_4	11
3	Ag_2O	25
4	AgO	12
5	AgTFA	trace
6	AgOPiv	27

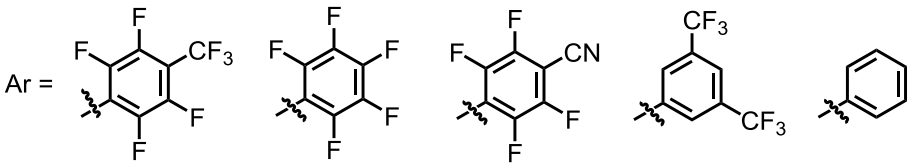
Base Effect:



Entry	Base	NMR Yield (%)
1	$Na_2HPO_4{\cdot}6H_2O$	29
2	NaOAc	29
3	$NaHCO_3$	28
4	NaOTs	40
5	Na_2CO_3	33
6	K_2HPO_4	45

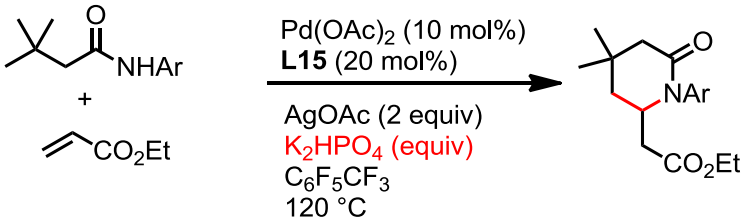
Auxiliary Groups:





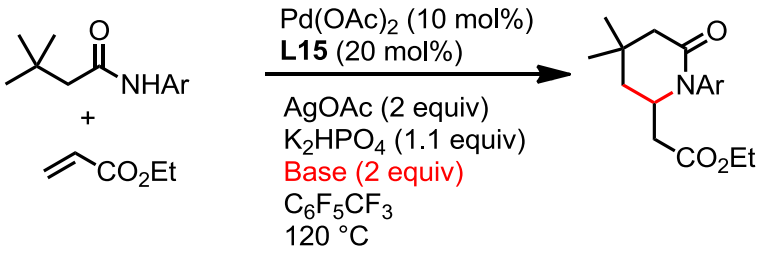
56% 16% 35% trace trace

Amount of K_2HPO_4:



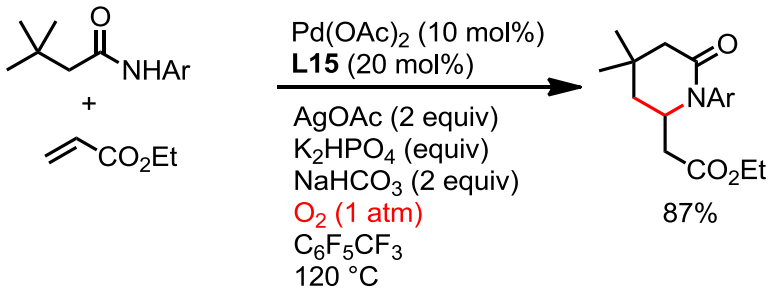
Entry	K_2HPO_4 (Equiv)	NMR Yield (%)
1	1.1	71
2	2	71
3	3	67

Additional Base:



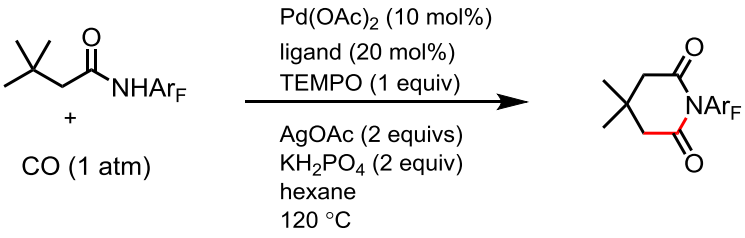
Entry	Base	NMR Yield (%)
1	-	71
2	Li_2CO_3 (1 equiv)	64
3	Na_2CO_3 (1 equiv)	77
4	K_2CO_3 (1 equiv)	58
5	$NaHCO_3$ (2 equiv)	82
6	$NaHCO_3$ (2 equiv) (without K_2HPO_4)	63
7	$KHCO_3$	64
8	NaOTs	68
9	LiOAc	72
10	CsF	32
11	K_3PO_4 (1 equiv)	71
12	LiCl	39
13	NaOAc	51
14	$Na_2HPO_4 \cdot 7H_2O$	67
15	NaTFA	52
16	NaCl	69
17	$NaNO_2$	45

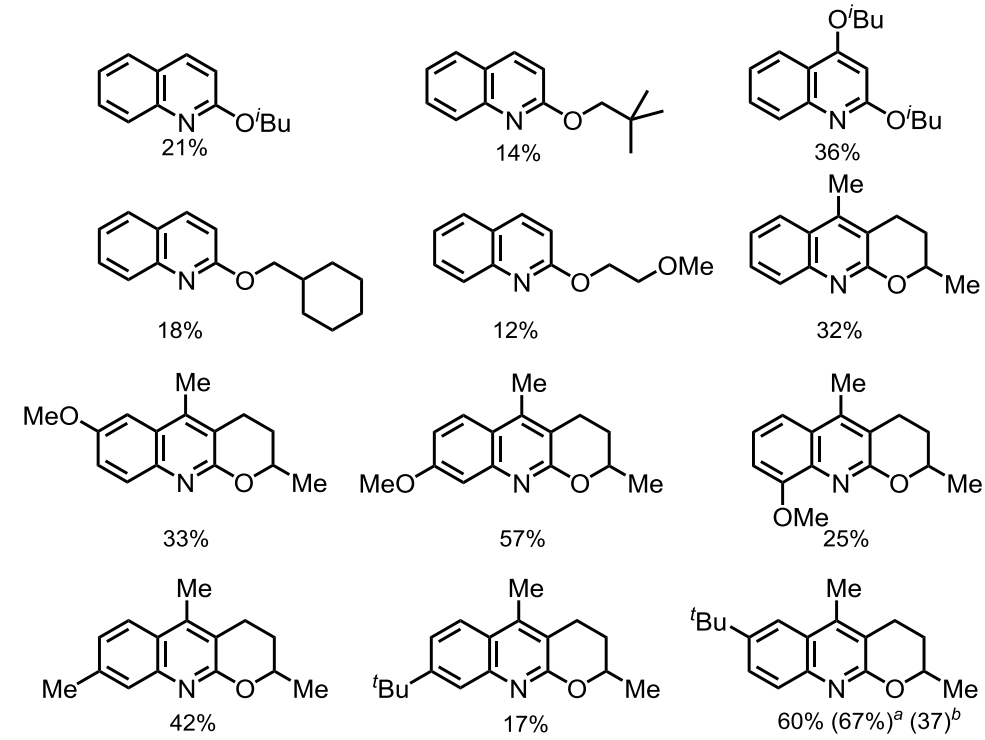
TEMPO and O_2:



with 20 mol% of TEMPO: 90% (NMR)
with 10 mol% of TEMPO: 95% (NMR)

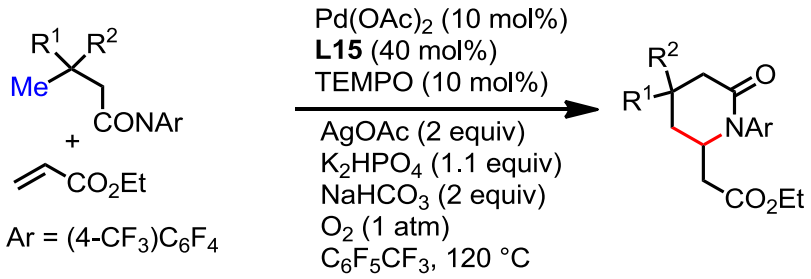
Ligand Screening in γ-carbonylation reaction:



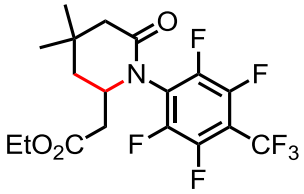


[a] *t*-butyl peroxide (2 equiv) was used instead of TEMPO in 150 °C. [b] Neither TEMPO nor *t*-butyl peroxide was used.

2.4 General Procedure for the Olefination of Amides

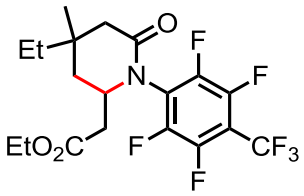


To an oven dried 50 mL Schlenk-type tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar were added substrate **1a** (33.1 mg, 0.1 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), **L15** (10.7 mg, 0.04 mmol), TEMPO (1.6 mg, 0.01 mmol), AgOAc (33.4 mg, 0.2 mmol), K_2HPO_4 (19.2 mg, 0.11 mmol), $NaHCO_3$ (16.8 mg, 0.2 mmol), and 1 mL of $C_6F_5CF_3$ followed by 0.05 mL of ethyl acrylate. The mixture was frozen with a dry ice/acetone bath. The reaction tube was evacuated and back-filled with O_2 (3 times, balloon) and heated to 120 ^oC for 20 hours under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with ethyl acetate and then filtered through a small pad of Celite. The solvents were removed under reduced pressure and the resulting mixture was purified by preparative TLC using hexanes/EtOAc as the eluent.



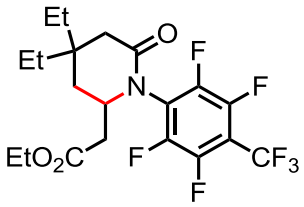
Ethyl 2-(4,4-dimethyl-6-oxo-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidin-2-yl)acetate (2a)

Substrate **1a** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 5/1), **2a** was obtained as a white solid (37.3 mg, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.35 (sext, J = 5.8 Hz, 1 H), 4.05-3.91 (m, 2 H), 2.50-2.34 (m, 4 H), 1.99 (ddd, J_1 = 13.6 Hz, J_2 = 4.6 Hz, J_3 = 2.0 Hz, 1 H), 1.71 (dd, J_1 = 13.6 Hz, J_2 = 11.2 Hz, 1 H), 1.19 (t, J = 7.2 Hz, 3 H), 1.13 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 169.8, 61.1, 53.6 (d, J = 2.9 Hz), 45.7, 42.0, 40.3, 30.4, 29.8, 24.5, 13.9; HRMS (ESI-TOF) Calcd for $C_{18}H_{19}F_7NO_3$ $[M+H]^+$: 430.1253; found: 430.1254.



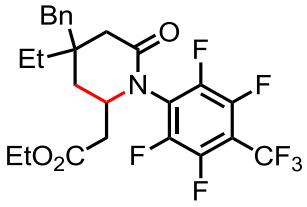
Ethyl 2-(4-ethyl-4-methyl-6-oxo-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidin-2-yl)acetate (2b)

Substrate **1b** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 5/1), **2b** was obtained as colorless oil (30.1 mg, 68%). The isomeric ratio (major/minor) was determined to be 56:44 by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45-4.23 (m, 1 H), 4.06-3.91 (m, 2 H), 2.54-2.30 (m, 4 H), 2.12 (ddd, J_1 = 13.8 Hz, J_2 = 5.0 Hz, J_3 = 3.0 Hz, 0.44 H), 1.97 (ddd, J_1 = 13.6 Hz, J_2 = 5.2 Hz, J_3 = 2.5 Hz, 0.56 H), 1.68-1.36 (m, 3 H), 1.23-1.16 (m, 3 H), 1.14 (s, 1.68 H), 1.05 (s, 1.33 H), 1.00-0.87 (m, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 170.2, 169.80, 169.75, 61.1, 53.4 (d, J = 2.9 Hz), 53.2 (d, J = 2.9 Hz), 44.8, 43.8, 40.4, 40.3, 40.0, 39.6, 35.7, 32.44, 32.37, 29.4, 26.3, 21.4, 13.93, 13.91, 8.1, 7.6; HRMS (ESI-TOF) Calcd for $C_{19}H_{21}F_7NO_3$ $[M+H]^+$: 444.1410; found: 444.1420.



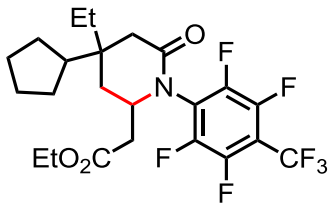
Ethyl 2-(4,4-diethyl-6-oxo-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidin-2-yl)acetate (2c)

Substrate **1c** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 5/1), **2c** was obtained as colorless oil (32.1 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (sext, J = 5.8 Hz, 1 H), 4.08-3.94 (m, 2 H), 2.53-2.27 (m, 4 H), 2.08 (ddd, J_1 = 13.7 Hz, J_2 = 4.8 Hz, J_3 = 3.2 Hz, 1 H), 1.62-1.50 (m, 3 H), 1.48-1.31 (m, 2 H), 1.20 (t, J = 7.2 Hz, 3 H), 0.96-0.84 (m, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 169.7, 61.0, 53.0 (d, J = 2.9 Hz), 42.6, 40.3, 37.8, 34.8, 30.7, 25.6, 13.9, 7.5, 7.1; HRMS (ESI-TOF) Calcd for $C_{20}H_{23}F_7NO_3$ $[M+H]^+$: 458.1566; found: 458.1567.



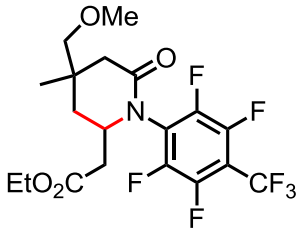
Ethyl 2-(4-benzyl-4-ethyl-6-oxo-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidin-2-yl)acetate (2d)

Substrate **1d** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 5/1), **2d** was obtained as yellow oil (25.2 mg, 49%). The isomeric ratio (major/minor) was determined to be 54:46 by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.23 (m, 3 H), 7.20-7.09 (m, 2 H), 4.62-4.51 (m, 0.46 H), 4.32-4.22 (m, 0.54 H), 4.06-3.94 (m, 2 H), 2.88 (d, *J* = 13.6 Hz, 0.47 H), 2.80 (d, *J* = 13.6 Hz, 0.47 H), 2.70 (d, *J* = 13.6 Hz, 0.53 H), 2.65 (d, *J* = 13.6 Hz, 0.53 H), 2.56-2.30 (m, 4 H), 2.14 (ddd, J_1 = 13.8 Hz, J_2 = 5.0 Hz, J_3 = 3.2 Hz, 0.54 H), 2.05 (ddd, J_1 = 13.8 Hz, J_2 = 5.5 Hz, J_3 = 2.9 Hz, 0.46 H), 1.75-1.50 (m, 1.82 H), 1.40-1.31 (m, 1.18 H), 1.23-1.15 (m, 3 H), 1.10 (t, *J* = 7.4 Hz, 1.59 H), 0.98 (t, *J* = 7.4 Hz, 1.41 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.34, 170.27, 169.71, 169.68, 136.7, 136.2, 130.5, 130.4, 128.3, 126.8, 126.6, 61.12, 61.07, 53.37 (d, *J* = 2.9 Hz), 52.85 (d, *J* = 2.9 Hz), 44.1, 42.4, 41.5, 40.6, 40.2, 39.8, 37.5, 37.0, 36.5, 35.9, 30.9, 27.0, 13.9, 7.9, 7.5; HRMS (ESI-TOF) Calcd for $C_{25}H_{25}F_7NO_3$ $[M+H]^+$: 520.1723; found: 520.1724.



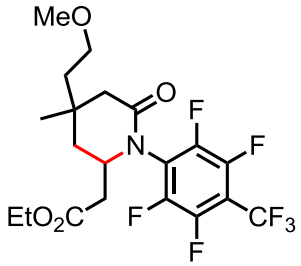
Ethyl 2-(4-cyclopentyl-4-ethyl-6-oxo-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidin-2-yl)acetate (2e)

Substrate **1e** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 5/1), **2e** was obtained as colorless oil (25.6 mg, 51%). The isomeric ratio (major/minor) was determined to be 55:45 by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40-4.31 (m, 0.45 H), 4.30-4.22 (m, 0.55 H), 4.06-3.96 (m, 2 H), 2.55-2.30 (m, 4 H), 2.23-1.95 (m, 2 H), 1.78-1.50 (m, 8 H), 1.47-1.23 (m, 3 H), 1.20 (t, *J* = 7.2 Hz, 3 H), 1.00-0.88 (m, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 171.1, 169.78, 169.75, 61.09, 61.06, 53.5 (d, *J* = 2.3 Hz), 52.8 (d, *J* = 2.6 Hz), 45.0, 44.7, 40.6, 40.3, 40.1, 39.1, 36.6, 36.5, 35.5, 27.7, 27.5, 26.4, 26.3, 26.2, 25.9, 25.6, 25.54, 25.49, 25.4, 13.9, 8.0, 7.5; HRMS (ESI-TOF) Calcd for $C_{23}H_{27}F_7NO_3$ $[M+H]^+$: 498.1879; found: 498.1888.



Ethyl 2-(4-(methoxymethyl)-4-methyl-6-oxo-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl) piperidin-2-yl)acetate (2f)

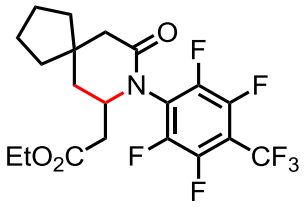
Substrate **1f** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 3/1), **2f** was obtained as yellow oil (28.3 mg, 62%). The isomeric ratio (major/minor) was determined to be 61:39 by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45-4.30 (m, 1 H), 4.05-3.90 (m, 2 H), 3.45-3.90 (m, 5 H), 2.72-2.16 (m, 4 H), 2.00-1.85 (m, 1.39 H), 1.72-1.64 (m, 0.61 H), 1.25-1.06 (m, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 170.1, 169.85, 169.77, 80.8, 78.5, 61.1, 61.0, 59.4, 59.3, 53.5 (d, J = 2.9 Hz), 53.2 (d, J = 2.7 Hz), 41.8, 40.6, 40.9, 40.32, 40.30, 38.6, 37.0, 34.1, 34.0, 26.0, 20.7, 13.9; HRMS (ESI-TOF) Calcd for $C_{19}H_{21}F_7NO_4$ $[M+H]^+$: 460.1359; found: 460.1359.



Ethyl 2-(4-(2-methoxyethyl)-4-methyl-6-oxo-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidin-2-yl)acetate (2g)

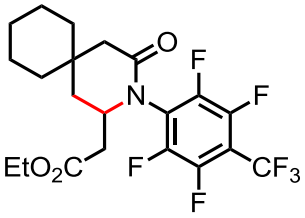
Substrate **1g** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 3/1), **2g** was obtained as colorless oil (24.2 mg, 51%). The isomeric ratio (major/minor) was determined to be 52:48 by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45-4.30 (m, 1 H), 4.06-3.90 (m, 2 H), 3.56-3.46 (m, 2 H), 3.33 (s, 3 H), 2.60-2.31 (m, 4 H), 22.19 (ddd, J_1 = 13.7 Hz, J_2 = 4.5 Hz, J = 3.3 Hz, 0.48 Hz), 2.07 (ddd, J_1 = 13.7 Hz, J_2 = 4.7 Hz, J = 2.3 Hz, 0.52 Hz), 1.90-1.64 (m, 3 H), 1.27-1.09 (m, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 169.9, 169.8, 169.7, 68.8, 68.6, 61.1, 61.0, 58.7, 58.6, 53.3 (d, J = 2.9 Hz), 53.2 (d, J = 2.9 Hz), 45.4, 44.5, 42.2, 40.6, 40.30, 40.28, 36.0, 31.92,

31.89, 27.2, 22.2, 13.92, 13.89.; HRMS (ESI-TOF) Calcd for $C_{20}H_{23}F_7NO_4$ $[M+H]^+$: 474.1515; found: 474.1516.



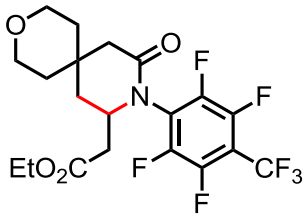
Ethyl 2-(9-oxo-8-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-8-azaspiro[4.5]decan-7-yl)acetate (2i)

Substrate **1i** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 5/1), **2i** was obtained as white soid (30.0 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (sext, J = 5.8 Hz, 1 H), 4.05-3.92 (m, 2 H), 2.59-2.38 (m, 4 H), 2.05 (ddd, J_1 = 13.5 Hz, J_2 = 4.3 Hz, J_3 = 2.9 Hz, 1 H), 1.85 (dd, J_1 = 13.6 Hz, J_2 = 11.2 Hz, 1 H), 1.81-1.50 (m, 8 H), 1.19 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 169.8, 61.1, 54.2 (d, J = 2.9 Hz), 44.1, 40.6, 40.4, 40.3, 40.0, 34.7, 24.4, 23.8, 13.9; HRMS (ESI-TOF) Calcd for $C_{20}H_{21}F_7NO_3$ $[M+H]^+$: 456.1410; found: 456.1411.



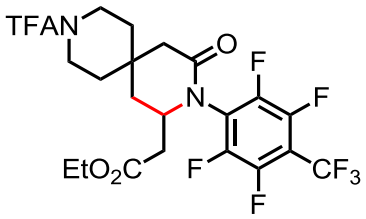
Ethyl 2-(4-oxo-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-3-azaspiro[5.5]undecan-2-yl)acetate (2j)

Substrate **1j** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 5/1), **2j** was obtained as white solid (32.1 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (sext, J = 5.8 Hz, 1 H), 4.05-3.92 (m, 2 H), 2.64 (dd, J_1 = 17.2 Hz, J_2 = 3.2 Hz, 1 H), 2.50-2.38 (m, 2 H), 2.32-2.17 (m, 2 H), 1.65-1.35 (m, 11 H), 1.19 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 169.8, 61.0, 52.8 (d, J = 2.9 Hz), 43.6, 40.3, 39.5, 39.1, 32.7, 32.4, 25.9, 21.6, 21.4, 13.9; HRMS (ESI-TOF) Calcd for $C_{21}H_{23}F_7NO_3$ $[M+H]^+$: 470.1566; found: 470.1569.



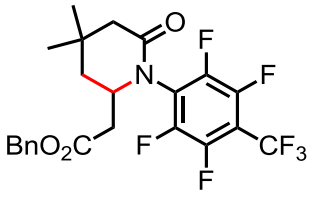
Ethyl 2-(10-oxo-9-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-3-oxa-9-azaspiro[5.5]undecan-8-yl)acetate (2k)

Substrate **1k** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 3/1), **2k** was obtained as yellow oil (39.2 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (sext, J = 5.8 Hz, 1 H), 4.08-3.92 (m, 2 H), 3.84-3.62 (m, 4 H), 2.83 (dd, J_1 = 17.2 Hz, J_2 = 3.2 Hz, 1 H), 2.55-2.41 (m, 2 H), 2.35 (d, J = 17.2 Hz, 1 H), 2.28 (ddd, J_1 = 14.0 Hz, J_2 = 5.2 Hz, J_3 = 3.2 Hz, 1 H), 1.90-1.45 (m, 5 H), 1.20 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 169.2, 63.3, 63.1, 61.2, 52.4 (d, J = 2.9 Hz), 42.5, 40.1, 39.7, 38.4, 32.8, 30.4, 13.9; HRMS (ESI-TOF) Calcd for $C_{20}H_{21}F_7NO_4$ $[M+H]^+$: 472.1359; found: 472.1361.



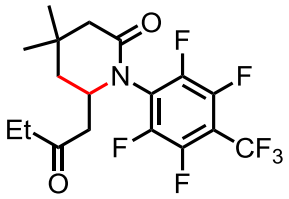
Ethyl 2-(4-oxo-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-9-(2,2,2-trifluoroacetyl)-3,9-diazaspiro[5.5] undecan-2-yl)acetate (2l)

Substrate **1l** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 2/1), **2l** was obtained as yellow oil (42.5 mg, 75%). The isomeric ratio (major/minor) was determined to be 1:1 by ^{13}C NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (hept, J = 6.0 Hz, 1 H), 4.08-3.96 (m, 2 H), 3.95-3.85 (m, 1 H), 3.80-3.65 (m, 1 H), 3.65-3.50 (m, 2 H), 2.78 (dd, J_1 = 17.2 Hz, J_2 = 3.2 Hz, 1 H), 2.55-2.37 (m, 3 H), 2.31-2.22 (m, 1 H), 1.86-1.72 (m, 3 H), 1.69-1.59 (m, 2 H), 1.20 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 169.4, 168.54, 168.51, 155.4 (q, J = 35.6 Hz), 155.3 (q, J = 35.6 Hz), 116.4 (q, J = 286.1 Hz), 61.32, 61.30, 52.5 (d, J = 2.9 Hz), 52.4 (d, J = 2.7 Hz), 41.9, 41.7, 41.6, 41.38, 41.36, 39.8, 39.3, 39.1, 39.0, 38.9, 38.2, 37.2, 32.5, 31.5, 31.4, 31.3, 13.9; HRMS (ESI-TOF) Calcd for $C_{22}H_{21}F_{10}N_2O_4$ $[M+H]^+$: 567.1342; found: 567.1345.



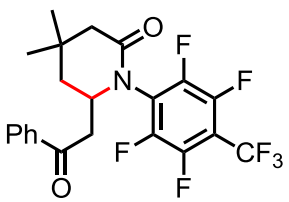
Benzyl 2-(4,4-dimethyl-6-oxo-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidin-2-yl)acetate (2aa)

Substrate **1a** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 3/1), **2aa** was obtained as yellow oil (39.2 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5 H), 4.99 (s, 2 H), 4.31 (sext, J = 5.8 Hz, 1 H), 2.54-2.30 (m, 4 H), 1.93 (ddd, J_1 = 13.7 Hz, J_2 = 5.1 Hz, J_3 = 2.5 Hz, 1 H), 1.72-1.64 (m, 1 H), 1.15 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 169.4, 134.9, 128.65, 128.63, 128.47, 66.8, 53.5 (d, J = 2.9 Hz), 45.7, 41.7, 40.1, 30.4, 29.7, 24.4; HRMS (ESI-TOF) Calcd for $C_{23}H_{21}F_7NO_3$ $[M+H]^+$: 492.1410; found: 492.1410.



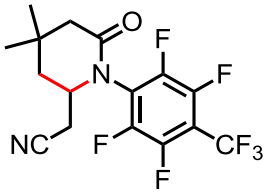
4,4-dimethyl-6-(2-oxobutyl)-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidin-2-one (2ab)

Substrate **1a** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 3/1), **2ab** was obtained as colorless oil (26.4 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (sext, J = 5.8 Hz, 1 H), 2.55 (d, J = 6.0 Hz, 2 H), 2.44-2.24 (m, 4 H), 2.00 (ddd, J_1 = 13.6 Hz, J_2 = 5.1 Hz, J_3 = 2.6 Hz, 1 H), 1.54 (dd, J_1 = 13.0 Hz, J_2 = 11.8 Hz, 1 H), 1.19 (s, 3 H), 1.11 (s, 3 H), 0.94 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.2, 170.3, 52.7 (d, J = 2.9 Hz), 47.6, 45.8, 42.1, 36.7, 30.5, 29.8, 24.5, 7.2; HRMS (ESI-TOF) Calcd for $C_{18}H_{19}F_7NO_2$ $[M+H]^+$: 414.1304; found: 414.1305.



4,4-dimethyl-6-(2-oxo-2-phenylethyl)-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidin-2-one (2ac)

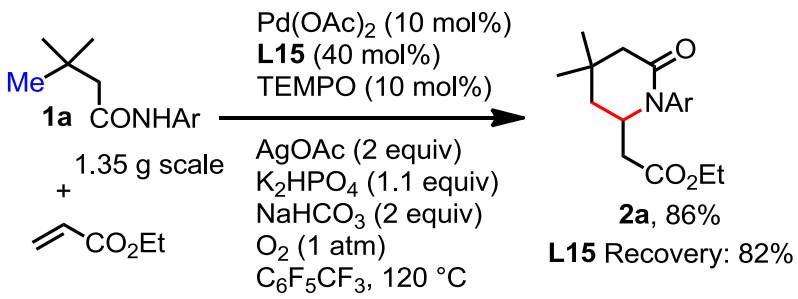
Substrate **1a** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 3/1), **2ac** was obtained as white solid (32.2 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.72 (m, 2 H), 7.62-7.55 (m, 1 H), 7.50-7.40 (m, 2 H), 4.70 (sext, J = 5.7 Hz, 1 H), 3.22 (dd, J_1 = 17.0 Hz, J_2 = 5.8 Hz, 1 H), 2.96 (dd, J_1 = 16.8 Hz, J_2 = 5.6 Hz, 1 H), 2.48-2.37 (m, 2 H), 2.08 (ddd, J_1 = 13.6 Hz, J_2 = 5.2 Hz, J_3 = 2.4 Hz, 1 H), 1.70 (dd, J_1 = 13.6 Hz, J_2 = 11.2 Hz, 1 H), 1.23 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 170.2, 135.8, 134.0, 128.8, 127.6, 53.7 (d, J = 2.7 Hz), 45.8, 43.5, 42.6, 30.5, 29.9, 24.5; HRMS (ESI-TOF) Calcd for $C_{22}H_{19}F_7NO_2$ $[M+H]^+$: 462.1298; found: 462.1299.



2-(4,4-dimethyl-6-oxo-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidin-2-yl)acetonitrile (2ad)

Substrate **1a** was olefinated following the general procedure. After purification by preparative TLC (eluent: hexanes/EtOAc = 3/1), **2ad** was obtained as white solid (27.9 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (sext, J = 5.1 Hz, 1 H), 2.55-2.35 (m, 4 H), 2.09 (ddd, J_1 = 13.8 Hz, J_2 = 5.2 Hz, J_3 = 1.8 Hz, 1 H), 1.87 (t, J = 12.6 Hz, 1 H), 1.19 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 115.2, 52.9 (d, J = 3.8 Hz), 45.5, 41.5, 30.2, 29.8, 24.30, 24.28; HRMS (ESI-TOF) Calcd for $C_{16}H_{14}F_7N_2O$ $[M+H]^+$: 383.0994; found: 383.0983.

Gram Scale Synthesis

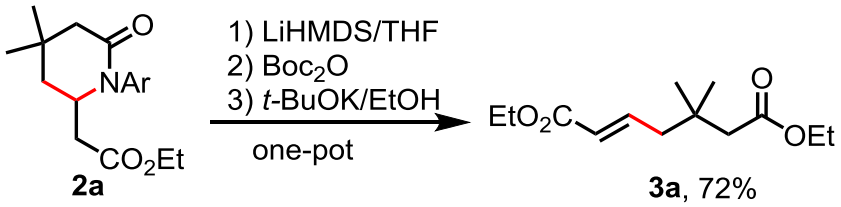


Ethyl 2-(4,4-dimethyl-6-oxo-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidin-2-yl)acetate (2a)

To an oven dried 350 mL Schlenk-type tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar were added substrate **1a** (1.3202 g, 4.0 mmol), $Pd(OAc)_2$ (89.0 mg, 0.4 mmol), **L15** (431.1 mg, 1.6 mmol), TEMPO (62.2 mg, 0.4 mmol), AgOAc (1.3401 g, 8.0 mmol), K_2HPO_4 (766.4 mg, 4.4 mmol), $NaHCO_3$ (672.0 mg, 8.0 mmol), and 20 mL of $C_6F_5CF_3$ followed by 1.0 mL of ethyl acrylate. The mixture was frozen with a dry ice/acetone bath. The reaction tube was evacuated and back-filled with O_2 (3 times, balloon) and heated to 120 ^oC (oil bath) for 20 hours under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with ethyl acetate and then filtered through a small pad of Celite. The solvents were removed under reduced pressure and the resulting mixture was purified by column chromatography on silica gel (hexanes/ethyl acetate = 10/1 ~ 2:1) to afford 1.4814 g of **2a** (86%) and 353.8 mg of **L14** (82%).

2.5 Procedure for Cleavage of Auxiliary

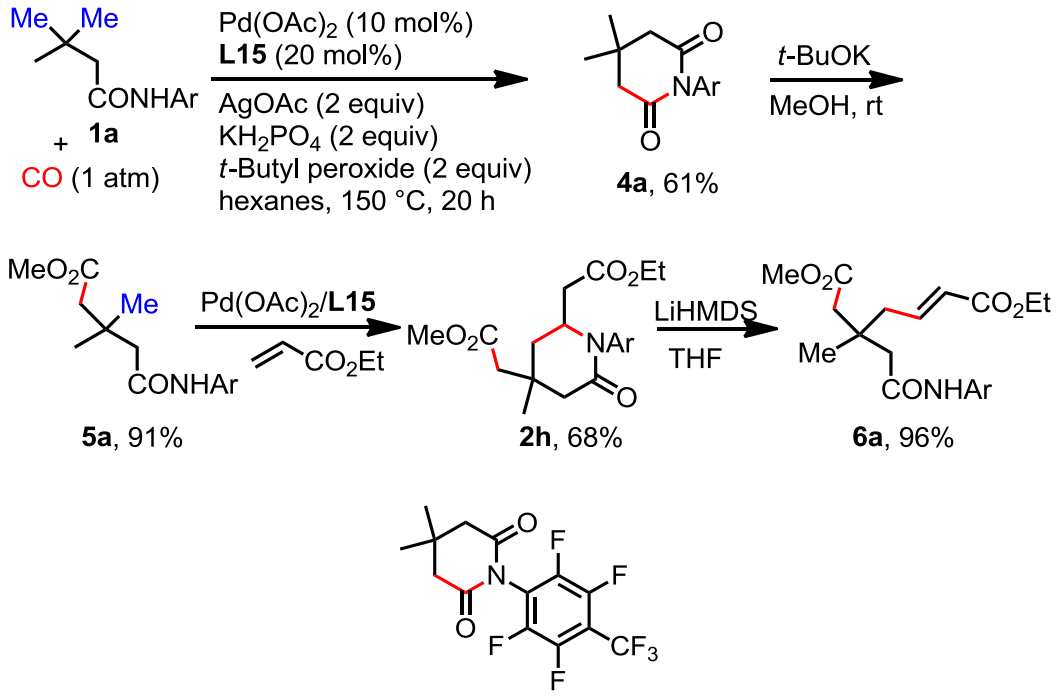
(*E*)-diethyl 5,5-dimethylhept-2-enedioate (3a)



To an oven dried 50 mL Schlenk-type tube equipped with a magnetic stir bar were added lactam (128.8 mg, 0.30 mmol) and 1 mL of anhydrous THF. After cooling to -78 ^oC, LiHMDS (0.5 M in 2-methyltetrahydrofuran, 1.5 mL, 0.75 mmol) was added dropwise within 5 minutes. The mixture was warmed up to -20 ^oC naturally in 40 minutes. Then Boc_2O (0.24 mL, d = 0.95 g/mL, 1.05 mmol) was added in -78 ^oC followed by warming up to room temperature naturally in 2 hours. EtOH (2 mL) and KO^tBu (168.3 mg, 1.5 mmol) were added at room temperature. After stirring at room temperature for 5 hours, the reaction was quenched with saturate NH_4Cl (5 mL) and extracted with ethyl acetate (6 mL × 3). The combined organic layer was washed with brine and dried over $MgSO_4$, filtrated and concentrated. The crude product was purified by preparative TLC using hexanes/EtOAc (10/1) as the eluent to afford 52.2 mg of **3a** (72%) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.21-6.92 (m, 1 H), 5.85 (dt, J_1 = 15.6 Hz, J_2 = 1.3 Hz, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 4.13 (q, J = 7.2 Hz, 2 H), 2.25 (dd, J_1 = 8.0 Hz, J_2 =

1.2 Hz, 2 H), 2.21 (s, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.05 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 167.2, 146.2, 125.0, 61.0, 60.9, 46.6, 45.2, 34.7, 28.2, 15.11, 15.09; HRMS (ESI-TOF) Calcd for $C_{13}H_{23}O_4$ $[M+H]^+$: 243.1596; found: 243.1594.

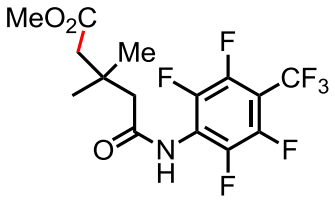
2.6 Procedure for Construction of Poly-functionalized Quaternary Carbon Centers



4,4-dimethyl-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidine-2,6-dione (4a)

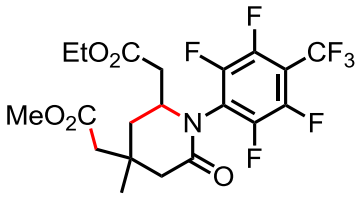
To an oven dried 350 mL Schlenk-type tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar were added substrate **1a** (1.3207 g, 4.0 mmol), $Pd(OAc)_2$ (89.8 mg, 0.4 mmol), **L15** (215.3 mg, 0.8 mmol), *Di*-tert-butyl peroxide (1.47 mL, d = 0.794 g/mL, 1.1698 g, 8 mmol), AgOAc (1.3350 g, 8.0 mmol), KH_2PO_4 (1.0887 g, 8.0 mmol) and 20 mL of hexanes. The mixture was frozen with a dry ice/acetone bath. The reaction tube was evacuated and back-filled with CO (3 times, balloon) and heated to 150 ^{o}C (oil bath) for 20 hours under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with ethyl acetate and then filtered through a small pad of Celite. The solvents were removed under reduced pressure and the resulting mixture was purified by column chromatography on silica gel (hexanes/ethyl acetate = 15/1) to afford 873.2 mg of **6a** (61%) as yellow soild. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (s, 4 H), 1.24 (s, 6 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 45.9, 29.6, 27.5; HRMS (ESI-TOF) Calcd for $C_{14}H_{11}F_7NO_2$ $[M+H]^+$: 358.0672; found: 358.0673.



3,3-dimethyl-5-oxo-5-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenylamino]-pentanoic acid methyl ester (5a)

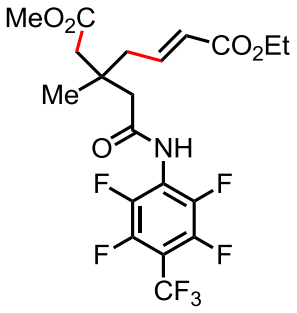
To a 100 mL of round bottle flask was added **6a** (714.4 mg, 2.0 mmol), MeOH (15 mL) and KO^{t}Bu (336.6 mg, 3.0 mmol). The mixture was stirred at room temperature for 6 hours. Upon completion, the reaction was quenched with sat. NH_4Cl and extracted with EtOAc (15 mL × 3). The organic layer was washed with brine and dried over $MgSO_4$, filtrated and concentrated. The crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate = 4/1) to afford 708.9 mg of **7a** (91%) as white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (br s, 1 H), 3.77 (s, 3 H), 2.54 (s, 2 H), 2.46 (s, 2 H), 1.14 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.8, 168.9, 52.2, 46.7, 44.4, 34.1, 28.9; HRMS (ESI-TOF) Calcd for $C_{15}H_{15}F_7NO_3$ $[M+H]^+$: 390.0940; found: 390.0939.



Ethyl 2-(4-(2-methoxy-2-oxoethyl)-4-methyl-6-oxo-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidin -2-yl)acetate (2h)

To an oven dried 250 mL Schlenk-type tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar were added substrate **7a** (389.3 g, 1.0 mmol), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), **L15** (107.7 mg, 0.4 mmol), TEMPO (15.6 mg, 0.1 mmol), AgOAc (334.0 mg, 2.0 mmol), K_2HPO_4 (191.6 mg, 4.4 mmol), $NaHCO_3$ (168.0 mg, 2.0 mmol), and 5 mL of $C_6F_5CF_3$ followed by 0.43 mL of ethyl acrylate. The mixture was frozen with a dry ice/acetone bath. The reaction tube was evacuated and

back-filled with O_2 (3 times, balloon) and heated to 120 ^oC (oil bath) for 20 hours under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with ethyl acetate and then filtered through a small pad of Celite. The solvents were removed under reduced pressure and the resulting mixture was purified by column chromatography on silica gel (hexanes/ethyl acetate = 10/1) to afford 332.1 g of **2h** (68%) as yellow oil. The isomeric ratio (major/minor) was determined to be 1:1 by ^1H NMR. ^1H NMR (400 MHz, $CDCl_3$) δ 4.45-4.30 (m, 1 H), 4.05-3.91 (m, 2 H), 3.72 (s, 1.5 H), 3.71 (s, 1.5 H), 2.70-2.15 (m, 7 H), 1.88 (t, J = 12.6 Hz, 0.5 H), 1.73 (dd, J_1 = 14.0 Hz, J_2 = 11.2 Hz, 0.5 H), 1.35-1.10 (m, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2, 170.9, 169.6, 169.5, 169.3, 169.1, 61.14, 61.12, 53.31 (d, J = 2.7 Hz), 53.10 (d, J = 2.7 Hz), 51.71, 51.66, 46.5, 45.0, 43.7, 40.9, 40.08, 40.06, 39.6, 39.5, 32.2, 32.0, 27.2, 22.5, 13.90, 13.89; HRMS (ESI-TOF) Calcd for $C_{20}H_{21}F_7NO_5$ $[M+H]^+$: 488.1308; found: 488.1306.



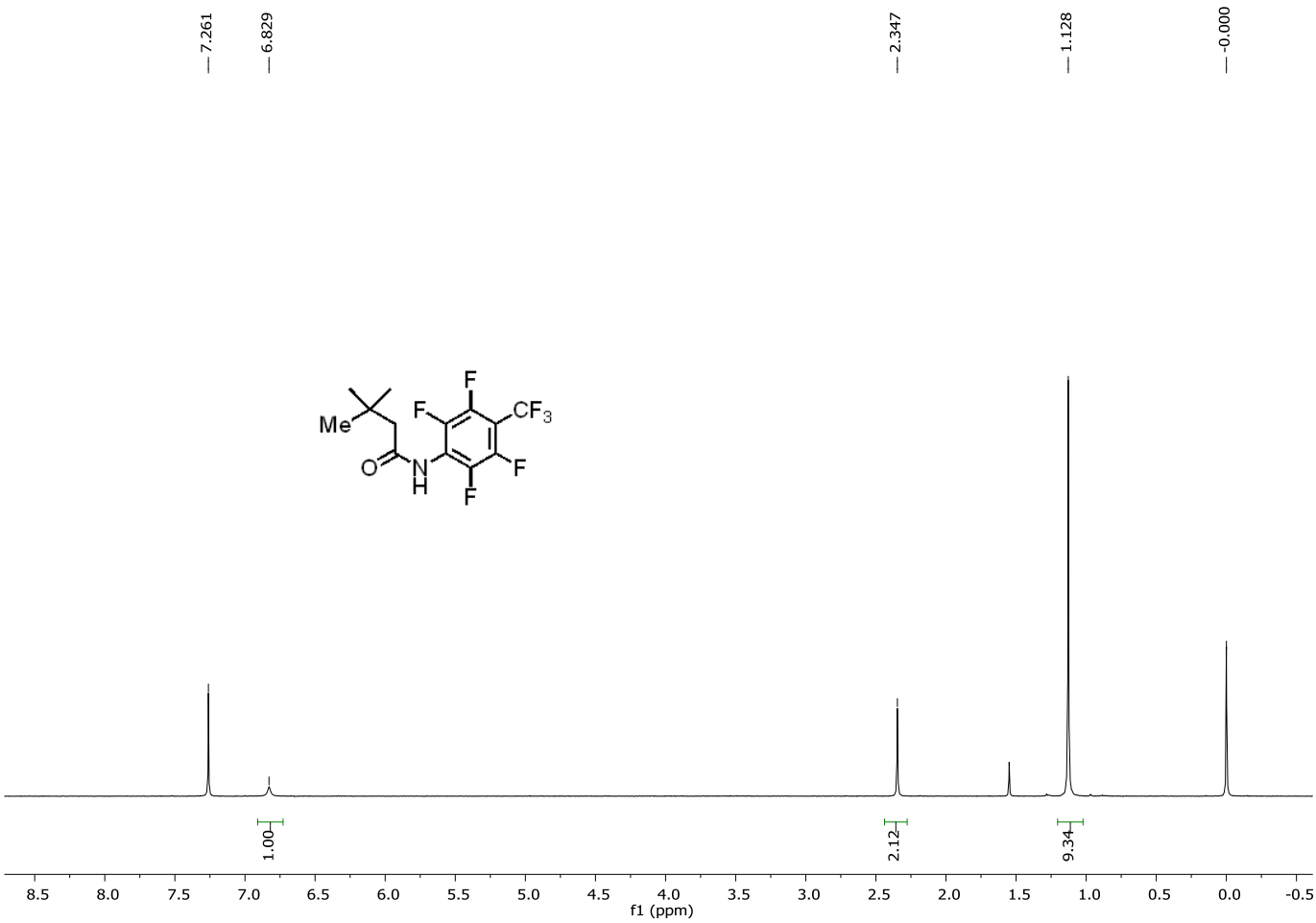
(*E*)-5-(2-oxo-2-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)amino)ethyl-5-methyl-2-heptenedioic acid 1-ethyl 7-methyl ester (6a)

To an oven dried 50 mL Schlenk-type tube equipped with a magnetic stir bar were added lactam (49.1 mg, 0.1 mmol) and 1 mL of anhydrous THF. After cooling to -78 ^oC, LiHMDS (0.5 M in 2-methyltetrahydrofuran, 1.0 mL, 0.50 mmol) was added dropwise within 5 minutes. The mixture was warmed up to -20 ^oC naturally in 40 minutes. Then the reaction was quenched with sat. NH_4Cl/AcOH (V/V = 20/1, 2 mL) in -78 ^oC and extracted with ethyl acetate (6 mL × 3). The combined organic layer was washed with brine and dried over $MgSO_4$, filtrated and concentrated. The crude product was purified by preparative TLC using hexanes/EtOAc (3/1) as the eluent to afford 45.7 mg of **8a** (93%) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1 H), 7.04-6.90 (m, 1 H), 5.93 (dt, J_1 = 15.6 Hz, J_2 = 1.4 Hz, 1 H), 4.21 (q, J = 7.1 Hz, 2 H), 3.77 (s, 3 H), 2.63 (d, J = 12.8 Hz, 1 H), 2.58 (d, J = 13.2 Hz, 1 H), 2.52 (d, J = 14.0 Hz, 1 H), 2.48 (d, J = 14.0 Hz, 1 H), 2.41-2.25 (m, 2 H), 1.30 (t, J = 7.2 Hz, 3 H), 1.15 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.1, 168.6, 166.0, 142.8, 125.7, 60.4, 52.2, 44.7, 43.2, 42.8, 37.1, 25.5, 14.2; HRMS (ESI-TOF) Calcd for $C_{20}H_{21}F_7NO_5$ $[M+H]^+$: 488.1308; found: 488.1307.

