

Supporting Information

Synthesis of Conformationally Constrained Esters and Amines by Pd-Catalyzed α -Arylation of Hindered Substrates

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General considerations

All reactions were carried out in pre-dried glassware under an argon or nitrogen atmosphere by using Schlenk techniques employing double-line argon-vacuum lines or by working in an argon-filled glove box, unless otherwise noted.

Commercial reagents were used without further purification, unless otherwise stated.

Analytical thin layer chromatography (TLC) was performed using EM Reagent 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains (KMnO₄, ninhydrin, and phosphomolybdic acid). Flash chromatography was performed using EM Silica Gel 60 (60-200 mesh) with the indicated solvent system, using gradients of increasing polarity in most cases.

¹H NMR, ¹³C NMR and ¹⁹F were recorded on a Bruker AV-300 (¹H: 300 MHz, ¹³C: 75.5 MHz), Bruker AV-400 (¹H: 400 MHz, ¹³C: 101 MHz, ¹⁹F: 376 MHz) and Bruker AV-500 Avance III (¹H: 500 MHz, ¹³C: 126 MHz, ¹⁹F: 470 MHz) using CDCl₃ as internal reference unless otherwise indicated. The chemical shift (δ) and coupling constants (*J*) are expressed in ppm and Hz respectively.

GC/MS analyses were performed on a Shimadzu QP2010 GC/MS apparatus, with injection on a DB-5ms column lined with a mass (EI 0.7 kV) detection system. High-resolution mass spectra were measured under electrospray ionization (ESI) or electronic impact (EI).

Infrared spectra were taken on a Thermo Scientific Nicolet iS10 FT-IR spectrometer and are reported in reciprocal centimeters (cm⁻¹).

Melting points were obtained on a Büchi melting point B-565 apparatus and are uncorrected.

Retention times (*R*_T) are given for analytical UPLC-MS using a « Acquity UPLC » system equipped with a Zorbax Eclipse C₁₈ column (1.8 μ m - 50 x 2.1 mm), a DAD UV detector (200 - 350 nm) and a SQD (ES) mass detection system.

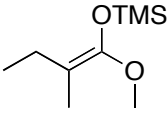
A Phenomenex C₁₈ Gemini NX column (150 x 30 mm; 10 μ m) was used for preparative HPLC separations using a Gilson PLC 2020 Personal Purification System equipped with a UV-visible diode array detector (190-600 nm).

Characterization data

General procedure A : synthesis of silyl ketene acetals (SKAs)

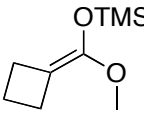
To a solution of diisopropylamine in THF was added *n*-BuLi (2.5 M in hexane) at -78°C. The resulted solution was stirred for 10 min at -78°C. Then, a solution of ester in THF was slowly added to the LDA solution at -78°C. After the solution was stirred for 1 h at -78°C, TMSCl was added dropwise at -78°C to the reaction mixture. The reaction mixture was stirred for 20 h at 20 °C. The reaction mixture was poured into ice water and hexane, and the aqueous layer was extracted with hexane. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The resulting crude oil was purified by distillation under reduced pressure to give the desired SKA.

((1-Methoxy-2-methylbut-1-en-1-yl)oxy)trimethylsilane (**5u**)

 Following procedure A, methyl 2-methylbutanoate (6 mL, 45.5 mmol, 1 equiv) in THF (18 mL) was reacted with diisopropylamine (7.6 mL, 54.5 mmol, 1.2 equiv), *n*-BuLi (21.8 mL, 54.5 mmol, 1.2 equiv) in THF (25 mL) and TMSCl (6.9 mL, 54.5 mmol, 1.2 equiv). The crude oil was purified by distillation (51 °C, 0.4-0.5 mbar) affording 6.9 g (36.86 mmol, 81 %) of **5u** as a colorless oil (9:1 mixture of isomers). Analytical data matched those reported in the literature.¹

¹H NMR (400 MHz, CDCl₃) δ 3.67 (s, 3H x 0.1), 3.50 (s, 3H x 0.9), 2.03 – 1.90 (m, 2H), 1.54 (s, 3H x 0.9), 1.50 (s, 3H x 0.1), 0.97 – 0.87 (m, 3H), 0.22 – 0.19 (m, 9H).

(Cyclobutylidene(methoxy)methoxy)trimethylsilane (**5w**)

 Following procedure A, methyl cyclobutanecarboxylate (2.0 mL, 17.52 mmol, 1 equiv) in THF (7 mL) was reacted with diisopropylamine (3.1 mL, 21.90 mmol, 1.25 equiv), *n*-BuLi (8.4 mL, 21.03 mmol, 1.2 equiv) in THF (11 mL) and TMSCl (2.7 mL, 21.03 mmol, 1.2 equiv). The crude oil was purified by distillation (43 °C, 0.4-0.5 mbar) affording 1.5 g (8.06 mmol, 46 %) of **5w** as a colorless oil (9:1 mixture of OSi/CSi isomers).

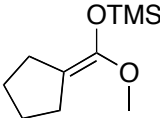
¹H NMR (300 MHz, CDCl₃) δ 3.66 (s, 3H x 0.1), 3.55 (s, 3H x 0.9), 2.78 – 2.68 (m, 2H x 0.9), 2.62 – 2.53 (m, 2H x 0.9), 2.50 (m, 2H x 0.1), 2.29 – 2.13 (m, 2H x 0.1), 2.01 – 1.78 (m, 2H x 0.9 and 2H x 0.1), 0.21 – 0.17 (m, 9H x 0.9), 0.09 (s, 9H x 0.1).

¹³C NMR (75 MHz, CDCl₃) δ 147.9, 92.8, 56.2, 51.4, 27.9, 26.9, 26.6, 25.4, 17.8, 17.6, 0.4, -4.1.

IR (neat) 2961, 1699, 1253, 1060, 840 cm⁻¹.

HRMS (ESI) : *m/z* calcd. for C₉H₁₈NaO₂Si [M+Na]⁺: 209.0968, found : 209.0969.

(Cyclopentylidene(methoxy)methoxy)trimethylsilane (**5x**)

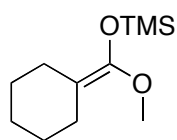
 Following procedure A, methyl cyclopentanecarboxylate (5 mL, 38.46 mmol, 1 equiv) in THF (15 mL) was reacted with diisopropylamine (6.0 mL, 42.31 mmol, 1.1 equiv), *n*-BuLi (16.9 mL, 42.31 mmol, 1.1 equiv) in THF (20 mL) and TMSCl (12.3 mL, 96.16 mmol, 2.5 equiv). The crude oil was purified by distillation (44 °C, 0.2-0.3 mbar) affording 4.68 g (23.36 mmol, 61 %) of **5x** as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 3.52 (s, 3H), 2.26 – 2.06 (m, 4H), 1.65 – 1.52 (m, 4H), 0.21 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 147.2, 100.9, 56.1, 28.5, 27.5, 27.2, 27.0, 0.3.

IR (neat) 2962, 1701, 1401, 1242, 1061, 871 cm⁻¹.

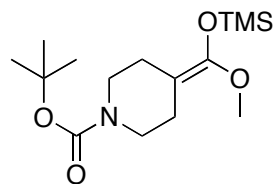
(Cyclohexylidene(methoxy)methoxy)trimethylsilane (**5y**)



Following procedure A, methyl cyclohexanecarboxylate (11.94 g, 83.97 mmol, 1 equiv) in THF (34 mL) was reacted with diisopropylamine (13.0 mL, 92.37 mmol, 1.1 equiv), *n*-BuLi (36.9 mL, 92.37 mmol, 1.1 equiv) in THF (42 mL) and TMSCl (26.6 mL, 209.92 mmol, 2.5 equiv). The crude oil was purified by distillation (70°C, 0.3-0.4 mbar) affording 15.56 g (72.57 mmol, 86 %) of **5y** as a colorless oil. Analytical data matched those reported in the literature.²

¹H NMR (300 MHz, CDCl₃) δ 3.50 (s, 3H), 2.13 – 2.06 (m, 2H), 2.06 – 1.98 (m, 2H), 1.52 – 1.39 (m, 6H), 0.22 – 0.18 (m, 9H).

tert-Butyl 4-(methoxy((trimethylsilyl)oxy)methylene)piperidine-1-carboxylate (**5z**)



Following procedure A, methyl 1-*tert*-butyl 4-methyl piperidine-1,4-dicarboxylate (5 g, 20.55 mmol, 1 equiv) in THF (9 mL) was reacted with diisopropylamine (4.0 mL, 28.77 mmol, 1.4 equiv), *n*-BuLi (10.4 mL, 25.89 mmol, 1.26 equiv) in THF (15 mL) and TMSCl (3.4 mL, 26.72 mmol, 1.3 equiv) to afford 3.2 g (10.07 mmol, 49 %) of **5z** as a slightly yellow oil which was used without further purification.

¹H NMR (300 MHz, CDCl₃) δ 3.51 (s, 3H), 3.38 – 3.29 (m, 4H), 2.22 – 2.14 (m, 2H), 2.13 – 2.05 (m, 2H), 1.46 (s, 9H), 0.21 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ 155.0, 148.7, 94.9, 79.3, 57.0, 45.3, 28.6, 26.6, 26.2, 0.1.

IR (neat) 2890, 1704, 1683, 1241, 869 cm⁻¹.