3. Reference:

1. Sridharan, V.; Ruiz, M.**;** Menéndez, J. C. *Synthesis* **2010**, 1053.

2. Zhang, Q.; Zhang, Z.; Yan, Z.; Liu, Q.; Wang, T. *Org. Lett.* **2007**, *9*, 3651.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H
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F
CF3
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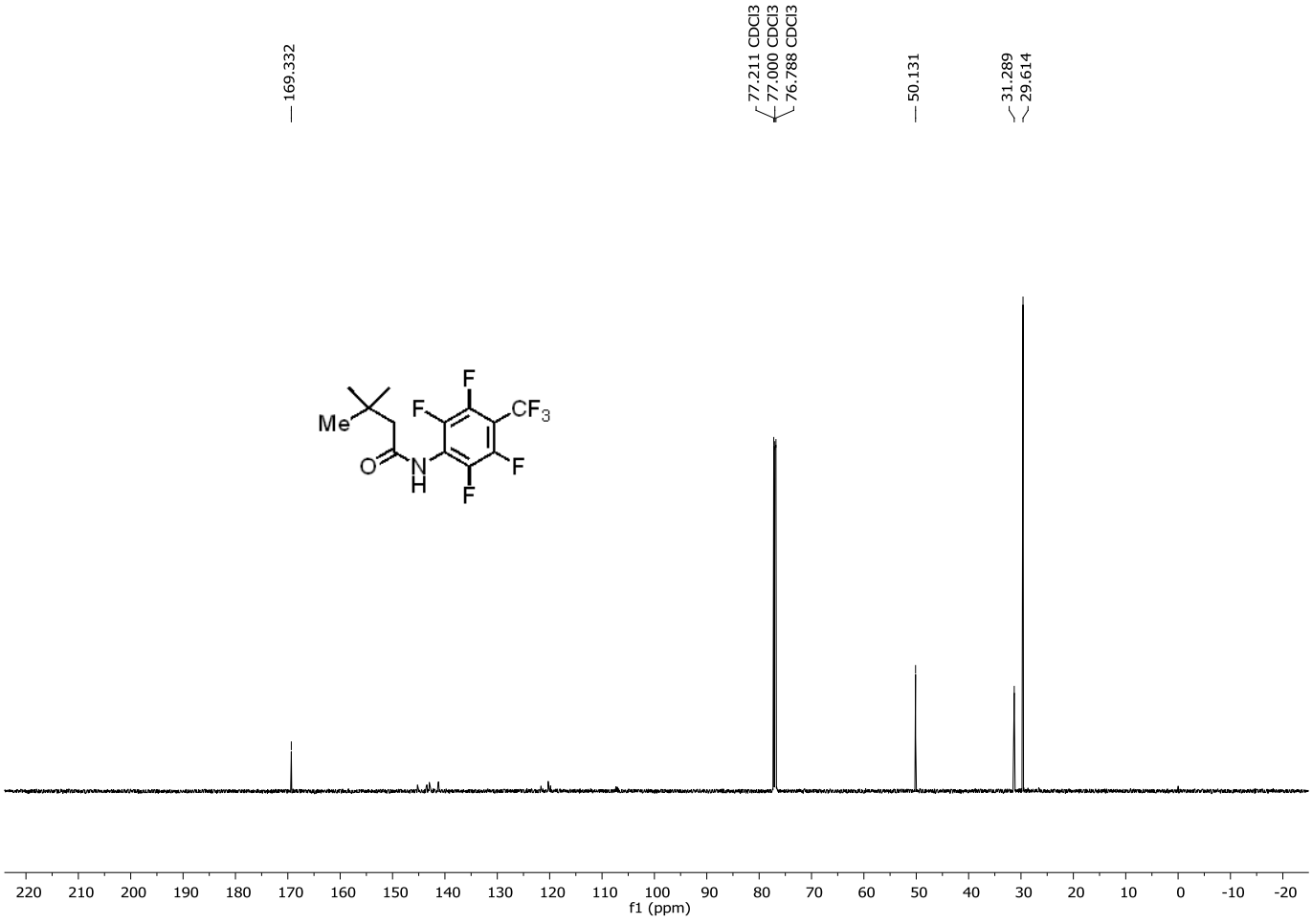
9.34
f1 (ppm)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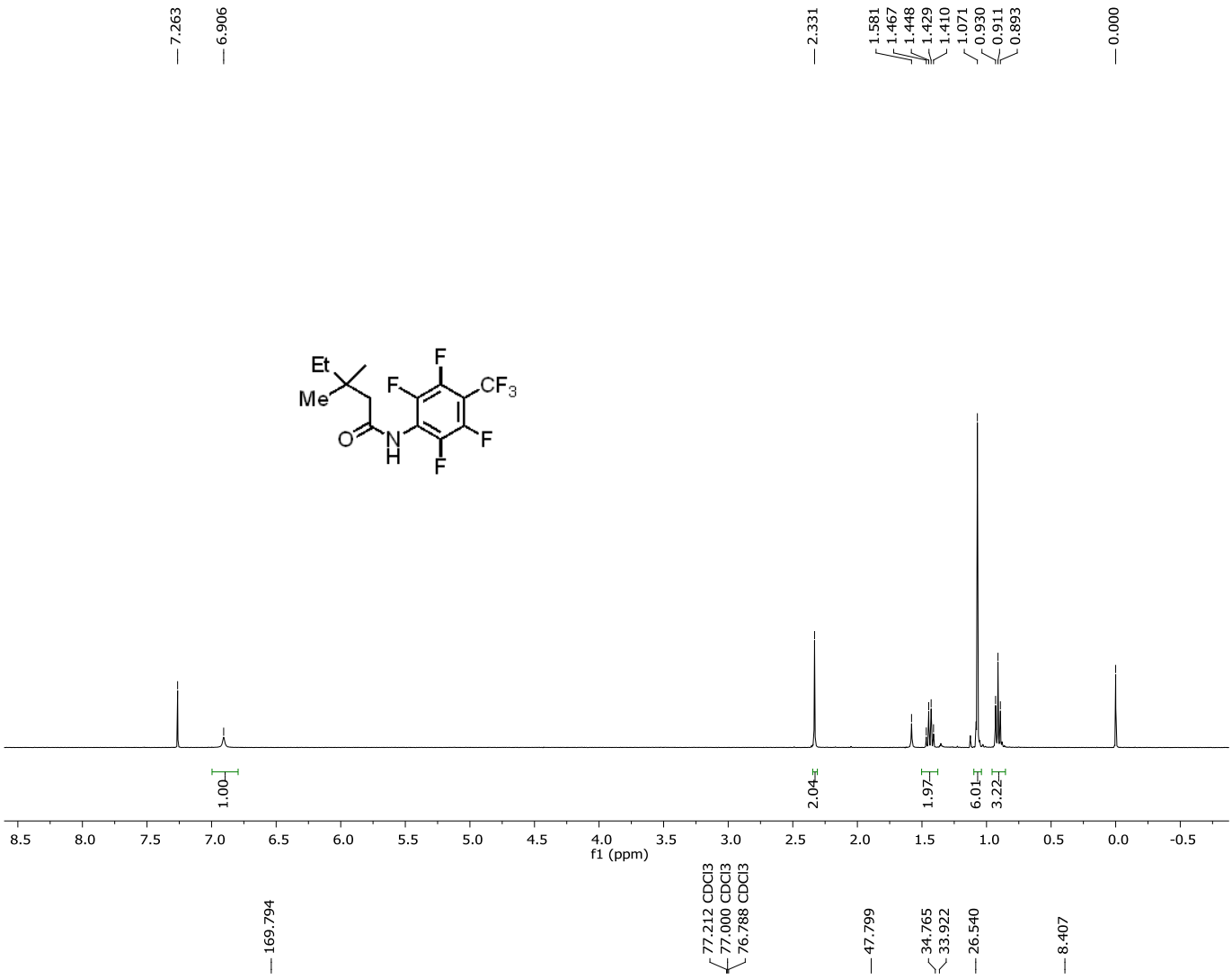
CF3
f1 (ppm)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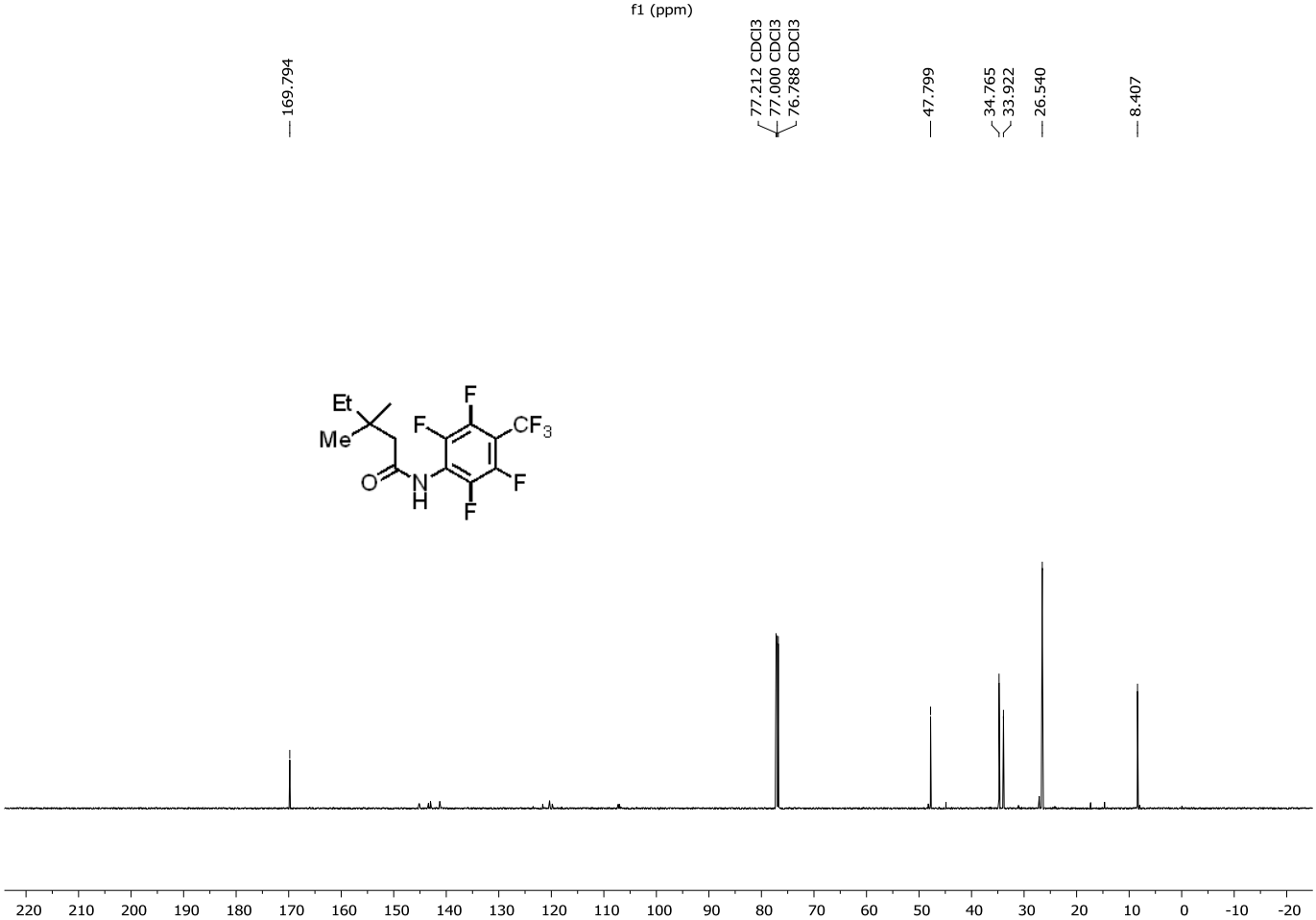
f1 (ppm)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H
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F
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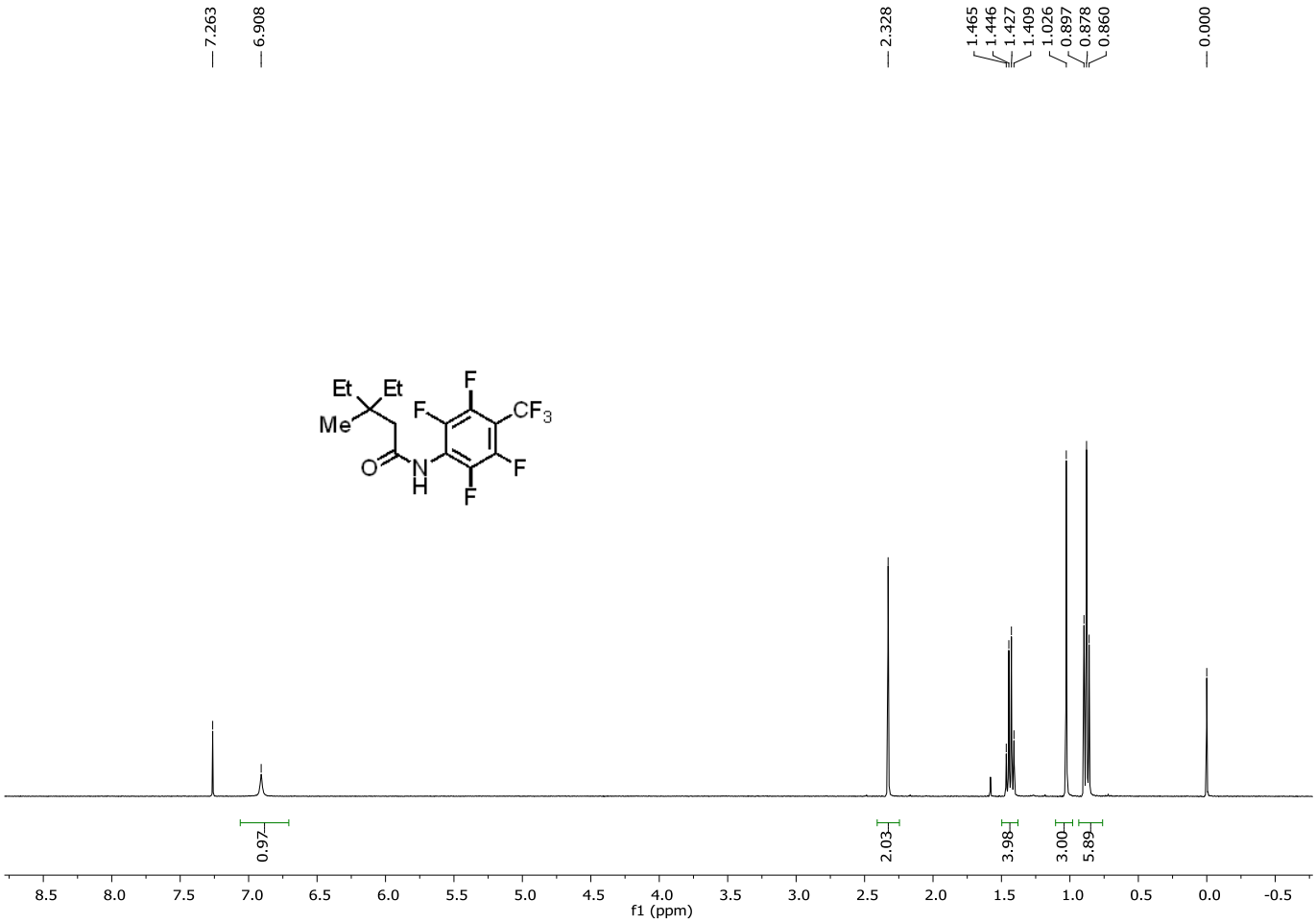
CF3
f1 (ppm)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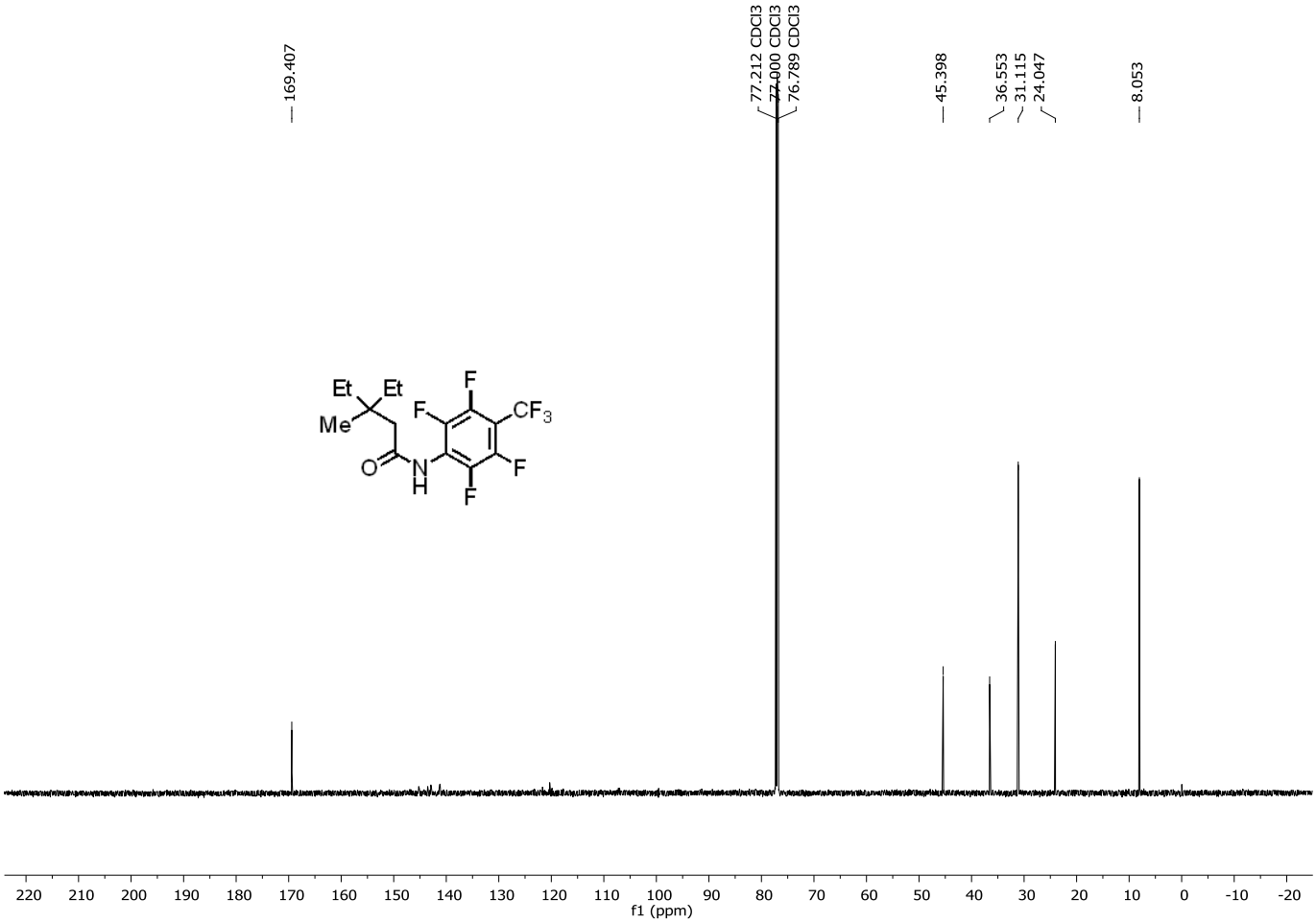
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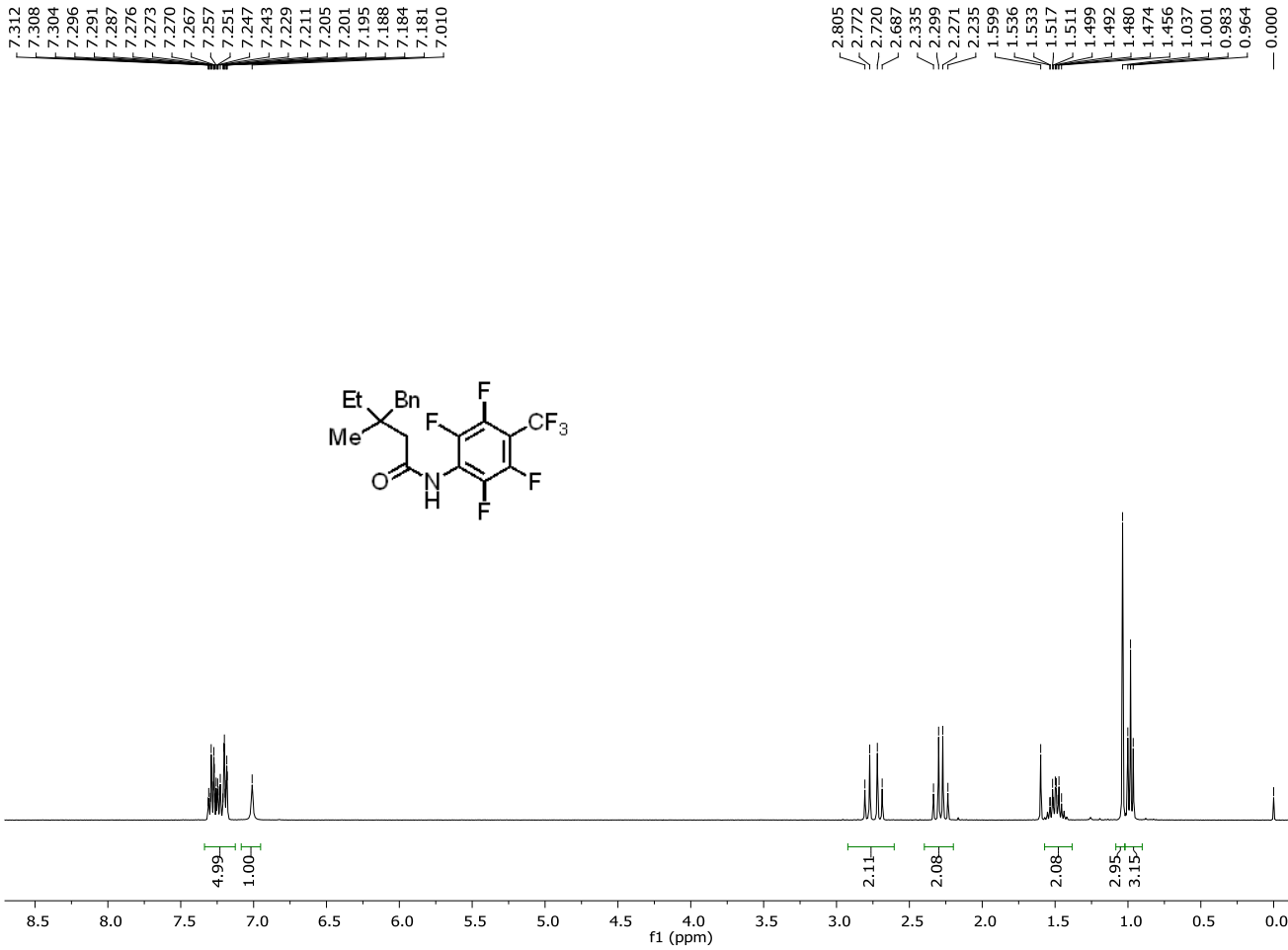
f1 (ppm)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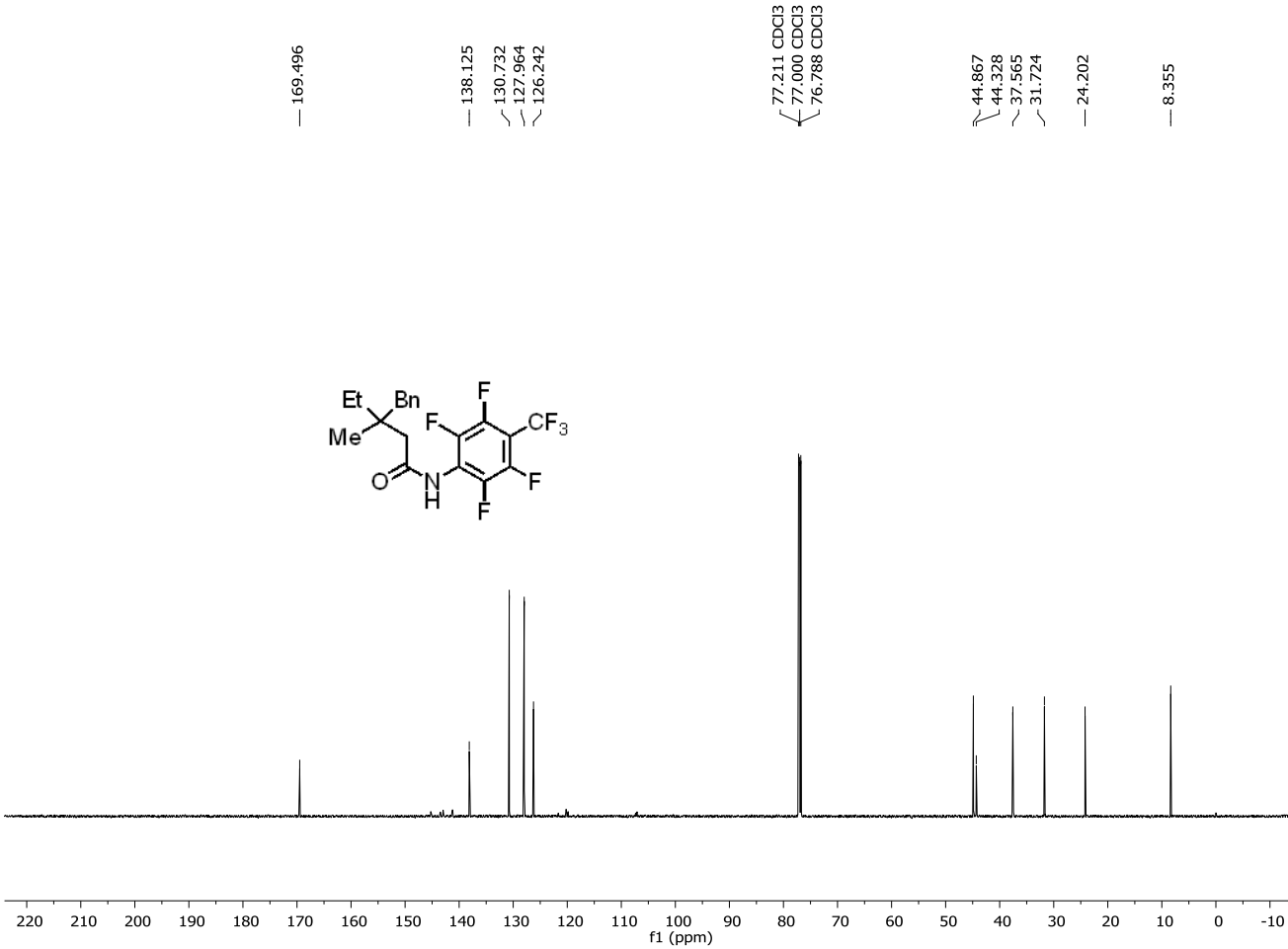
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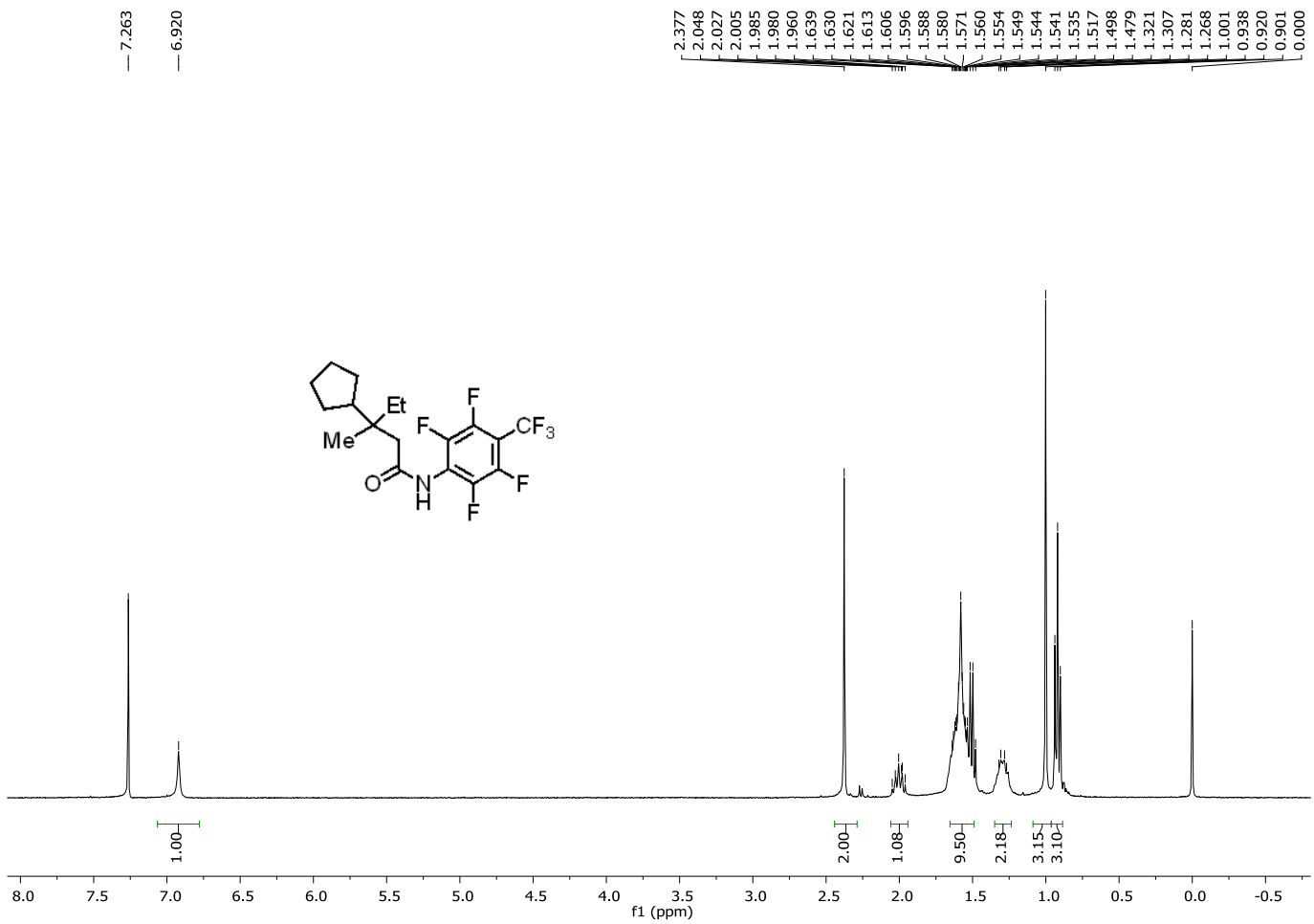
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2.00
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3.10
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6.5
6.0
5.5
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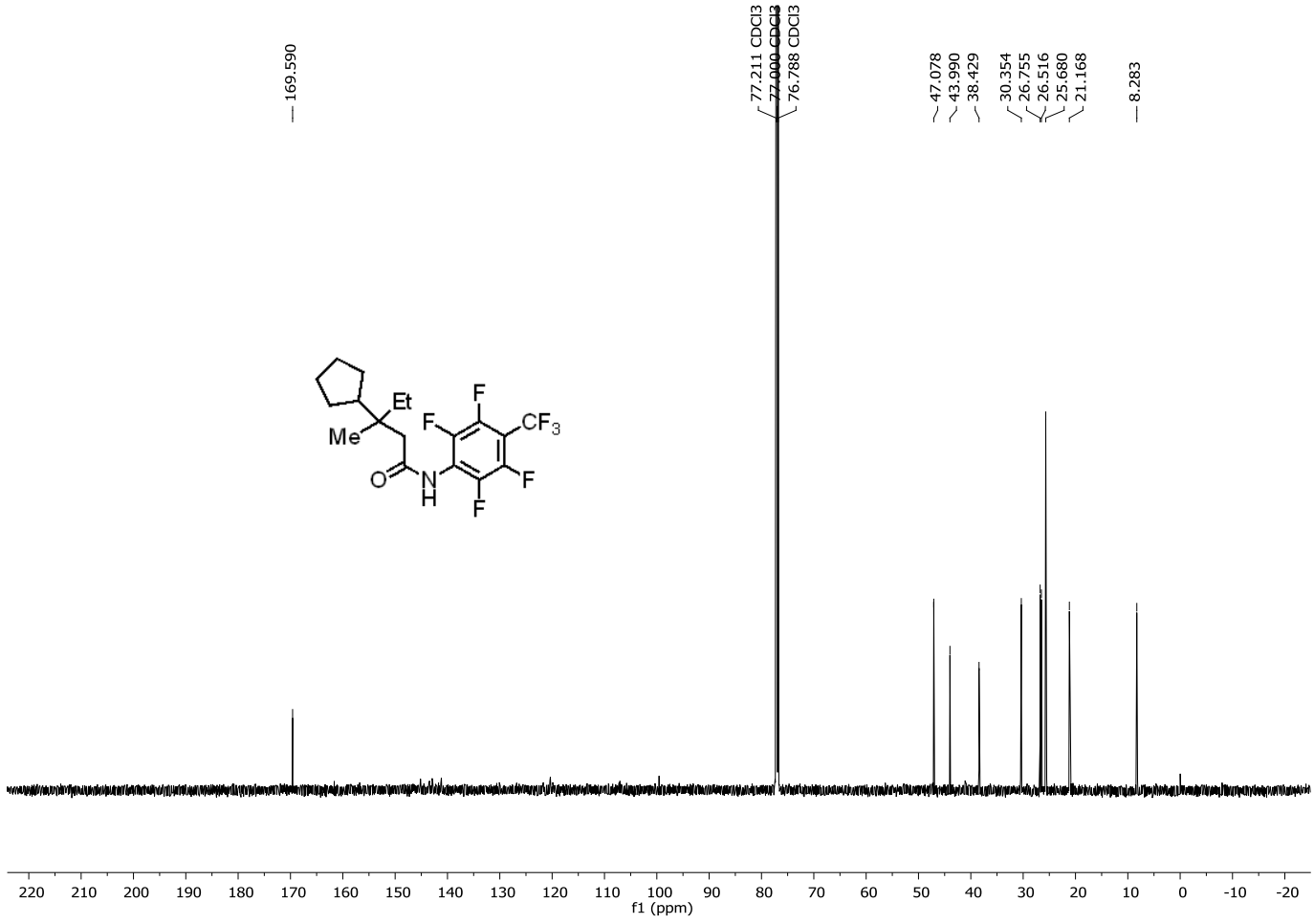
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180
170
160
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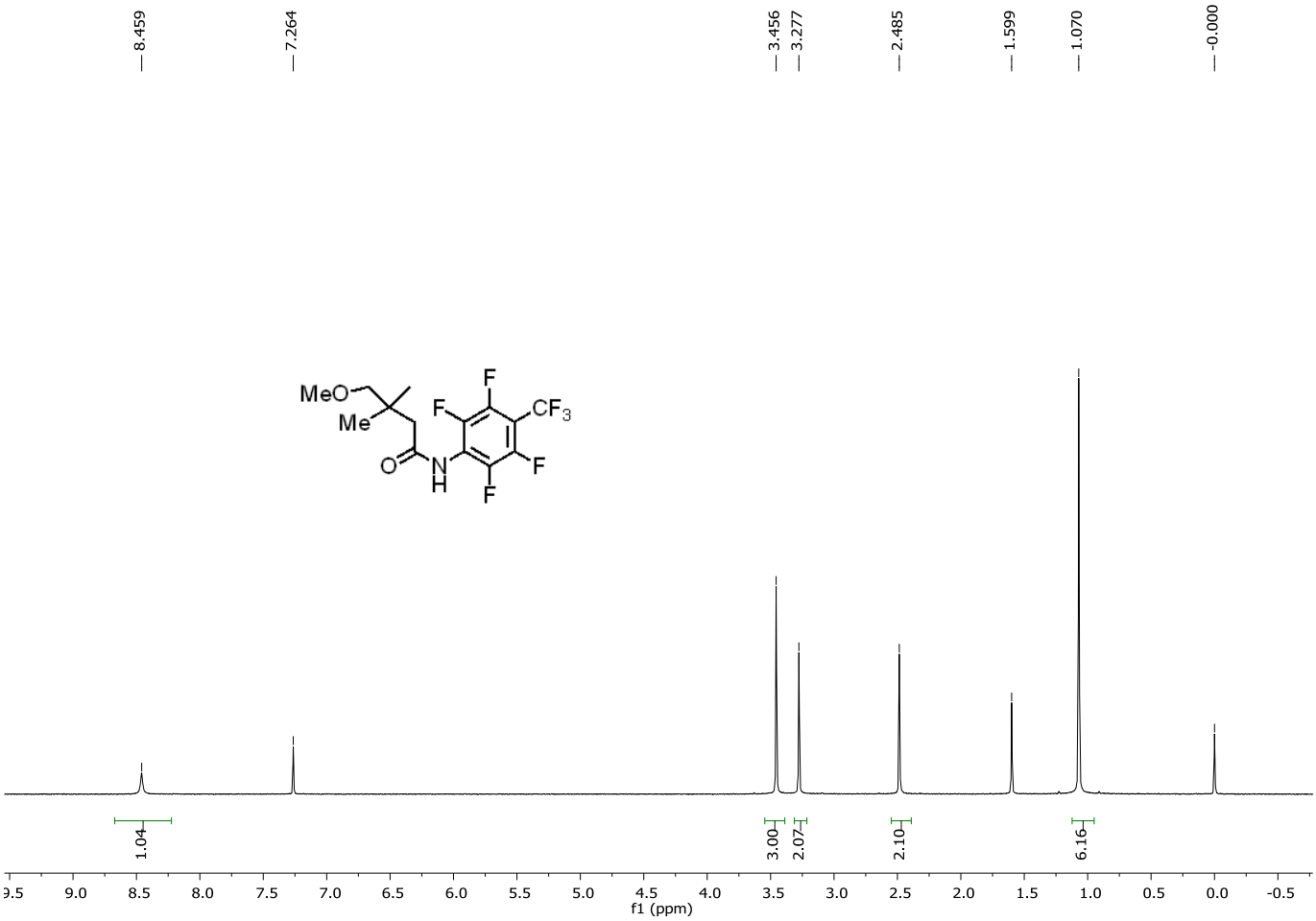
f1 (ppm)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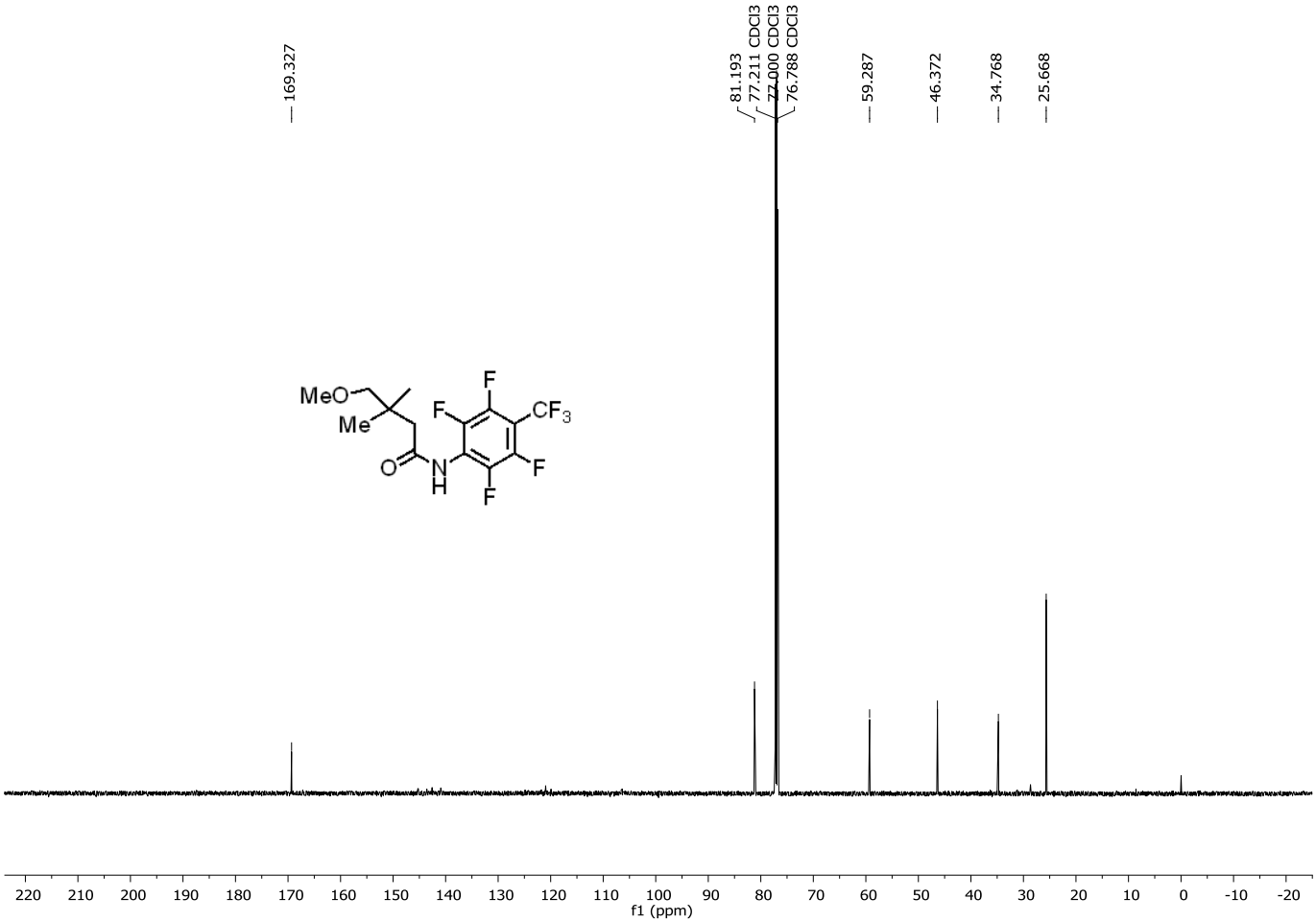
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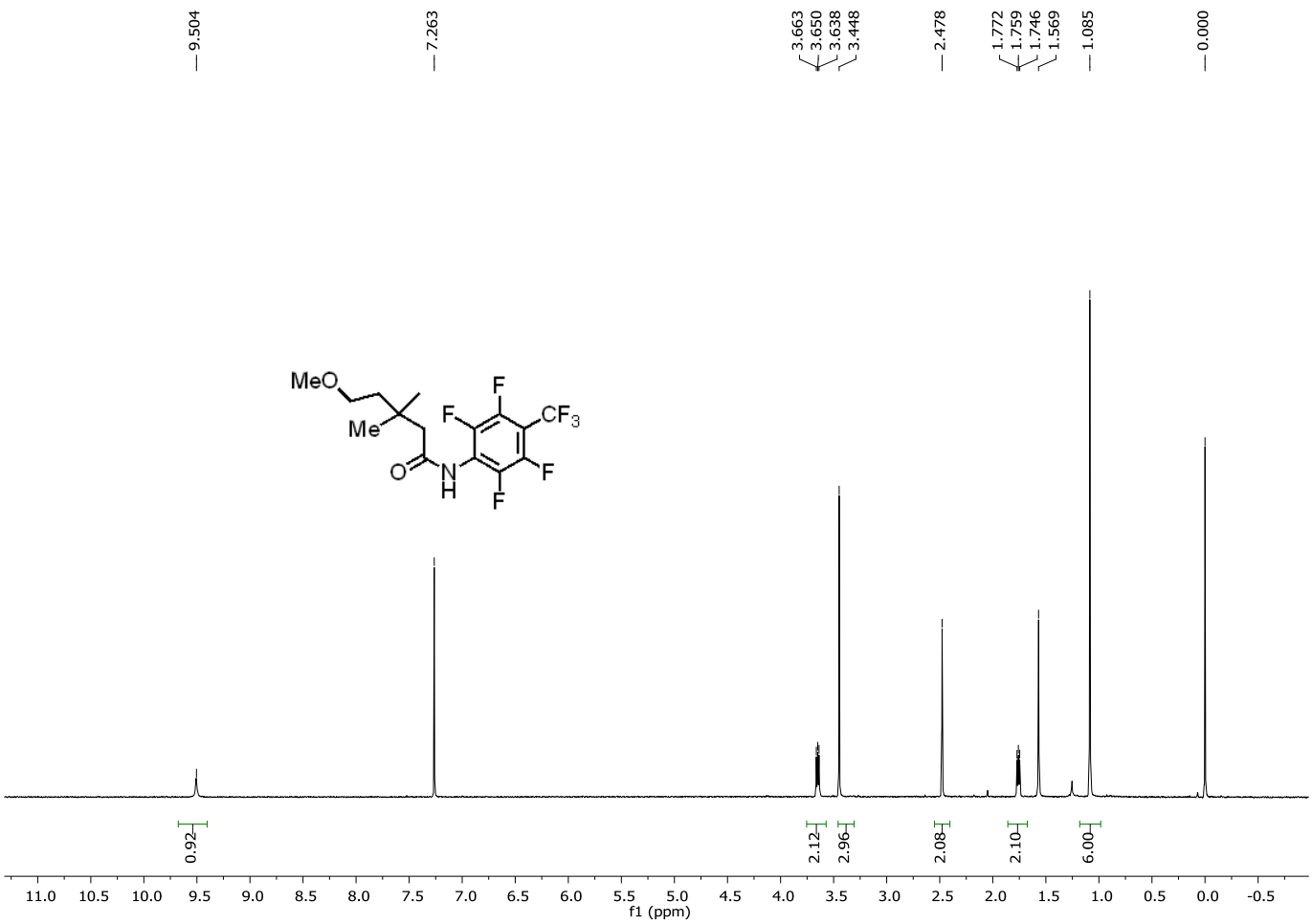
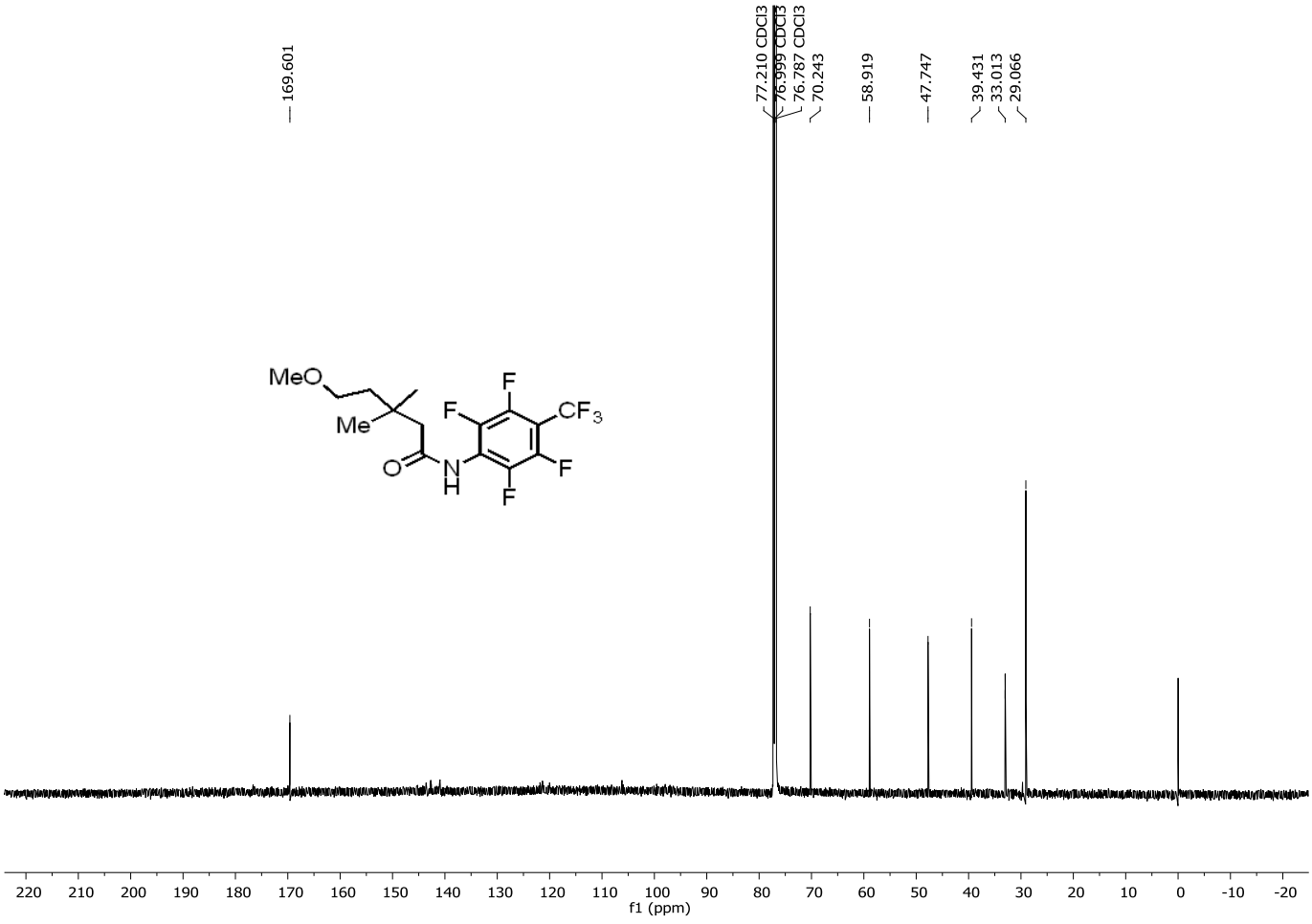
F
F
CF3
f1 (ppm)