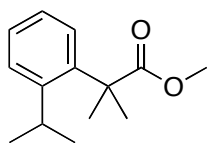
General procedure B : cross-coupling using Pd(PtBu₃)₂ as catalyst

Pd(PtBu₃)₂ and ZnF₂ were weighed in the glovebox in an oven-dried vial. The vial was capped with a septum, brought outside the glovebox and degassed DMF was added under argon. The aryl bromide was added, followed by the SKA. The reaction mixture was warmed to the indicated temperature for the indicated time. After completion, the reaction mixture was diluted in diethyl ether and quenched with a mixture of sat. aq. NH₄Cl/water (1:1). The aqueous layer was extracted twice with diethyl ether then the combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration and evaporation, the crude mixture was purified by preparative HPLC.

General procedure C : cross-coupling using palladacycle 6 as catalyst

Palladacycle **6** and ZnF₂ were weighed in an oven-dried vial. The vial was sealed, flushed with dry nitrogen, and degassed DMF was added. The aryl bromide was added, followed by the SKA. NEt₃ was added in one portion and the reaction mixture was warmed to the indicated temperature for the indicated time. After completion, the reaction mixture was diluted with diethyl ether and quenched with a mixture of sat. aq. NH₄Cl/water (1:1). The aqueous layer was extracted twice with diethyl ether, then the combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration and evaporation, the crude mixture was purified by preparative HPLC.

Methyl 2-(2-isopropylphenyl)-2-methylpropanoate (**2a**)



Following general procedure B, **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 2-bromocumene (230 μ L, 1.5 mmol, 1 equiv), ZnF₂ (155.1 mg, 1.5 mmol, 1 equiv) and Pd(PtBu₃)₂ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 304 mg (1.38 mmol, 92 %) of **2a** as a colorless oil.

Following general procedure C **5a** (488 μ L, 2.4 mmol, 1.6 equiv,) was reacted with 2-bromocumene (230 μ L, 1.5 mmol, 1 equiv), ZnF₂ (155.1 mg, 1.5 mmol, 1 equiv), **6** (35.2 mg, 0.06 mmol, 4 mol%) and NEt₃ (8.3 μ L, 0.06 mmol, 4 mol%) in DMF (9 mL) at 110 °C for 15 h to give 237 mg (1.08 mmol, 72 %) of **2a** as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 7.38 – 7.23 (m, 3H), 7.23 – 7.13 (m, 1H), 3.66 (s, 3H), 2.94 – 2.78 (m, 1H), 1.59 (s, 6H), 1.18 (d, J = 6.7 Hz, 6H).

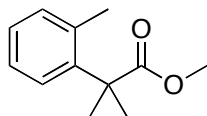
¹³C NMR (75 MHz, CDCl₃) δ 179.3, 147.4, 141.2, 127.4, 127.2, 125.9, 125.0, 52.3, 46.3, 29.3, 28.0, 24.4.

IR (neat) 1730, 1446, 1255, 1140, 756 cm⁻¹.

HRMS (ESI) : m/z calcd. for C₁₄H₂₀NaO₂ [M+Na]⁺ : 243.1356, found : 243.1355.

R_T = 2.38 min.

Methyl 2-methyl-2-(o-tolyl)propanoate (**2b**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 2-bromotoluene (181 μ L, 1.5 mmol, 1 equiv), ZnF₂ (155.1 mg, 1.5 mmol, 1 equiv) and Pd(PtBu₃)₂ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 283 mg (1.47 mmol, 98 %) of **2b** as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 7.40 – 7.33 (m, 1H), 7.25 – 7.11 (m, 3H), 3.67 (s, 3H), 2.21 (s, 3H), 1.58 (s, 6H).

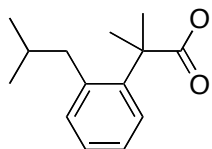
¹³C NMR (75 MHz, CDCl₃) δ 178.9, 143.0, 136.0, 131.9, 126.9, 126.2, 125.1, 52.4, 46.5, 27.0, 20.1.

IR (neat) 1730, 1468, 1250, 1142, 750, 726 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{12}\text{H}_{16}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 215.1043, found : 215.1041.

R_T = 2.04 min.

Methyl 2-(2-isobutylphenyl)-2-methylpropanoate (**2c**)



Following general procedure B **5a** (488 μL , 2.4 mmol, 1.6 equiv) was reacted with 1-bromo-2-isobutylbenzene (320 mg, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 110 $^\circ\text{C}$ for 15 h to give 288 mg (1.23 mmol, 82 %) of **2c** as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.38 (dd, J = 7.4, 1.9 Hz, 1H), 7.29 – 7.17 (m, 3H), 3.65 (s, 3H), 2.37 (d, J = 7.3 Hz, 2H), 2.15 – 2.02 (m, 1H), 1.58 (s, 6H), 0.92 (d, J = 6.6 Hz, 6H).

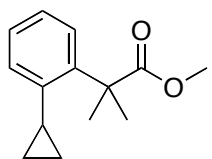
^{13}C NMR (101 MHz, CDCl_3) δ 178.9, 142.8, 139.4, 129.5, 126.7, 125.8, 125.2, 52.2, 46.2, 40.5, 28.2, 27.7, 22.6.

IR (neat) 1730, 1451, 1257, 761 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{15}\text{H}_{22}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 257.1512, found : 257.1505.

R_T = 2.57 min.

Methyl 2-(2-cyclopropylphenyl)-2-methylpropanoate (**2d**)



Following general procedure B **5a** (488 μL , 2.4 mmol, 1.6 equiv,) was reacted with 1-bromo-2-cyclopropylbenzene (296 mg, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 110 $^\circ\text{C}$ for 15 h to give 278 mg (1.27 mmol, 85 %) of **2d** as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.39 – 7.34 (m, 1H), 7.21 – 7.14 (m, 2H), 6.82 – 6.77 (m, 1H), 3.67 (s, 3H), 1.81 – 1.71 (m, 1H), 1.65 (s, 6H), 0.96 – 0.89 (m, 2H), 0.75 – 0.69 (m, 2H).

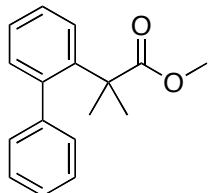
^{13}C NMR (101 MHz, CDCl_3) δ 179.2, 143.1, 141.1, 127.1, 125.5, 124.9, 123.5, 52.2, 46.3, 27.4, 12.2, 9.7.

IR (neat) 3061, 2984, 1731, 1449, 1261, 1258, 1139, 757 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{14}\text{H}_{18}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 241.1199, found : 241.1192.

R_T = 2.20 min.

Methyl 2-([1,1'-biphenyl]-2-yl)-2-methylpropanoate (**2e**)



Following general procedure B **5a** (488 μL , 2.4 mmol, 1.6 equiv) was reacted with 2-bromobiphenyl (259 μL , 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 $^\circ\text{C}$ for 15 h to give 275 mg (1.08 mmol, 72 %) of **2e** as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.50 (dd, J = 8.0, 1.2 Hz, 1H), 7.41 – 7.31 (m, 4H), 7.31 – 7.23 (m, 2H), 7.22 – 7.17 (m, 2H), 7.08 (dd, J = 7.5, 1.6 Hz, 1H), 3.37 (s, 3H), 1.49 (s, 6H).

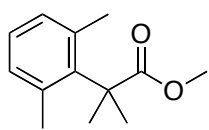
^{13}C NMR (75 MHz, CDCl_3) δ 177.5, 142.6, 142.1, 141.9, 132.2, 130.2, 127.7, 127.5, 127.3, 126.4, 125.9, 51.9, 46.9, 28.6.

IR (neat) 1735, 1476, 1436, 1243, 1190, 1142, 1112, 754, 705 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{17}\text{H}_{18}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 277.1199, found : 277.1203.

$R_T = 2.35$ min.

Methyl 2-(2,6-dimethylphenyl)-2-methylpropanoate (**2g**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 2-bromo-1,3-dimethylbenzene (201 μ L, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 $^\circ\text{C}$ for 15 h to give 90 mg (0.44 mmol, 29 %) of **2g** as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.07 – 6.92 (m, 3H), 3.70 (s, 3H), 2.34 (s, 6H), 1.68 (s, 6H).

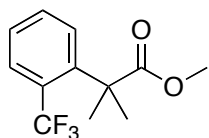
^{13}C NMR (75 MHz, CDCl_3) δ 180.0, 141.4, 136.6, 131.0, 126.3, 52.4, 49.3, 27.8, 23.3.

IR (neat) 1729, 1454, 1238, 1145, 1127, 767 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{13}\text{H}_{18}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 229.1199, found : 229.1196.

$R_T = 2.19$ min.

Methyl 2-methyl-2-(2-(trifluoromethyl)phenyl)propanoate (**2h**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 2-bromobenzotrifluoride (205 μ L, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 $^\circ\text{C}$ for 15 h to give 41 mg (0.17 mmol, 11 %) of **2h** as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.68 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.59 – 7.50 (m, 2H), 7.41 (dddd, $J = 7.9, 6.9, 1.7, 1.0$ Hz, 1H), 3.64 (s, 3H), 1.65 (s, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 175.2, 140.2, 129.9, 126.7 (q, $J = 5.5$ Hz), 126.2 (q, $J = 30.5$ Hz), 125.2, 125.2, 123.0 (q, $J = 274.1$ Hz), 50.1, 44.8, 26.3 (d, $J = 1.6$ Hz).

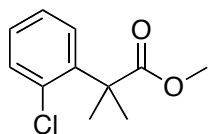
^{19}F NMR (376 MHz, CDCl_3) δ -55.5.

IR (neat) 1738, 1309, 1176, 1145, 1108, 1038, 764 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{12}\text{H}_{13}\text{F}_3\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 269.0760, found : 269.0753.

$R_T = 2.13$ min.

Methyl 2-(2-chlorophenyl)-2-methylpropanoate (**2i**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 1-bromo-2-chlorobenzene (174 μ L, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 $^\circ\text{C}$ for 15 h to give 128 mg (0.60 mmol, 40 %) of **2i** as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.44 – 7.17 (m, 4H), 3.68 (s, 3H), 1.62 (s, 6H).

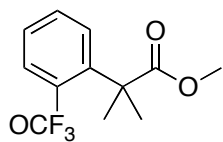
^{13}C NMR (75 MHz, CDCl_3) δ 177.6, 142.5, 133.9, 130.8, 128.2, 127.1, 126.9, 52.6, 46.8, 26.2.

IR (neat) 1734, 1474, 1432, 1250, 1145, 1110, 1040, 748 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{11}\text{H}_{13}\text{ClNaO}_2$ $[\text{M}+\text{Na}]^+$: 235.0496, found : 235.0491.

$R_T = 2.03$ min.

Methyl 2-methyl-2-(2-(trifluoromethoxy)phenyl)propanoate (**2j**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 1-bromo-2-(trifluoromethoxy)benzene (223 μ L, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 200 mg (0.76 mmol, 51 %) of **2j** as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.42 (dd, J = 7.9, 1.8 Hz, 1H), 7.33 – 7.21 (m, 3H), 3.66 (s, 3H), 1.56 (s, 7H).

^{13}C NMR (101 MHz, CDCl_3) δ 177.2, 147.6, 136.1, 128.3, 126.9, 126.0, 120.6 (q, J = 259.0 Hz), 117.7 (q, J = 2.2 Hz), 52.3, 44.7, 26.2.

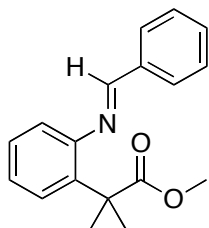
^{19}F NMR (376 MHz, CDCl_3) δ -55.8.

IR (neat) 1743, 1493, 1449, 1244, 1213, 1144, 756 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{12}\text{H}_{13}\text{F}_3\text{NaO}_3$ $[\text{M}+\text{Na}]^+$: 285.0709, found : 285.0703.

R_T = 2.25 min.

Methyl 2-(2-(benzylideneamino)phenyl)-2-methylpropanoate (**2k**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with N-benzylidene-2-bromoaniline (390 mg, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 330 mg (1.17 mmol, 78 %) of **2k** as a slightly yellow oil.

^1H NMR (300 MHz, CDCl_3) δ 8.48 (s, 1H), 7.98 – 7.88 (m, 2H), 7.56 – 7.49 (m, 3H), 7.49 – 7.44 (m, 1H), 7.40 – 7.27 (m, 2H), 7.16 – 7.11 (m, 1H), 3.57 (s, 3H), 1.63 (s, 6H).

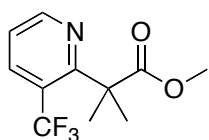
^{13}C NMR (75 MHz, CDCl_3) δ 178.5, 158.9, 148.9, 140.5, 136.7, 131.5, 129.3, 129.0, 128.0, 126.6, 125.3, 117.5, 52.1, 45.4, 26.7.

IR (neat) 1738, 1654, 1450, 1253, 1128 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{18}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 282.1494, found : 282.1489.

R_T = 2.52 min.

Methyl 2-methyl-2-(3-(trifluoromethyl)pyridin-2-yl)propanoate (**2l**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 2-bromo-3-(trifluoromethyl)pyridine (339 mg, 1.5 mmol, 1 equiv), ZnF_2 (155 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 152 mg (0.62 mmol, 41 %) of **2l** as a slightly yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 8.73 (dd, J = 4.6, 1.1 Hz, 1H), 7.96 (dd, J = 8.0, 1.6 Hz, 1H), 7.35 (ddd, J = 7.9, 4.7, 0.9 Hz, 1H), 3.66 (s, 3H), 1.66 (s, 6H) ;

^{13}C NMR (126 MHz, CDCl_3) δ 176.6, 159.6, 150.8, 136.4 (q, J = 5.1 Hz), 124.5 (q, J = 32.3 Hz), 124.2 (q, J = 273.6 Hz), 121.7, 52.1, 50.6, 26.8 (d, J = 1.7 Hz) ;

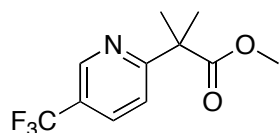
^{19}F NMR (376 MHz, CDCl_3) δ -56.9 ;

IR (neat) 1741, 1593, 1565, 1435, 1313, 1151, 1123, 1028 cm^{-1} ;

HRMS (ESI) : m/z calcd. for $\text{C}_{11}\text{H}_{13}\text{F}_3\text{NO}_2$ $[\text{M}+\text{H}]^+$: 248.0893, found : 248.0905.

R_T = 1.97 min.

Methyl 2-methyl-2-(5-(trifluoromethyl)pyridin-2-yl)propanoate (**2m**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 2-bromo-5-(trifluoromethyl)pyridine (339 mg, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 252 mg (1.02 mmol, 68 %) of **2m** as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 8.46 (dd, J = 4.7, 1.4 Hz, 1H), 7.56 – 7.50 (m, 1H), 7.30 – 7.23 (m, 1H), 3.68 (s, 3H), 1.59 (s, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 176.5, 154.5, 145.8, 144.3, 125.1 (q, J = 2.1 Hz), 123.0, 121.1 (q, J = 260.0 Hz), 52.3, 47.8, 25.0.

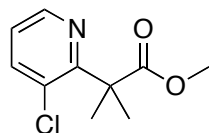
^{19}F NMR (376 MHz, CDCl_3) δ -56.1.

IR (neat) 1735, 1437, 1249, 1207, 1170, 1150, 1089, 805 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{11}\text{H}_{13}\text{F}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$: 264.0842, found : 264.0838.

R_T = 2.57 min.

Methyl 2-(3-chloropyridin-2-yl)-2-methylpropanoate (**2p**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 2-bromo-3-chloropyridine (289 mg, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 269 mg (1.26 mmol, 84 %) of **2p** as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 8.47 (dd, J = 4.6, 1.5 Hz, 1H), 7.64 (dd, J = 8.0, 1.5 Hz, 1H), 7.17 (dd, J = 8.0, 4.7 Hz, 1H), 3.69 (s, 3H), 1.64 (s, 6H).

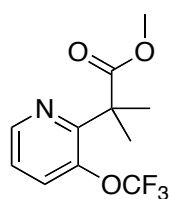
^{13}C NMR (75 MHz, CDCl_3) δ 176.9, 159.6, 146.5, 138.0, 131.2, 123.2, 52.5, 49.5, 25.1.

IR (neat) 1736, 1417, 1254, 1152, 1121, 1037, 796 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{10}\text{H}_{12}\text{ClNNaO}_2$ $[\text{M}+\text{Na}]^+$: 236.0449, found : 236.0457.

R_T = 1.68.

Methyl 2-methyl-2-(3-(trifluoromethoxy)pyridin-2-yl)propanoate (**2q**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 2-bromo-3-(trifluoromethoxy)pyridine (363 mg, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 241 mg (0.92 mmol, 61 %) of **2q** as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 8.46 (dd, J = 4.7, 1.4 Hz, 1H), 7.56 – 7.50 (m, 1H), 7.30 – 7.23 (m, 1H), 3.68 (s, 3H), 1.59 (s, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 176.5, 154.5, 145.8, 144.3, 125.1 (q, J = 2.1 Hz), 123.0, 121.1 (q, J = 260.0 Hz), 52.3, 47.8, 25.0.

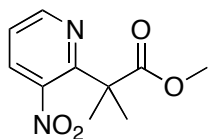
^{19}F NMR (376 MHz, CDCl_3) δ -56.1.

IR (neat) 1735, 1437, 1249, 1207, 1170, 1150, 1089, 805 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{11}\text{H}_{13}\text{F}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$: 264.0842, found : 264.0838.

R_T = 1.95 min.

Methyl 2-methyl-2-(3-nitropyridin-2-yl)propanoate (**2r**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 2-bromo-3-nitropyridine (305 mg, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 215 mg (0.96 mmol, 64 %) of **2r** as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 8.79 (dd, J = 4.6, 1.6 Hz, 1H), 8.23 (dd, J = 8.2, 1.6 Hz, 1H), 7.40 (dd, J = 8.2, 4.6 Hz, 1H), 3.66 (s, 3H), 1.71 (s, 7H).

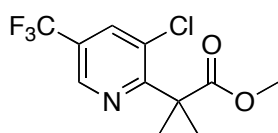
^{13}C NMR (75 MHz, CDCl_3) δ 175.6, 159.9, 157.2, 152.0, 133.3, 122.5, 52.2, 50.1, 26.3.

IR (neat) 1741, 1726, 1523, 1354, 1252, 1153, 1119, 867 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 247.0689, found : 247.0686.

R_T = 1.61 min.