9.504
7.263
3.663
3.650
3.638
3.448
2.478
1.772
1.759
1.746
1.569
1.085
0.000
MeO
Me
O
N
H
F
F
F
F
CF3
0.92
2.12
2.96
2.08
2.10
6.00
11.0 10.5 10.0 9.5 9.0 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 0.0 -0.5
f1 (ppm)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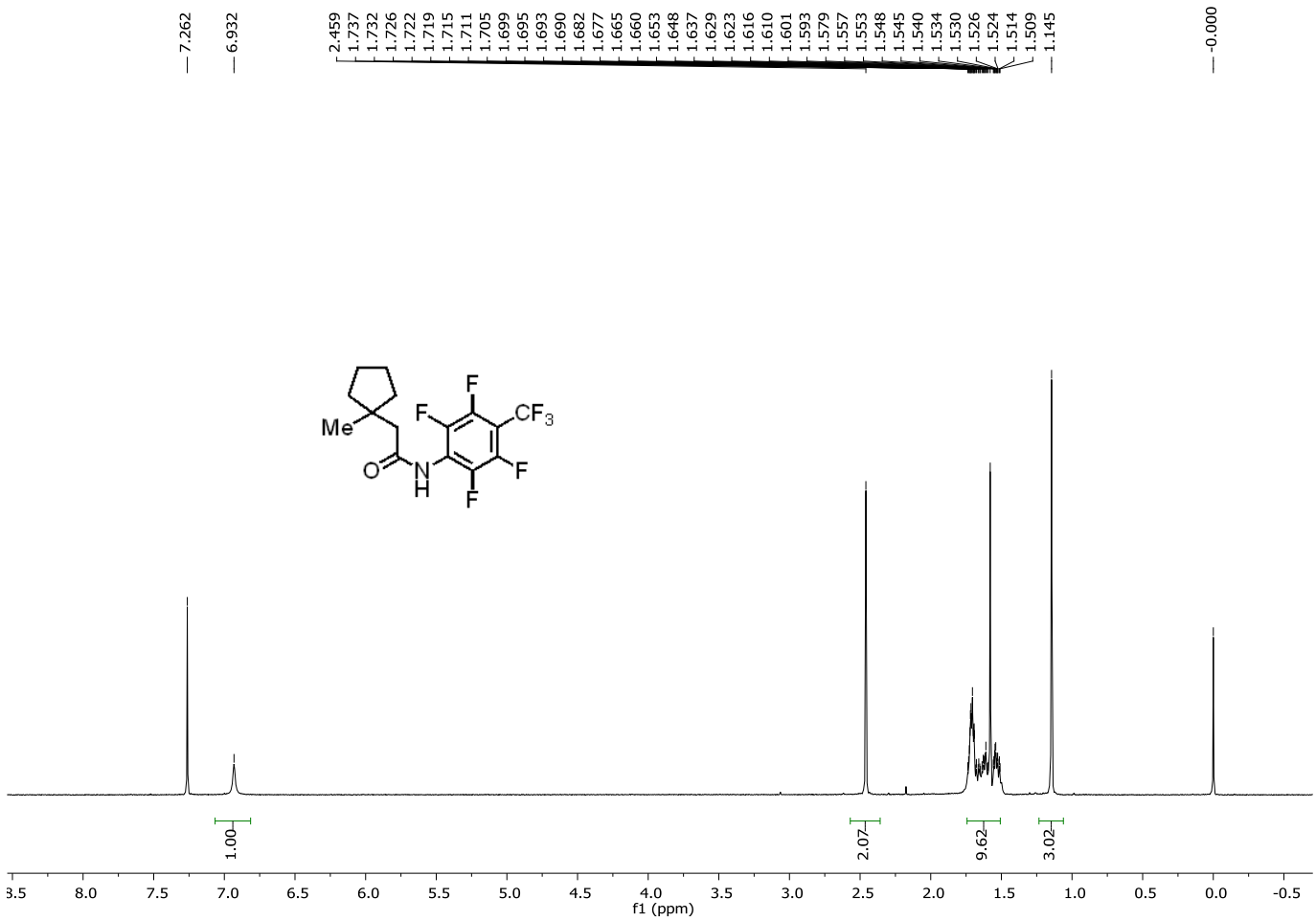
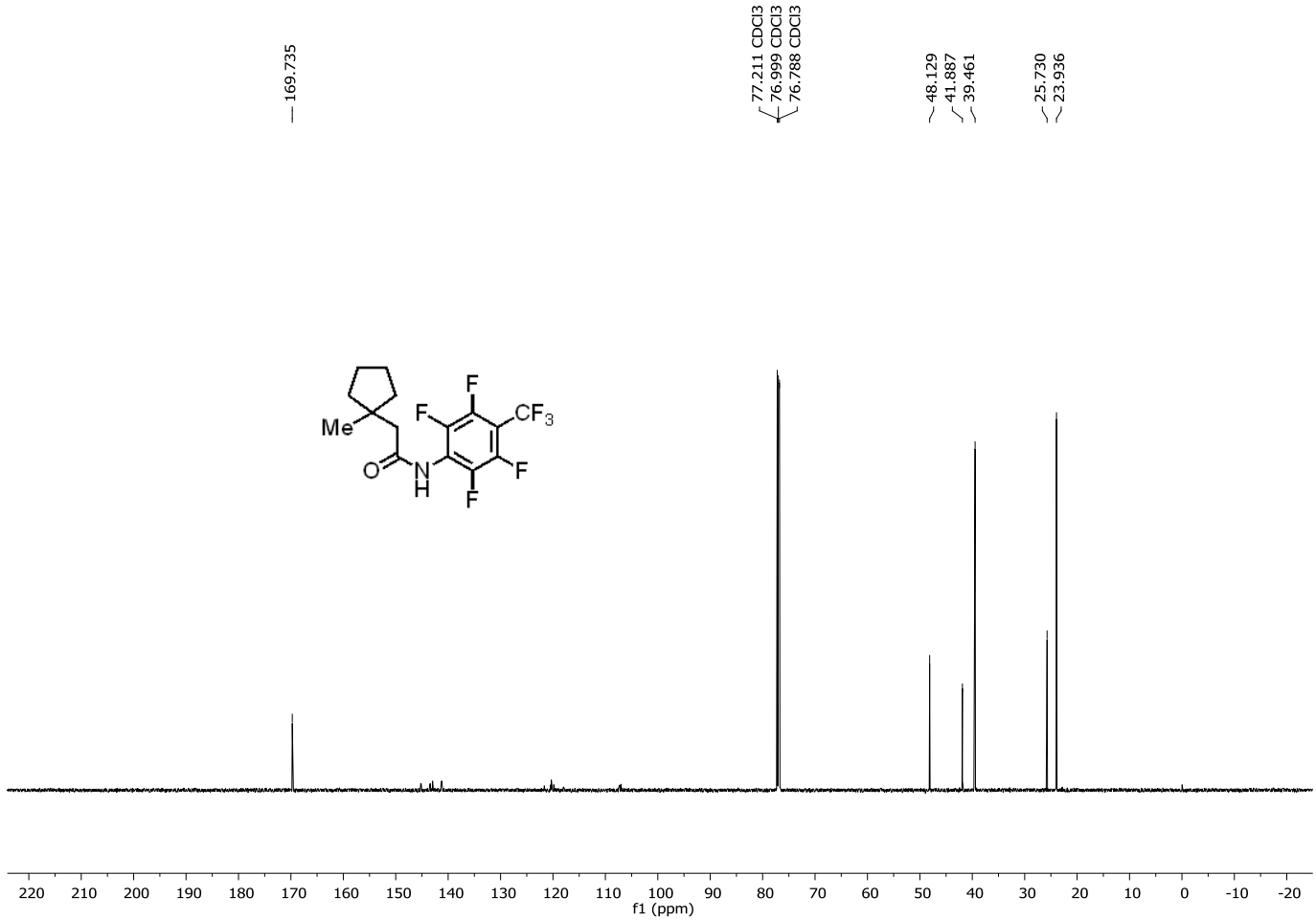
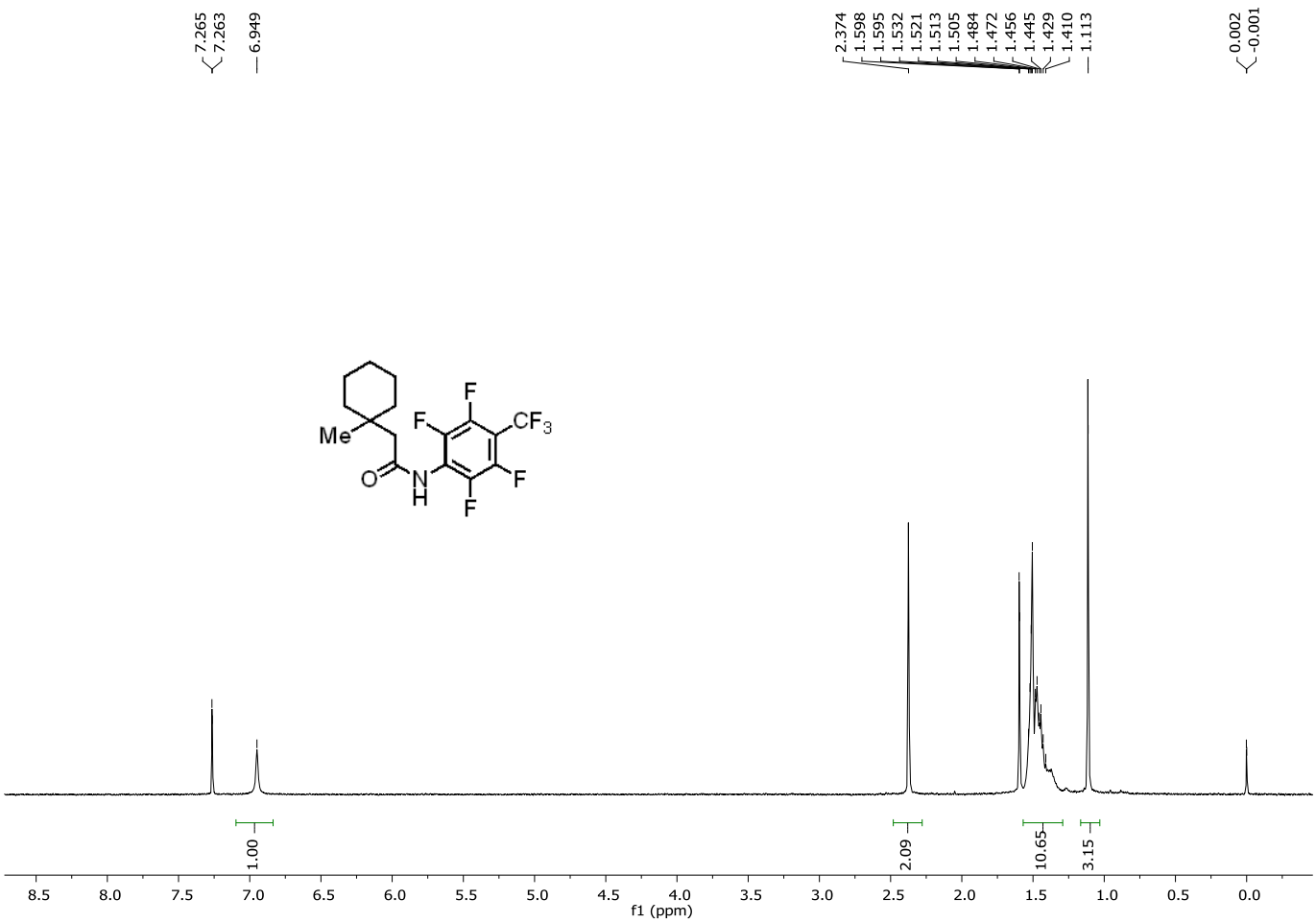
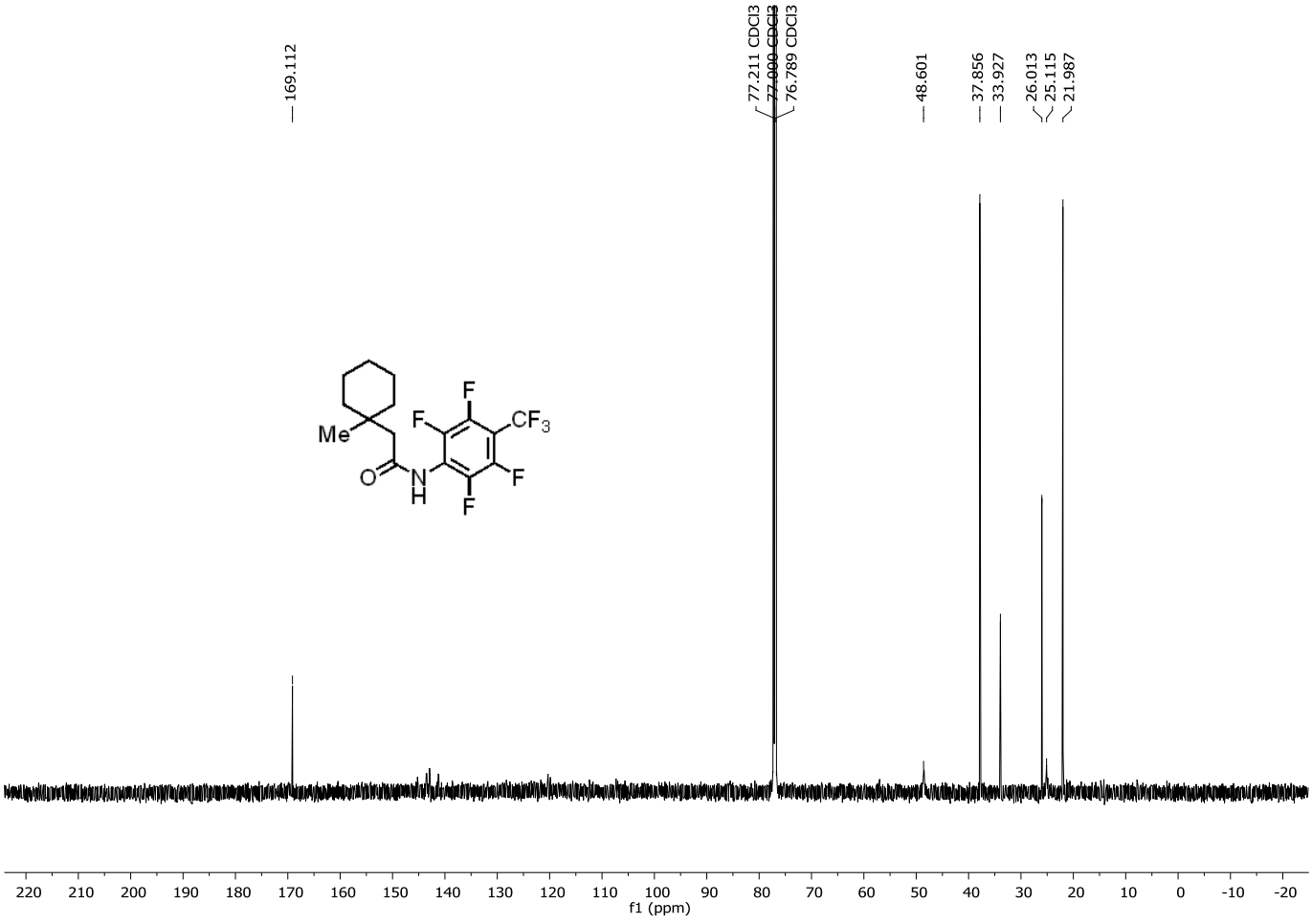
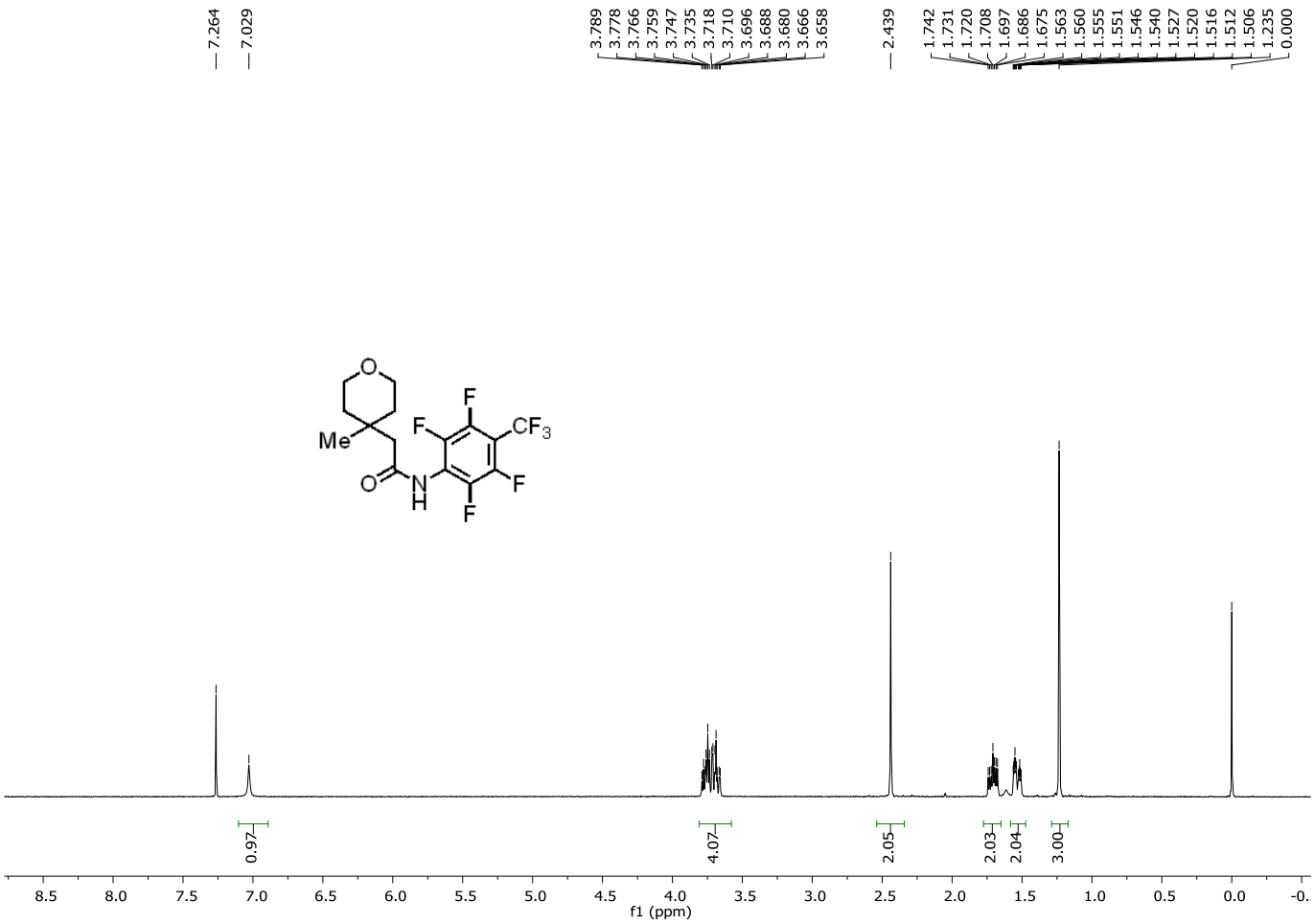
77.210 CDCl3
76.999 CDCl3
76.787 CDCl3
70.243
58.919
47.747
39.431
33.013
29.066
MeO
Me
O
N
H
F
F
F
F
CF3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

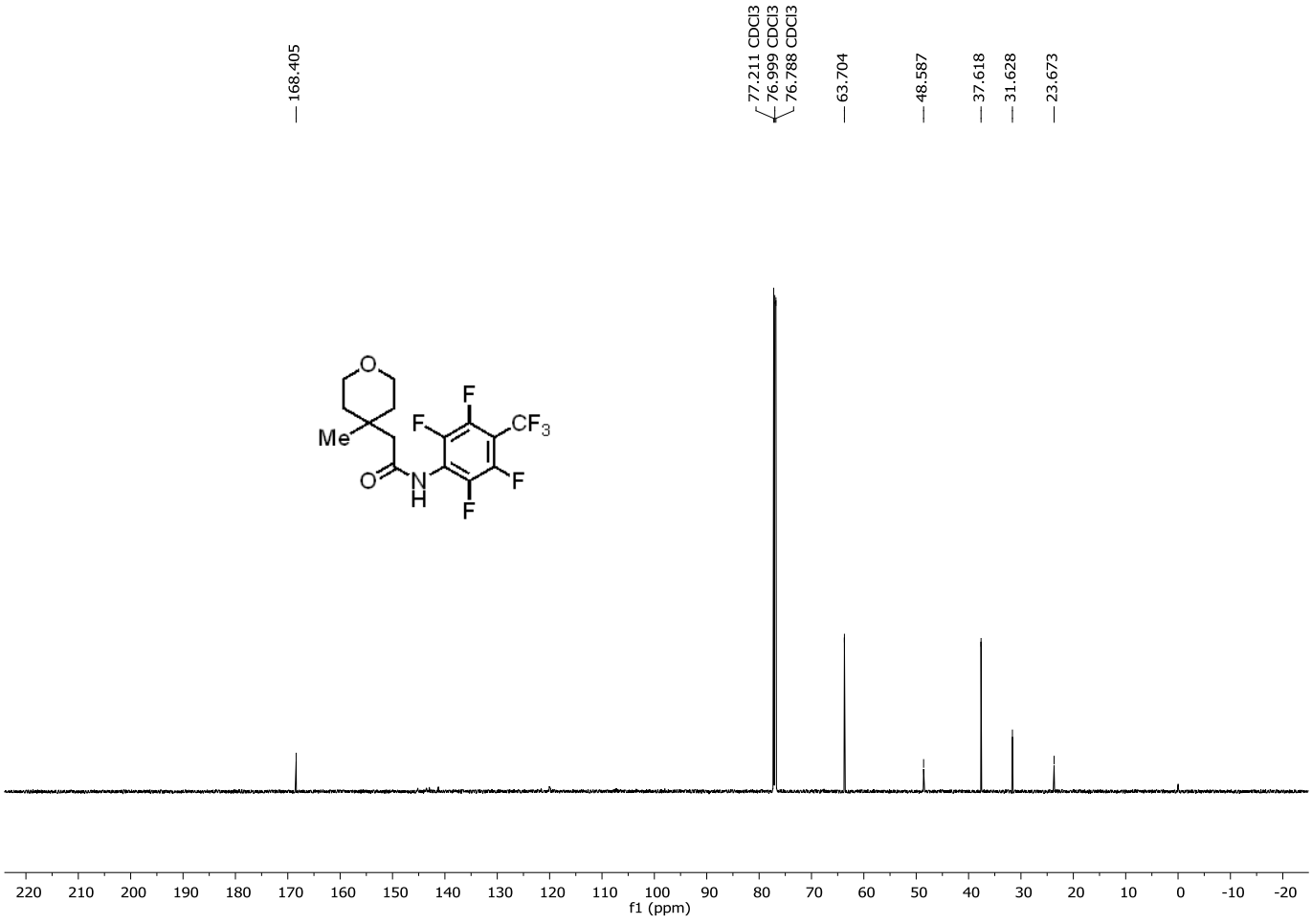

7.262
6.932
2.459
1.737
1.732
1.726
1.722
1.719
1.715
1.711
1.705
1.699
1.695
1.693
1.690
1.682
1.677
1.665
1.660
1.653
1.648
1.637
1.629
1.623
1.616
1.610
1.601
1.593
1.579
1.557
1.553
1.548
1.545
1.540
1.534
1.530
1.526
1.524
1.514
1.509
1.145
-0.000
Me
O
N
H
F
F
CF3
F
F
1.00
2.07
9.62
3.02
f1 (ppm)

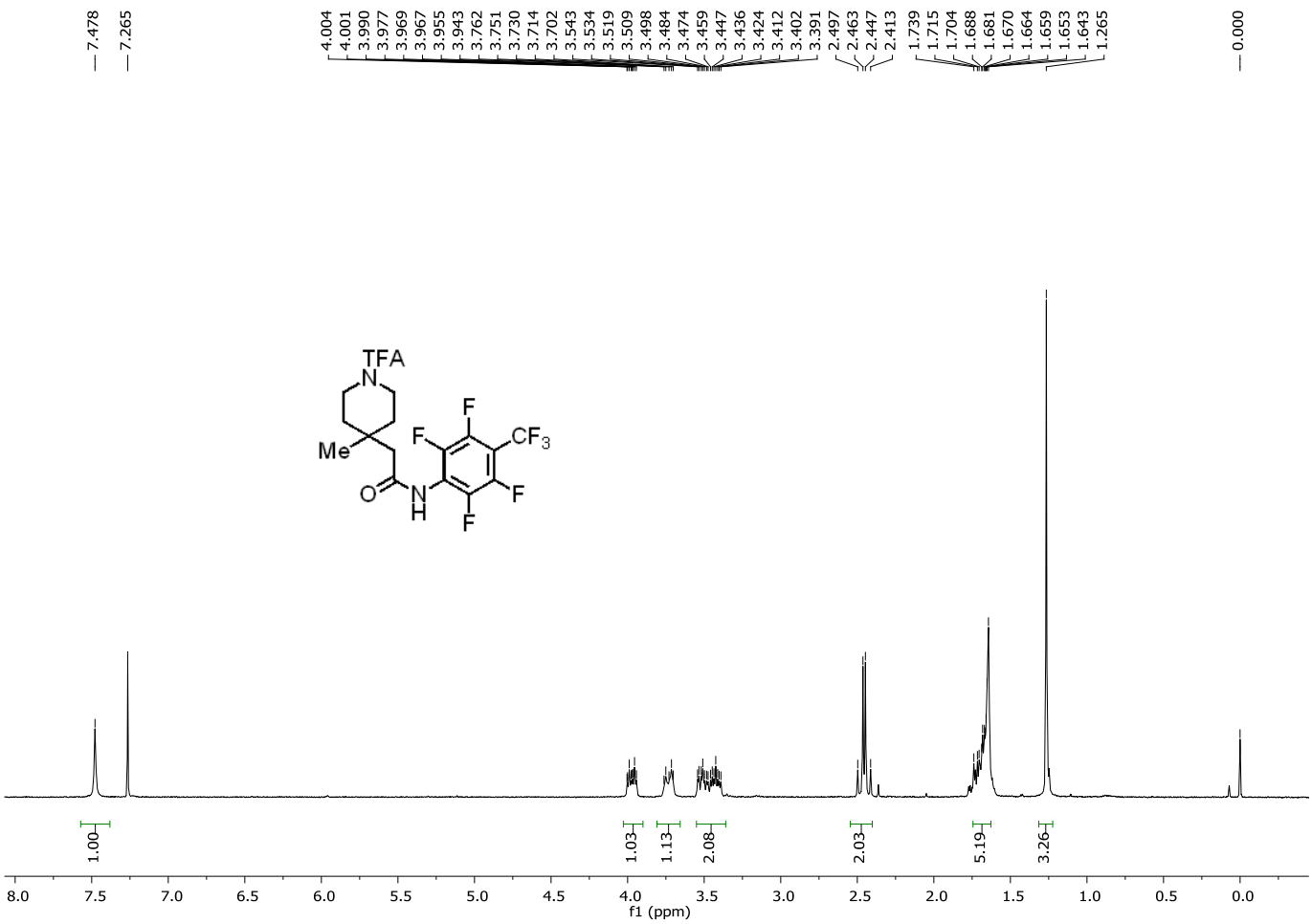

169.735
77.211 CDCl3
76.999 CDCl3
76.788 CDCl3
48.129
41.887
39.461
25.730
23.936
Me
O
N
H
F
F
CF3
F
F
f1 (ppm)

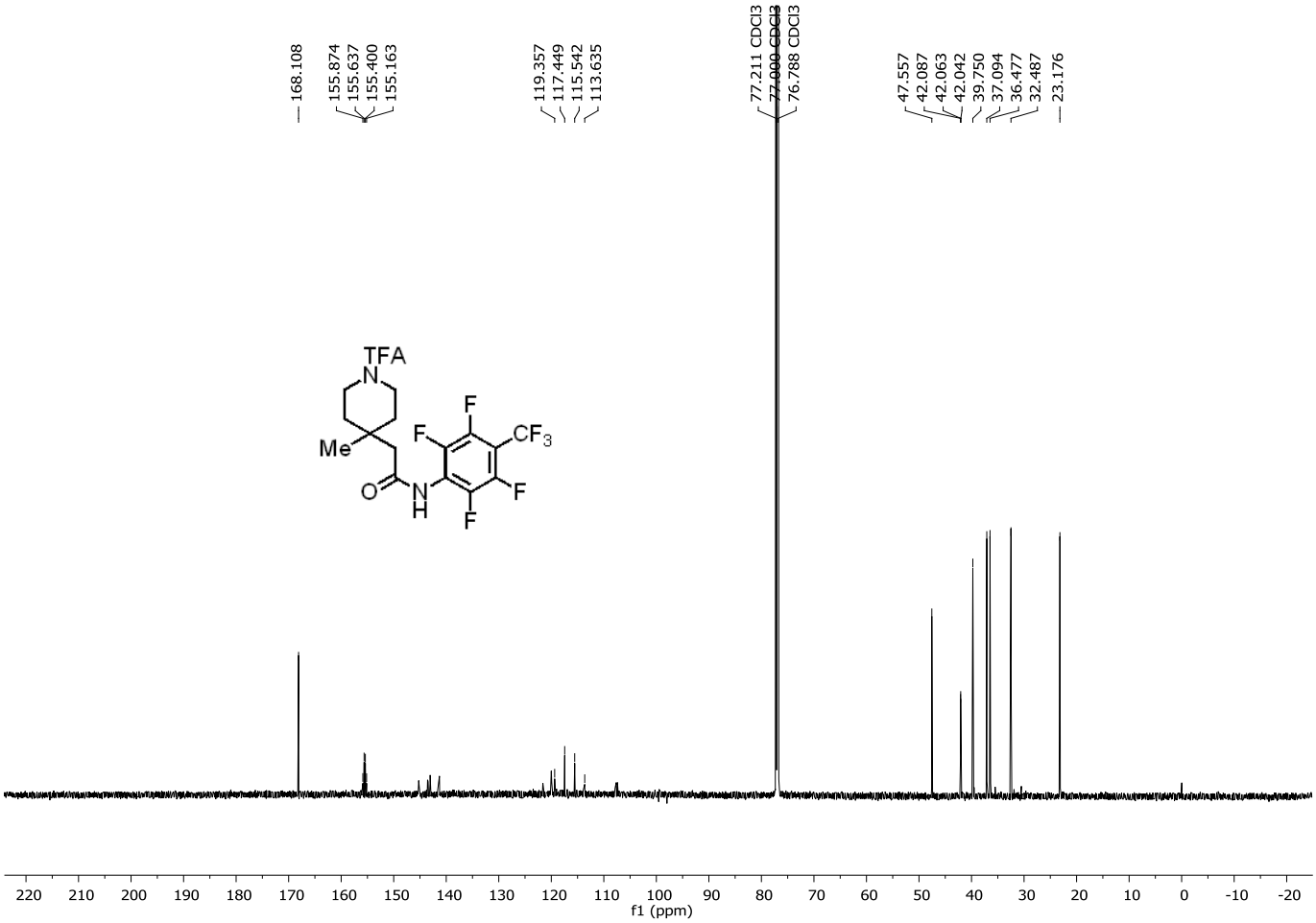

7.265
7.263
6.949
2.374
1.598
1.595
1.532
1.521
1.513
1.505
1.484
1.472
1.456
1.445
1.429
1.410
1.113
0.002
-0.001
Me
F
F
CF3
O
N
H
F
F
1.00
2.09
10.65
3.15
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

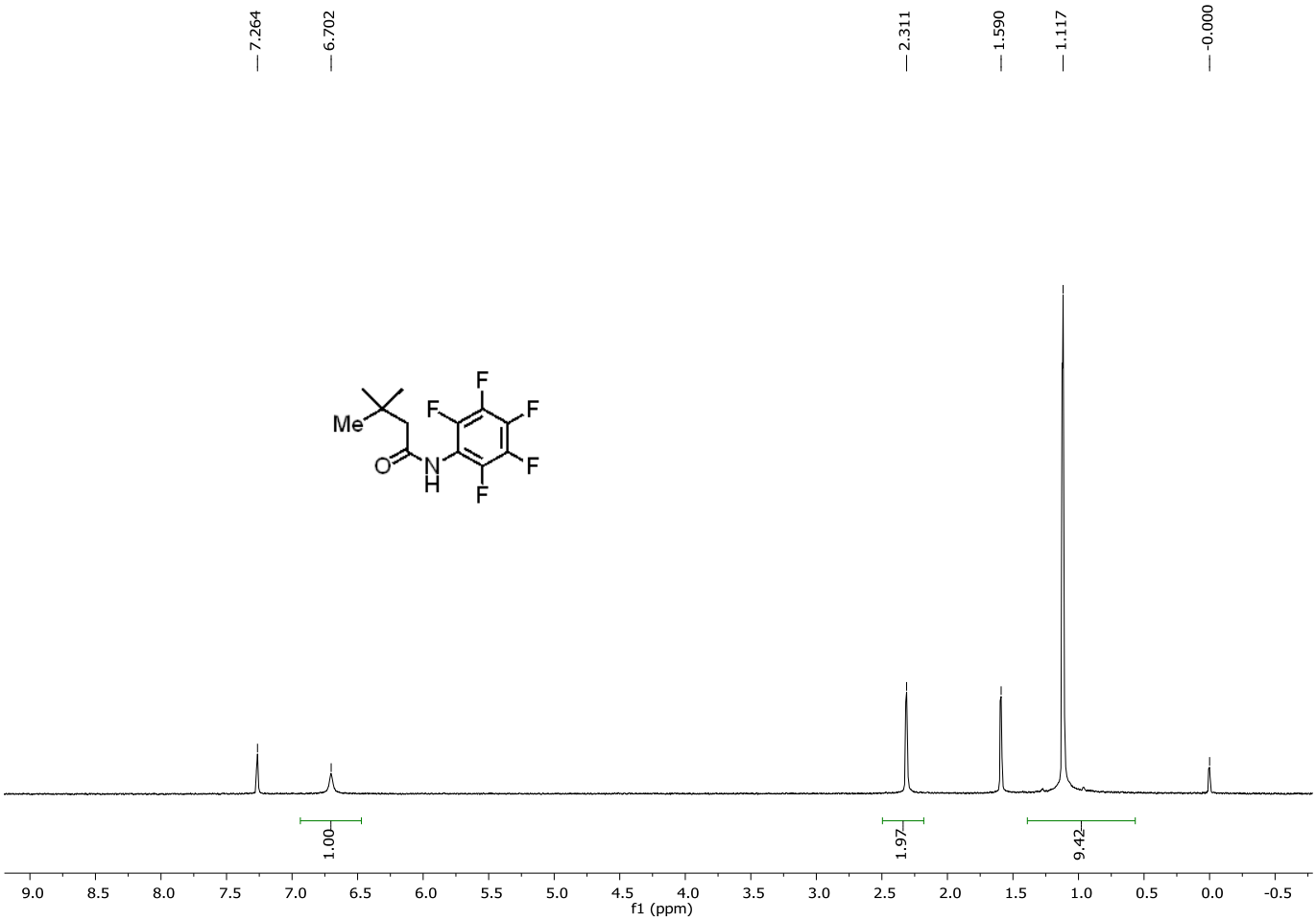

169.112
77.211 CDCl3
77.000 CDCl3
76.789 CDCl3
48.601
37.856
33.927
26.013
25.115
21.987
Me
F
F
CF3
O
N
H
F
F
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

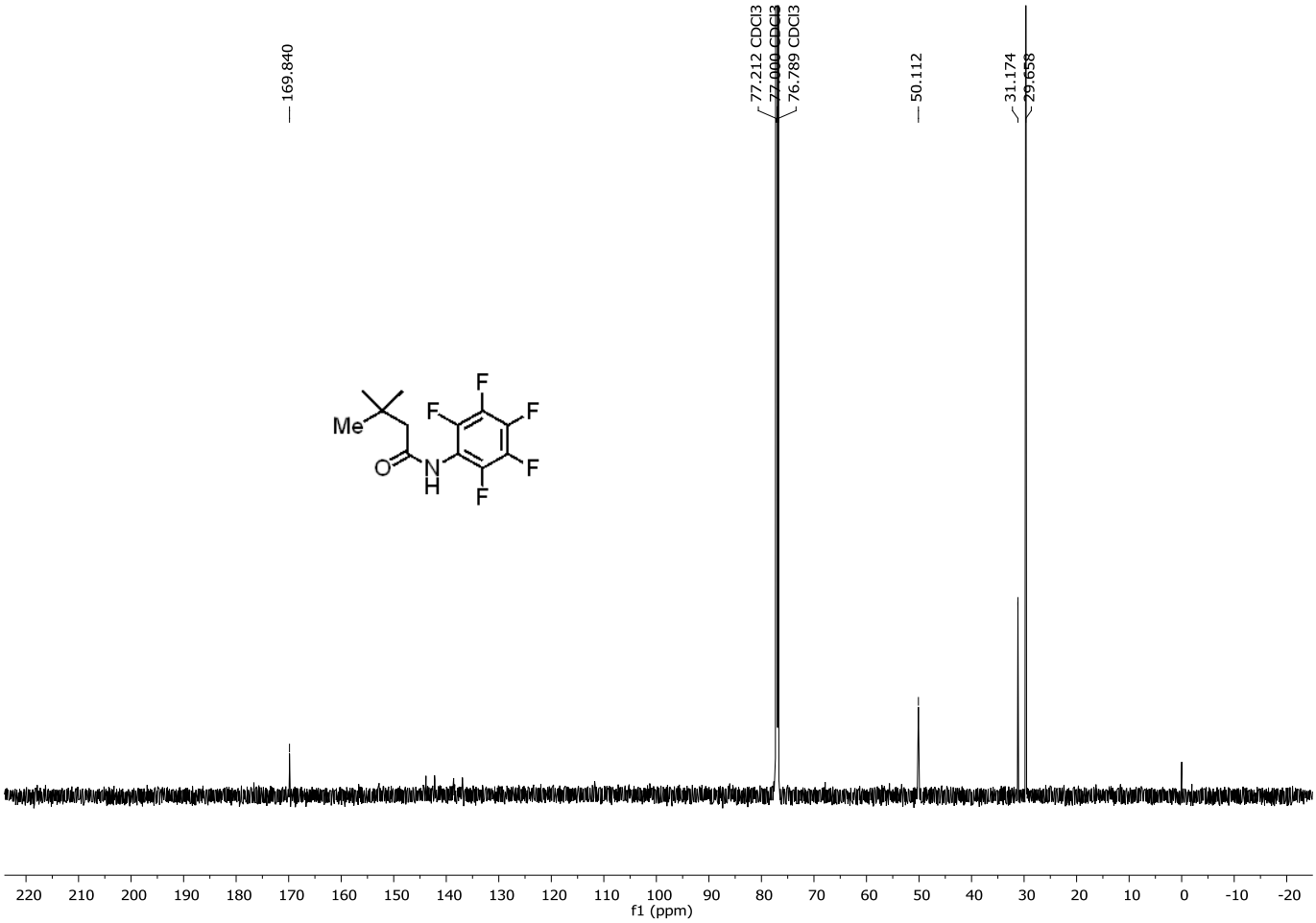

7.264
7.029
3.789
3.778
3.766
3.759
3.747
3.735
3.718
3.710
3.696
3.688
3.680
3.666
3.658
2.439
1.742
1.731
1.720
1.708
1.697
1.686
1.675
1.563
1.560
1.555
1.551
1.546
1.540
1.527
1.520
1.516
1.512
1.506
1.235
0.000
Me
O
N
H
F
CF3
0.97
4.07
2.05
2.03
2.04
3.00
f1 (ppm)