Methyl 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-methylpropanoate (**2s**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 2,3-dichloro-5-(trifluoromethyl)pyridine (209 μ L, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 376 mg (1.34 mmol, 89 %) of **2s** as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 8.75 – 8.71 (m, 1H), 7.90 – 7.86 (m, 1H), 3.70 (s, 3H), 1.66 (s, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 176.0, 163.5, 143.3 (q, J = 4.0 Hz), 135.0 (q, J = 3.5 Hz), 131.3, 126.1 (t, J = 33.6 Hz), 122.9 (q, J = 272.7 Hz), 52.7, 49.8, 24.9.

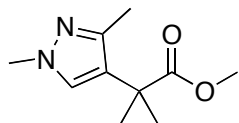
^{19}F NMR (376 MHz, CDCl_3) δ -62.3.

IR (neat) 1743, 1320, 1249, 1127, 1051 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{11}\text{H}_{12}\text{ClF}_3\text{NO}_2$ $[\text{M}+\text{H}]^+$: 282.0503, found : 282.0516.

R_T = 2.33 min.

Methyl 2-(1,3-dimethyl-1H-pyrazol-4-yl)-2-methylpropanoate (**2t**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 4-bromo-1,3-dimethyl-1H-pyrazole (177 μ L, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 197 mg (1.00 mmol, 67 %) of **2t** as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.15 (s, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 2.17 (s, 3H), 1.51 (s, 6H).

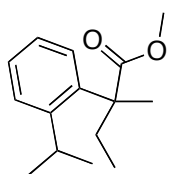
^{13}C NMR (101 MHz, CDCl_3) δ 177.2, 145.7, 128.4, 123.8, 52.4, 40.6, 38.7, 26.6, 13.0.

IR (neat) 3101, 2960, 1732, 1231, 1099, 864, 738 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{10}\text{H}_{16}\text{N}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 219.1104, found : 219.1096.

R_T = 1.09 min.

Methyl 2-(2-isopropylphenyl)-2-methylbutanoate (2u)



Following general procedure B **5u** (513 μ L, 2.4 mmol, 1.6 equiv,) was reacted with 1-bromo-2-isopropylbenzene (230 μ L, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 327 mg (1.40 mmol, 93 %) of **2u** as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.33–7.13 (m, 4H), 3.65 (s, 3H), 2.95–2.81 (m, 1H), 2.18–1.92 (m, 2H), 1.54 (s, 3H), 1.16 (dd, J = 6.7, 4.7 Hz, 6H), 0.72 (t, J = 7.5 Hz, 3H).

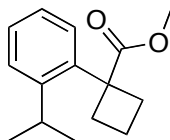
^{13}C NMR (75 MHz, CDCl_3) δ 178.9, 147.5, 139.8, 127.2, 127.2, 126.1, 125.6, 52.1, 50.0, 31.5, 29.2, 24.6, 24.5, 24.3, 8.9 ;

IR (neat) 1726, 1448, 1236, 1134, 1111, 753 cm^{-1} ;

HRMS (ESI) : m/z calcd. for $\text{C}_{15}\text{H}_{22}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 257.1512, found : 257.1502.

R_T = 2.58 min.

Methyl 1-(2-isopropylphenyl)cyclobutanecarboxylate (2w)



Following general procedure B **5w** (447 mg, 2.4 mmol, 1.6 equiv) was reacted with 1-bromo-2-isopropylbenzene (230 μ L, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 213 mg (0.92 mmol, 61 %) of **2w** as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.29 – 7.14 (m, 4H), 3.63 (s, 3H), 2.97 – 2.78 (m, 3H), 2.64 – 2.50 (m, 2H), 2.28 – 2.09 (m, 1H), 1.94 – 1.77 (m, 1H), 1.13 (d, J = 6.8 Hz, 6H).

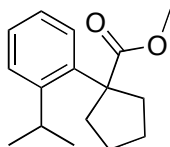
^{13}C NMR (75 MHz, CDCl_3) δ 176.9, 147.4, 140.6, 127.2, 126.9, 126.5, 125.5, 52.7, 52.3, 33.2, 29.0, 24.2, 17.0.

IR (neat) 1727, 1486, 1439, 1205, 1122, 756 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{15}\text{H}_{20}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 255.1356, found : 255.1353.

R_T = 2.56 min.

Methyl 1-(2-isopropylphenyl)cyclopentanecarboxylate (2x)



Following general procedure B **5x** (481 mg, 2.4 mmol, 1.6 equiv) was reacted with 1-bromo-2-isopropylbenzene (230 μ L, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 193 mg (0.80 mmol, 53 %) as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.35 – 7.12 (m, 4H), 3.61 (s, 3H), 3.03 (dt, J = 13.4, 6.7 Hz, 1H), 2.55 – 2.40 (m, 2H), 2.13 – 2.00 (m, 2H), 1.87 – 1.65 (m, 4H), 1.15 (d, J = 6.7 Hz, 6H).

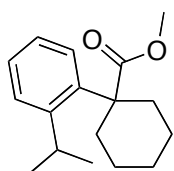
^{13}C NMR (75 MHz, CDCl_3) δ 178.4, 147.9, 140.7, 127.2, 125.6, 125.6, 57.8, 52.3, 37.7, 29.5, 24.7, 24.4.

IR (neat) 1727, 1488, 1446, 1434, 1232, 1153, 753 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{16}\text{H}_{22}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 269.1512, found : 269.1501.

R_T = 2.67 min.

Methyl 1-(2-isopropylphenyl)cyclohexanecarboxylate (**2y**)



Following general procedure B **5y** (515 mg, 2.4 mmol, 1.6 equiv) was reacted with 1-bromo-2-isopropylbenzene (230 μ L, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 355 mg (1.36 mmol, 91 %) of **2y** as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.42 (dd, J = 7.8, 1.3 Hz, 1H), 7.31 (dd, J = 7.7, 1.8 Hz, 1H), 7.28 – 7.14 (m, 2H), 3.62 (s, 3H), 3.30 – 3.15 (m, 1H), 2.41 – 2.28 (m, 2H), 1.90 – 1.57 (m, 7H), 1.45 – 1.25 (m, 1H), 1.15 (d, J = 6.7 Hz, 6H).

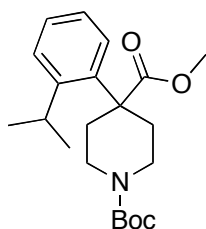
^{13}C NMR (75 MHz, CDCl_3) δ 177.7, 147.9, 141.0, 127.4, 127.0, 125.8, 125.7, 51.8, 50.2, 35.8, 28.4, 25.8, 24.5, 22.8.

IR (neat) 1726, 1486, 1449, 1215, 1127, 753 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{17}\text{H}_{24}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 283.1669, found : 283.1660.

R_T = 2.86 min.

1-*tert*-Butyl 4-methyl 4-(2-isopropylphenyl)piperidine-1,4-dicarboxylate (**2z**)



Following general procedure B **5z** (757 mg, 2.4 mmol, 1.6 equiv,) was reacted with 1-bromo-2-isopropylbenzene (230 μ L, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 267 mg (0.74 mmol, 49 %) of **2z** as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.35 – 7.27 (m, 3H), 7.26 – 7.15 (m, 1H), 4.00 – 3.74 (br s, 2H), 3.64 (s, 3H), 3.49 – 3.25 (br s, 2H), 3.25 – 3.10 (m, 1H), 2.43 – 2.30 (m, 2H), 2.09 – 1.81 (br s, 2H), 1.45 (s, J = 3.2 Hz, 9H), 1.16 (d, J = 6.7 Hz, 6H).

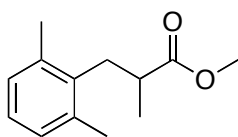
^{13}C NMR (75 MHz, CDCl_3) δ 176.8, 155.0, 148.0, 139.6, 127.8, 127.7, 126.1, 125.5, 79.7, 53.6, 52.2, 48.7, 34.8, 28.6, 24.5.

IR (neat) 1725, 1681, 1480, 1221, 1861, 745 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{21}\text{H}_{31}\text{NNaO}_4$ $[\text{M}+\text{Na}]^+$: 384.2145, found : 384.2136.

R_T = 2.79 min.

Methyl 3-(2,6-dimethylphenyl)-2-methylpropanoate (**7g**)



The same experiment described above for **2g** gave 96 mg (0.47 mmol, 31 %) of **7g** as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.06 – 6.97 (m, 3H), 3.65 (s, 3H), 3.12 – 3.00 (m, 1H), 2.85 – 2.67 (m, 2H), 2.33 (s, 6H), 1.15 (d, J = 6.7 Hz, 3H) ;

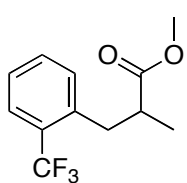
^{13}C NMR (75 MHz, CDCl_3) δ 177.1, 137.0, 136.4, 128.5, 126.3, 51.8, 39.6, 33.2, 20.4, 16.6.

IR (neat) 1737, 1460, 1167, 770 cm^{-1} ;

HRMS (ESI) : m/z calcd. for $\text{C}_{13}\text{H}_{18}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 229.1199, found : 229.1194.

R_T = 2.31 min.

Methyl 2-methyl-3-(2-(trifluoromethyl)phenyl)propanoate (**7h**)

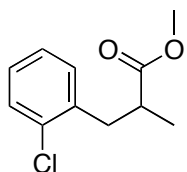


The same experiment described above for **2h** gave 259 mg (1.05 mmol, 70 %) of **7h** as a colorless oil. Analytical data matched those reported in the literature.³

¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.42 (m, 1H), 7.35 – 7.27 (m, 2H), 3.64 (s, 3H), 3.23 – 3.15 (m, 1H), 2.94 – 2.76 (m, 2H), 1.20 (d, *J* = 6.9 Hz, 3H).

R_T = 2.27 min.

Methyl 3-(2-chlorophenyl)-2-methylpropanoate (**7i**)

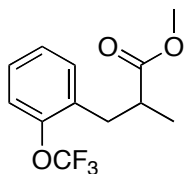


The same experiment described above for **2i** gave 166 mg (0.78 mmol, 52 %) of **7i** as a colorless oil. Analytical data matched those reported in the literature.³

¹H NMR (300 MHz, CDCl₃) δ 7.38 – 7.31 (m, 1H), 7.21 – 7.13 (m, 3H), 3.63 (s, 3H), 3.18 – 3.06 (m, 1H), 2.95 – 2.77 (m, 2H), 1.19 (d, *J* = 6.8 Hz, 3H).

R_T = 2.24 min.

Methyl 2-methyl-3-(2-(trifluoromethoxy)phenyl)propanoate (**7j**)



The same experiment described above for **2j** gave 122 mg (0.47 mmol, 31 %) of **7j** as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.17 (m, 4H), 3.63 (s, 3H), 3.09 – 3.00 (m, 1H), 2.85 – 2.74 (m, 2H), 1.17 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 176.4, 148.0 (d, *J* = 1.3 Hz), 131.9, 131.6, 128.0, 126.7, 120.7 (d, *J* = 257.4 Hz), 120.3 (d, *J* = 1.4 Hz), 51.8, 40.0, 34.0, 17.0.

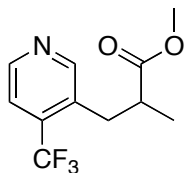
¹⁹F NMR (376 MHz, CDCl₃) δ -56.9.

IR (neat) 1739, 1493, 1454, 1249, 1212, 1156, 1124, 761 cm⁻¹.

HRMS (ESI) : *m/z* calcd. for C₁₂H₁₃F₃NaO₃ [M+Na]⁺ : 285.0709, found : 285.0703.

R_T = 2.36 min.

Methyl 2-methyl-3-(4-(trifluoromethyl)pyridin-3-yl)propanoate (**7n**)



Following general procedure B **5a** (488 μL, 2.4 mmol, 1.6 equiv) was reacted with 3-bromo-4-(trifluoromethyl)pyridine (339 mg, 1.5 mmol, 1 equiv), ZnF₂ (155.1 mg, 1.5 mmol, 1 equiv) and Pd(PtBu₃)₂ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 289 mg (1.17 mmol, 78 %) of **7n** as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 8.70 – 8.58 (m, 2H), 7.51 (d, *J* = 5.0 Hz, 1H), 3.65 (s, 3H), 3.21 (dd, *J* = 14.1, 8.0 Hz, 1H), 2.93 – 2.85 (m, 1H), 2.85 – 2.76 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 2H).

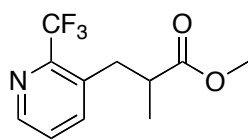
¹³C NMR (101 MHz, CDCl₃) δ 175.8, 153.0, 148.8, 136.6 (q, *J* = 31.5 Hz), 132.3, 123.3 (q, *J* = 274.8 Hz), 119.8, 52.0, 40.8, 33.7, 17.5.

IR (neat) 1743, 1459, 1320, 1201, 1112, 861, 804 cm⁻¹.

HRMS (ESI) : *m/z* calcd. for C₁₁H₁₃F₃NO₂ [M+H]⁺ : 248.0893, found : 248.0890.

R_T = 1.72 min.

Methyl 2-methyl-3-(2-(trifluoromethyl)pyridin-3-yl)propanoate (**7o**)



Following general procedure B **5a** (488 μ L, 2.4 mmol, 1.6 equiv) was reacted with 3-bromo-2-(trifluoromethyl)pyridine (339 mg, 1.5 mmol, 1 equiv), ZnF_2 (155.1 mg, 1.5 mmol, 1 equiv) and $\text{Pd}(\text{PtBu}_3)_2$ (15.3 mg, 0.03 mmol, 2 mol%) in DMF (9 mL) at 90 °C for 15 h to give 312 mg (1.26 mmol, 84 %) of **7o** as a colorless oil.

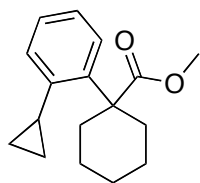
^1H NMR (300 MHz, CDCl_3) δ 8.58 (d, J = 3.7 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.42 (dd, J = 7.9, 4.7 Hz, 1H), 3.63 (s, 3H), 3.18 (dd, J = 14.2, 8.6 Hz, 1H), 2.93 (dd, J = 14.2, 6.3 Hz, 1H), 2.87 – 2.74 (m, 1H), 1.23 (d, J = 7.0 Hz, 3H) ;

^{13}C NMR (75 MHz, CDCl_3) δ 175.9, 147.2, 140.1, 134.1, 126.1, 51.8, 40.8, 34.9, 17.5.

IR (neat) 1734, 1457, 1324, 1179, 1119, 1079, 1055, 805 cm^{-1} ;

HRMS (ESI) : m/z calcd. for $\text{C}_{11}\text{H}_{13}\text{F}_3\text{NO}_2$ $[\text{M}+\text{H}]^+$: 248.0893, found : 248.0892.

R_T = 1.69 min.

Methyl 1-(2-cyclopropylphenyl)cyclohexanecarboxylate (2aa)

Pd(PtBu₃)₂ (454 mg, 0.89 mmol, 5 mol%) and ZnF₂ (1.84 g, 17.76 mmol, 1 equiv) were weighed in the glovebox in an oven-dried round bottom flask. The flask was sealed with a rubber septum, brought outside the glovebox and degassed DMF (110 mL) was added. 1-Bromo-2-cyclopropylbenzene (3.5 g, 17.76 mmol, 1 equiv) was added followed by **5y** (6.09 g, 28.42 mmol, 1.6 equiv). The reaction mixture was heated to 110°C for 15h. The reaction mixture was diluted in diethyl ether and quenched with a mixture of sat. aq. NH₄Cl/water (1:1). The aqueous layer was extracted twice with diethyl ether then the combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration and evaporation, the crude mixture was purified by silica gel chromatography (pentane/EtOAc : 100:0 to 95:5) to give 4.08 g (89 %) of **2aa** as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.49 – 7.41 (m, 1H), 7.21 – 7.13 (m, 2H), 6.82 – 6.76 (m, 1H), 3.64 (s, 3H), 2.50 – 2.41 (m, 2H), 2.08 – 1.99 (m, 1H), 1.97 – 1.86 (m, 2H), 1.84 – 1.60 (m, 5H), 1.42 – 1.30 (m, 1H), 0.97 – 0.89 (m, 2H), 0.73 – 0.66 (m, 2H).

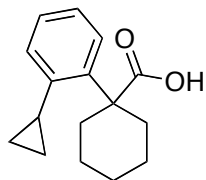
¹³C NMR (101 MHz, CDCl₃) δ 177.7, 143.2, 141.7, 127.0, 125.9, 125.5, 123.9, 52.0, 50.6, 35.5, 26.0, 22.9, 12.4, 10.0.

IR (neat) 3058, 2964, 1734, 1501, 1448, 1190, 1131 cm⁻¹.

HRMS (ESI) : m/z calcd. for C₁₇H₂₂NaO₂ [M+Na]⁺ : 281.1512, found : 281.1514.

Mp : 72 - 73 °C

R_T = 2.78 min.

1-(2-Cyclopropylphenyl)cyclohexanecarboxylic acid (8)

Compound **2aa** (75 mg, 0.29 mmol, 1 equiv) and KOH (326 mg, 5.80 mmol, 20 equiv) were added in a microwave vial followed by water (1 mL), THF (1 mL) and MeOH (1 mL). The vial was sealed and irradiated under microwave for 30 min at 150 °C. The reaction mixture was diluted in EtOAc and quenched with an aqueous HCl (1M) solution. The aqueous layer was extracted twice with EtOAc then the combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration and evaporation, the crude mixture was purified by preparative HPLC to give 53 mg (75 %) of **8** as a white solid.

¹H NMR (400 MHz, DMSO) δ 12.27 (s, 1H), 7.49 – 7.27 (m, 1H), 7.22 – 7.03 (m, 2H), 6.91 – 6.67 (m, *J* = 4.5 Hz, 1H), 2.45 – 2.25 (m, 2H), 2.24 – 2.07 (m, 1H), 1.90 – 1.76 (m, 2H), 1.76 – 1.64 (m, 2H), 1.64 – 1.48 (m, 3H), 1.42 – 1.23 (m, 1H), 0.99 – 0.82 (m, 2H), 0.76 – 0.60 (m, 2H).

¹³C NMR (101 MHz, DMSO) δ 177.7, 143.1, 141.3, 126.5, 125.8, 125.1, 123.4, 49.8, 34.7, 25.4, 22.5, 12.2, 10.2.