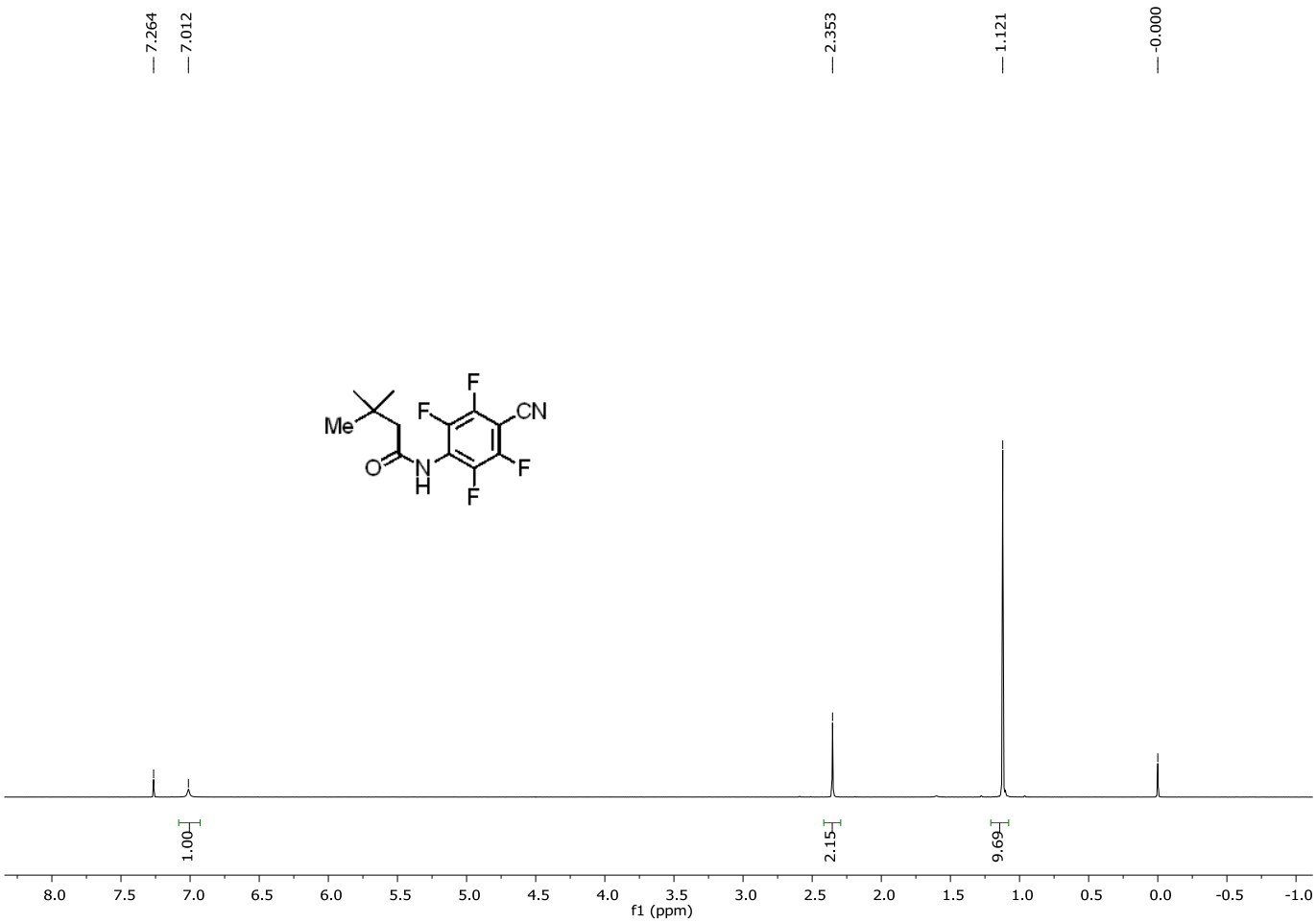

168.405
77.211 CDCl3
76.999 CDCl3
76.788 CDCl3
63.704
48.587
37.618
31.628
23.673
Me
O
N
H
F
CF3
f1 (ppm)

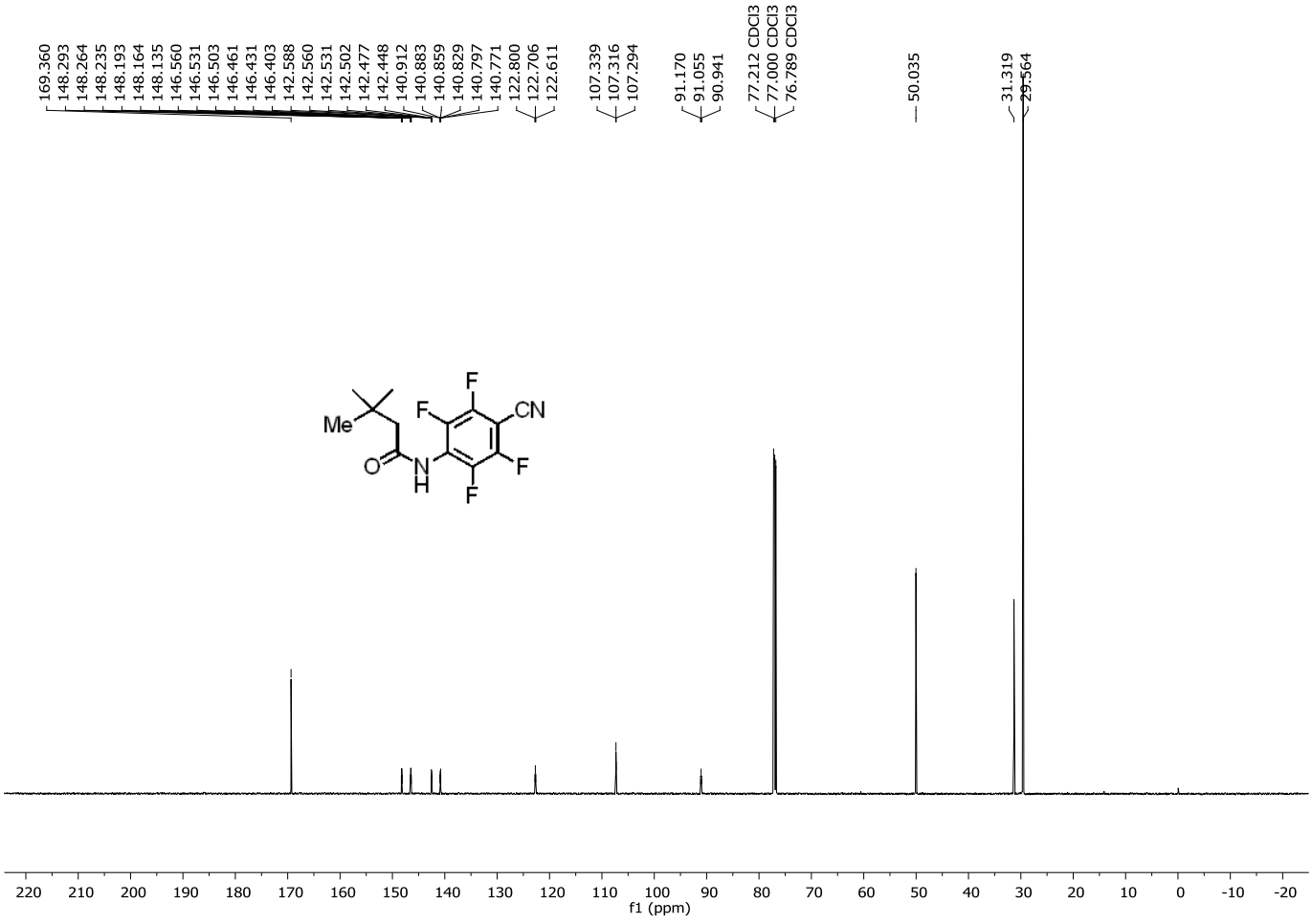

7.478
7.265
4.004
4.001
3.990
3.977
3.969
3.967
3.955
3.943
3.762
3.751
3.730
3.714
3.702
3.543
3.534
3.519
3.509
3.498
3.484
3.474
3.459
3.447
3.436
3.424
3.412
3.402
3.391
2.497
2.463
2.447
2.413
1.739
1.715
1.704
1.688
1.681
1.670
1.664
1.659
1.653
1.643
1.265
0.000
TFA
N
Me
O
N
H
F
F
CF3
F
F
1.00
1.03
1.13
2.08
2.03
5.19
3.26
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
0.0
f1 (ppm)

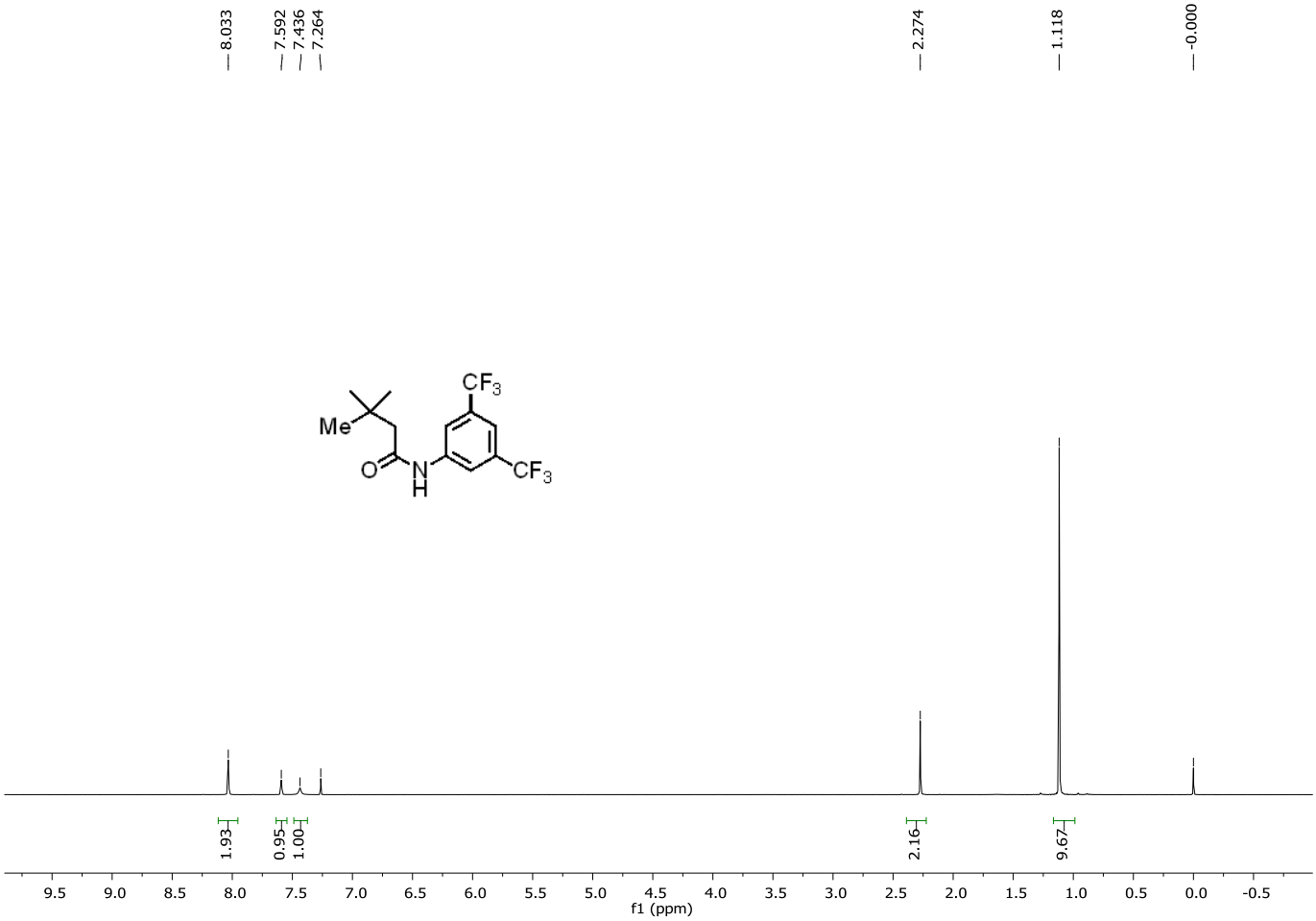

168.108
155.874
155.637
155.400
155.163
119.357
117.449
115.542
113.635
77.211 CDCl3
77.000 CDCl3
76.788 CDCl3
47.557
42.087
42.063
42.042
39.750
37.094
36.477
32.487
23.176
TFA
N
Me
O
N
H
F
F
CF3
F
F
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

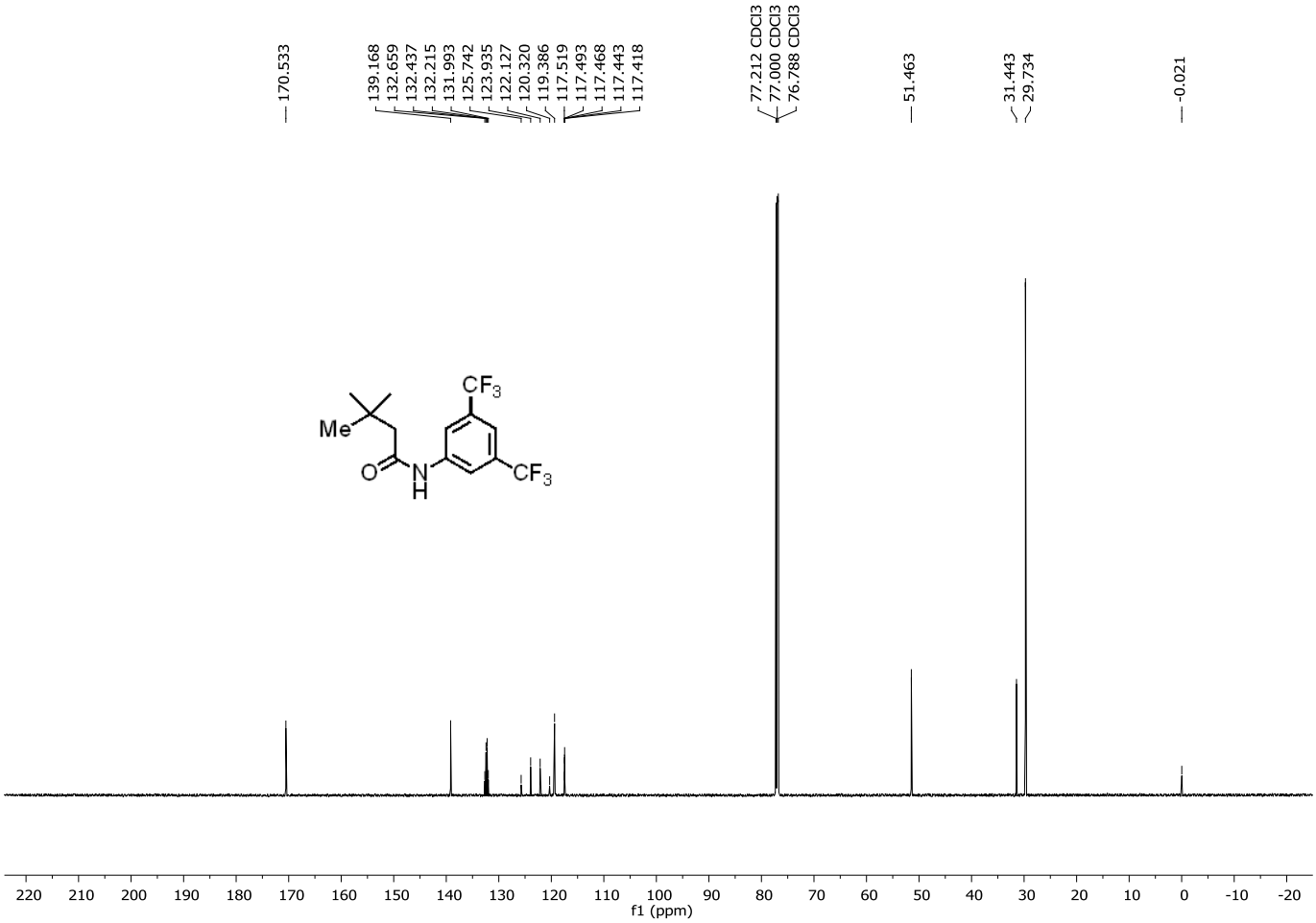

7.264
6.702
2.311
1.590
1.117
-0.000
Me
O
N
H
F
F
F
F
F
1.00
1.97
9.42
f1 (ppm)

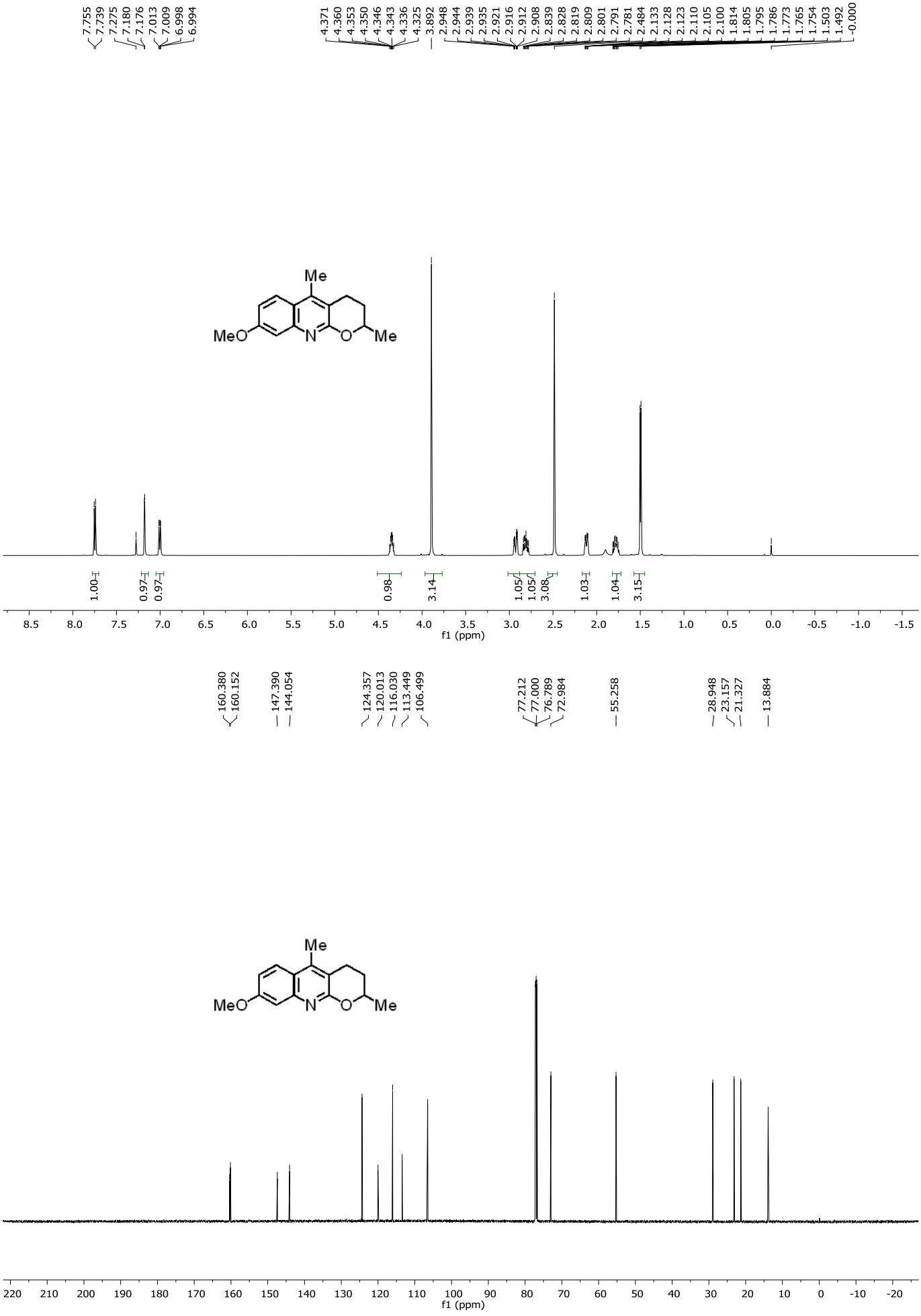

169.840
77.212 CDCl3
77.000 CDCl3
76.789 CDCl3
50.112
31.174
29.658
Me
O
N
H
F
F
F
F
F
f1 (ppm)

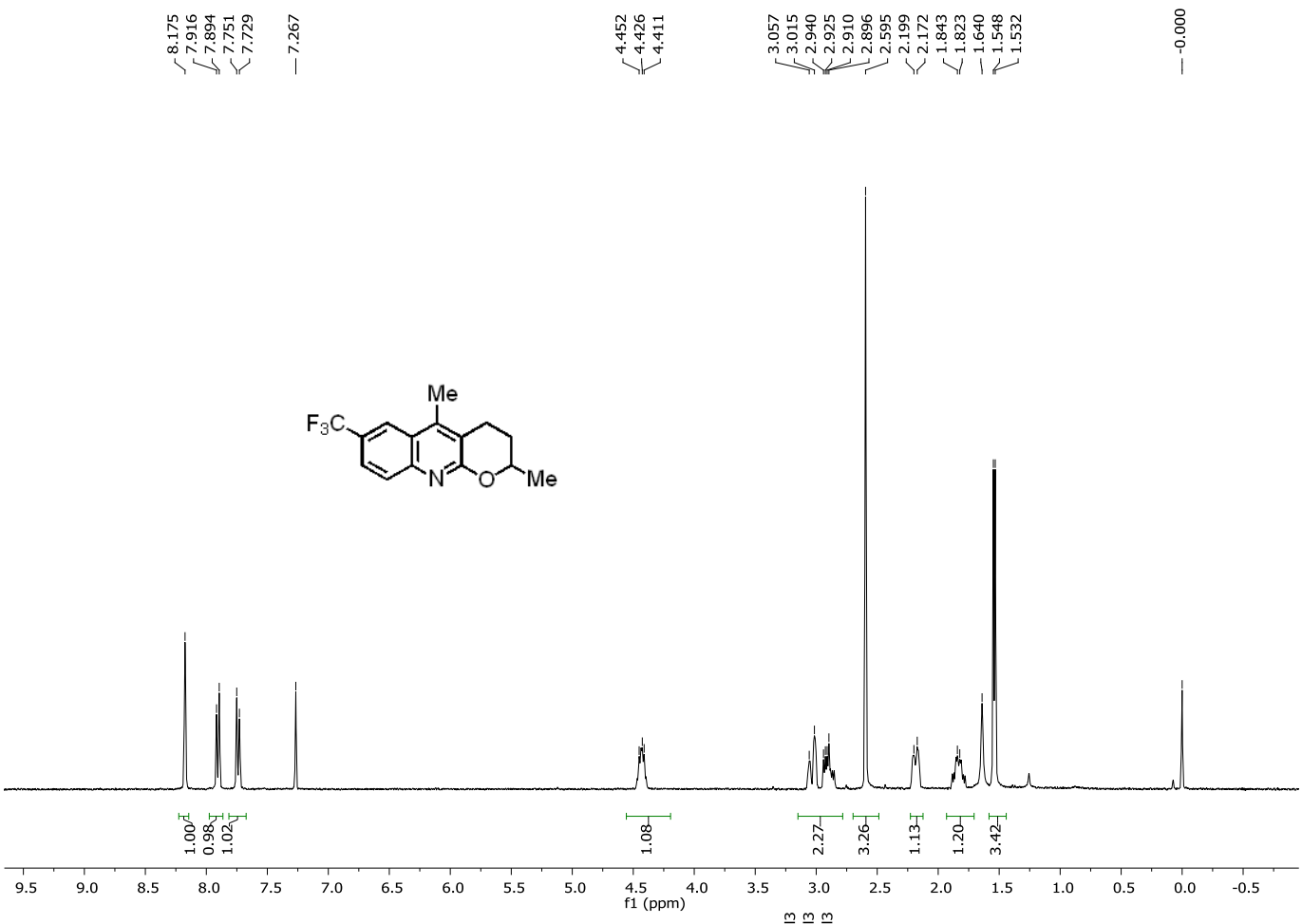

7.264
7.012
2.353
1.121
-0.000
Me
F
CN
O
N
H
1.00
2.15
9.69
f1 (ppm)


169.360
148.293
148.264
148.235
148.193
148.164
148.135
146.560
146.531
146.503
146.461
146.431
146.403
142.588
142.560
142.531
142.502
142.477
142.448
140.912
140.883
140.859
140.829
140.797
140.771
122.800
122.706
122.611
107.339
107.316
107.294
91.170
91.055
90.941
77.212 CDCl3
77.000 CDCl3
76.789 CDCl3
50.035
31.319
29.564
Me
F
CN
O
N
H
f1 (ppm)


8.033
7.592
7.436
7.264
2.274
1.118
-0.000
CF3
Me
O
N
H
CF3
1.93
0.95
1.00
2.16
9.67
f1 (ppm)


170.533
139.168
132.659
132.437
132.215
131.993
125.742
123.935
122.127
120.320
119.386
117.519
117.493
117.468
117.443
117.418
77.212 CDCl3
77.000 CDCl3
76.788 CDCl3
51.463
31.443
29.734
-0.021
CF3
Me
O
N
H
CF3
f1 (ppm)


7.755
7.739
7.275
7.180
7.176
7.013
7.009
6.998
6.994
4.371
4.360
4.353
4.350
4.346
4.343
4.336
4.325
3.892
2.948
2.944
2.939
2.935
2.921
2.916
2.912
2.908
2.839
2.828
2.819
2.809
2.801
2.791
2.781
2.484
2.133
2.128
2.123
2.110
2.105
2.100
1.814
1.805
1.795
1.786
1.773
1.765
1.754
1.503
1.492
-0.000
Me
MeO
N
O
Me
1.00
0.97
0.97
0.98
3.14
1.05
1.05
3.08
1.03
1.04
3.15
f1 (ppm)
160.380
160.152
147.390
144.054
124.357
120.013
116.030
113.449
106.499
77.212
77.000
76.789
72.984
55.258
28.948
23.157
21.327
13.884
Me
MeO
N
O
Me
f1 (ppm)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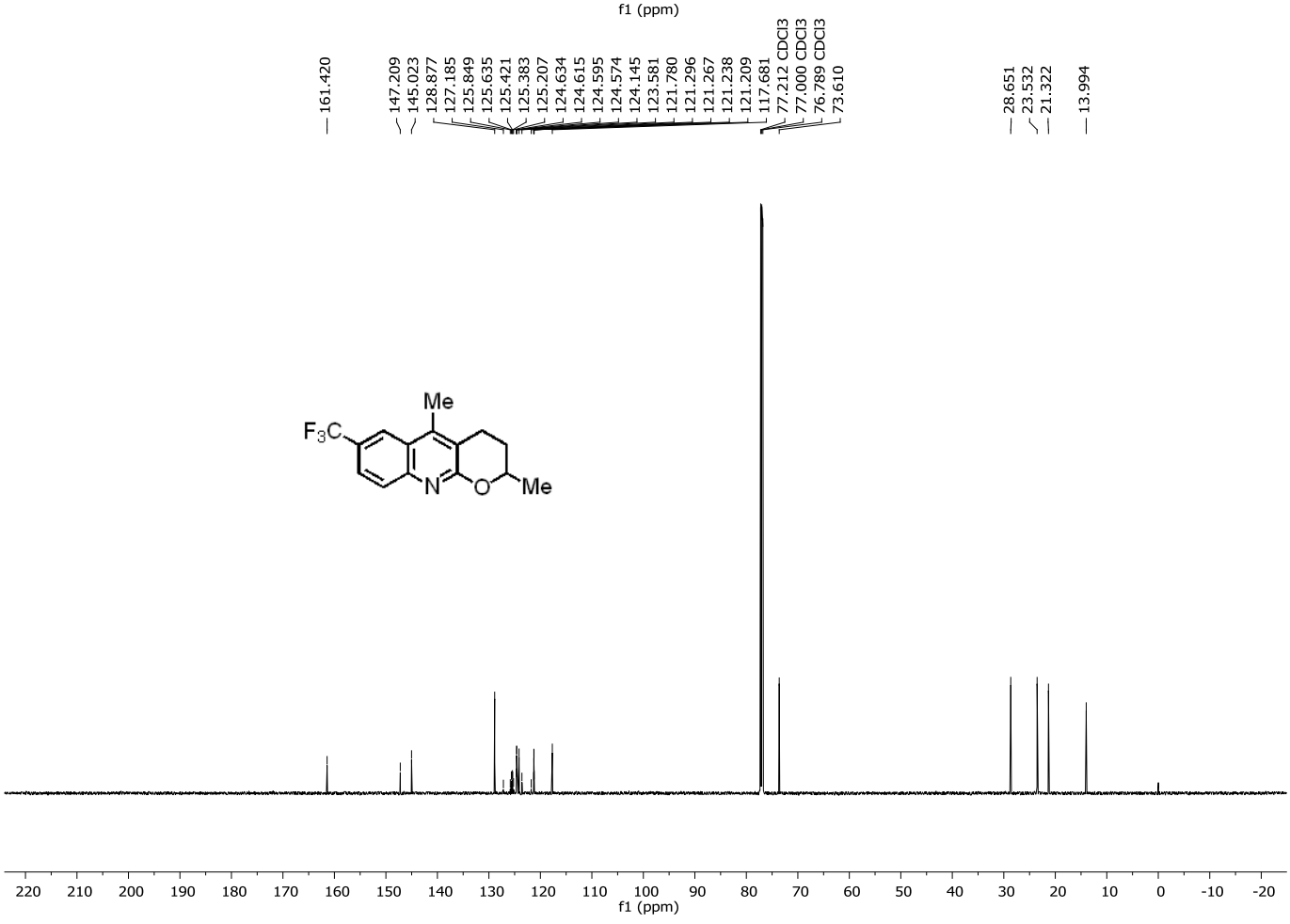
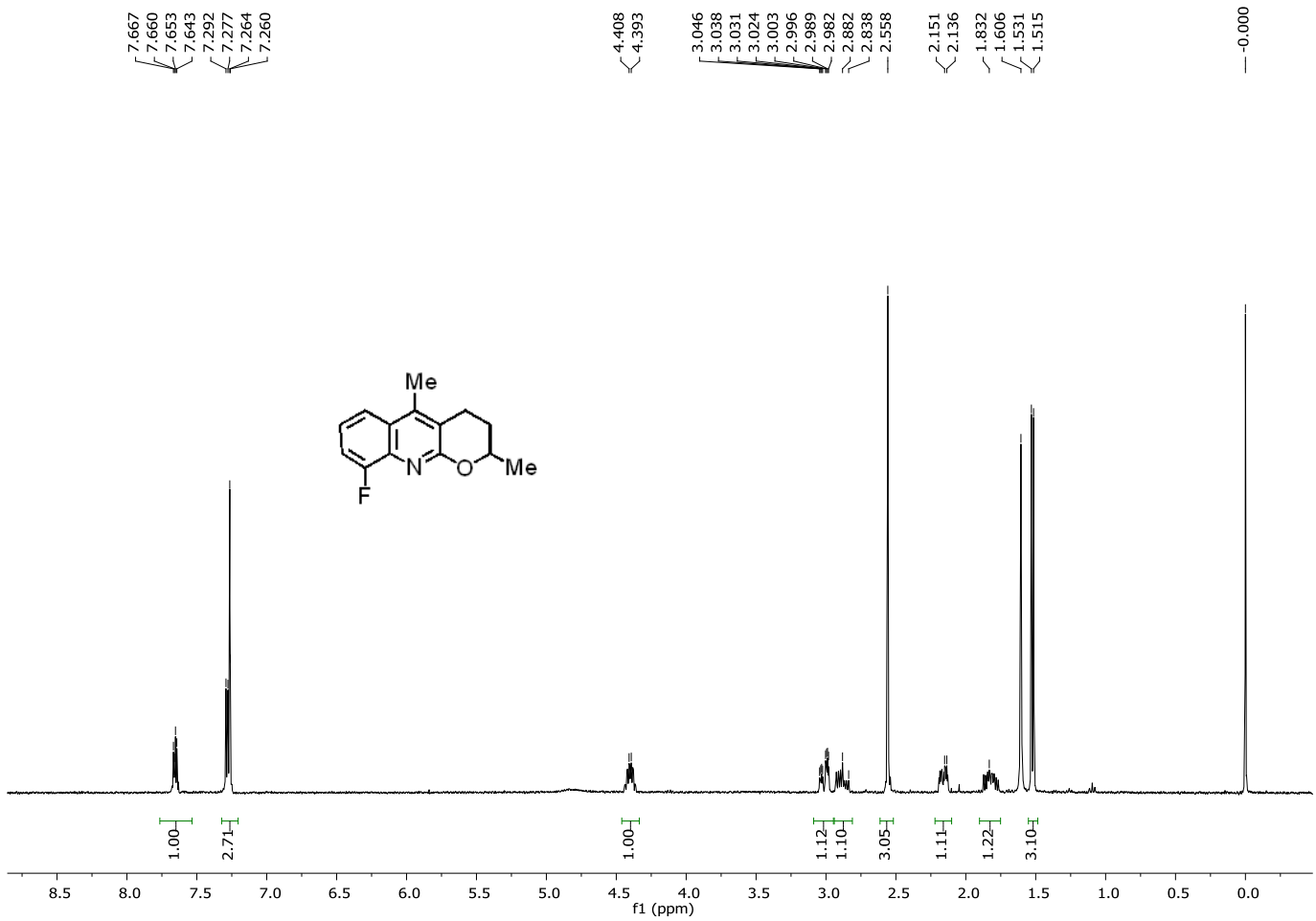
7.916
7.894
7.751
7.729
7.267
4.452
4.426
4.411
3.057
3.015
2.940
2.925
2.910
2.896
2.595
2.199
2.172
1.843
1.823
1.640
1.548
1.532
-0.000
Me
F3C
N
O
Me
1.00
0.98
1.02
1.08
2.27
3.26
1.13
1.20
3.42
f1 (ppm)


161.420
147.209
145.023
128.877
127.185
125.849
125.635
125.421
125.383
125.207
124.634
124.615
124.595
124.574
124.145
123.581
121.780
121.296
121.267
121.238
121.209
117.681
77.212 CDCl3
77.000 CDCl3
76.789 CDCl3
73.610
28.651
23.532
21.322
13.994
Me
F3C
N
O
Me
f1 (ppm)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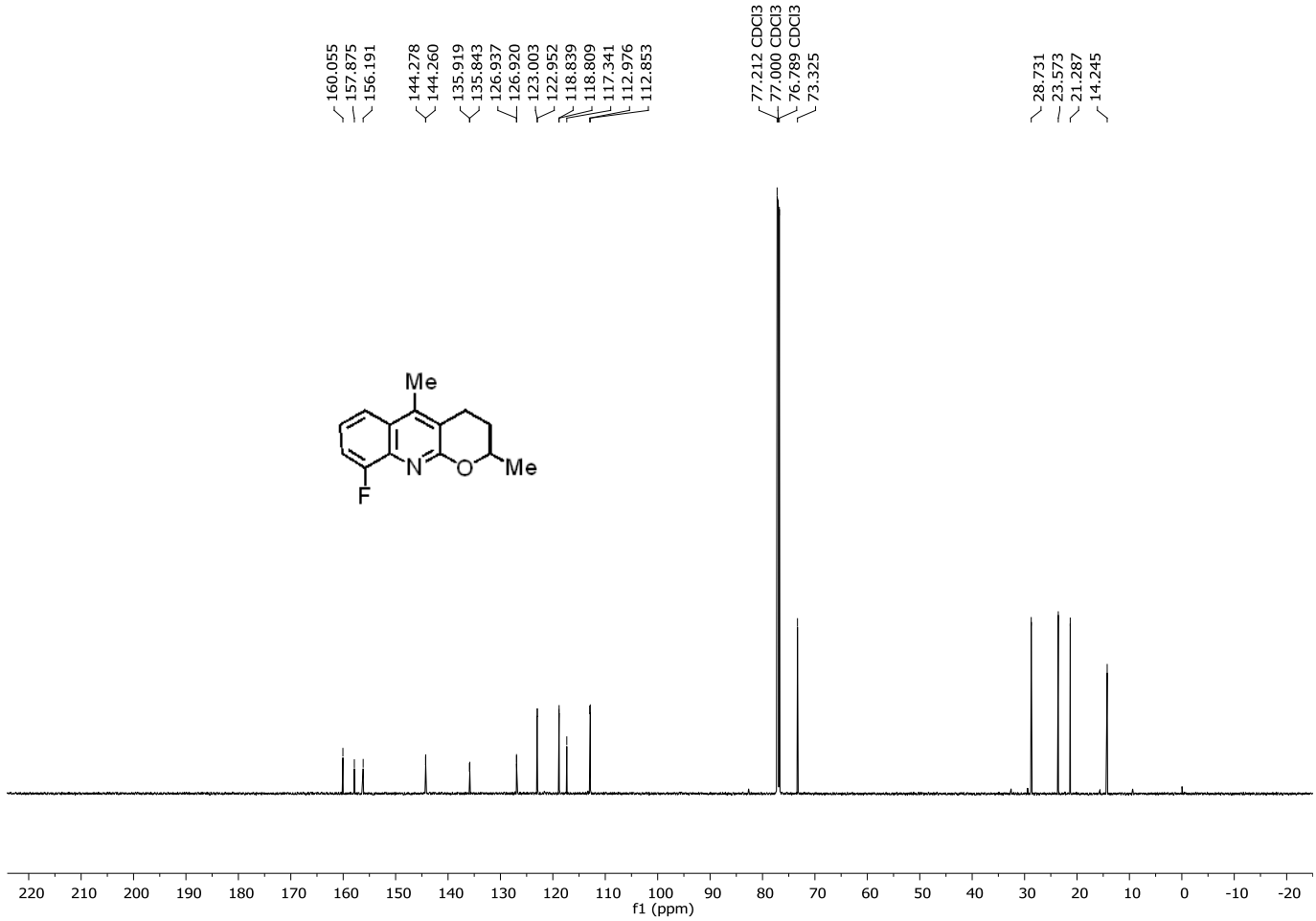
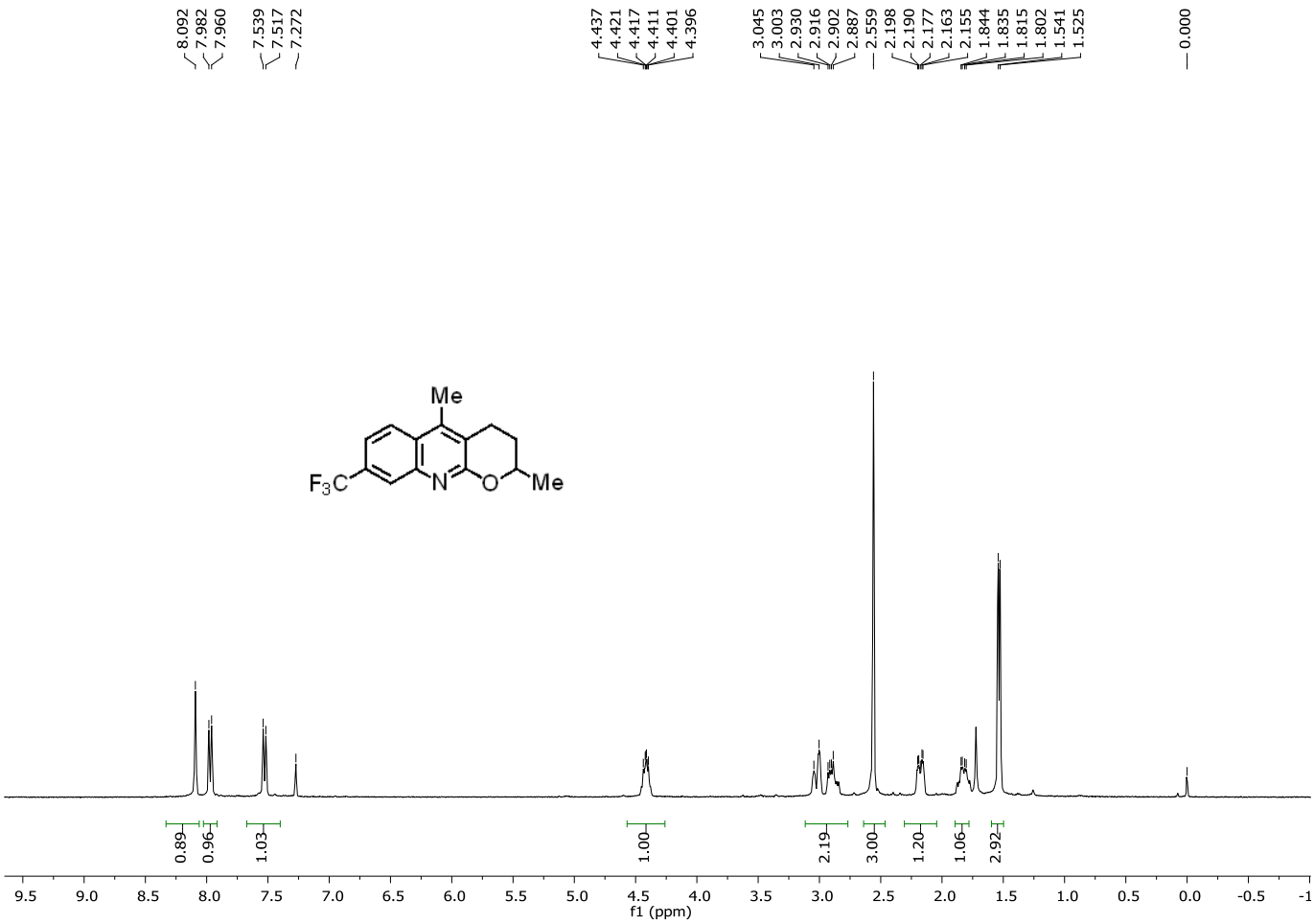
7.660
7.653
7.643
7.292
7.277
7.264
7.260
4.408
4.393
3.046
3.038
3.031
3.024
3.003
2.996
2.989
2.982
2.882
2.838
2.558
2.151
2.136
1.832
1.606
1.531
1.515
-0.000
Me
N
O
Me
F
1.00
2.71
1.00
1.12
1.10
3.05
1.11
1.22
3.10
f1 (ppm)