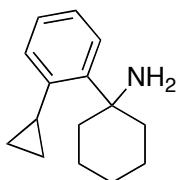
IR (neat) 3060, 2995, 1714, 1498, 1231, 1124 cm⁻¹.

HRMS (ESI) : m/z calcd. for C₁₆H₂₀NaO₂ [M+Na]⁺ : 267.1356, found : 267.1355.

Mp : 112 - 113 °C

R_T = 2.27 min.

1-(2-Cyclopropylphenyl)cyclohexanamine (9)



Compound **8** (75 mg, 0.30 mmol, 1 equiv) was added to a microwave vial followed by toluene (1.4 mL). To this solution were added DPPA (69 μ L, 0.31 mmol, 1.04 equiv) and NEt_3 (49 μ L, 0.35 mmol, 1.15 equiv). The vial was sealed and irradiated under microwave for 45 min at 110 $^{\circ}\text{C}$. LC/MS showed full conversion to the isocyanate intermediate. The crude mixture was diluted in THF (1.5 mL) and aqueous HCl (37% w/w) solution (3 mL) was added at 0 $^{\circ}\text{C}$. The reaction mixture was allowed to warm to 25 $^{\circ}\text{C}$ and stirred for 15 h. The reaction mixture was diluted with Et_2O and quenched with an aqueous NaOH (30% w/w) solution. The aqueous layer was extracted twice with Et_2O then the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . After filtration and evaporation, the crude mixture was purified by preparative HPLC to give 55 mg (83 %) of **9** as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.48 – 7.42 (m, 1H), 7.17 – 7.09 (m, 2H), 6.89 – 6.84 (m, 1H), 2.99 – 2.88 (m, 1H), 2.13 – 1.96 (m, 4H), 1.78 – 1.59 (m, 5H), 1.39 – 1.24 (m, 1H), 1.06 – 0.98 (m, 2H), 0.85 – 0.77 (m, 2H).

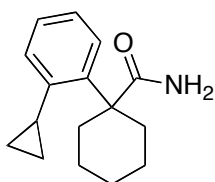
^{13}C NMR (101 MHz, CDCl_3) δ 147.4, 142.1, 126.8, 125.8, 125.2, 124.7, 55.3, 39.2, 26.0, 22.7, 14.2, 10.7.

IR (neat) 3356, 3058, 1434, 1321, 871, 753 cm^{-1} .

HRMS (ESI) : calcd. m/z for $\text{C}_{15}\text{H}_{21}\text{NNa}$ $[\text{M}+\text{Na}]^+$: 238.1566, found : 238.1566.

R_T = 0.91 min.

1-(2-Cyclopropylphenyl)cyclohexanecarboxamide (10)



Compound **8** (290 mg, 1.18 mmol, 1 equiv) was added to a vial followed by CH_2Cl_2 (4.7 mL) and oxalyl chloride (114 μ L, 1.30 mmol, 1.1 equiv). A drop of DMF was added and the reaction mixture was stirred for 15 h at 25 $^{\circ}\text{C}$. LC/MS showed full conversion to the corresponding acid chloride. The solvent was removed under vacuum and THF (2.5 mL) was added, followed by an aqueous NH_4OH (28 % w/w) solution (2.5 mL). The reaction mixture was stirred for 2 h at 25 $^{\circ}\text{C}$. The reaction mixture was diluted with EtOAc and quenched with an aqueous HCl (1M) solution. The aqueous layer was extracted twice with EtOAc , then the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . After filtration and evaporation, the crude mixture was purified by preparative HPLC to give 214 mg (74 %) of **10** as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.53 – 7.47 (m, 1H), 7.23 – 7.13 (m, 2H), 6.82 – 6.75 (m, 1H), 5.15 (br s, 2H), 2.39 – 2.25 (m, 2H), 2.25 – 2.12 (m, 2H), 2.10 – 1.96 (m, 1H), 1.91 – 1.73 (m, 2H), 1.57 – 1.42 (m, 4H), 1.06 – 0.96 (m, 2H), 0.78 – 0.68 (m, 2H).

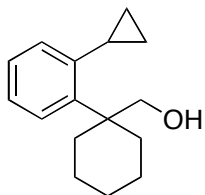
^{13}C NMR (75 MHz, CDCl_3) δ 181.1, 143.3, 141.9, 127.5, 127.3, 125.4, 123.9, 50.9, 35.1, 26.1, 22.8, 13.0, 11.0.

IR (neat) 3061, 2997, 1628, 1439, 1169, 1118, 738 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{16}\text{H}_{21}\text{NNaO}$ $[\text{M}+\text{Na}]^+$: 266.1515, found : 266.1520.

R_T = 1.92 min.

(1-(2-Cyclopropylphenyl)cyclohexyl)methanol (**11**)



To a solution of LiAlH_4 (735 mg, 19.3 mmol, 5 equiv) in THF (30 mL) at 0 °C was added **2aa** (1 g, 3.87 mmol, 1 equiv) in solution in THF (8 mL). The reaction mixture was stirred for 30 min at 0 °C then for 15 h at 25 °C. The reaction mixture was diluted with diethyl ether and quenched with sat. aq. NH_4Cl . The aqueous layer was extracted twice with diethyl ether, then the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . After filtration and evaporation, the crude mixture was purified by preparative HPLC to give 855 mg (96 %) of **11** as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.45 – 7.37 (m, 1H), 7.22 – 7.12 (m, 2H), 7.10 – 7.03 (m, 1H), 3.82 (s, 2H), 2.71 – 2.55 (m, 2H), 2.29 – 2.14 (m, 1H), 1.74 – 1.51 (m, 5H), 1.51 – 1.35 (m, 3H), 1.06 – 0.90 (m, 3H), 0.86 – 0.77 (m, 2H).

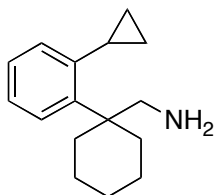
^{13}C NMR (75 MHz, CDCl_3) δ 141.7, 141.5, 130.5, 127.6, 126.8, 126.0, 70.3, 47.0, 34.2, 26.9, 22.0, 16.4, 9.6.

IR (neat) 3451, 3324, 3051, 1428, 1321, 1014 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{16}\text{H}_{23}\text{O}$ $[\text{M}+\text{H}]^+$: 231.1749, found : 231.1747.

R_T = 2.34 min.

(1-(2-Cyclopropylphenyl)cyclohexyl)methanamine (**12**)



To a solution of alcohol **11** (475 mg, 2.06 mmol, 1 equiv) in THF (10.3 mL) was added PPh_3 (649 mg, 2.47 mmol, 1.2 equiv). The solution was cooled to 0 °C and DIAD (487 μL , 2.47 mmol, 1.2 equiv) was added in one portion. DPPA (533 μL , 2.47 mmol, 1.2 equiv) in solution in THF (4.1 mL) was then added dropwise at 0 °C. The resulting mixture was warmed to 25 °C and stirred for 15 h. LC/MS showed full conversion to the corresponding azide. PPh_3 (703 mg, 2.68 mmol, 1.3 equiv) in solution in THF (1 mL) was then added to the solution. The reaction mixture was stirred for 30 min at 25 °C, then warmed to 60 °C for 4 h. LC/MS showed full conversion to the corresponding iminophosphorane. Water (5 mL) was added to the reaction mixture, which was heated to 80 °C for 1 h. The reaction mixture was cooled down to room temperature, diluted with Et_2O and quenched with an aqueous NaOH (1M) solution. The aqueous layer was extracted twice with Et_2O , then the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . After filtration and evaporation, the crude mixture was purified by preparative HPLC to give 321 mg (68 %) of **12** as a white solid.

^1H NMR (300 MHz, CDCl_3) δ 7.77 (br s, 2H), 7.43 – 7.36 (m, 1H), 7.21 – 7.08 (m, 3H), 3.24 (s, 2H), 2.77 – 2.61 (m, 2H), 2.12 – 1.97 (m, 1H), 1.79 – 1.33 (m, 8H), 1.04 – 0.91 (m, 2H), 0.91 – 0.80 (m, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ 141.3, 139.1, 130.2, 128.8, 127.6, 126.6, 48.1, 43.6, 34.9, 26.3, 22.3, 16.7, 9.4.

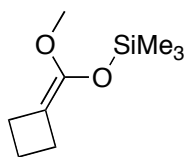
IR (neat) 3361, 3102, 1398, 1254, 834 cm^{-1} .

HRMS (ESI) : m/z calcd. for $\text{C}_{16}\text{H}_{24}\text{N}$ $[\text{M}+\text{H}]^+$: 230.1909, found : 230.1903.

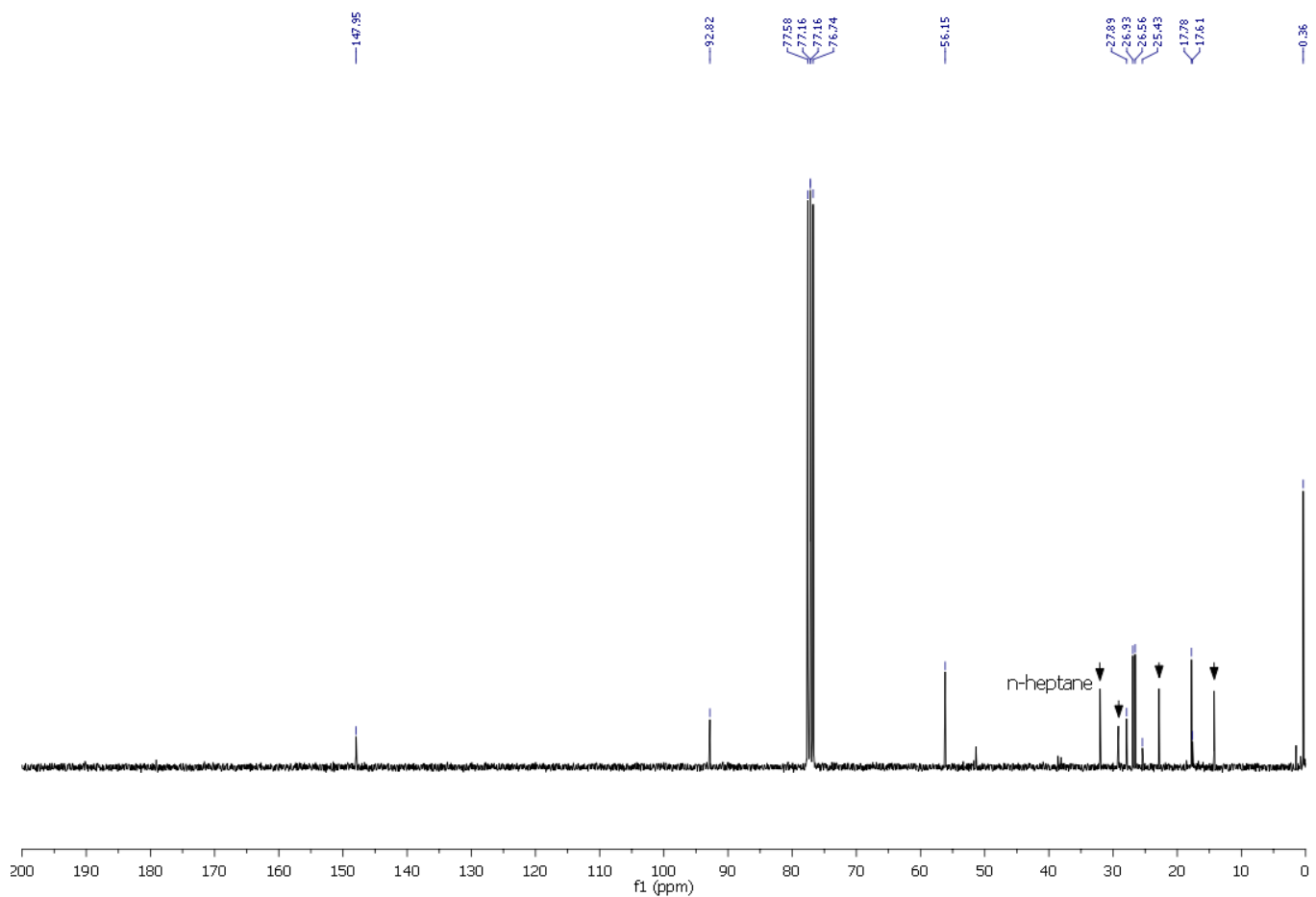
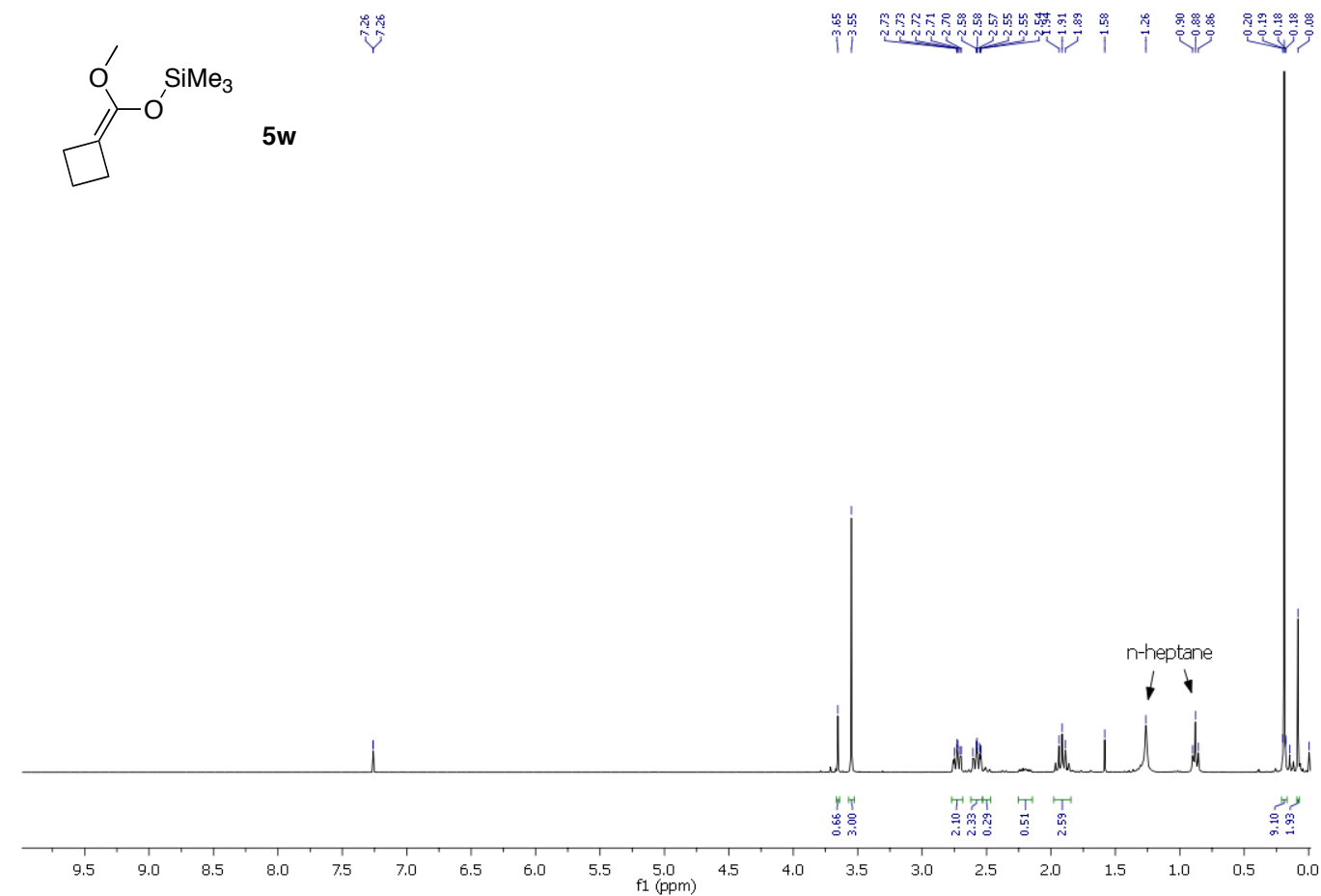
Mp : 199 - 200 °C

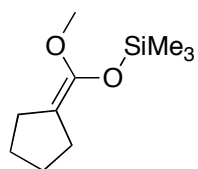
R_T = 1.16 min.