160.055
157.875
156.191
144.278
144.260
135.919
135.843
126.937
126.920
123.003
122.952
118.839
118.809
117.341
112.976
112.853
77.212 CDCl3
77.000 CDCl3
76.789 CDCl3
73.325
28.731
23.573
21.287
14.245
Me
N
O
Me
F
f1 (ppm)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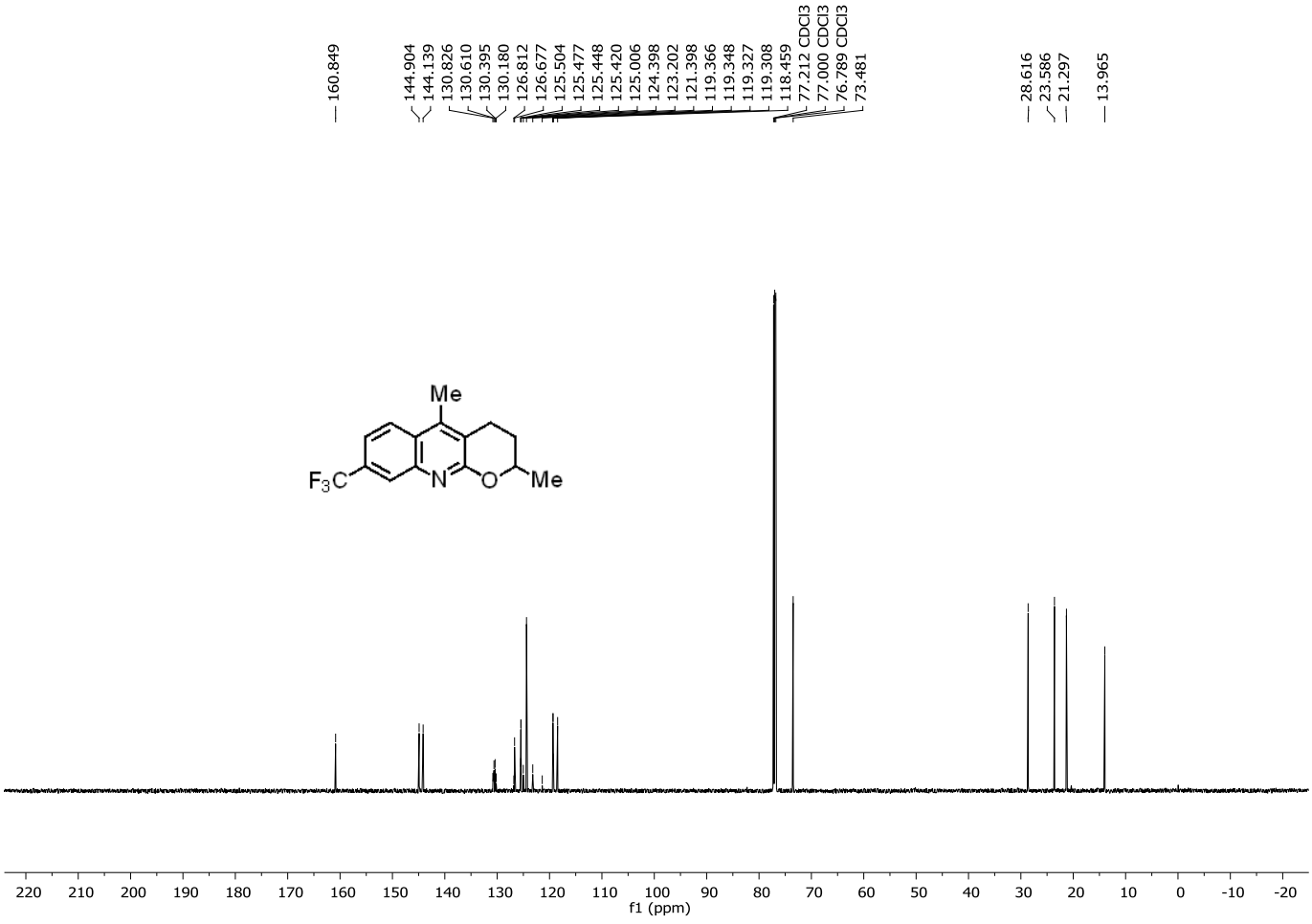
7.982
7.960
7.539
7.517
7.272
4.437
4.421
4.417
4.411
4.401
4.396
3.045
3.003
2.930
2.916
2.902
2.887
2.559
2.198
2.190
2.177
2.163
2.155
1.844
1.835
1.815
1.802
1.541
1.525
0.000
Me
F3C
N
O
Me
0.89
0.96
1.03
1.00
2.19
3.00
1.20
1.06
2.92
f1 (ppm)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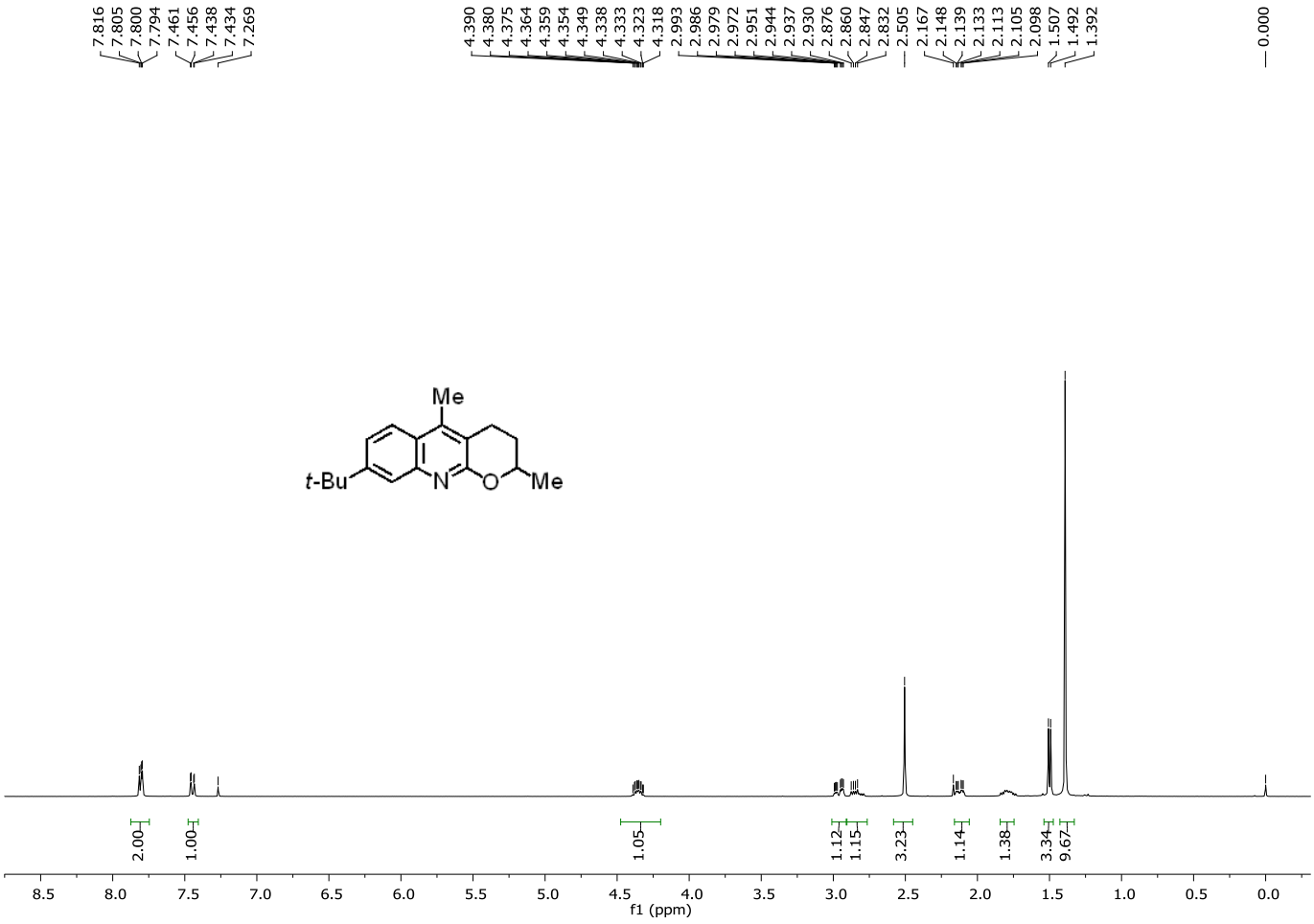
144.904
144.139
130.826
130.610
130.395
130.180
126.812
126.677
125.504
125.477
125.448
125.420
125.006
124.398
123.202
121.398
119.366
119.348
119.327
119.308
118.459
77.212 CDCl3
77.000 CDCl3
76.789 CDCl3
73.481
28.616
23.586
21.297
13.965
Me
F3C
N
O
Me
f1 (ppm)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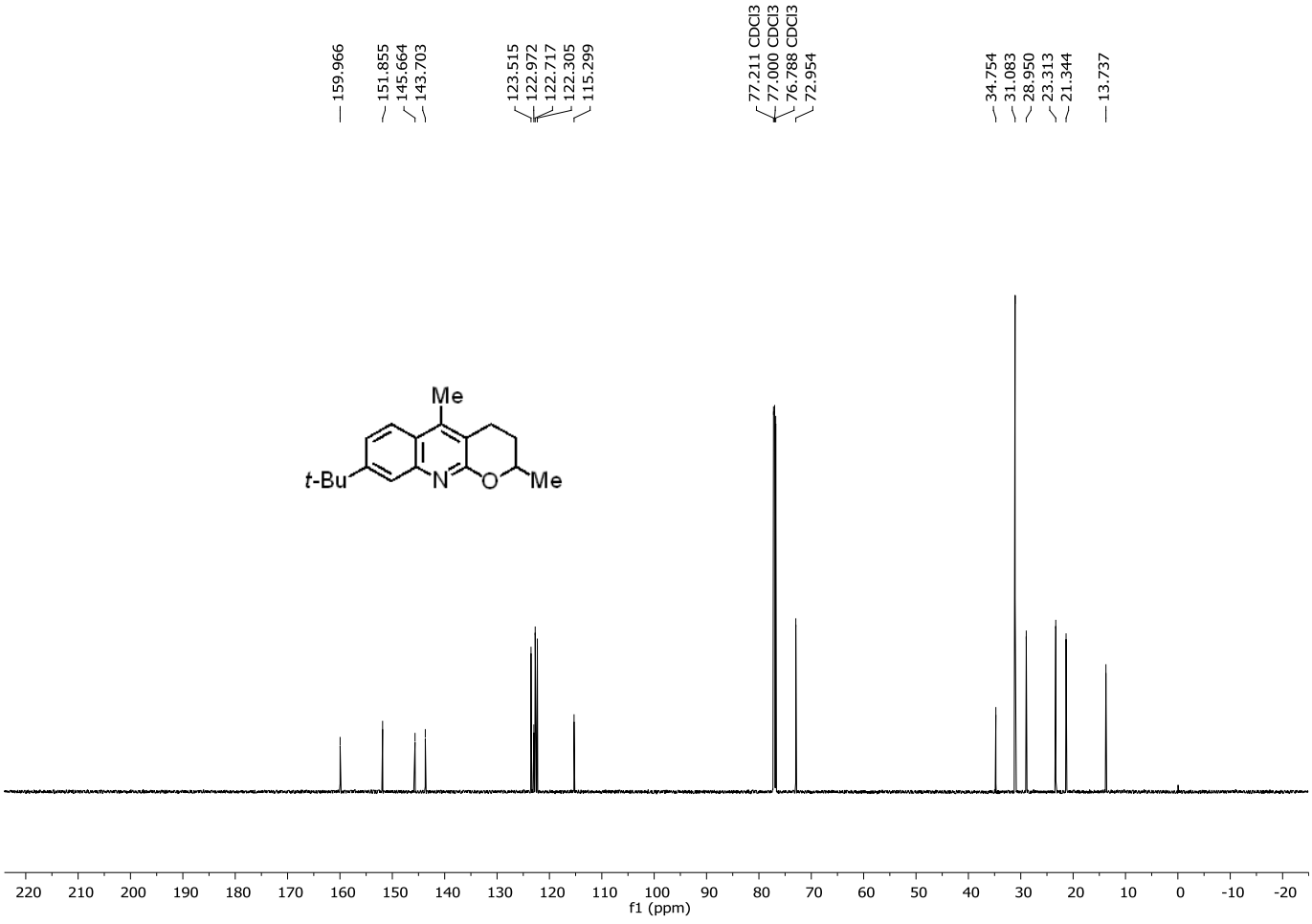
7.800
7.794
7.461
7.456
7.438
7.434
7.269
4.390
4.380
4.375
4.364
4.359
4.354
4.349
4.338
4.333
4.323
4.318
2.993
2.986
2.979
2.972
2.951
2.944
2.937
2.930
2.876
2.860
2.847
2.832
2.505
2.167
2.148
2.139
2.133
2.113
2.105
2.098
1.507
1.492
1.392
0.000
Me
t-Bu
N
O
Me
2.00
1.00
1.05
1.12
1.15
3.23
1.14
1.38
3.34
9.67
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
0.0
f1 (ppm)


159.966
151.855
145.664
143.703
123.515
122.972
122.717
122.305
115.299
77.211 CDCl3
77.000 CDCl3
76.788 CDCl3
72.954
34.754
31.083
28.950
23.313
21.344
13.737
Me
t-Bu
N
O
Me
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
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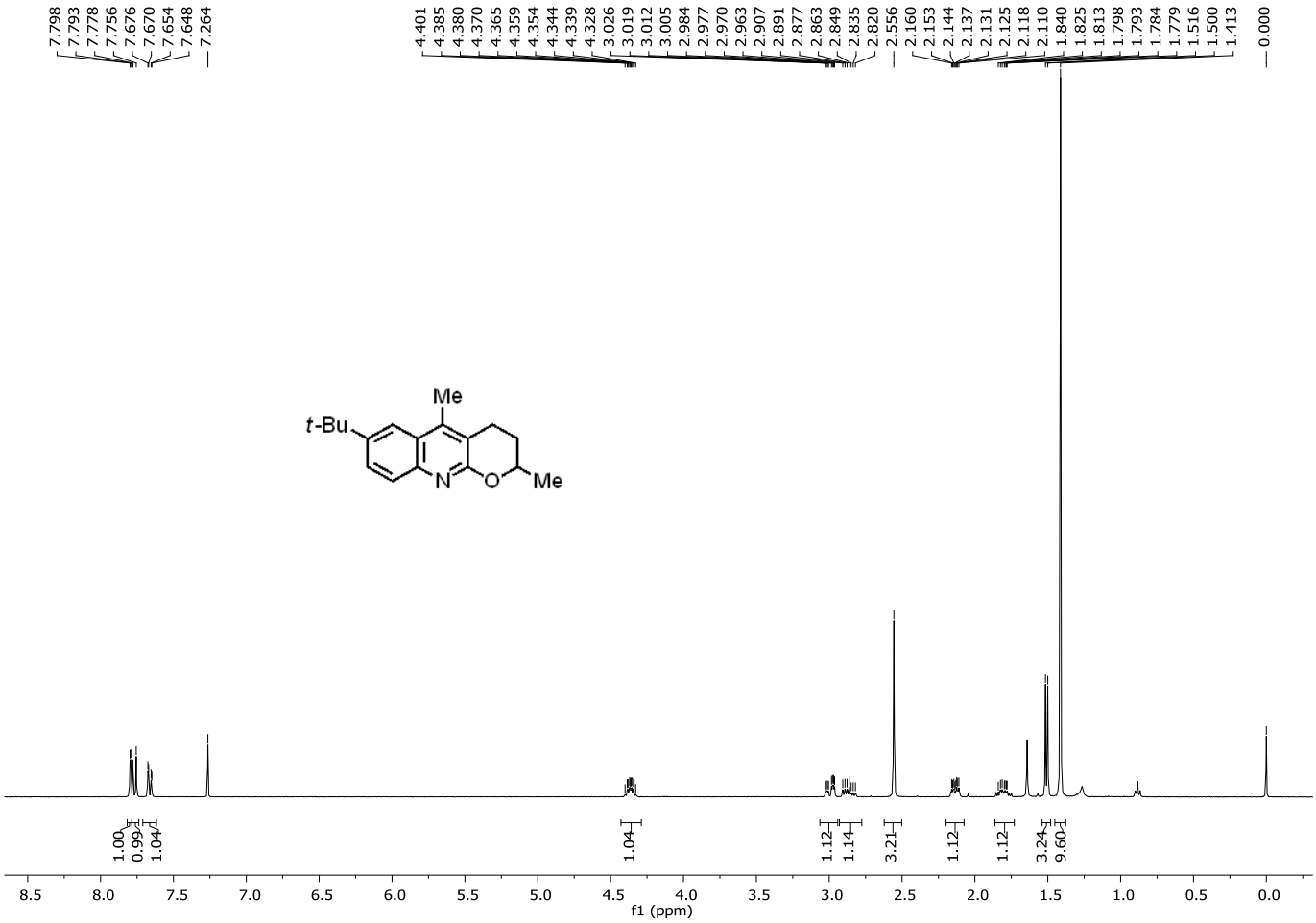
f1 (ppm)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4.359
4.354
4.344
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3.019
3.012
3.005
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2.977
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2.963
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2.877
2.863
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2.835
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2.153
2.144
2.137
2.131
2.125
2.118
2.110
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1.798
1.793
1.784
1.779
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1.413
0.000
Me
t-Bu
N
O
Me
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0.99
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1.04
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1.12
1.12
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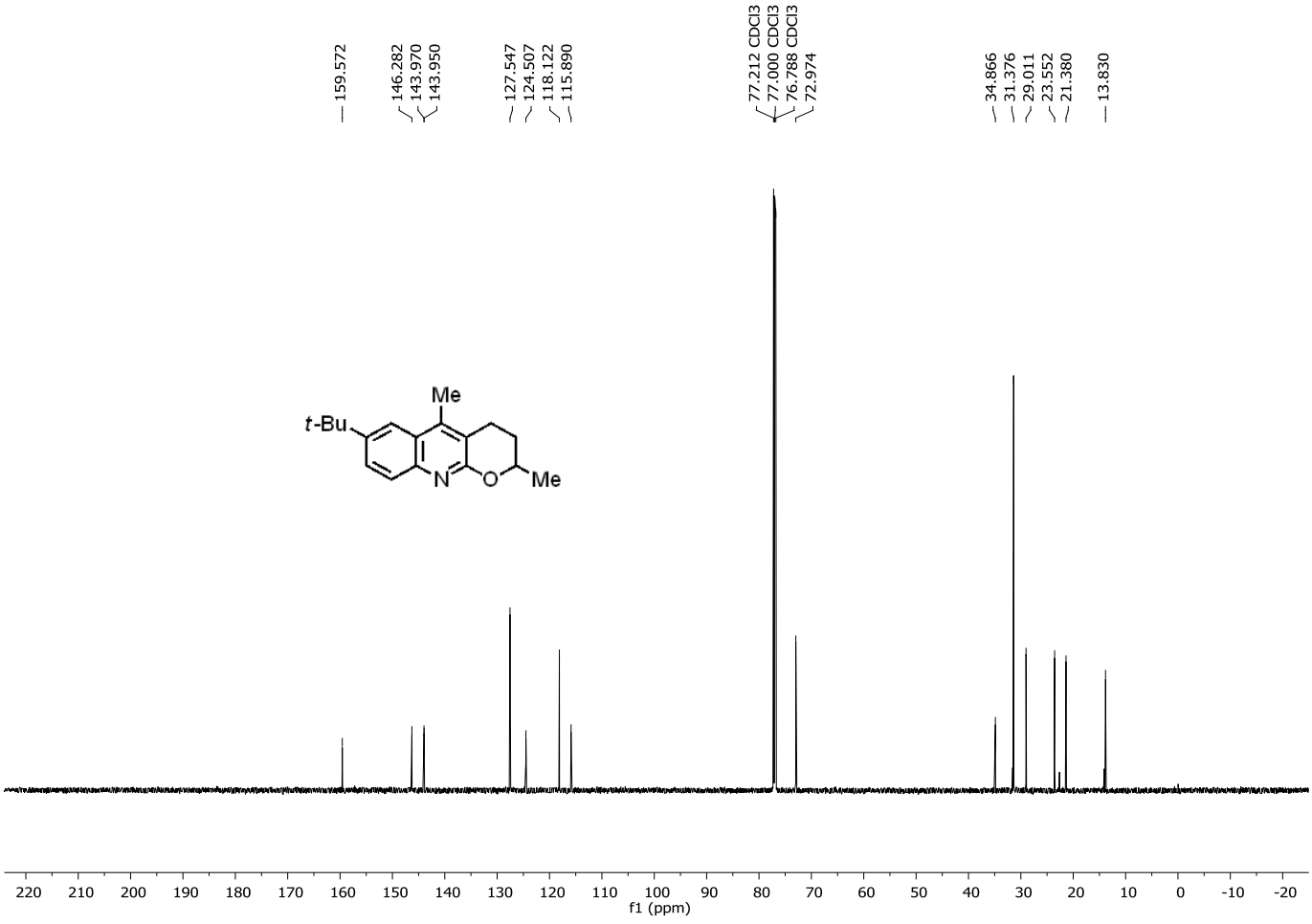
f1 (ppm)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76.788 CDCl3
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29.011
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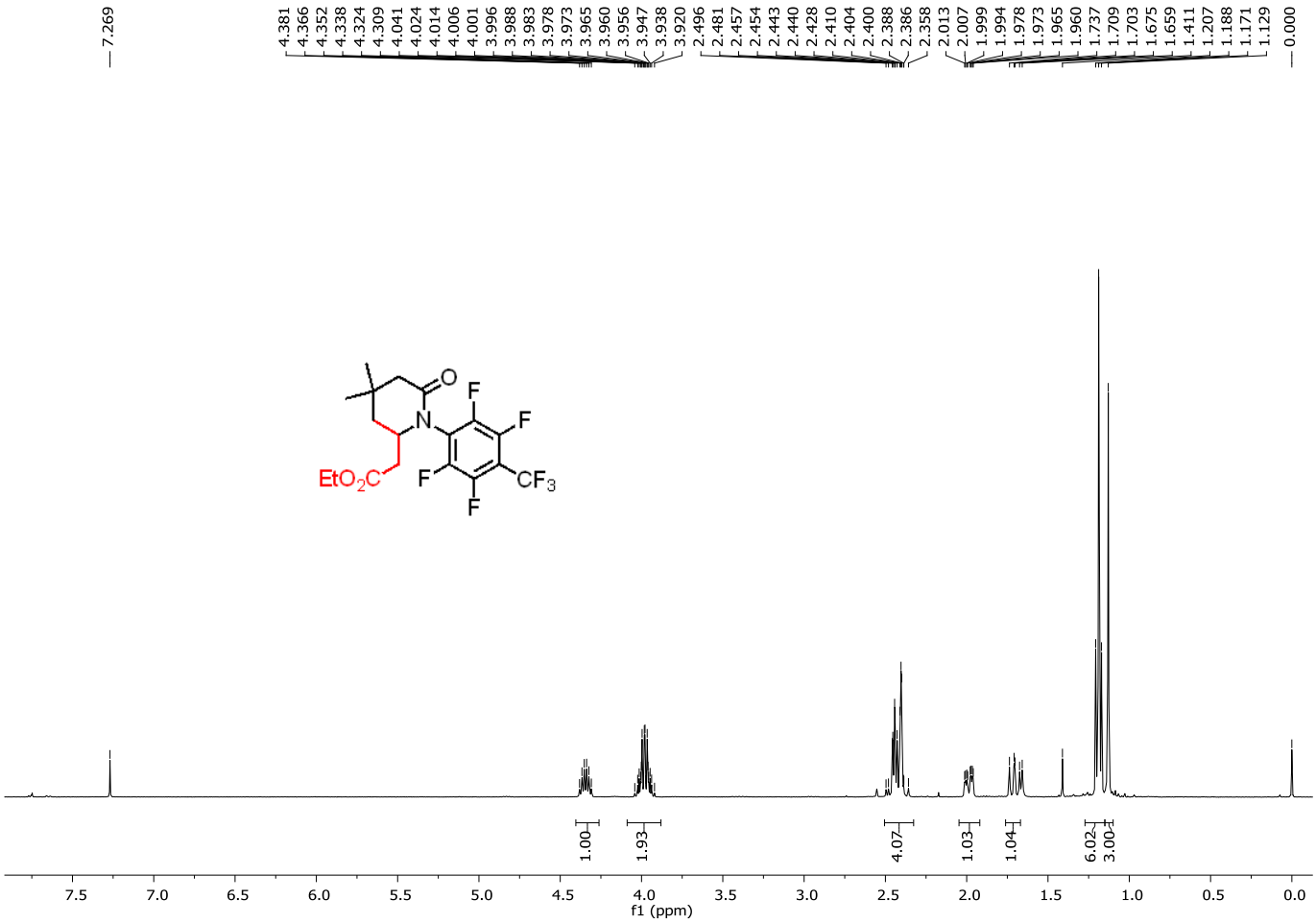
Me
t-Bu
N
O
Me
f1 (ppm)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3.920
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2.481
2.457
2.454
2.443
2.440
2.428
2.410
2.404
2.400
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1.659
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1.207
1.188
1.171
1.129
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O
N
F
F
F
F
CF3
EtO2C
1.00
1.93
4.07
1.03
1.04
6.02
3.00
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6.5
6.0
5.5
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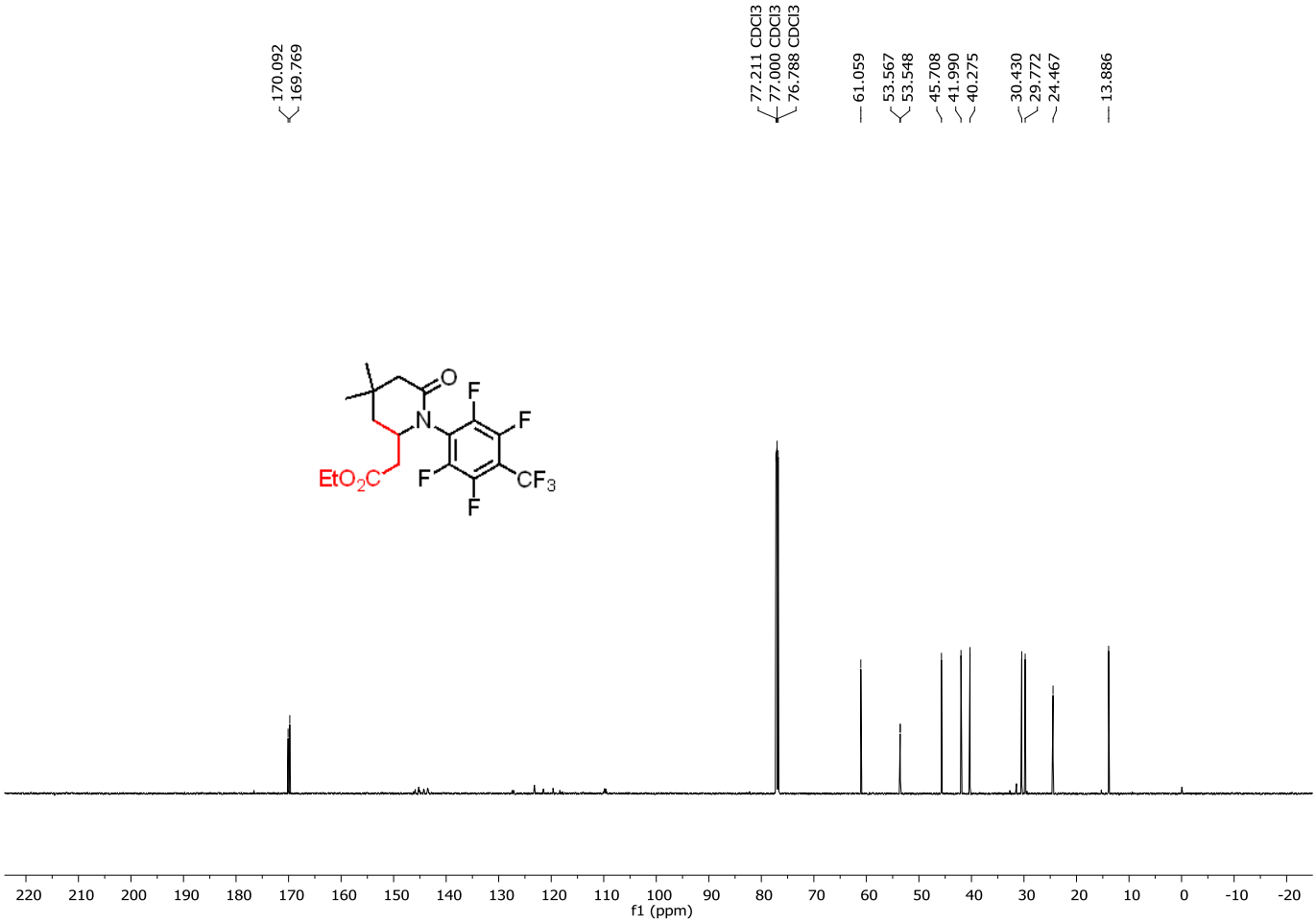
f1 (ppm)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40.275
30.430
29.772
24.467
13.886
O
N
F
F
F
F
CF3
EtO2C
220
210
200
190
180
170
160
150
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100
90
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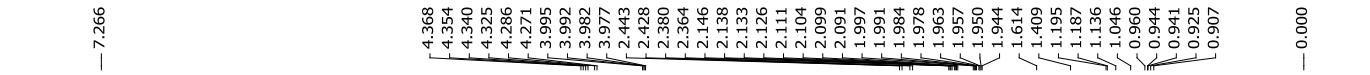
-20
f1 (ppm)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3.977
2.443
2.428
2.380
2.364
2.146
2.138
2.133
2.126
2.111
2.104
2.099
2.091
1.997
1.991
1.984
1.978
1.963
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1.944
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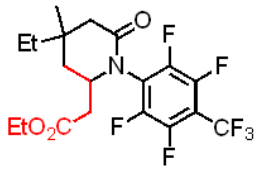
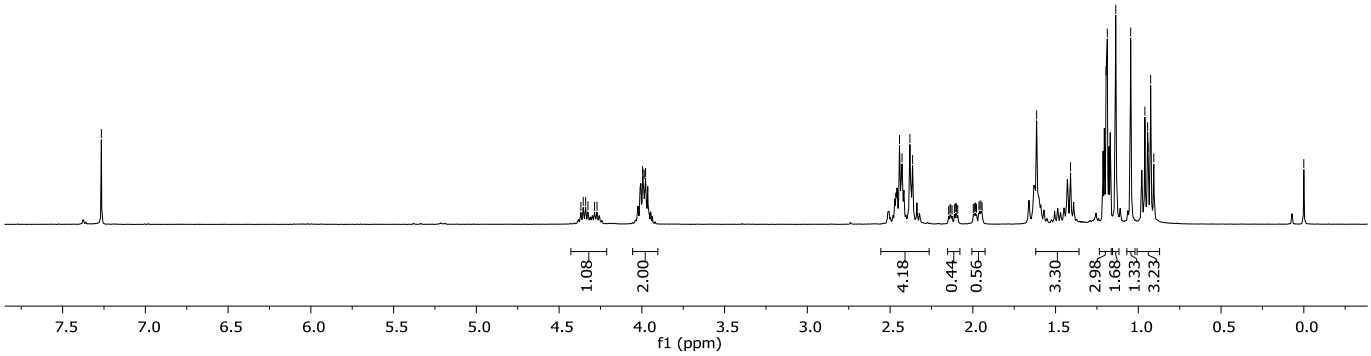
0.000


Et
O
N
F
F
F
F
EtO2C
CF3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1.68
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3.23
7.5
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6.5
6.0
5.5
5.0
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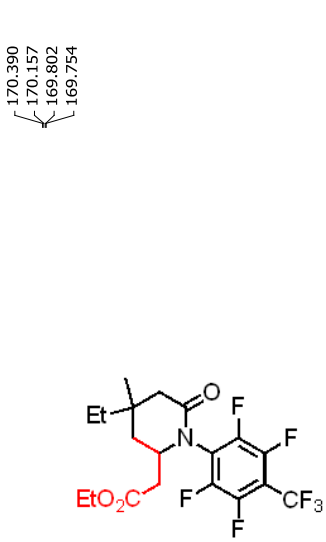
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Et
O
N
F
F
F
F
EtO2C
CF3

170.390
170.157
169.802
169.754
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77.000 CDCl3
76.788 CDCl3
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53.445
53.426
53.166
53.147
44.799
43.815
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40.271
40.018
39.571
35.701
32.440
32.372
29.351
26.295
21.416
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7.584
220
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200
190
180
170
160
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90
80
70
60
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20
10
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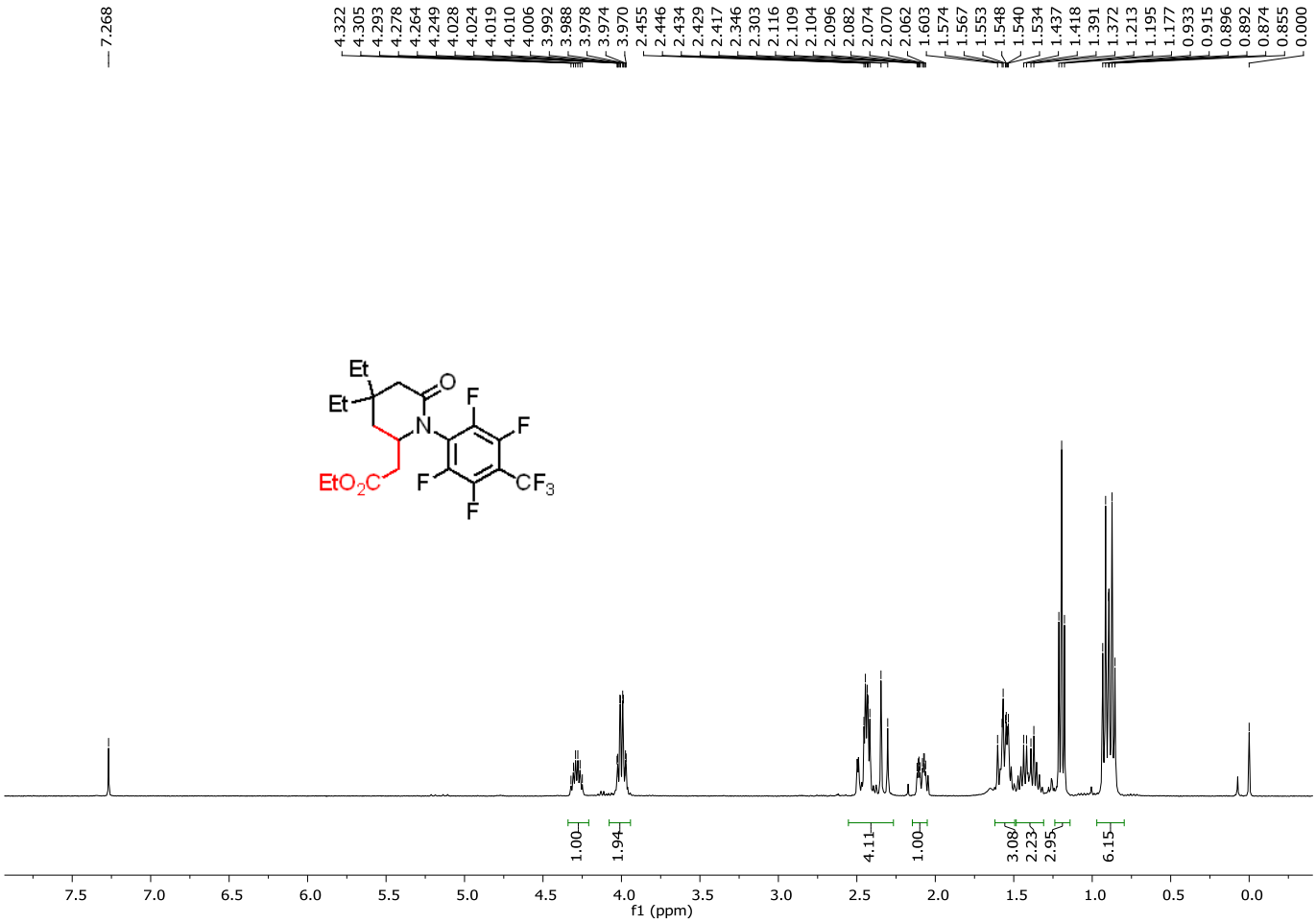
-10
-20
f1 (ppm)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2.303
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2.109
2.104
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2.082
2.074
2.070
2.062
1.603
1.574
1.567
1.553
1.548
1.540
1.534
1.437
1.418
1.391
1.372
1.213
1.195
1.177
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0.915
0.896
0.892
0.874
0.855
0.000
Et
Et
O
N
F
F
F
F
CF3
EtO2C
1.00
1.94
4.11
1.00
3.08
2.23
2.95
6.15
7.5
7.0
6.5
6.0
5.5
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3.5
3.0
2.5
2.0
1.5
1.0
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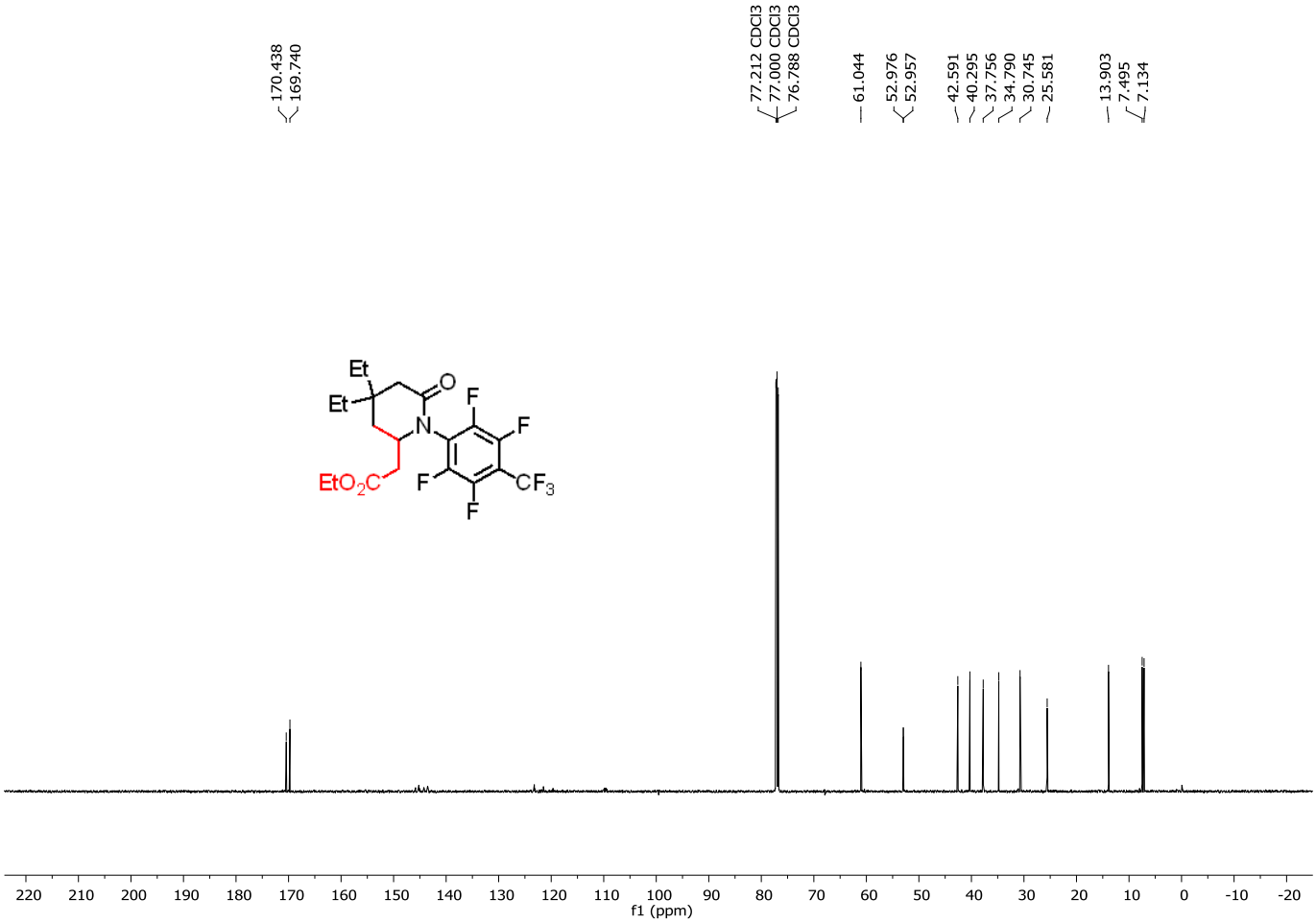
0.0
f1 (ppm)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42.591
40.295
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34.790
30.745
25.581
13.903
7.495
7.134
Et
Et
O
N
F
F
F
F
CF3
EtO2C
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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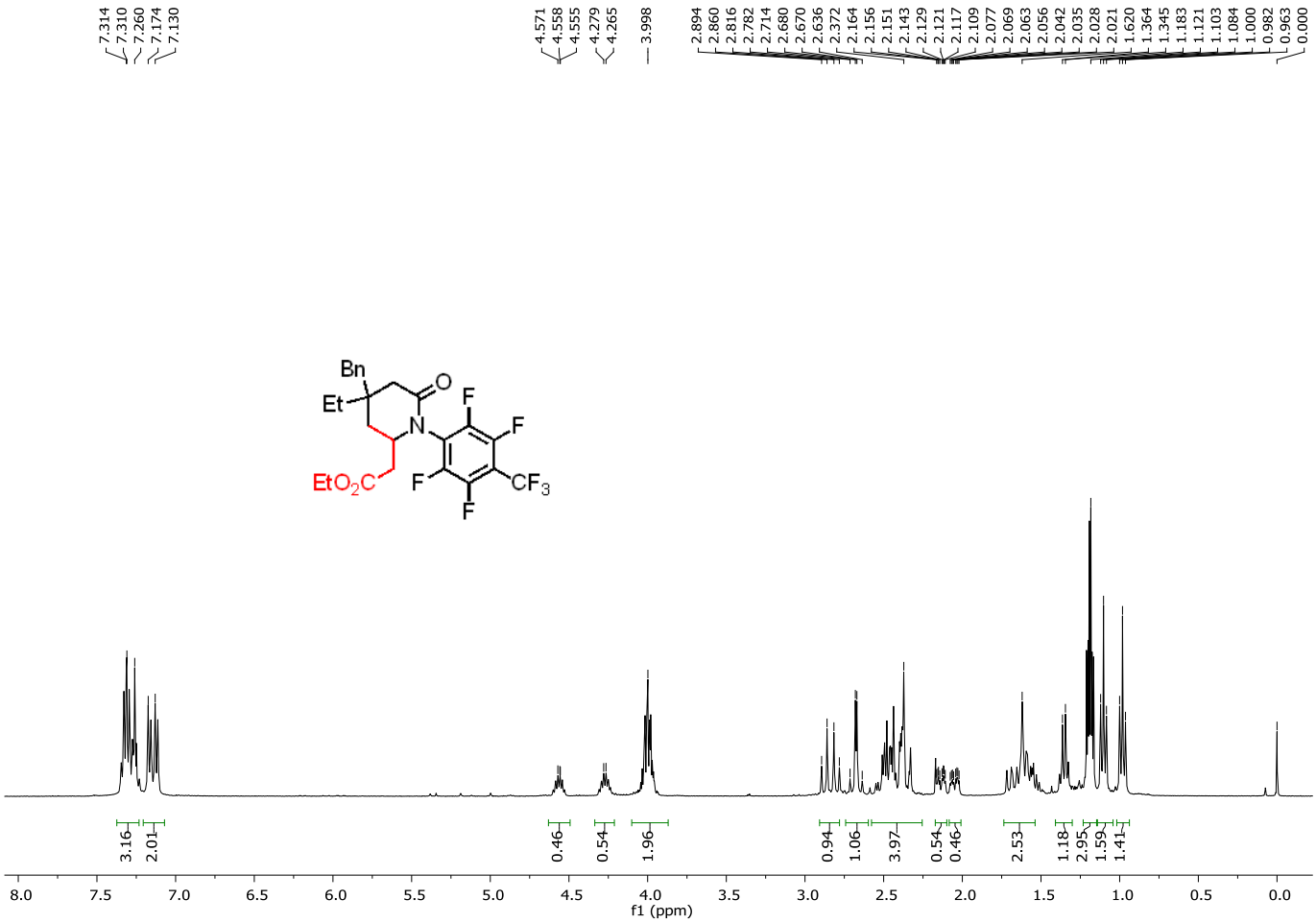
-10
-20
f1 (ppm)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2.816
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2.714
2.680
2.670
2.636
2.372
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2.151
2.143
2.129
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2.117
2.109
2.077
2.069
2.063
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2.035
2.028
2.021
1.620
1.364
1.345
1.183
1.121
1.103
1.084
1.000
0.982
0.963
0.000
Bn
Et
O
N
F
F
F
F
CF3
EtO2C
3.16
2.01
0.46
0.54
1.96
0.94
1.06
3.97
0.54
0.46
2.53
1.18
2.95
1.59
1.41
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
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1.0
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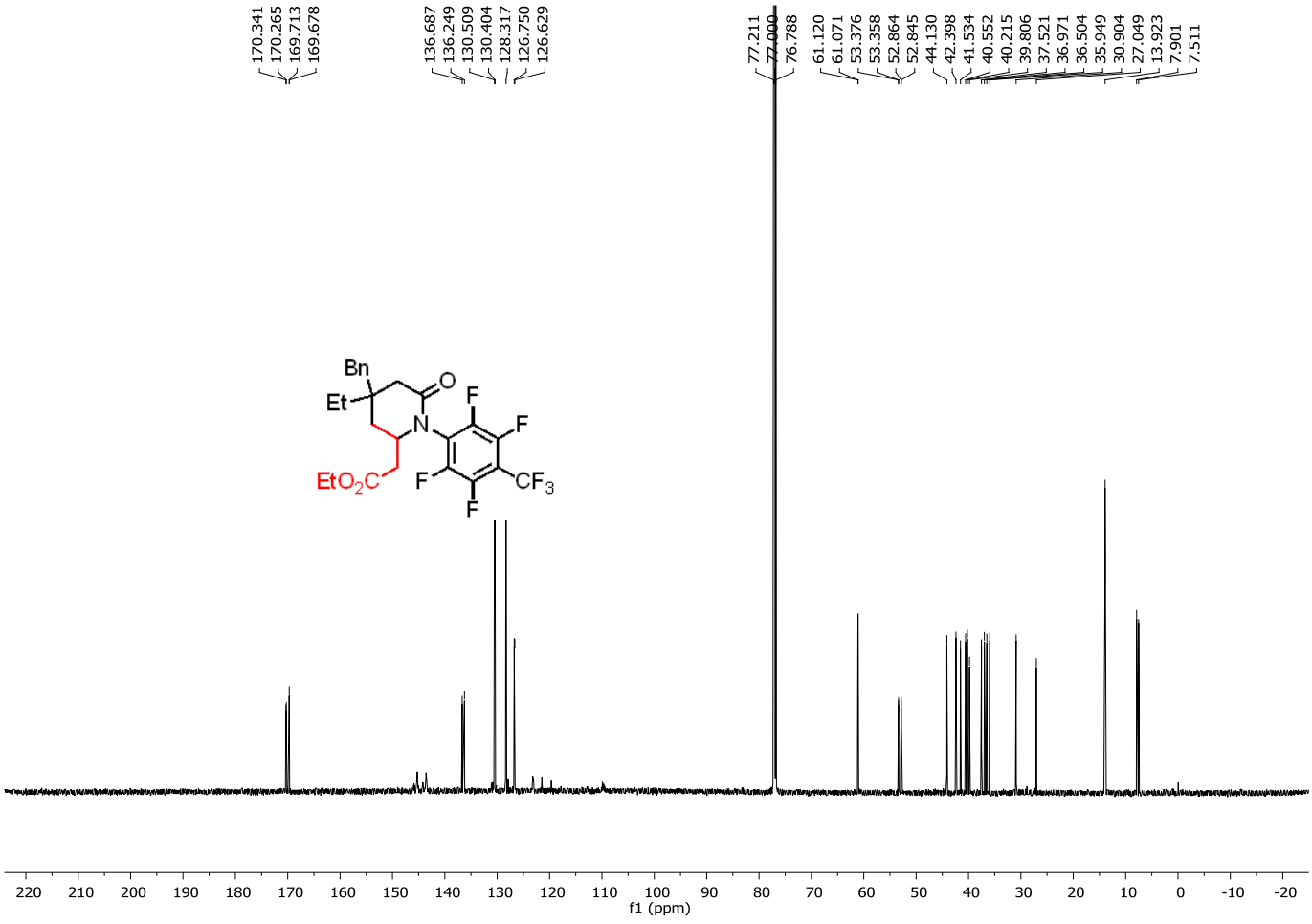
f1 (ppm)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77.000
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61.071
53.376
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52.864
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44.130
42.398
41.534
40.552
40.215
39.806
37.521
36.971
36.504
35.949
30.904
27.049
13.923
7.901
7.511
Bn
Et
O
N
F
F
F
F
CF3
EtO2C
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
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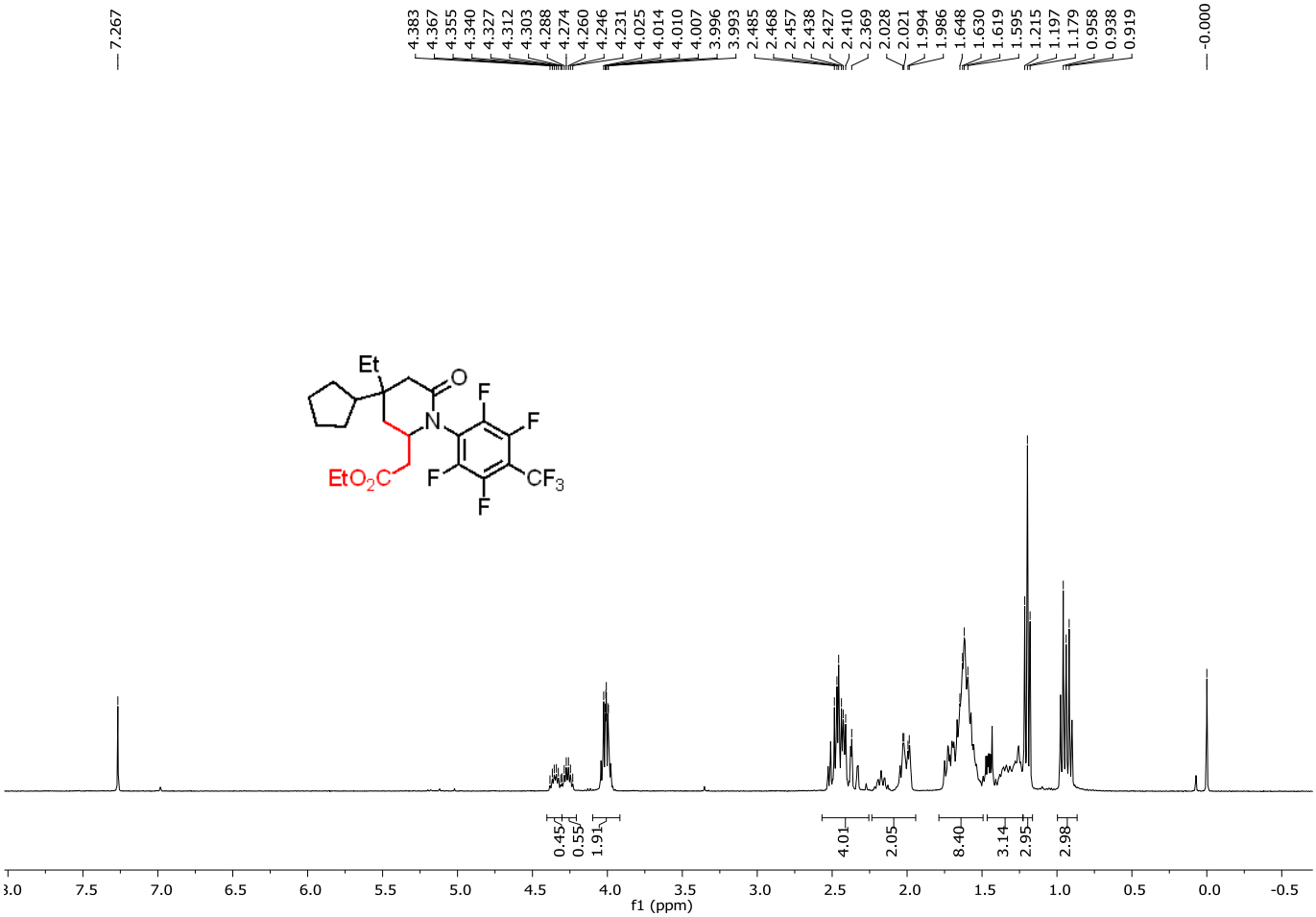
-20
f1 (ppm)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4.231
4.025
4.014
4.010
4.007
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3.993
2.485
2.468
2.457
2.438
2.427
2.410
2.369
2.028
2.021
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1.986
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1.630
1.619
1.595
1.215
1.197
1.179
0.958
0.938
0.919
-0.000
Et
O
N
F
F
F
F
F
CF_3
EtO_2C
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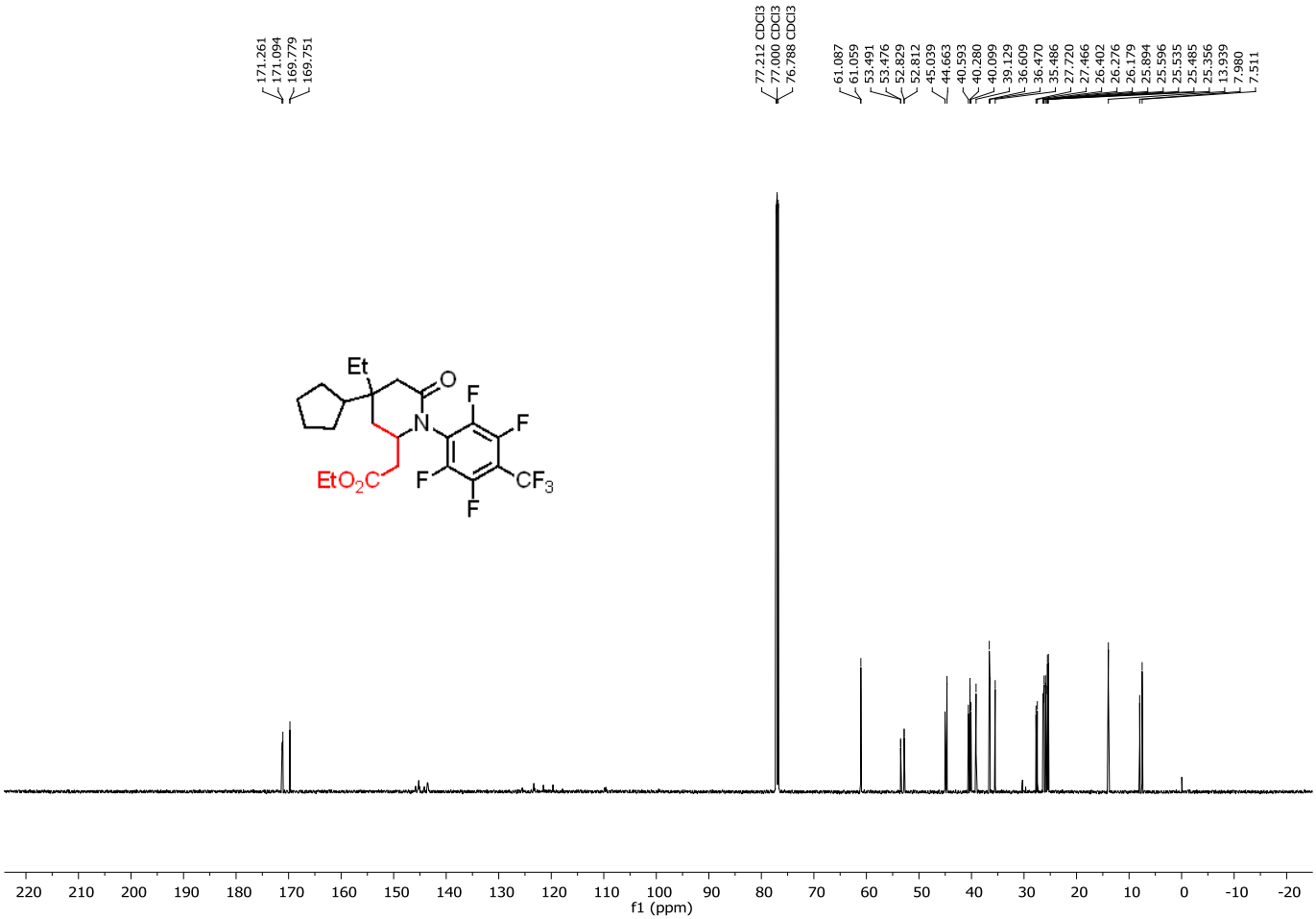
f1 (ppm)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39.129
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36.470
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27.720
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26.402
26.276
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25.894
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25.535
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25.356
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7.511
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N
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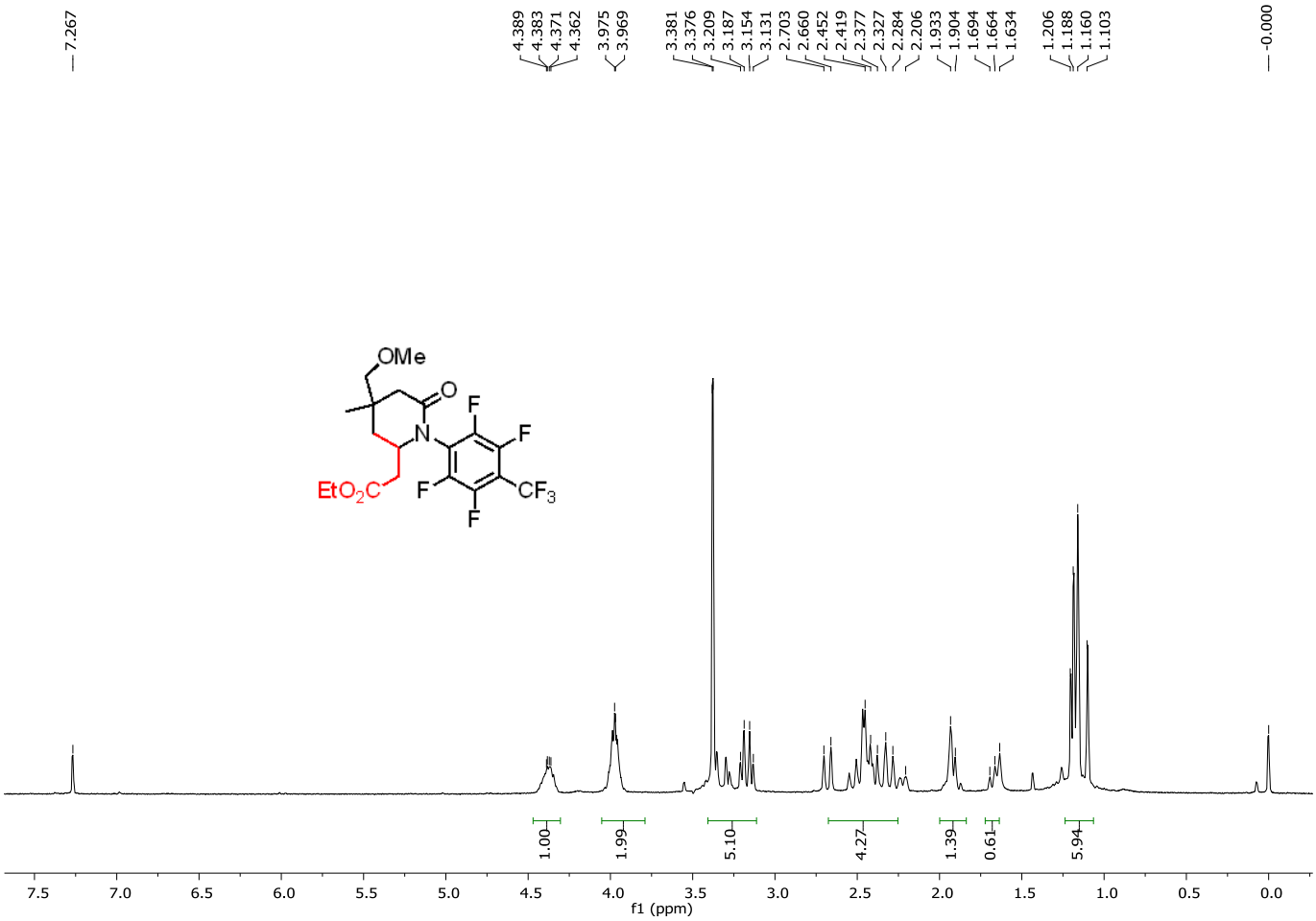
F
F
F
F
CF_3
EtO_2C
f1 (ppm)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3.131
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2.377
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1.904
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1.188
1.160
1.103
-0.000
OMe
O
N
F
F
F
F
CF3
EtO2C
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1.99
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1.39
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6.5
6.0
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1.0
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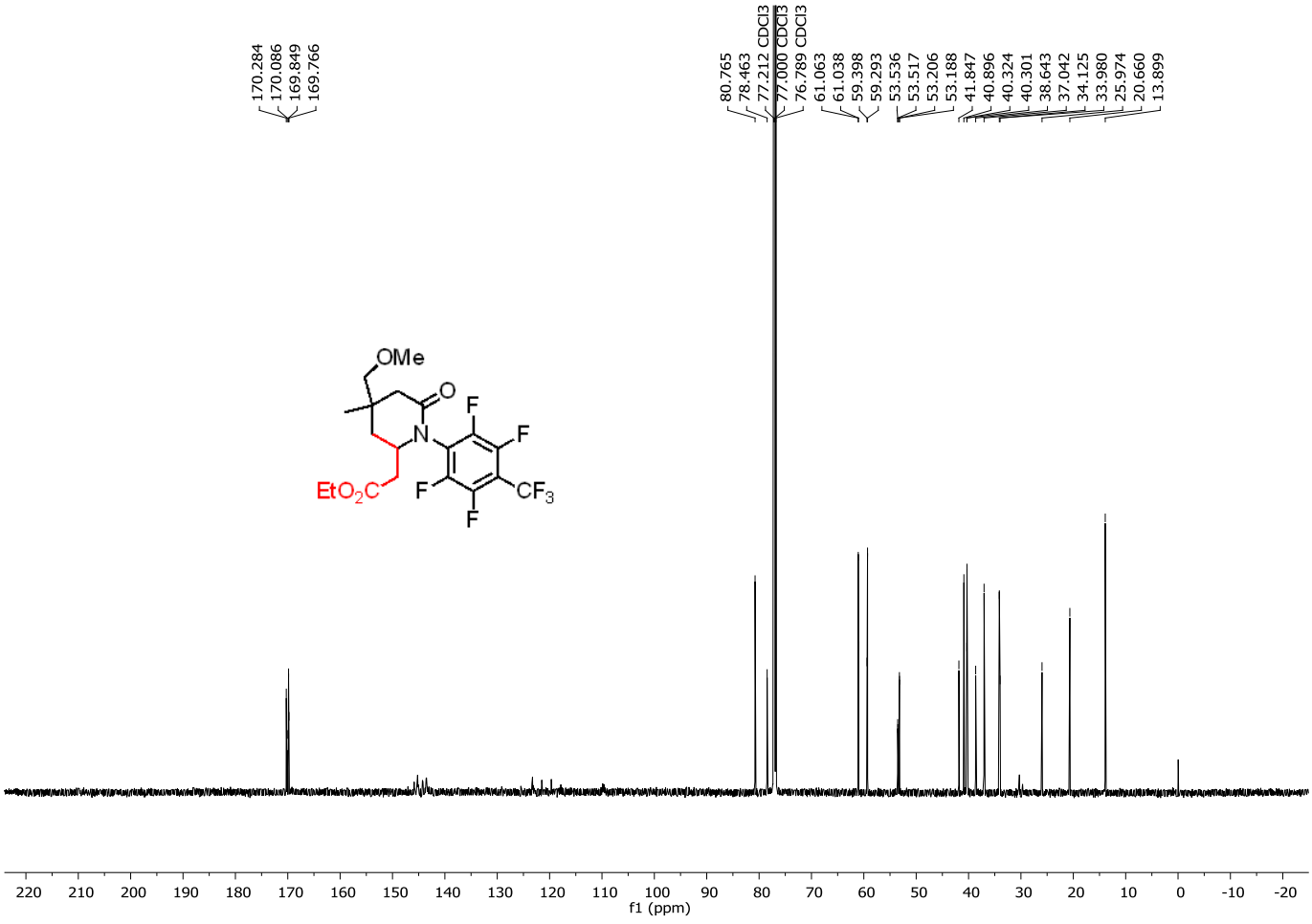
f1 (ppm)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53.188
41.847
40.896
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40.301
38.643
37.042
34.125
33.980
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20.660
13.899
OMe
O
N
F
F
F
F
CF3
EtO2C
220
210
200
190
180
170
160
150
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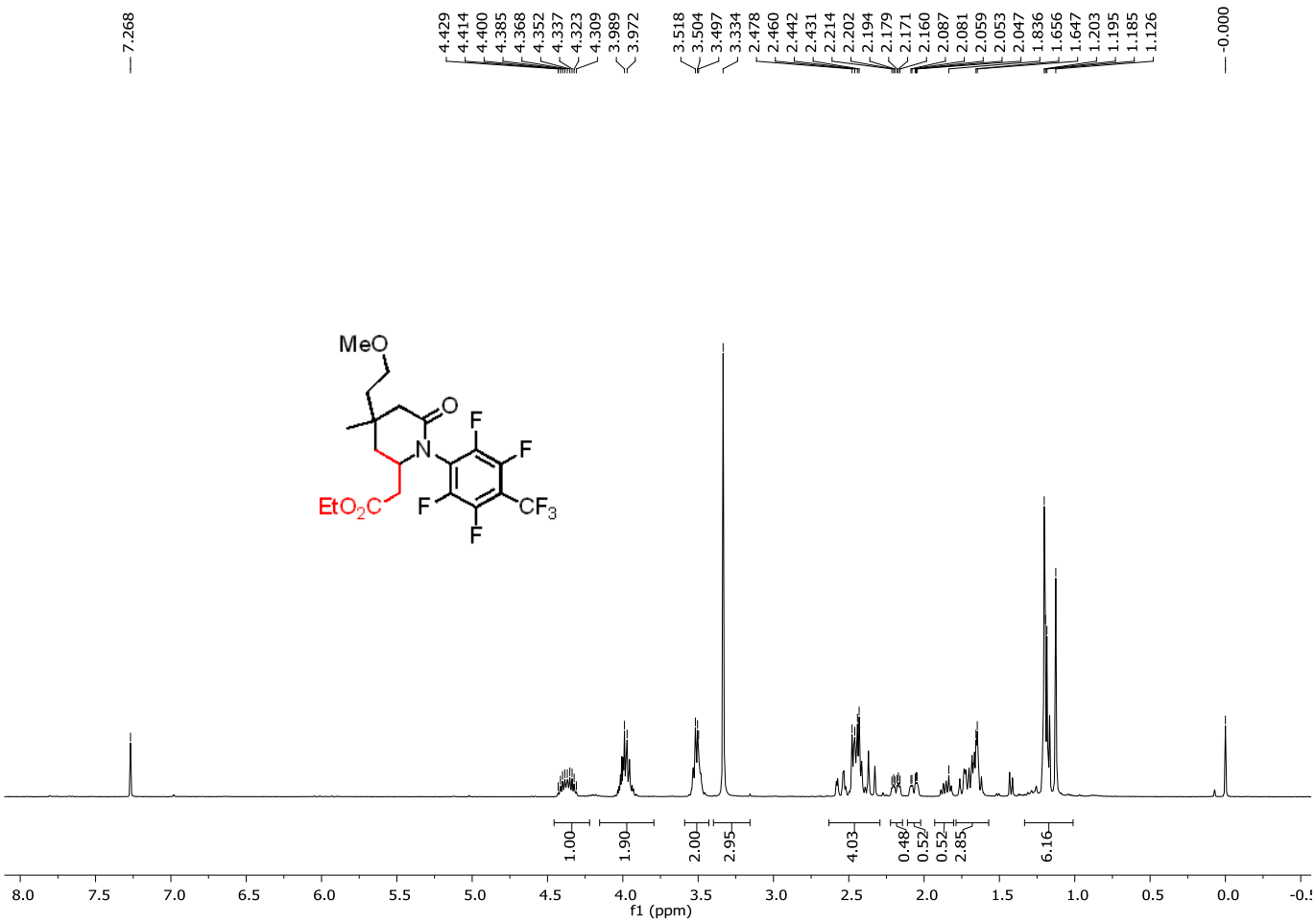
f1 (ppm)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3.334
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2.431
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2.202
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2.179
2.171
2.160
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MeO
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N
F
F
F
F
CF3
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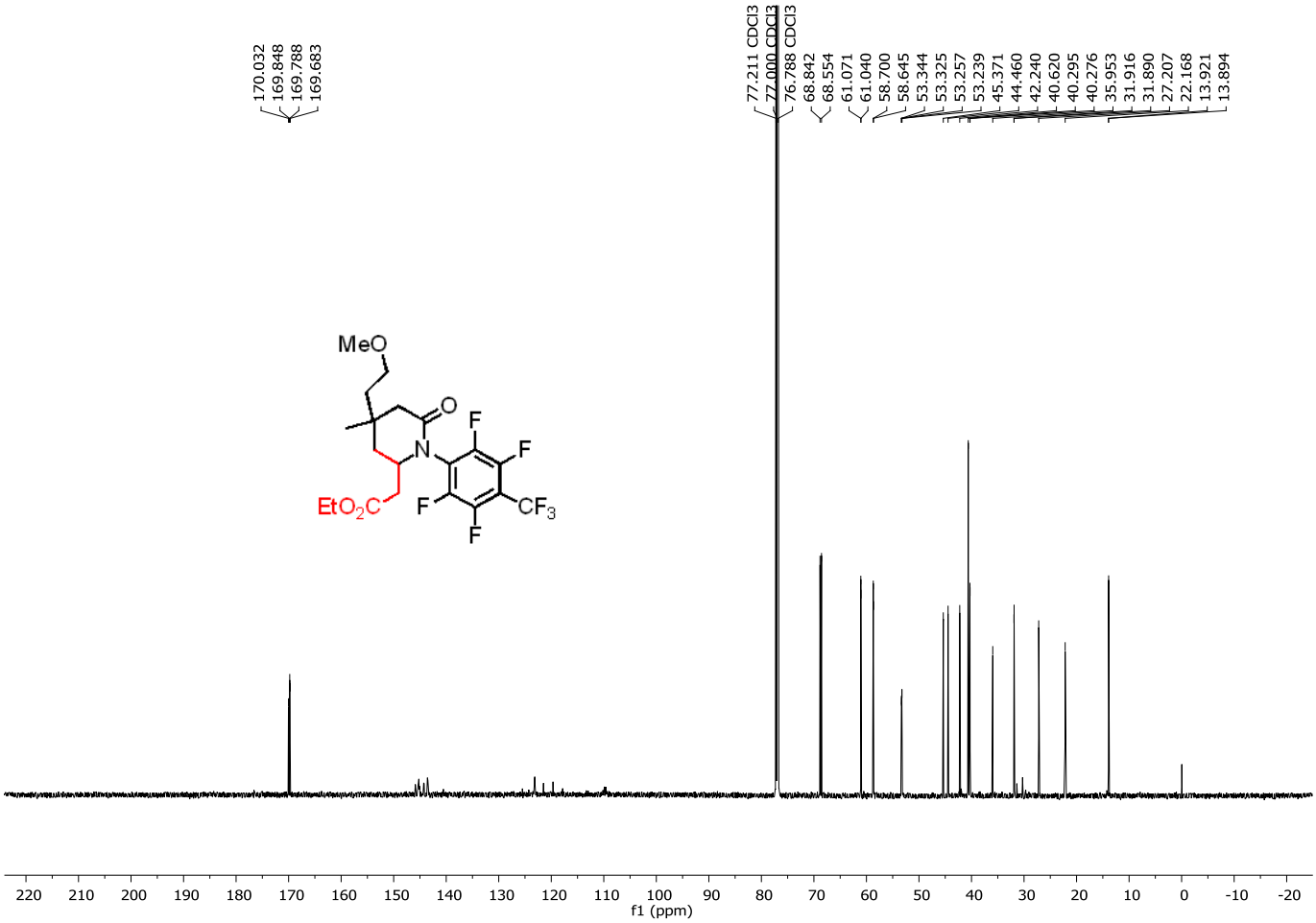
6.16
f1 (ppm)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76.788 CDCl3
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58.645
53.344
53.325
53.257
53.239
45.371
44.460
42.240
40.620
40.295
40.276
35.953
31.916
31.890
27.207
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13.894
MeO
O
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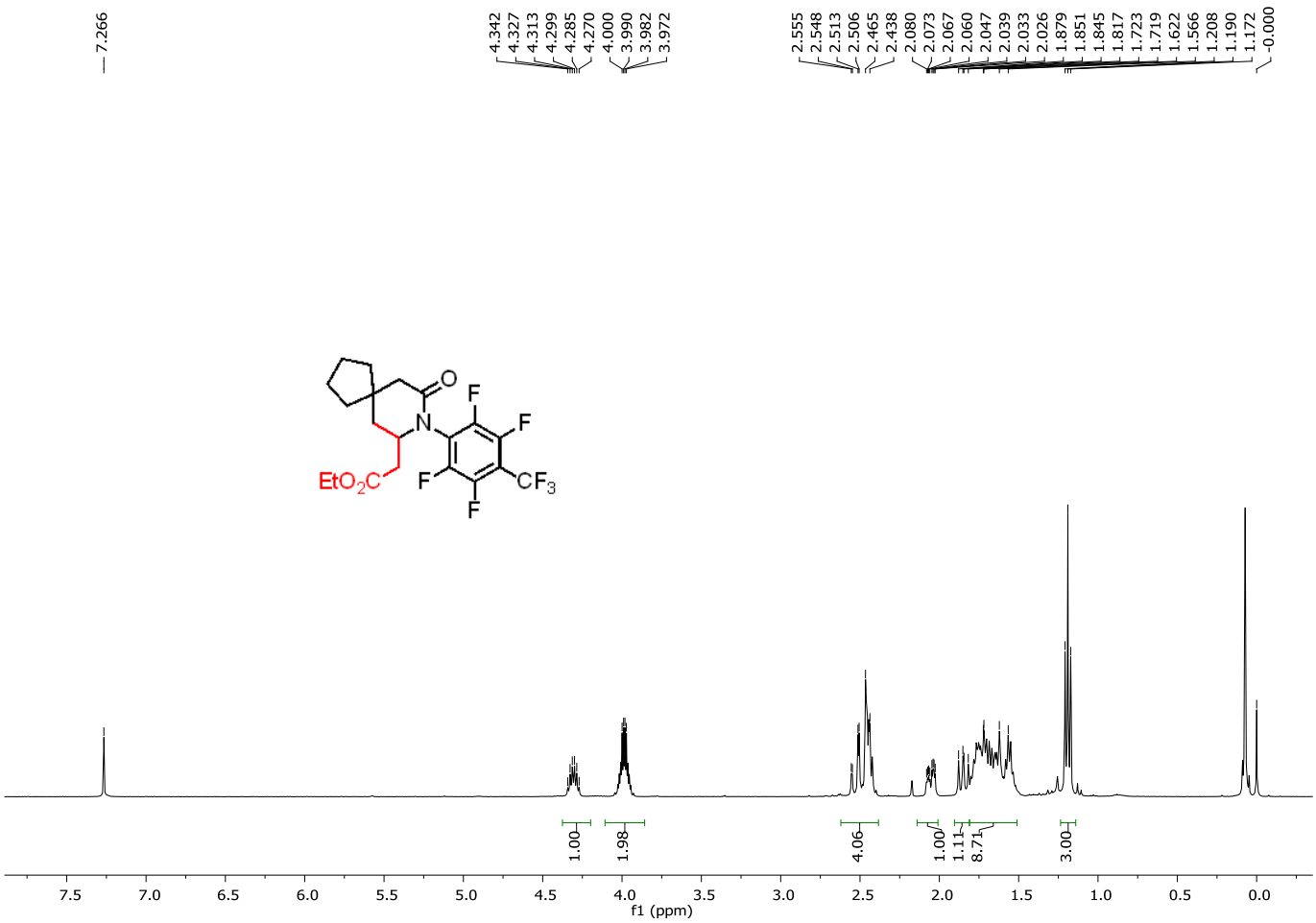
F
F
CF3
EtO2C
f1 (ppm)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2.555
2.548
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1.851
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1.817
1.723
1.719
1.622
1.566
1.208
1.190
1.172
-0.000
O
N
F
F
F
F
CF3
EtO2C
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1.98
4.06
1.00
1.11
8.71
3.00
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6.5
6.0
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2.5
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1.0
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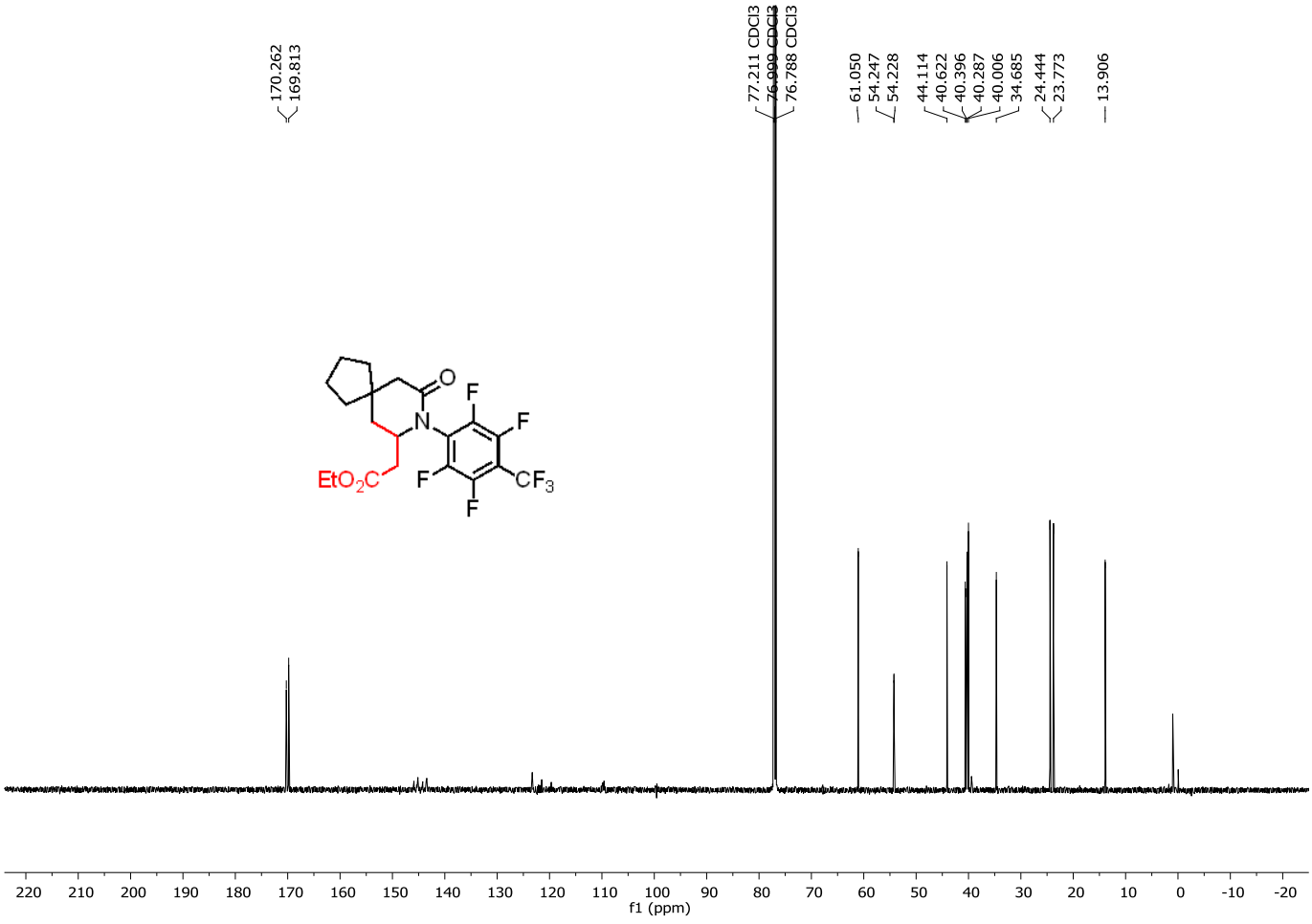
f1 (ppm)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76.999 CDCl3
76.788 CDCl3
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54.228
44.114
40.622
40.396
40.287
40.006
34.685
24.444
23.773
13.906
O
N
F
F
F
F
CF3
EtO2C
220
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200
190
180
170
160
150
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40
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20
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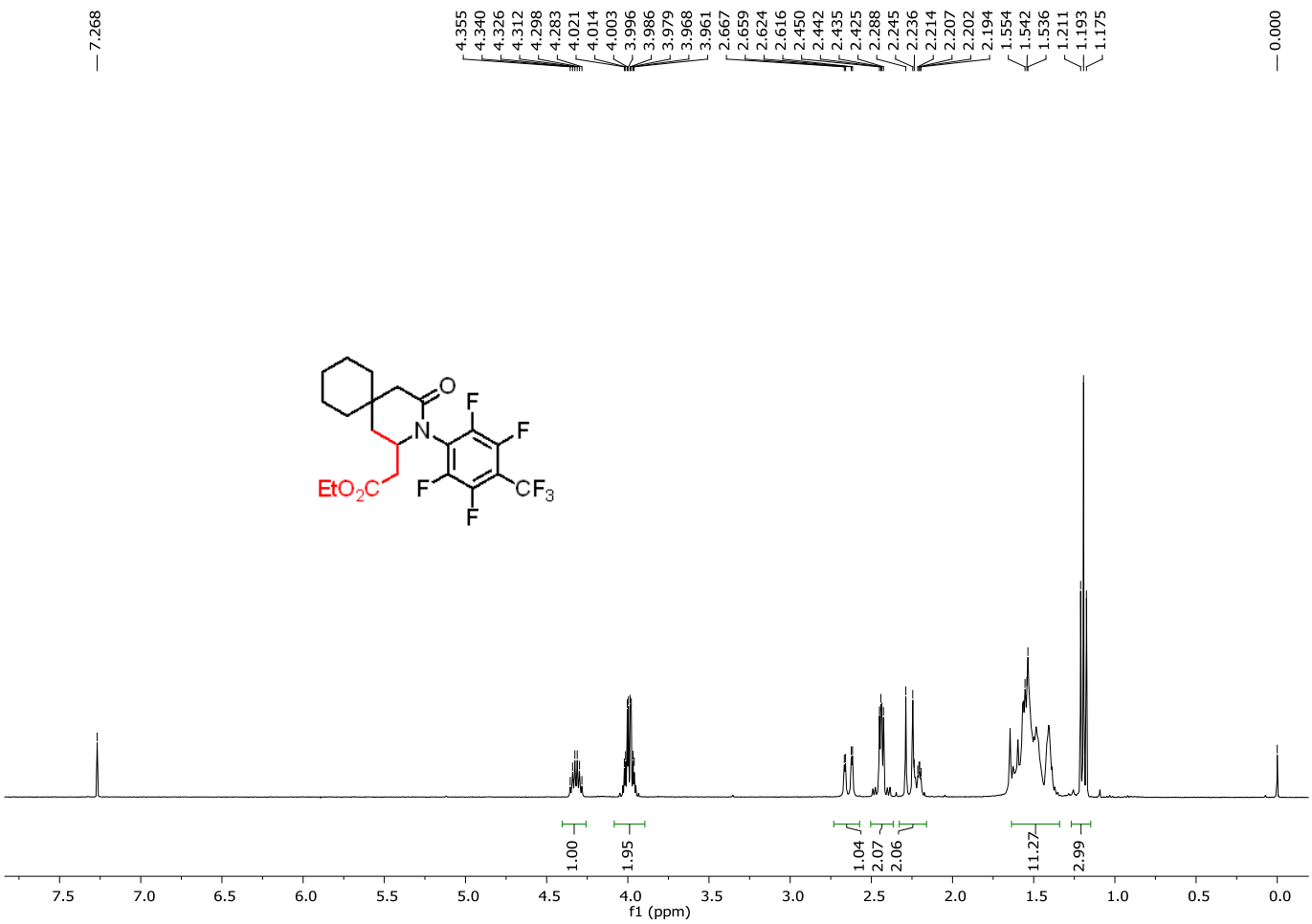
0
-10
-20
f1 (ppm)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2.236
2.214
2.207
2.202
2.194
1.554
1.542
1.536
1.211
1.193
1.175
0.000
O
N
F
F
F
F
F
EtO2C
CF3
1.00
1.95
1.04
2.07
2.06
11.27
2.99
7.5
7.0
6.5
6.0
5.5
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1.5
1.0
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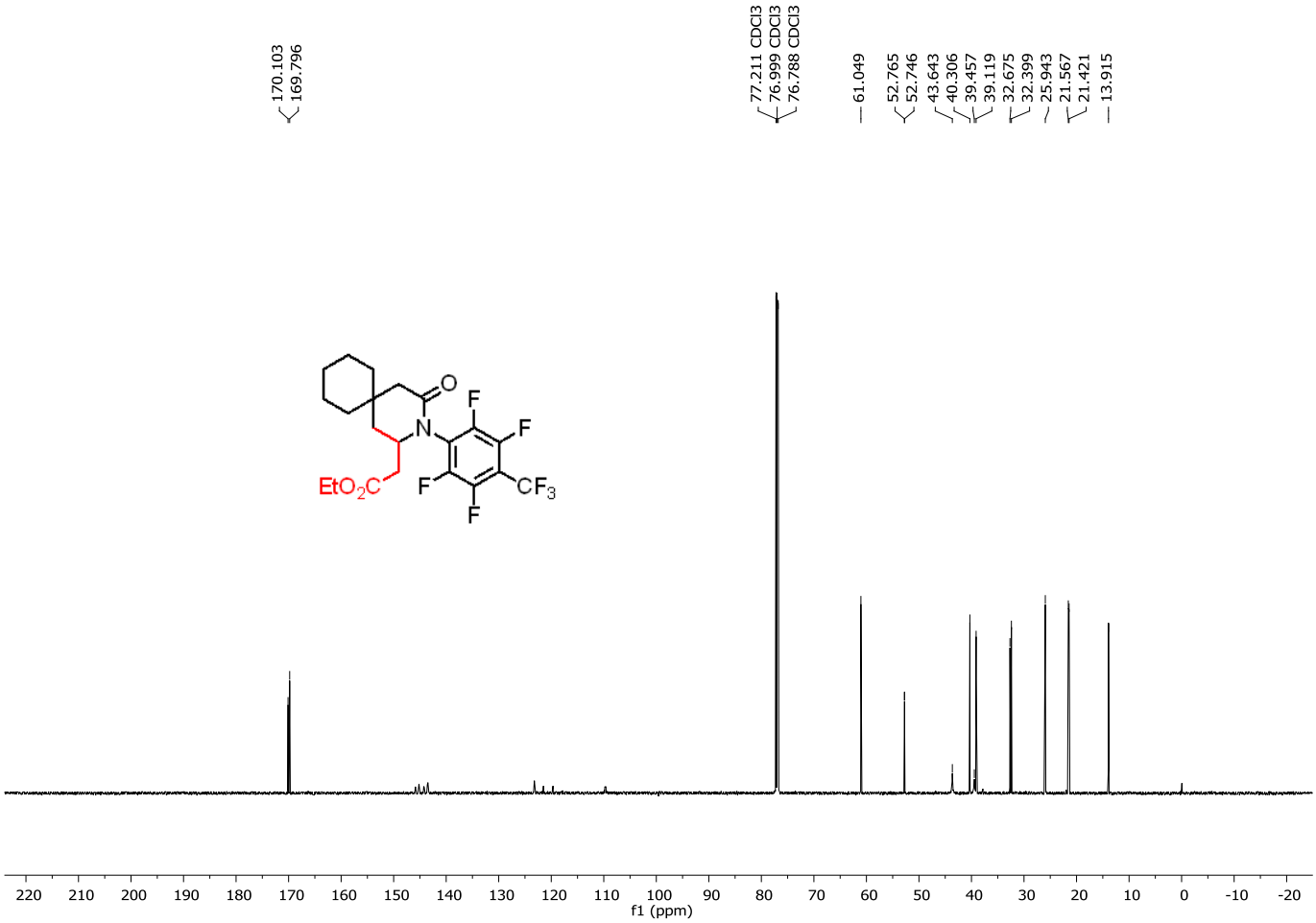
f1 (ppm)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39.457
39.119
32.675
32.399
25.943
21.567
21.421
13.915
O
N
F
F
F
F
F
EtO2C
CF3
220
210
200
190
180
170
160
150
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100
90
80
70
60
50
40
30
20
10
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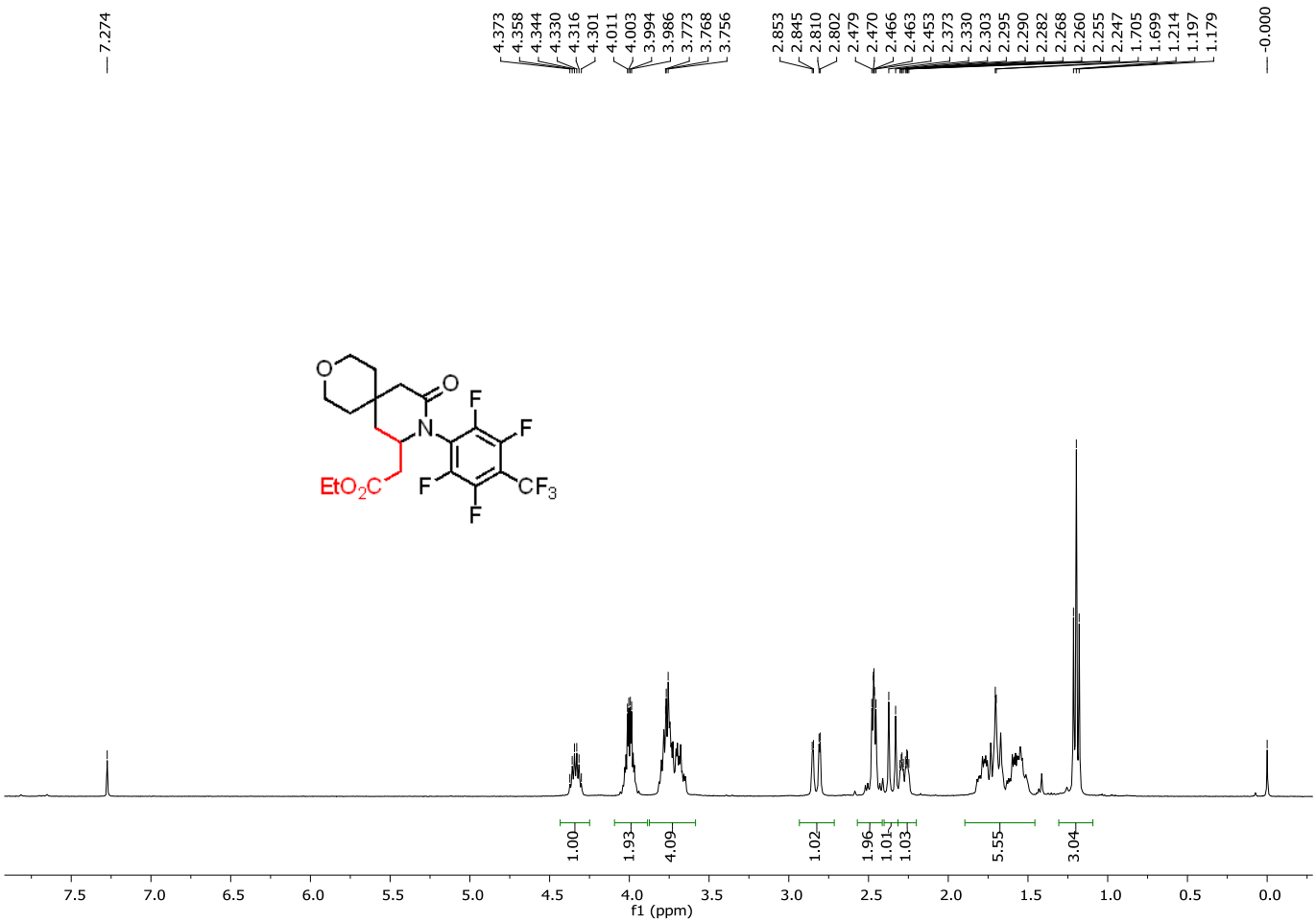
-10
-20
f1 (ppm)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3.986
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3.768
3.756
2.853
2.845
2.810
2.802
2.479
2.470
2.466
2.463
2.453
2.373
2.330
2.303
2.295
2.290
2.282
2.268
2.260
2.255
2.247
1.705
1.699
1.214
1.197
1.179
-0.000
EtO2C
F
F
F
F
CF3
O
O
N
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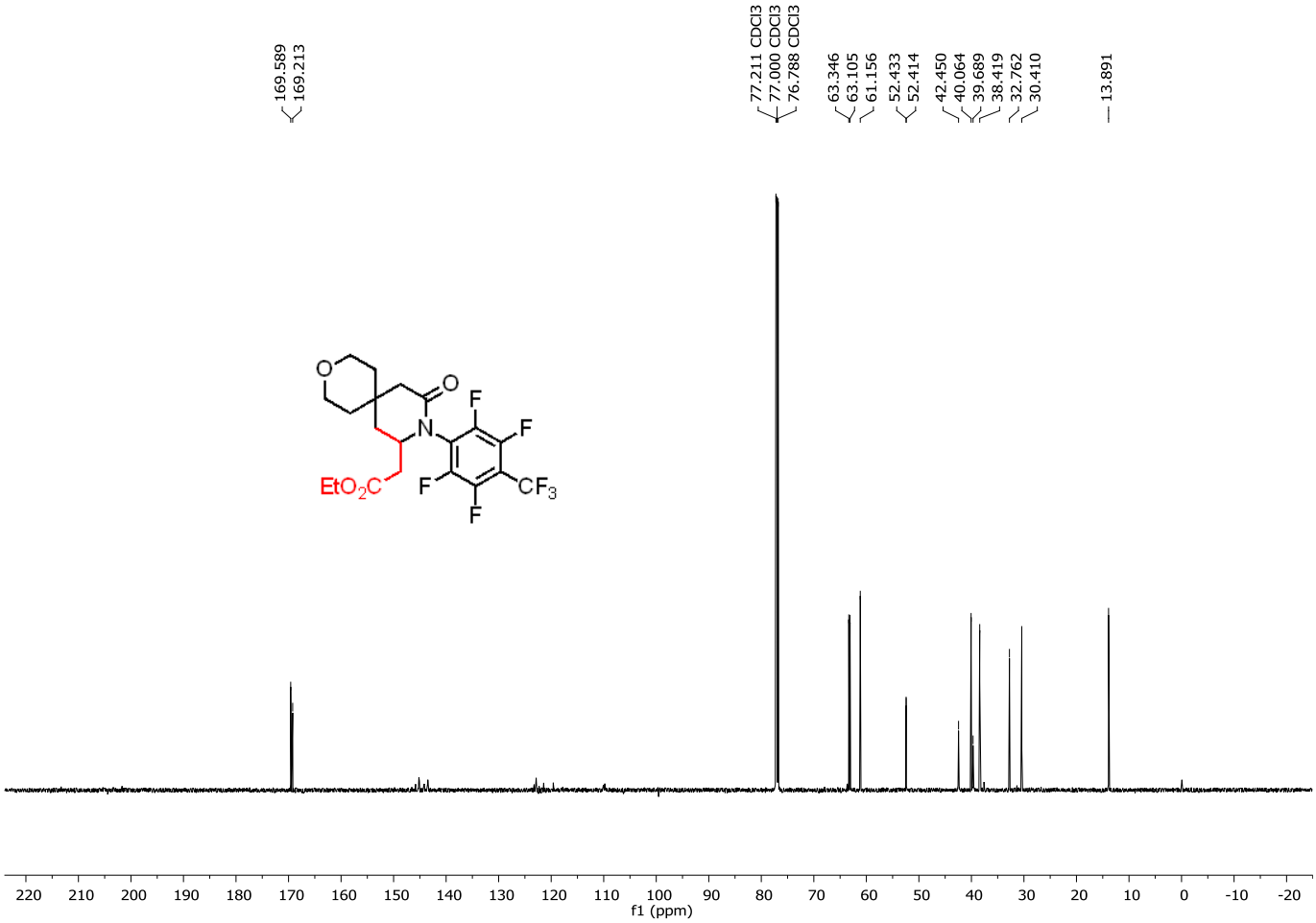
1.93
4.09
1.02
1.96
1.01
1.03
5.55
3.04
f1 (ppm)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40.064
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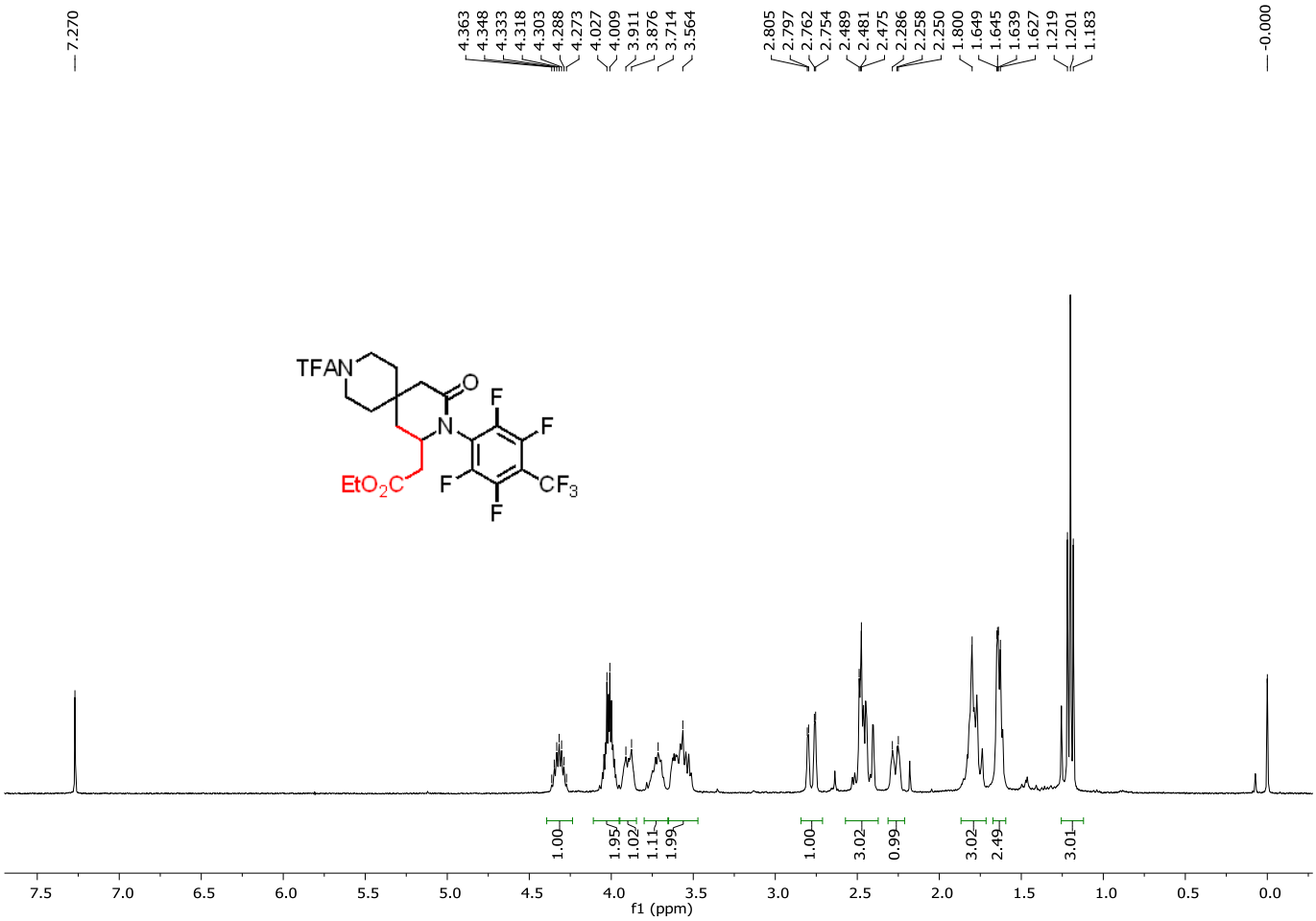
30.410
13.891
EtO2C
F
F
F
F
CF3
O
O
N
f1 (ppm)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4.273
4.027
4.009
3.911
3.876
3.714
3.564
2.805
2.797
2.762
2.754
2.489
2.481
2.475
2.286
2.258
2.250
1.800
1.649
1.645
1.639
1.627
1.219
1.201
1.183
-0.000
TFAN
O
N
F
F
F
F
CF3
EtO2C
1.00
1.95
1.02
1.11
1.99
1.00
3.02
0.99
3.02
2.49
3.01
7.5
7.0
6.5
6.0
5.5
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
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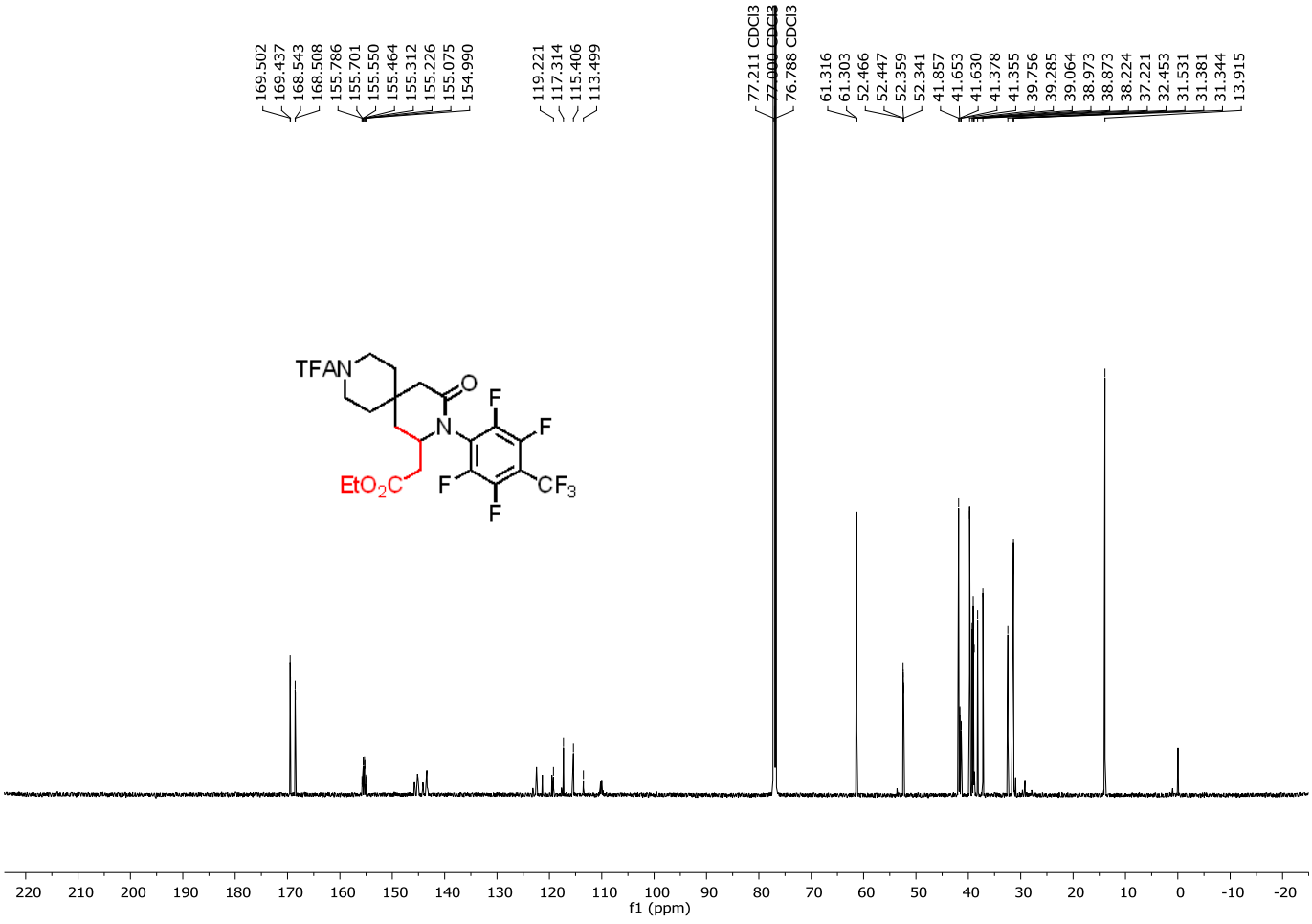
0.0
f1 (ppm)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155.464
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155.075
154.990
119.221
117.314
115.406
113.499
77.211 CDCl3
77.000 CDCl3
76.788 CDCl3
61.316
61.303
52.466
52.447
52.359
52.341
41.857
41.653
41.630
41.378
41.355
39.756
39.285
39.064
38.973
38.873
38.224
37.221
32.453
31.531
31.381
31.344
13.915
TFAN
O
N
F
F
F
F
CF3
EtO2C
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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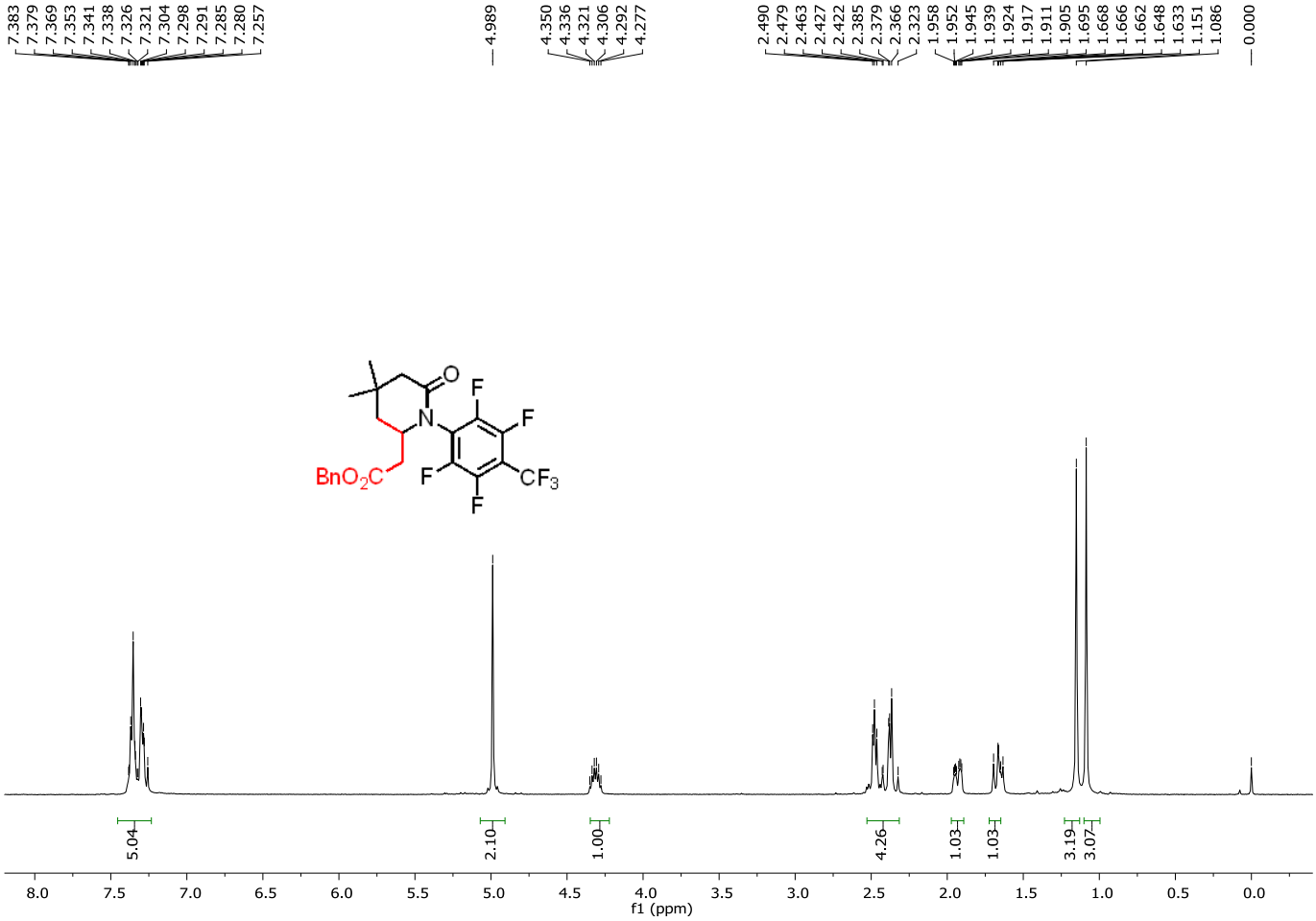
-10
-20
f1 (ppm)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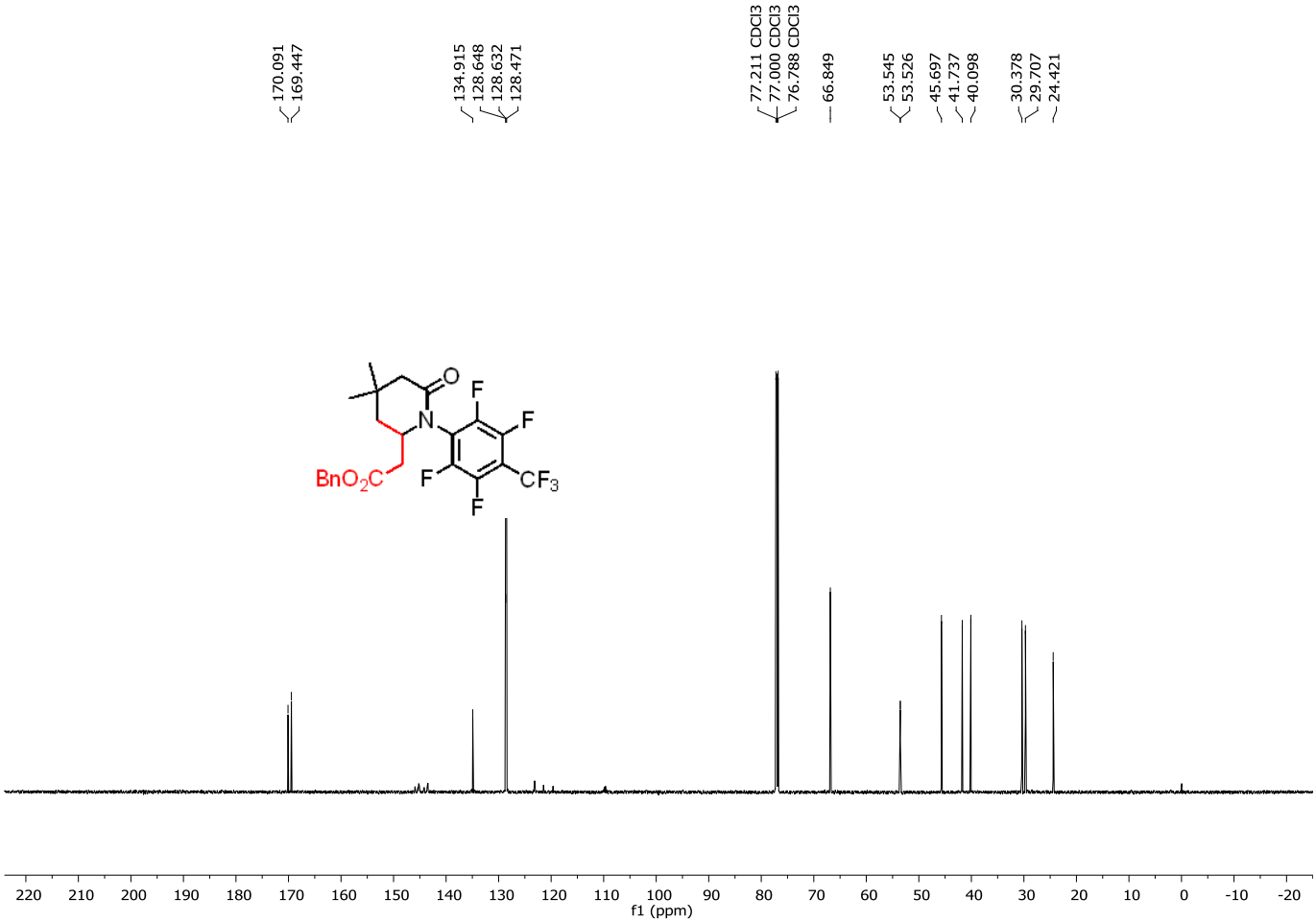
7.369
7.353
7.341
7.338
7.326
7.321
7.304
7.298
7.291
7.285
7.280
7.257
4.989
4.350
4.336
4.321
4.306
4.292
4.277
2.490
2.479
2.463
2.427
2.422
2.385
2.379
2.366
2.323
1.958
1.952
1.945
1.939
1.924
1.917
1.911
1.905
1.695
1.668
1.666
1.662
1.648
1.633
1.151
1.086
0.000
BnO2C
F
F
F
F
CF3
O
N
5.04
2.10
1.00
4.26
1.03
1.03
3.19
3.07
f1 (ppm)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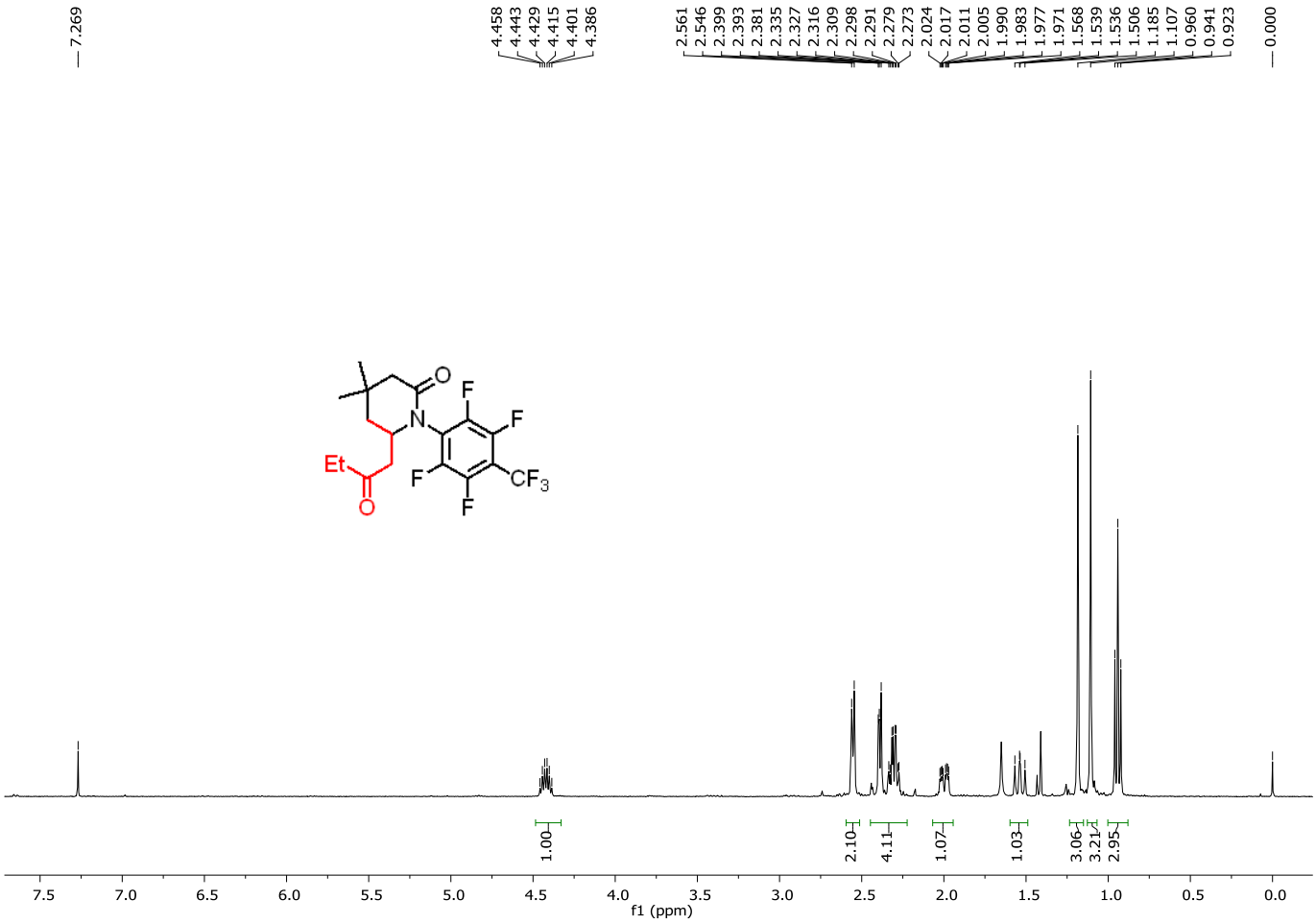
169.447
134.915
128.648
128.632
128.471
77.211 CDCl3
77.000 CDCl3
76.788 CDCl3
66.849
53.545
53.526
45.697
41.737
40.098
30.378
29.707
24.421
BnO2C
F
F
F
F
CF3
O
N
f1 (ppm)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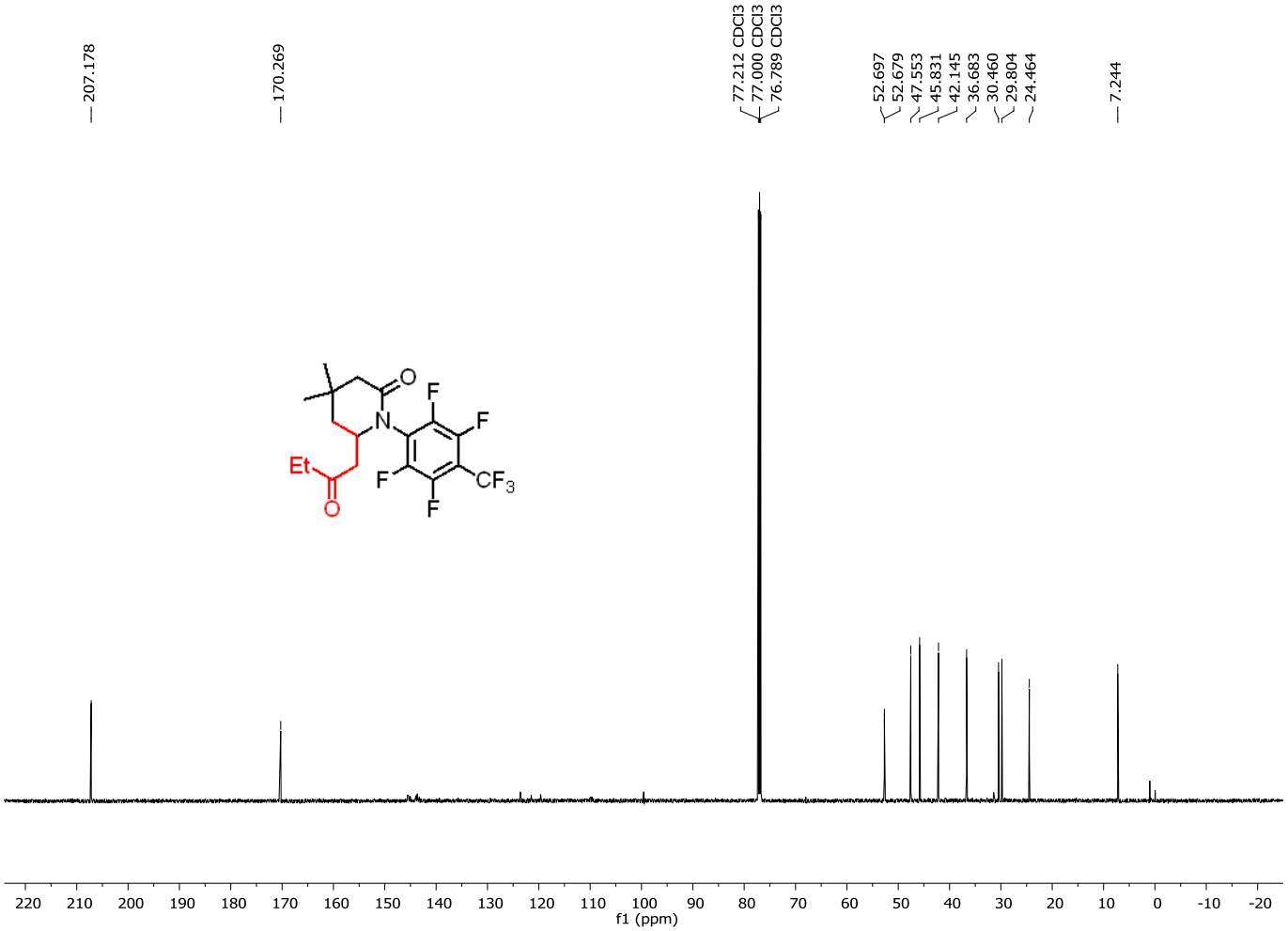
4.415
4.401
4.386
2.561
2.546
2.399
2.393
2.381
2.335
2.327
2.316
2.309
2.298
2.291
2.279
2.273
2.024
2.017
2.011
2.005
1.990
1.983
1.977
1.971
1.568
1.539
1.536
1.506
1.185
1.107
0.960
0.941
0.923
0.000
O
N
F
F
F
F
CF3
Et
O
1.00
2.10
4.11
1.07
1.03
3.06
3.21
2.95
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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170.269
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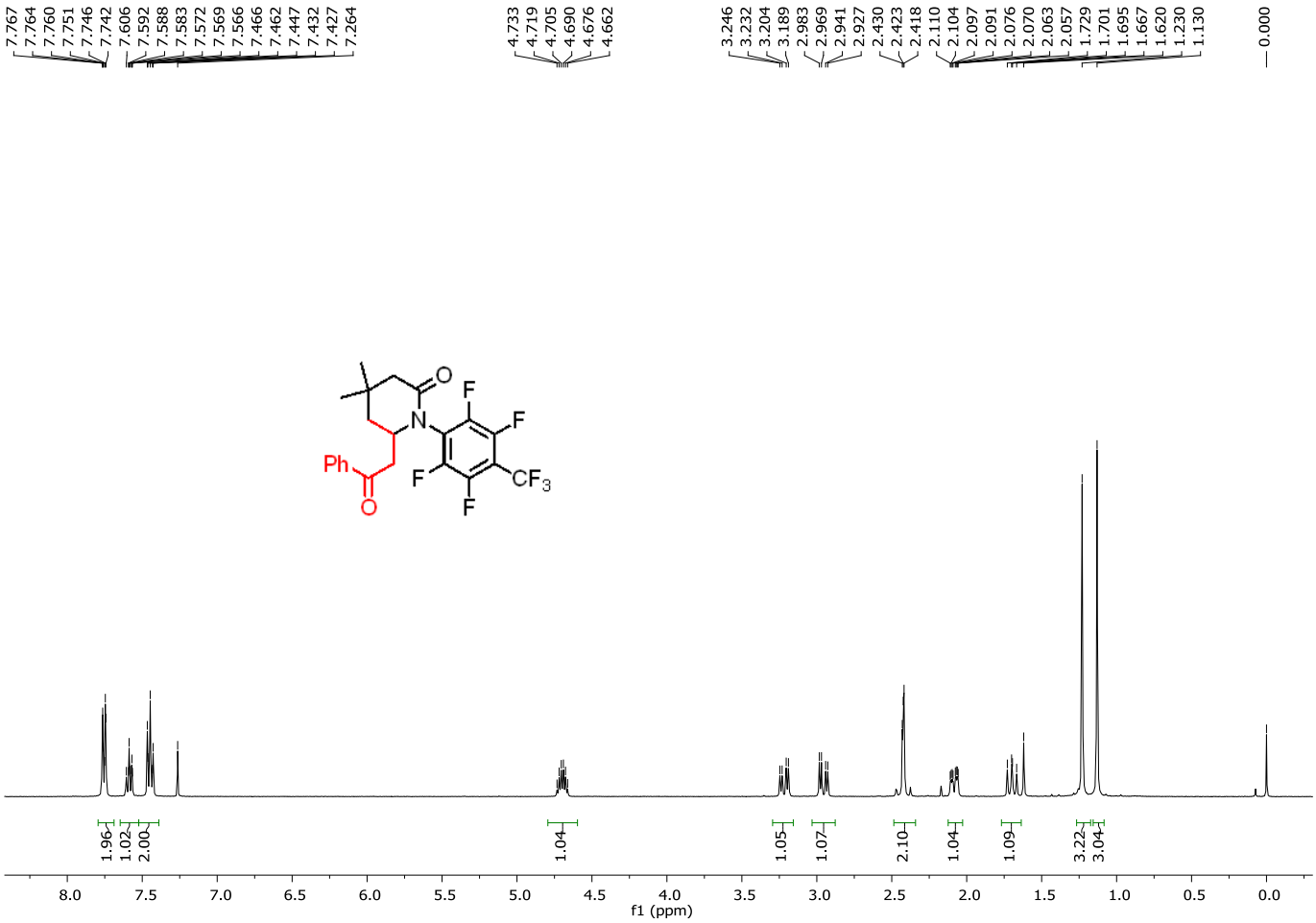
76.789 CDCl3
52.697
52.679
47.553
45.831
42.145
36.683
30.460
29.804
24.464
7.244
O
N
F
F
F
F
CF3
Et
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)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7.764
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7.751
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7.606
7.592
7.588
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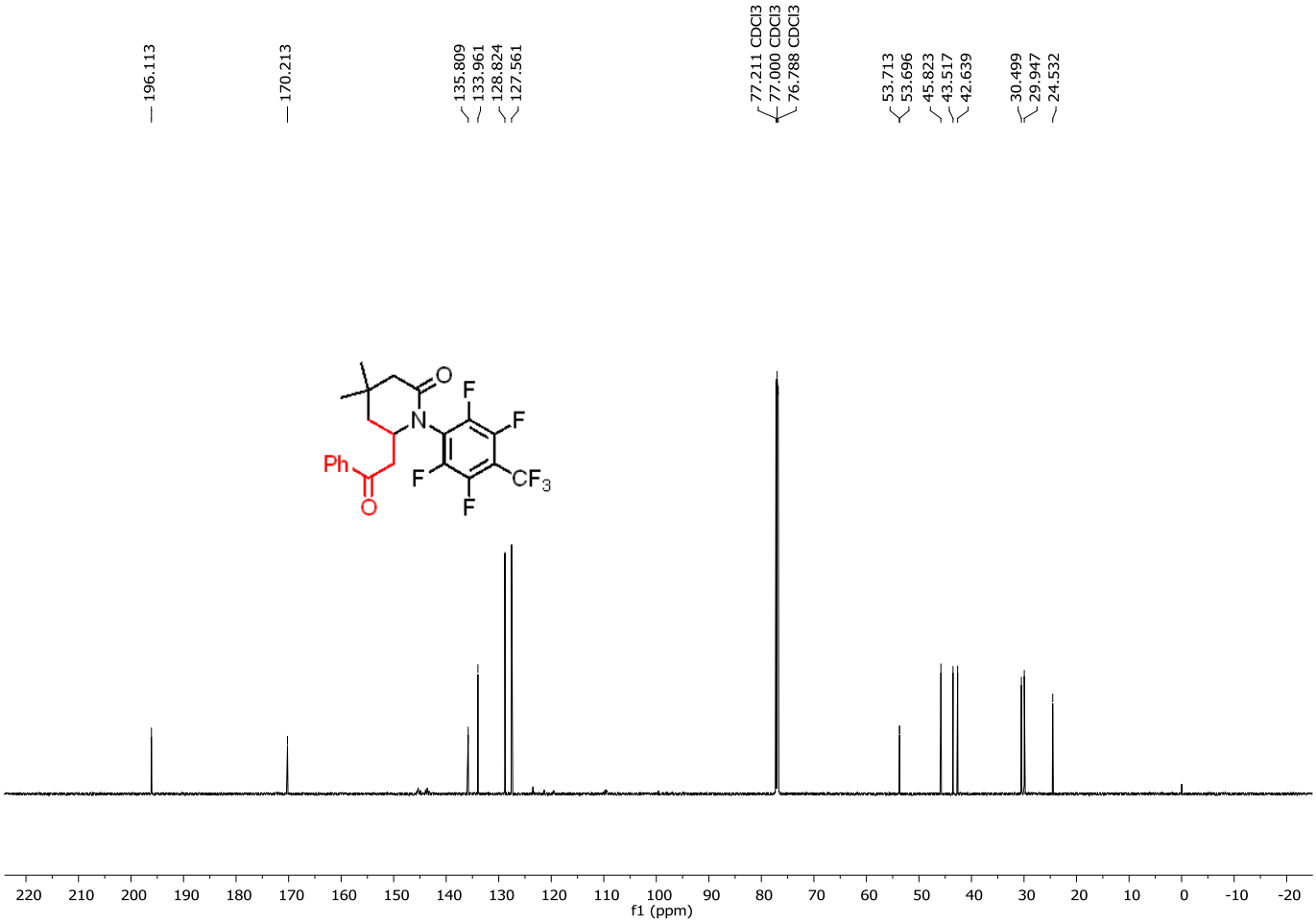
7.569
7.566
7.466
7.462
7.447
7.432
7.427
7.264
4.733
4.719
4.705
4.690
4.676
4.662
3.246
3.232
3.204
3.189
2.983
2.969
2.941
2.927
2.430
2.423
2.418
2.110
2.104
2.097
2.091
2.076
2.070
2.063
2.057
1.729
1.701
1.695
1.667
1.620
1.230
1.130
0.000
O
N
F
F
F
F
CF3
Ph
O
1.96
1.02
2.00
1.04
1.05
1.07
2.10
1.04
1.09
3.22
3.04
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
0.0
f1 (ppm)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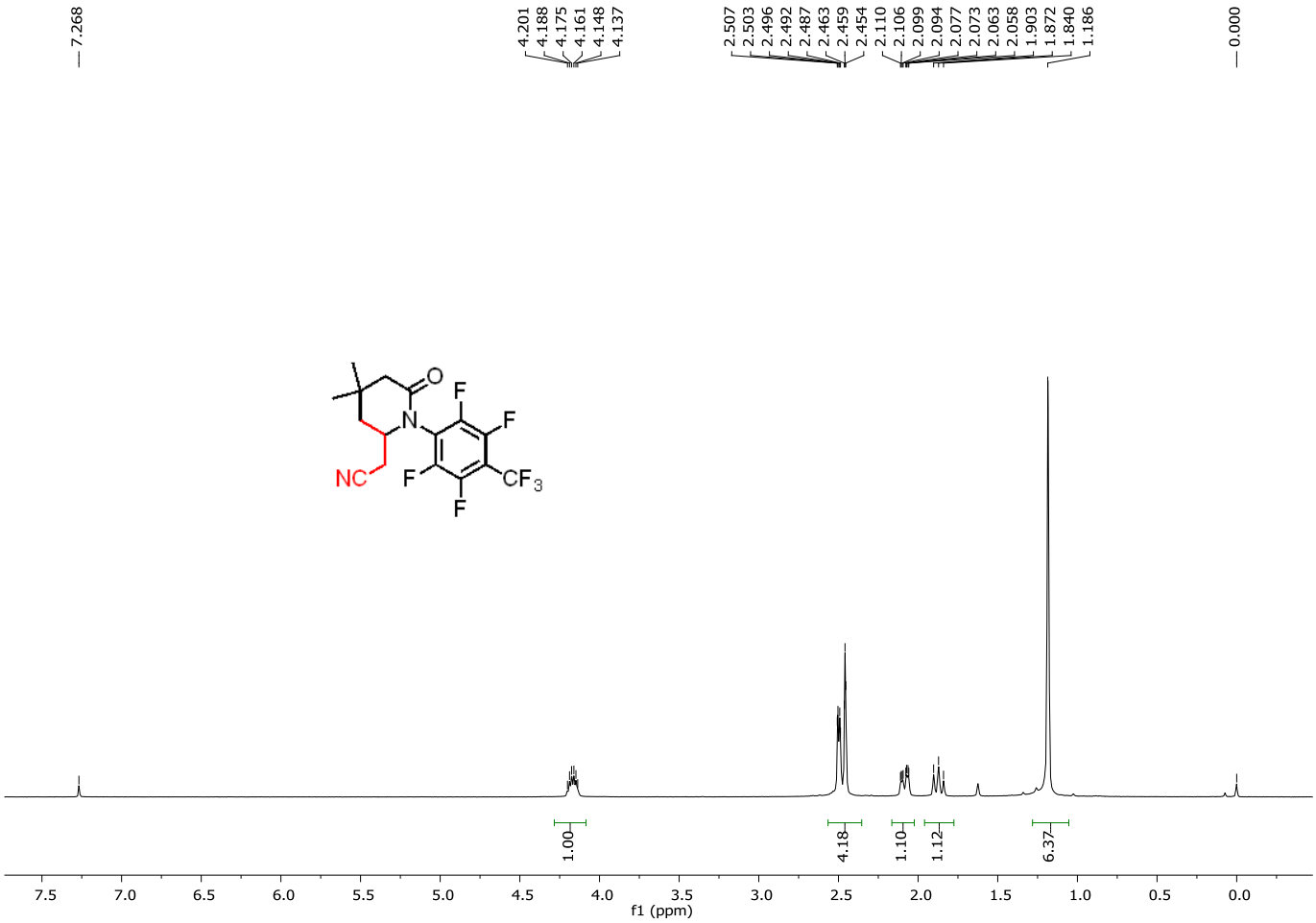
170.213
135.809
133.961
128.824
127.561
77.211 CDCl3
77.000 CDCl3
76.788 CDCl3
53.713
53.696
45.823
43.517
42.639
30.499
29.947
24.532
O
N
F
F
F
F
CF3
Ph
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)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4.161
4.148
4.137
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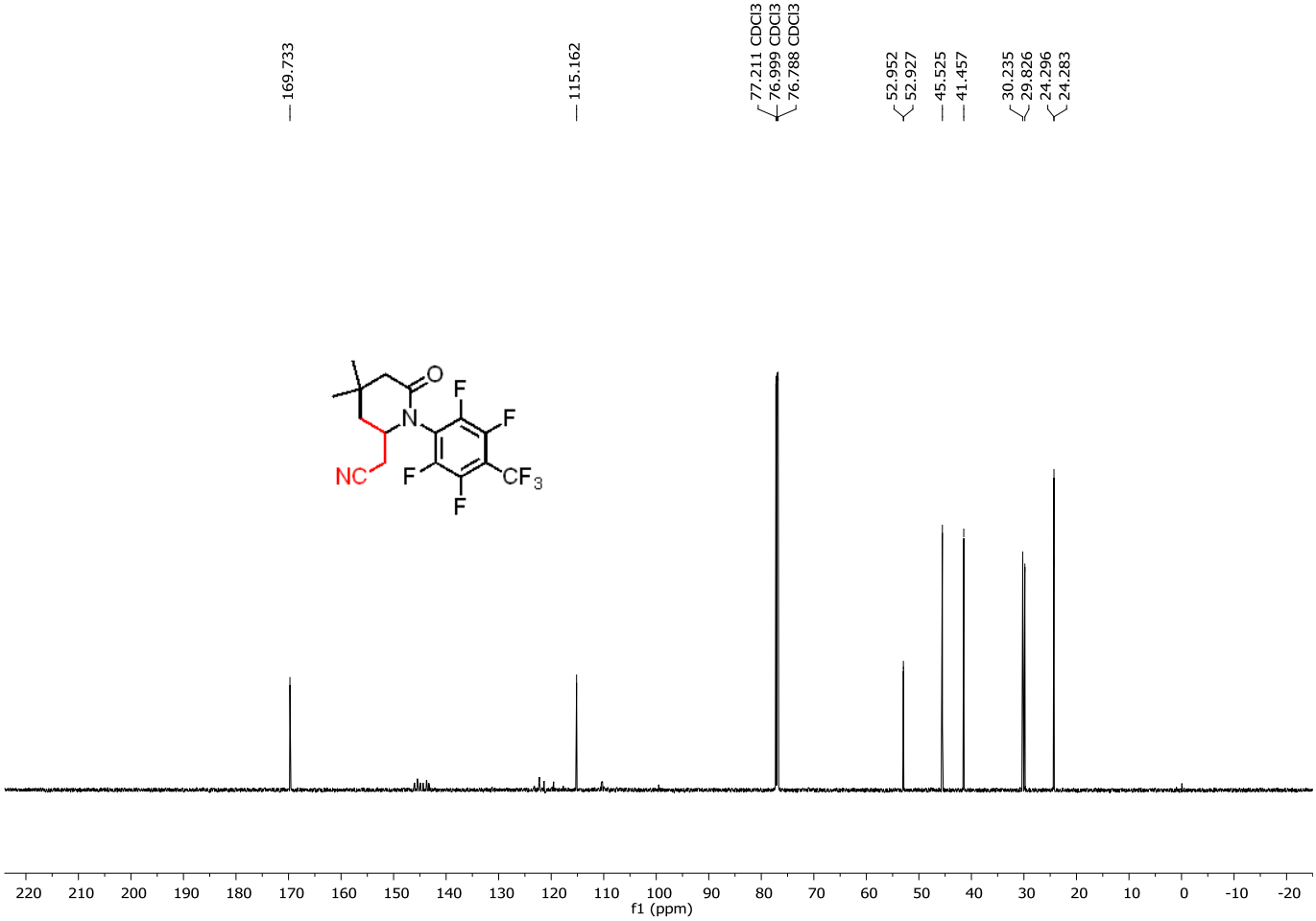
2.503
2.496
2.492
2.487
2.463
2.459
2.454
2.110
2.106
2.099
2.094
2.077
2.073
2.063
2.058
1.903
1.872
1.840
1.186
0.000
O
N
F
F
F
F
F
NC
CF3
1.00
4.18
1.10
1.12
6.37
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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76.788 CDCl3
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52.927
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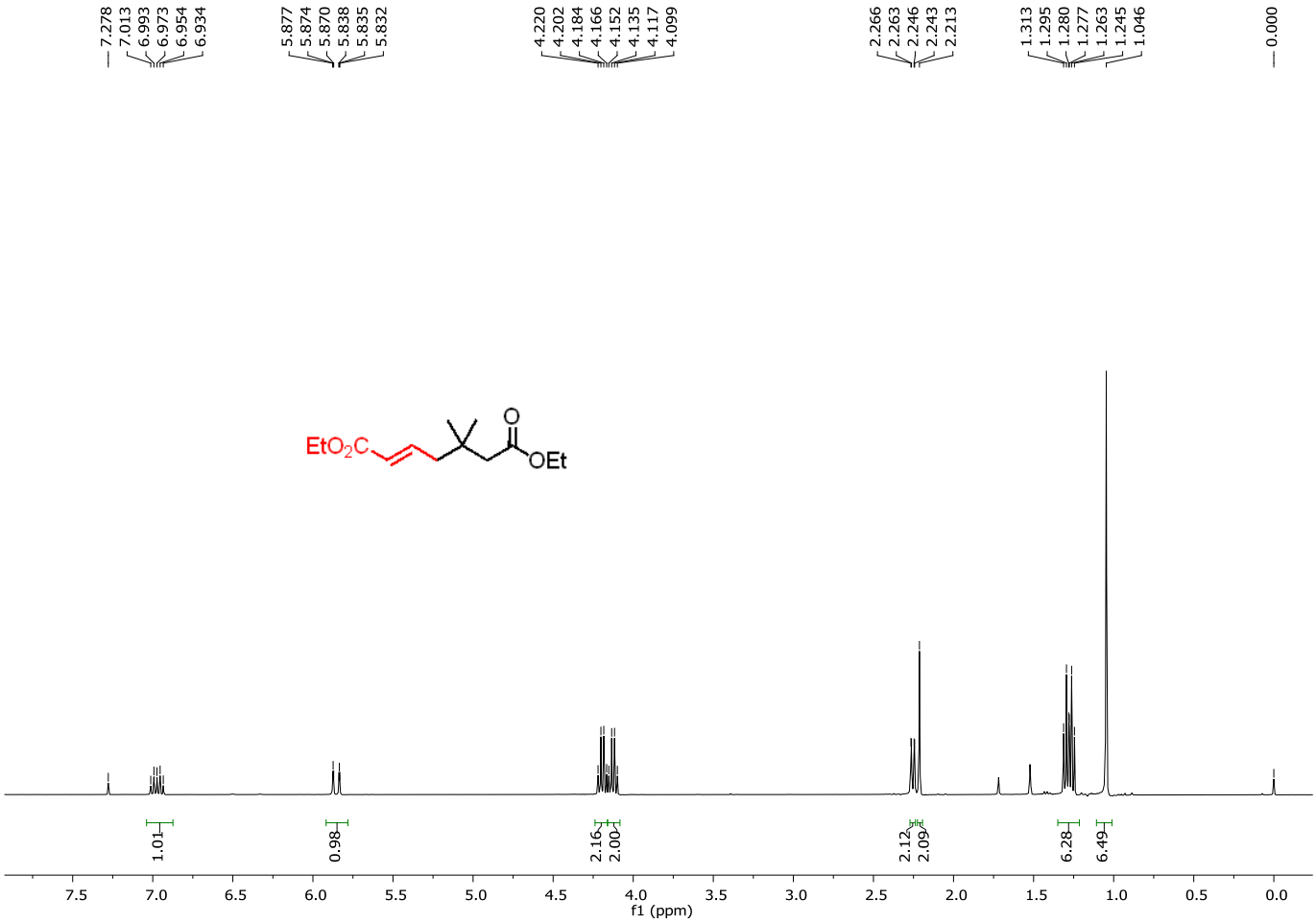
41.457
30.235
29.826
24.296
24.283
O
N
F
F
F
F
F
NC
CF3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)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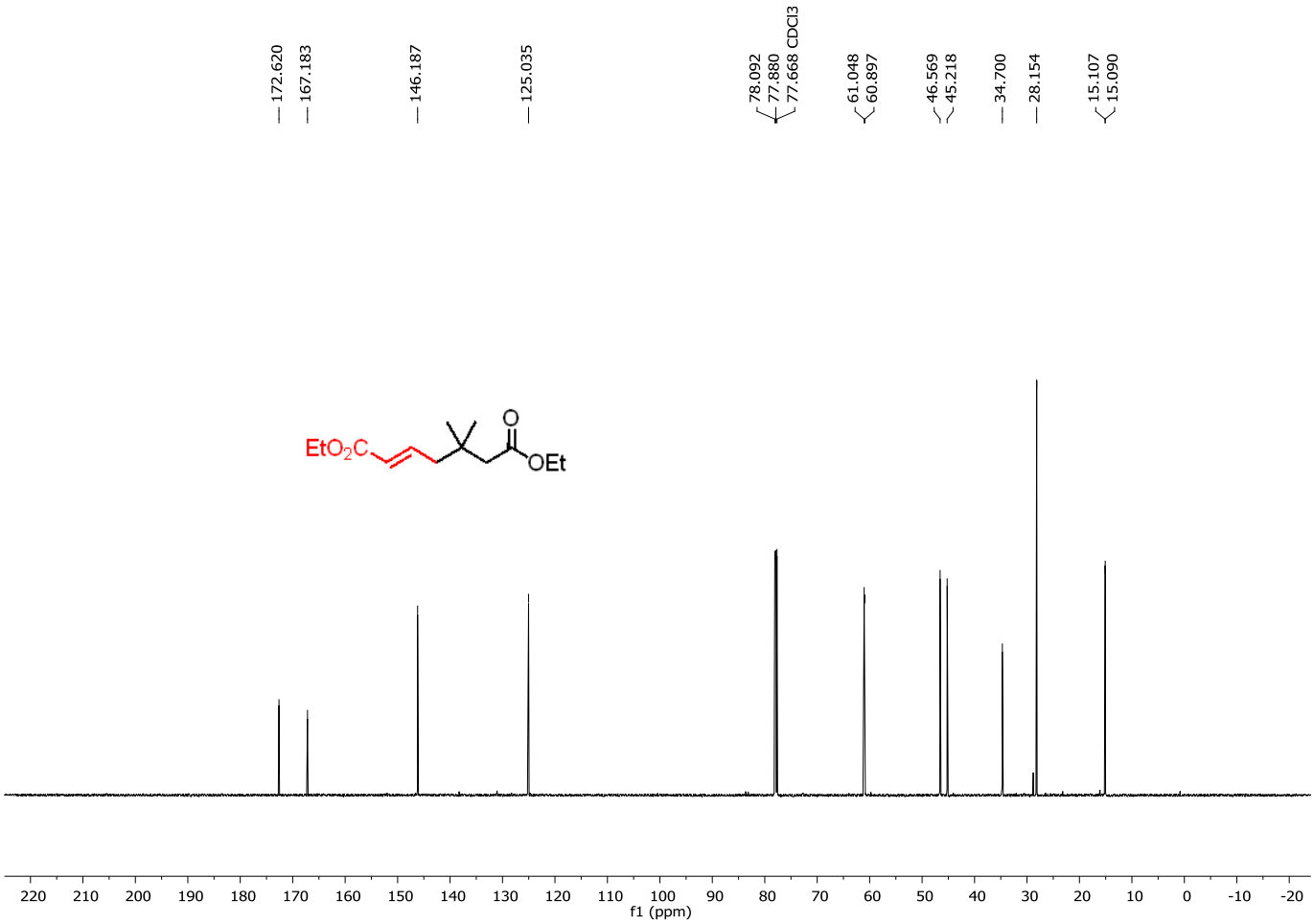
5.835
5.832
4.220
4.202
4.184
4.166
4.152
4.135
4.117
4.099
2.266
2.263
2.246
2.243
2.213
1.313
1.295
1.280
1.277
1.263
1.245
1.046
0.000
EtO2C
OEt
1.01
0.98
2.16
2.00
2.12
2.09
6.28
6.49
f1 (ppm)


172.620
167.183
146.187
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77.668 CDCl3
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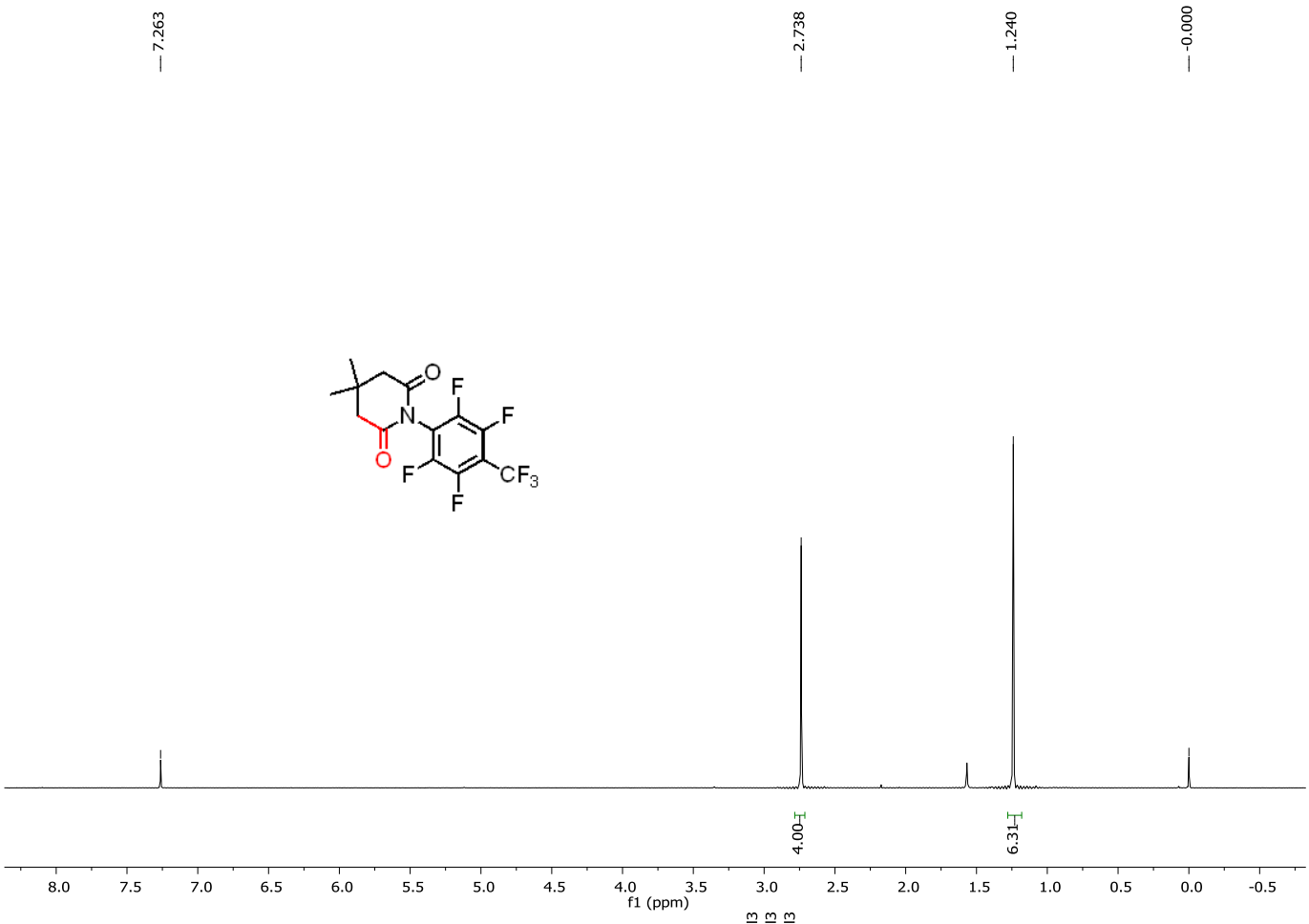
46.569
45.218
34.700
28.154
15.107
15.090
EtO2C
OEt
f1 (ppm)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4.00
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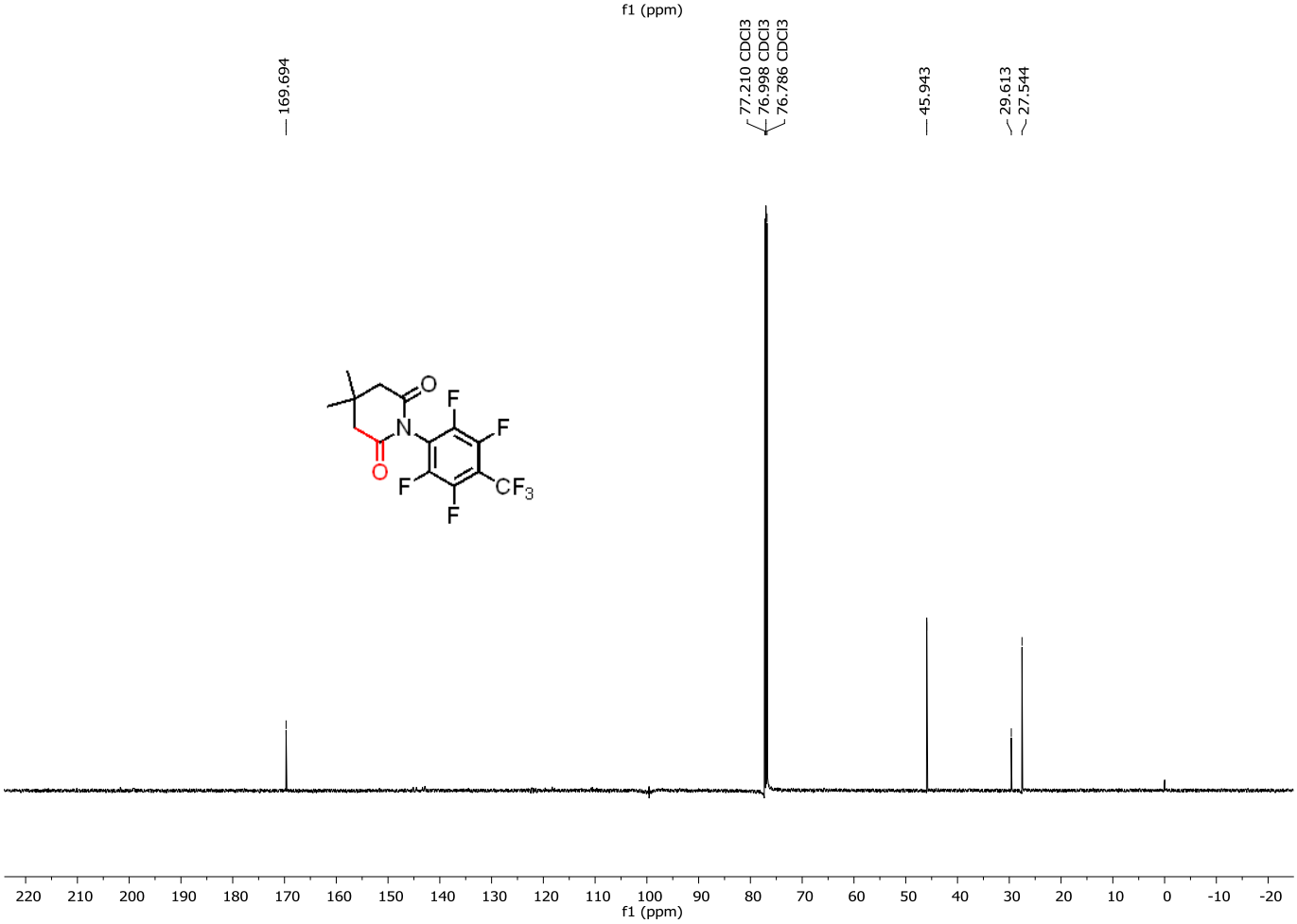
f1 (ppm)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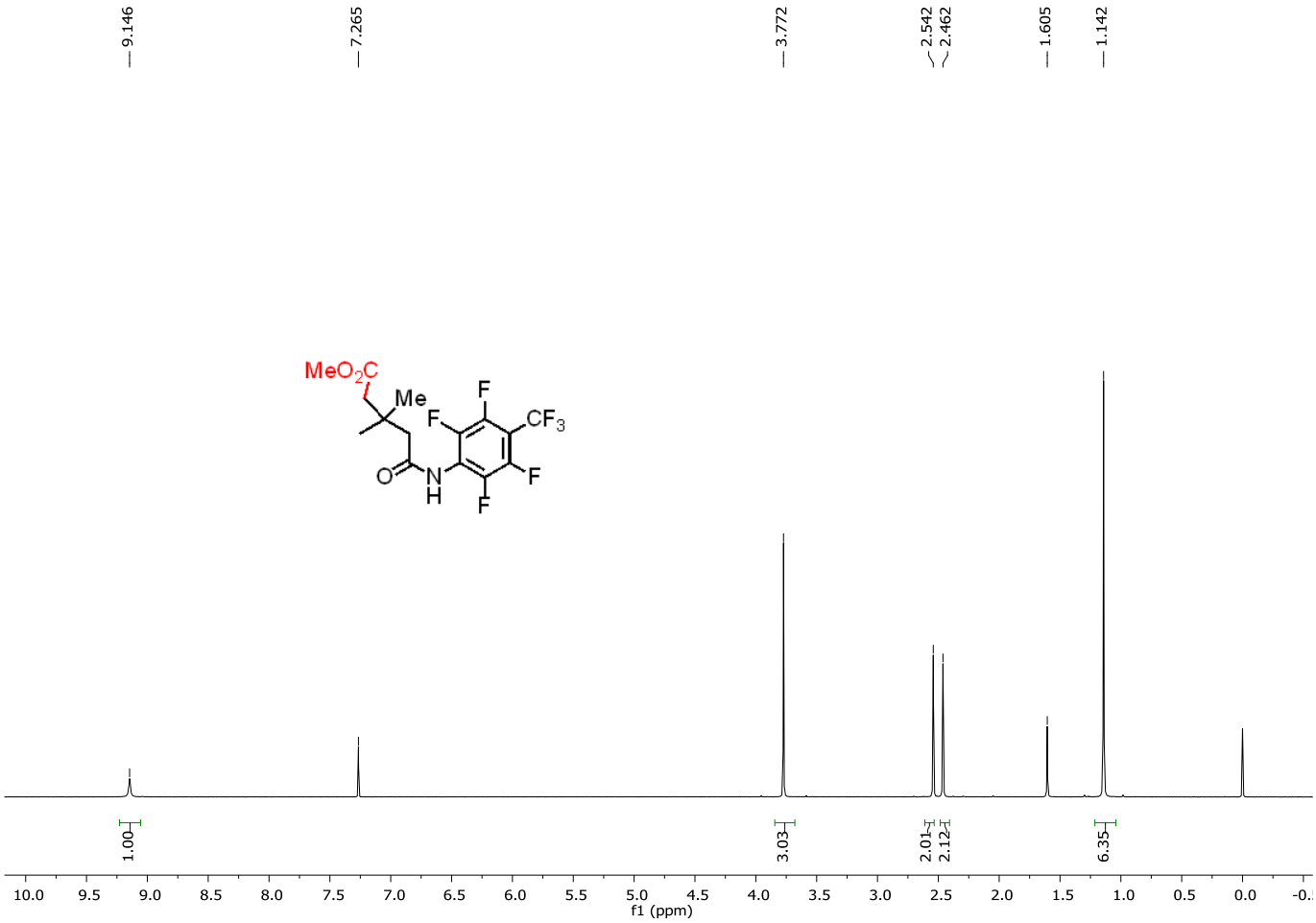
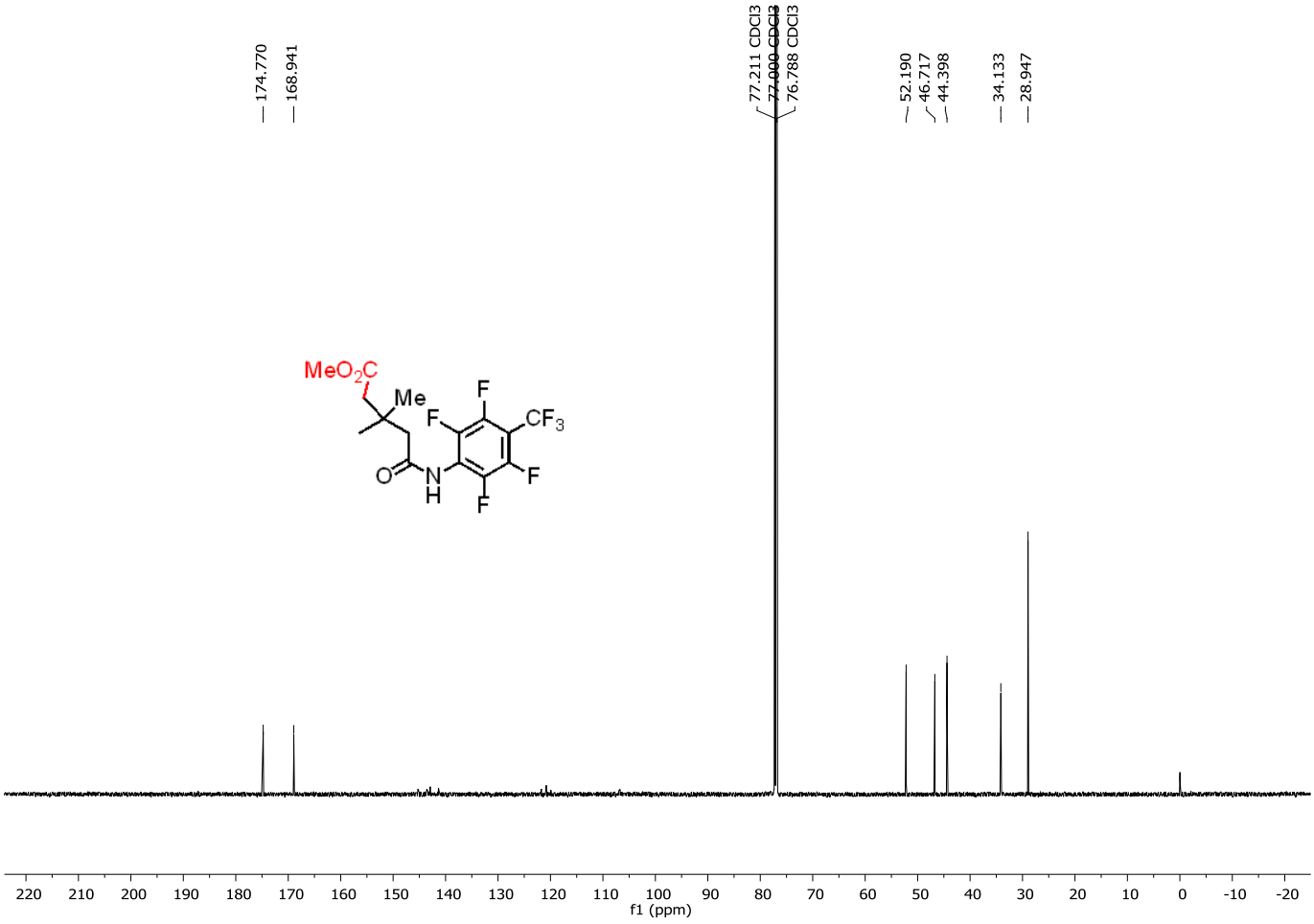
29.613
27.544
f1 (ppm)


9.146
7.265
3.772
2.542
2.462
1.605
1.142
MeO2C
Me
F
F
CF3
O
N
H
F
F
1.00
3.03
2.01
2.12
6.35
f1 (ppm)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76.788 CDCl3
52.190
46.717
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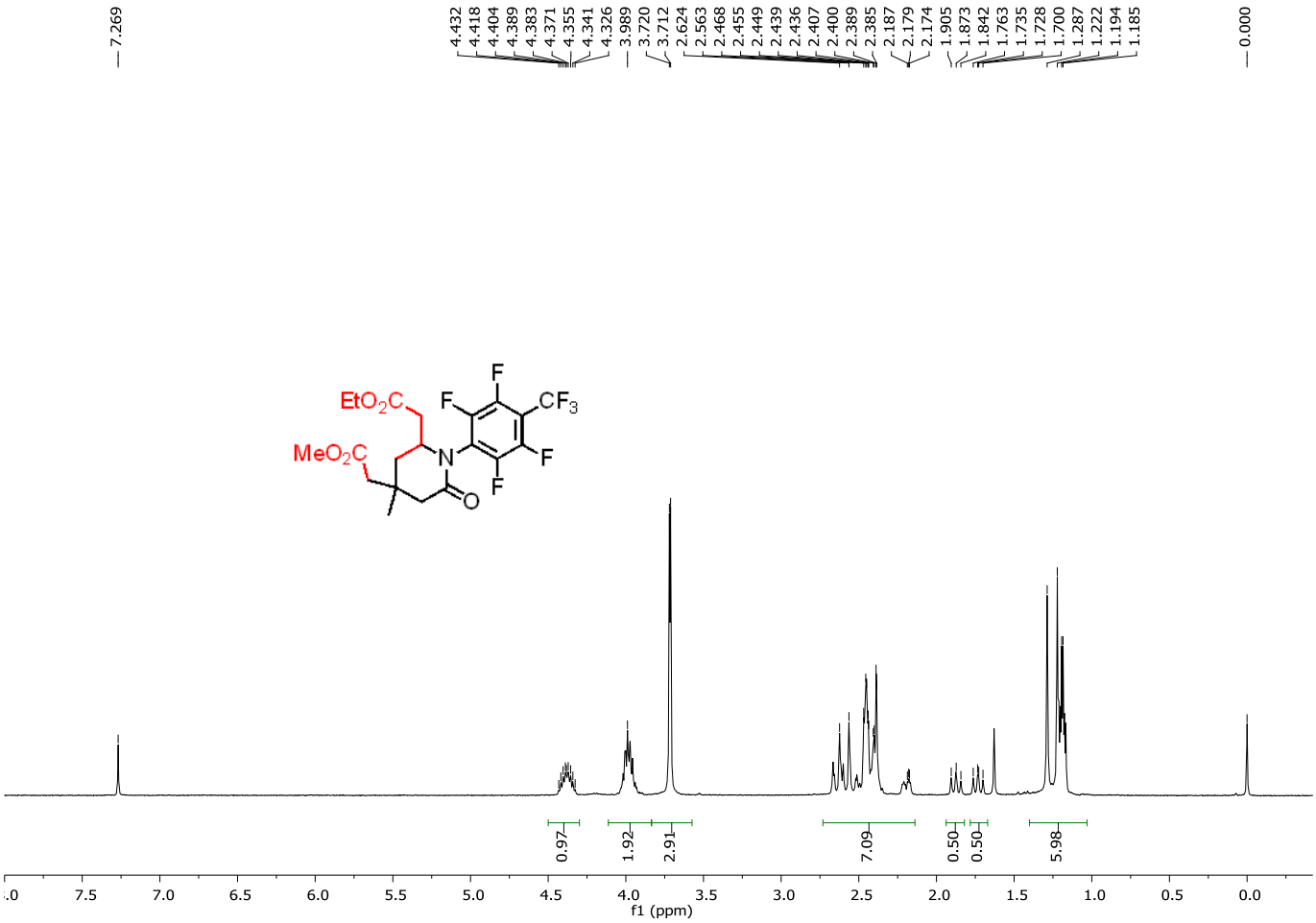
34.133
28.947
MeO2C
Me
F
F
CF3
O
N
H
F
F
f1 (ppm)


7.269
4.432
4.418
4.404
4.389
4.383
4.371
4.355
4.341
4.326
3.989
3.720
3.712
2.624
2.563
2.468
2.455
2.449
2.439
2.436
2.407
2.400
2.389
2.385
2.187
2.179
2.174
1.905
1.873
1.842
1.763
1.735
1.728
1.700
1.287
1.222
1.194
1.185
0.000
EtO2C
MeO2C
F
CF3
N
O
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2.91
7.09
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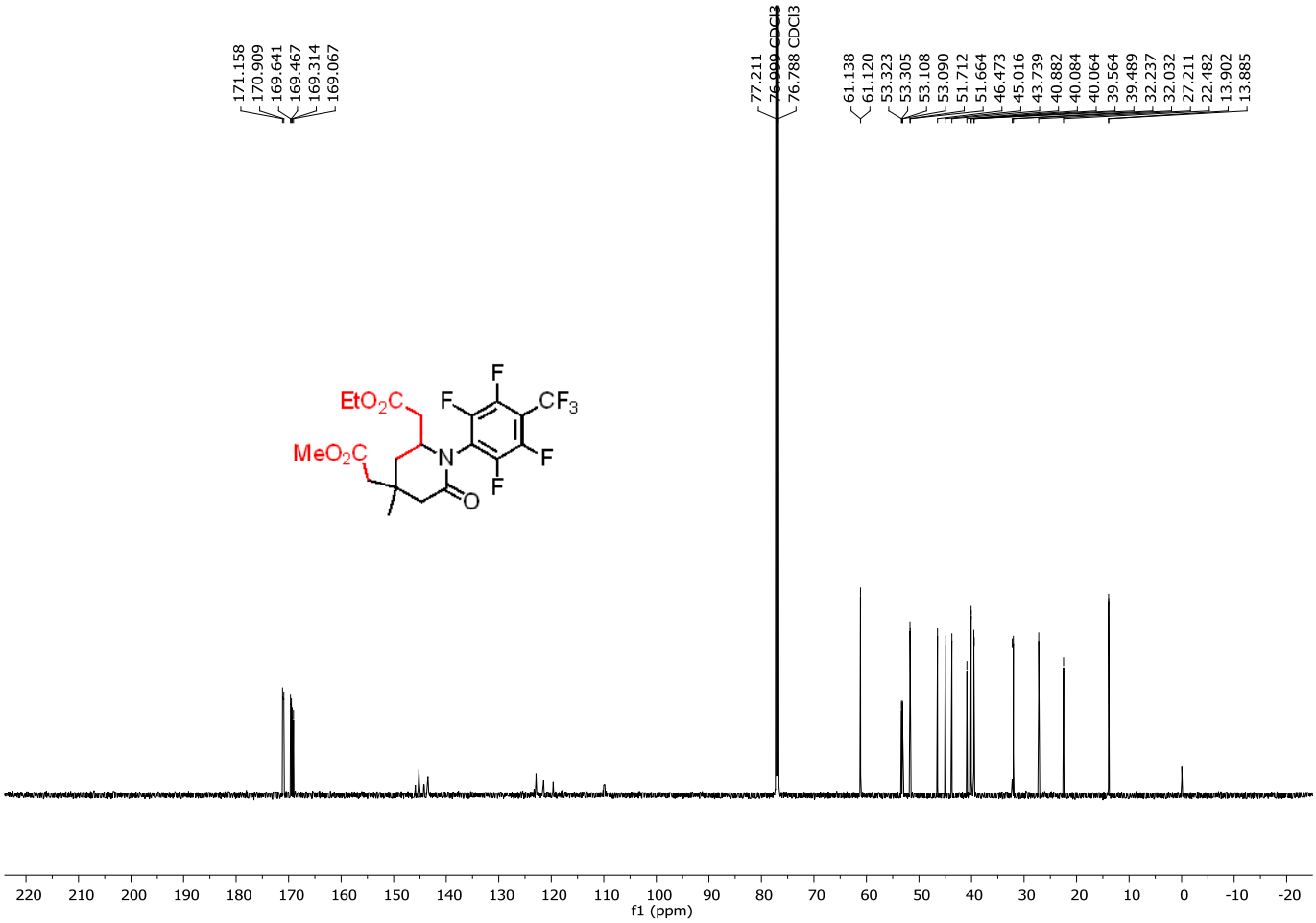
0.50
5.98
f1 (ppm)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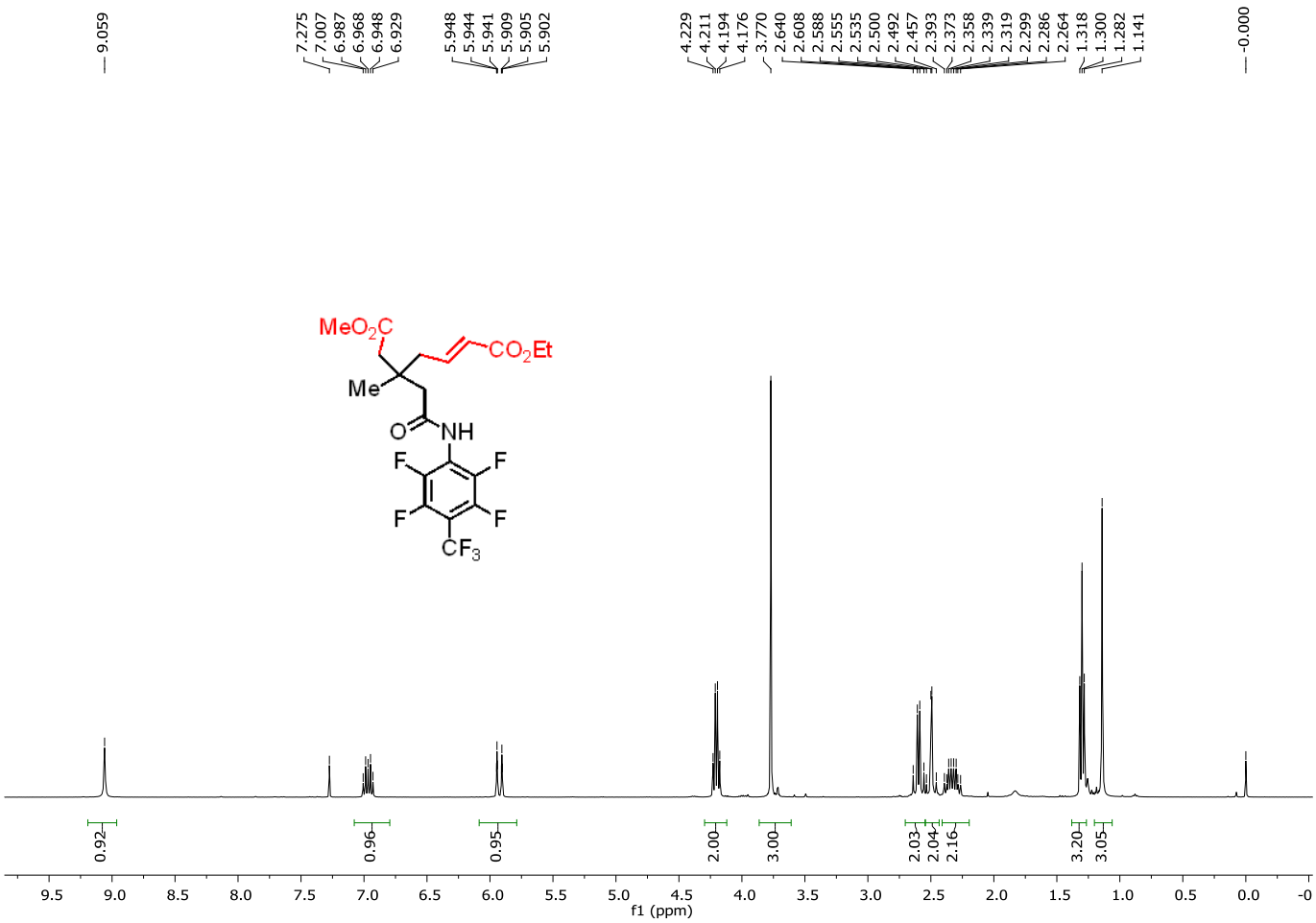
169.467
169.314
169.067
77.211
76.999 CDCl3
76.788 CDCl3
61.138
61.120
53.323
53.305
53.108
53.090
51.712
51.664
46.473
45.016
43.739
40.882
40.084
40.064
39.564
39.489
32.237
32.032
27.211
22.482
13.902
13.885
EtO2C
MeO2C
F
CF3
N
O
f1 (ppm)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6.968
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6.929
5.948
5.944
5.941
5.909
5.905
5.902
4.229
4.211
4.194
4.176
3.770
2.640
2.608
2.588
2.555
2.535
2.500
2.492
2.457
2.393
2.373
2.358
2.339
2.319
2.299
2.286
2.264
1.318
1.300
1.282
1.141
-0.000
MeO2C
CO2Et
Me
O
NH
F
F
F
F
CF3
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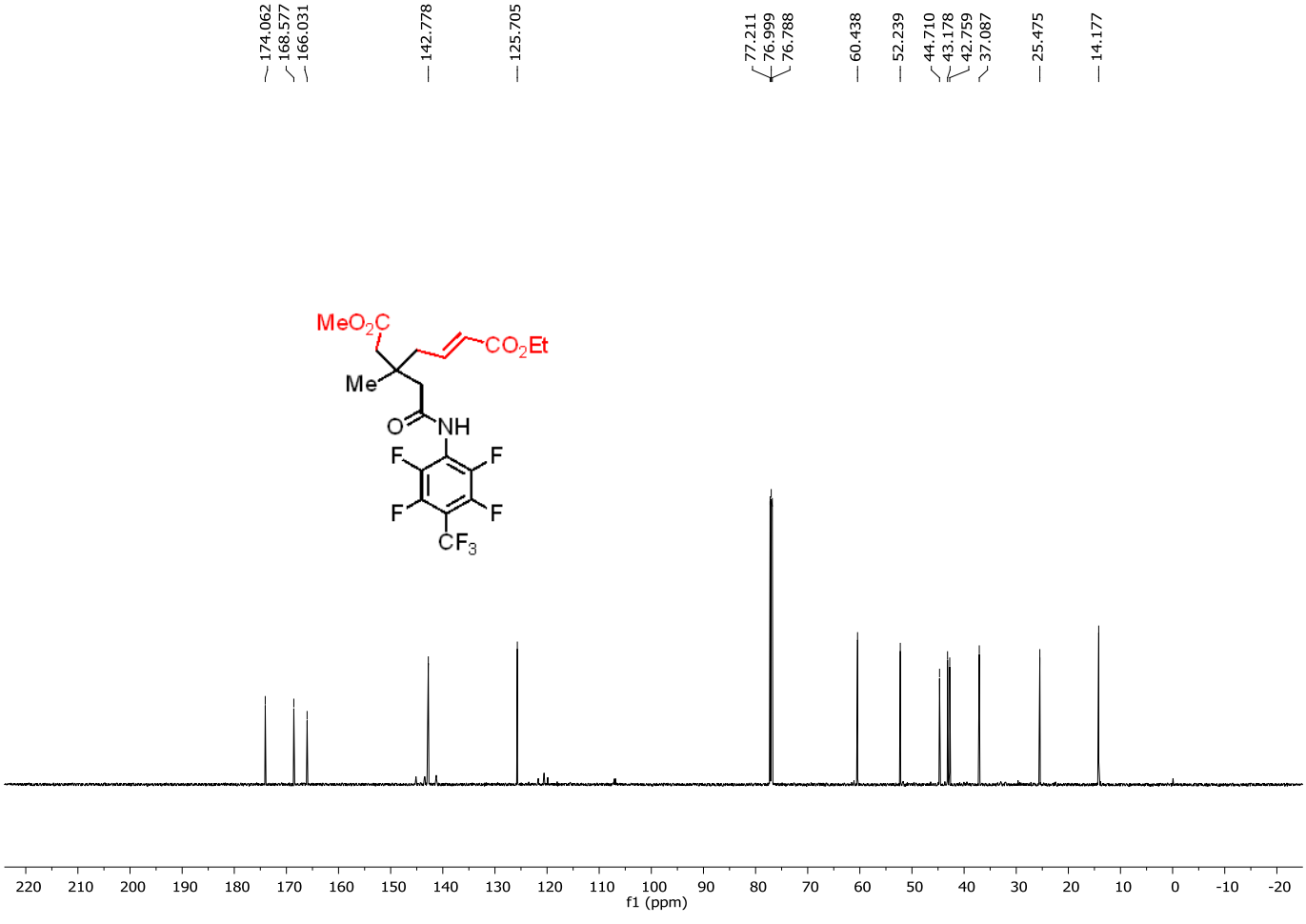
0.96
0.95
2.00
3.00
2.03
2.04
2.16
3.20
3.05
f1 (ppm)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77.211
76.999
76.788
60.438
52.239
44.710
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42.759
37.087
25.475
14.177
MeO2C
CO2Et
Me
O
NH
F
F
F
F
CF3
f1 (ppm)