NMR Spectra

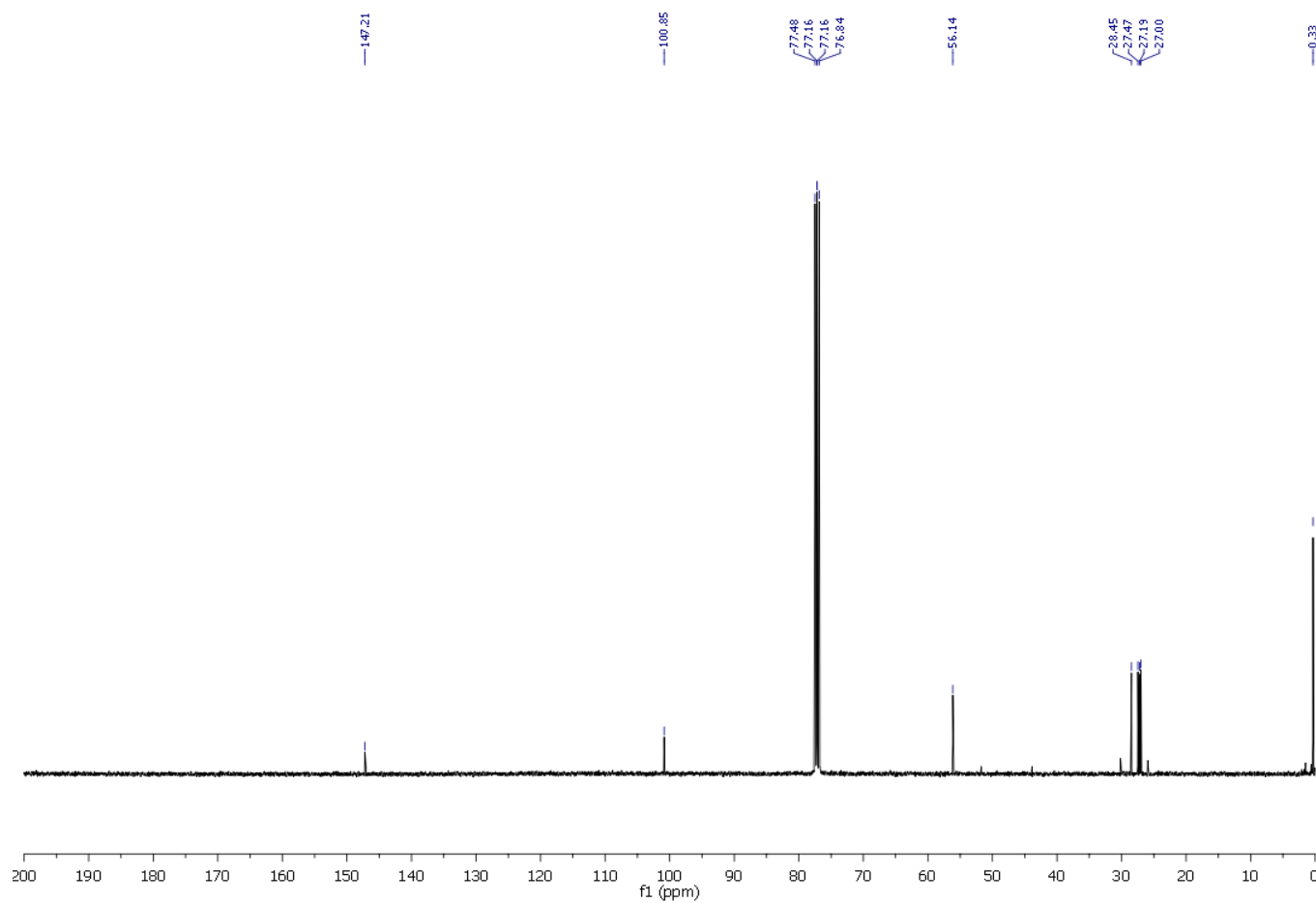
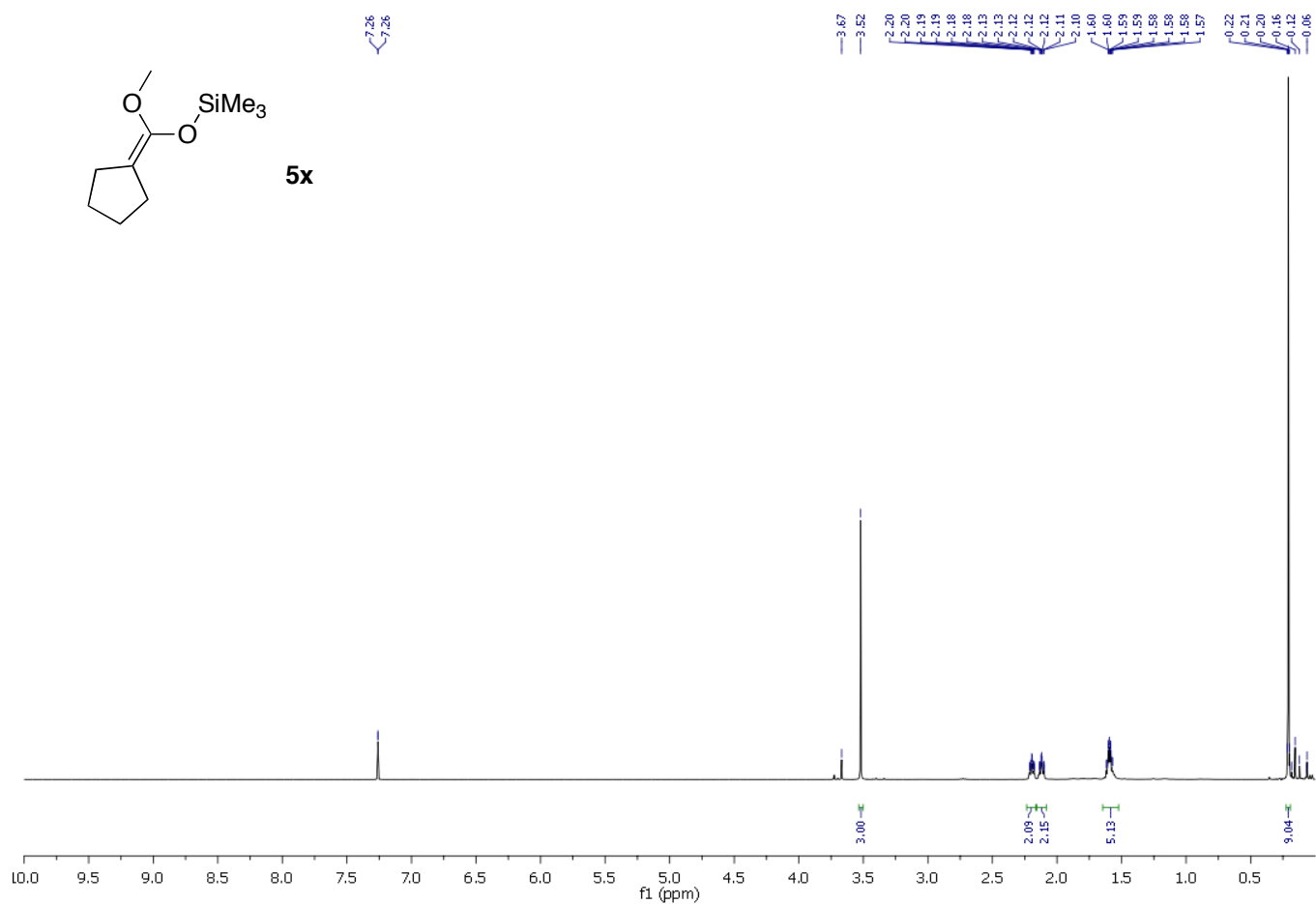


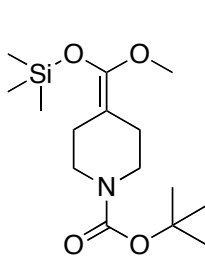
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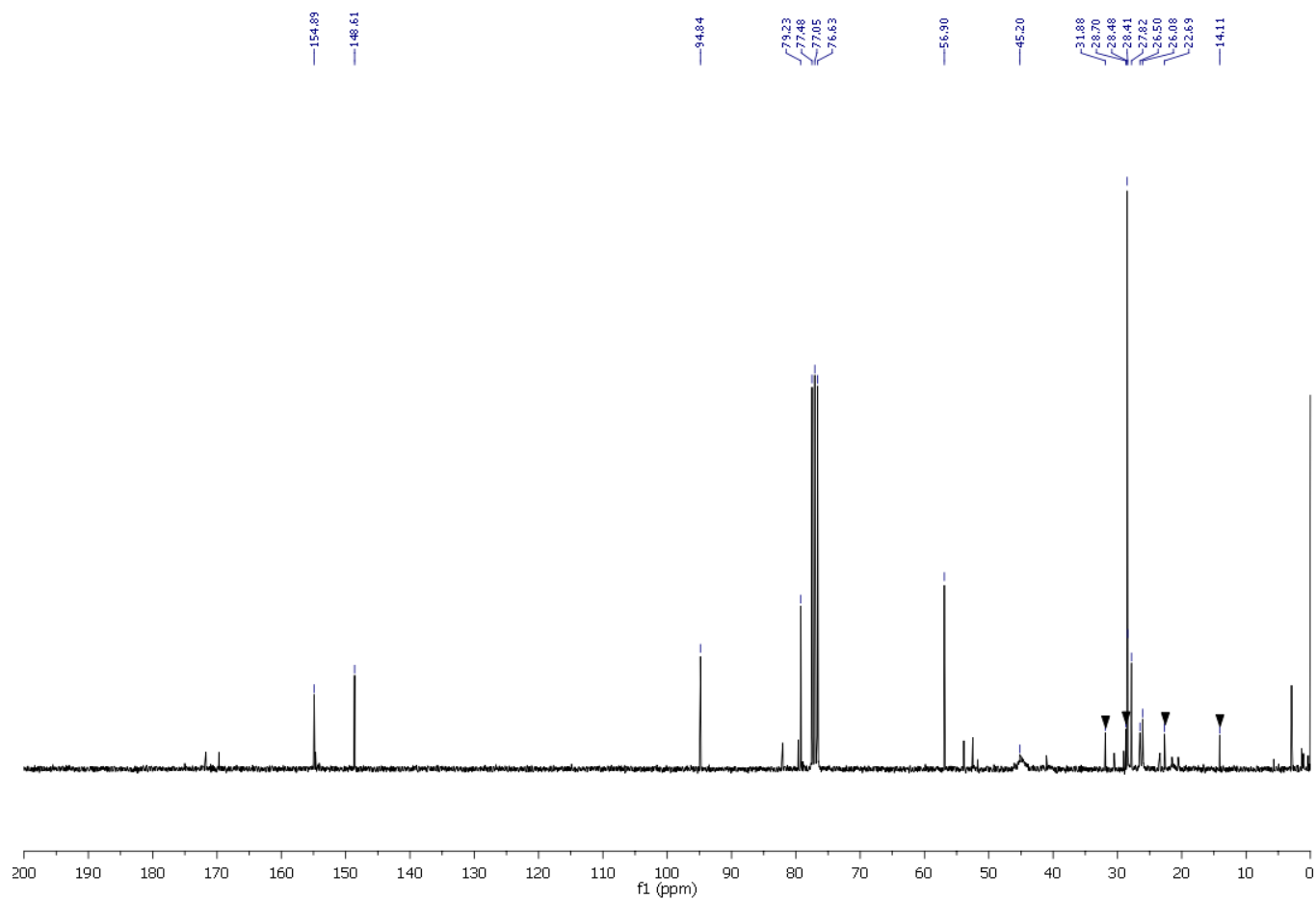
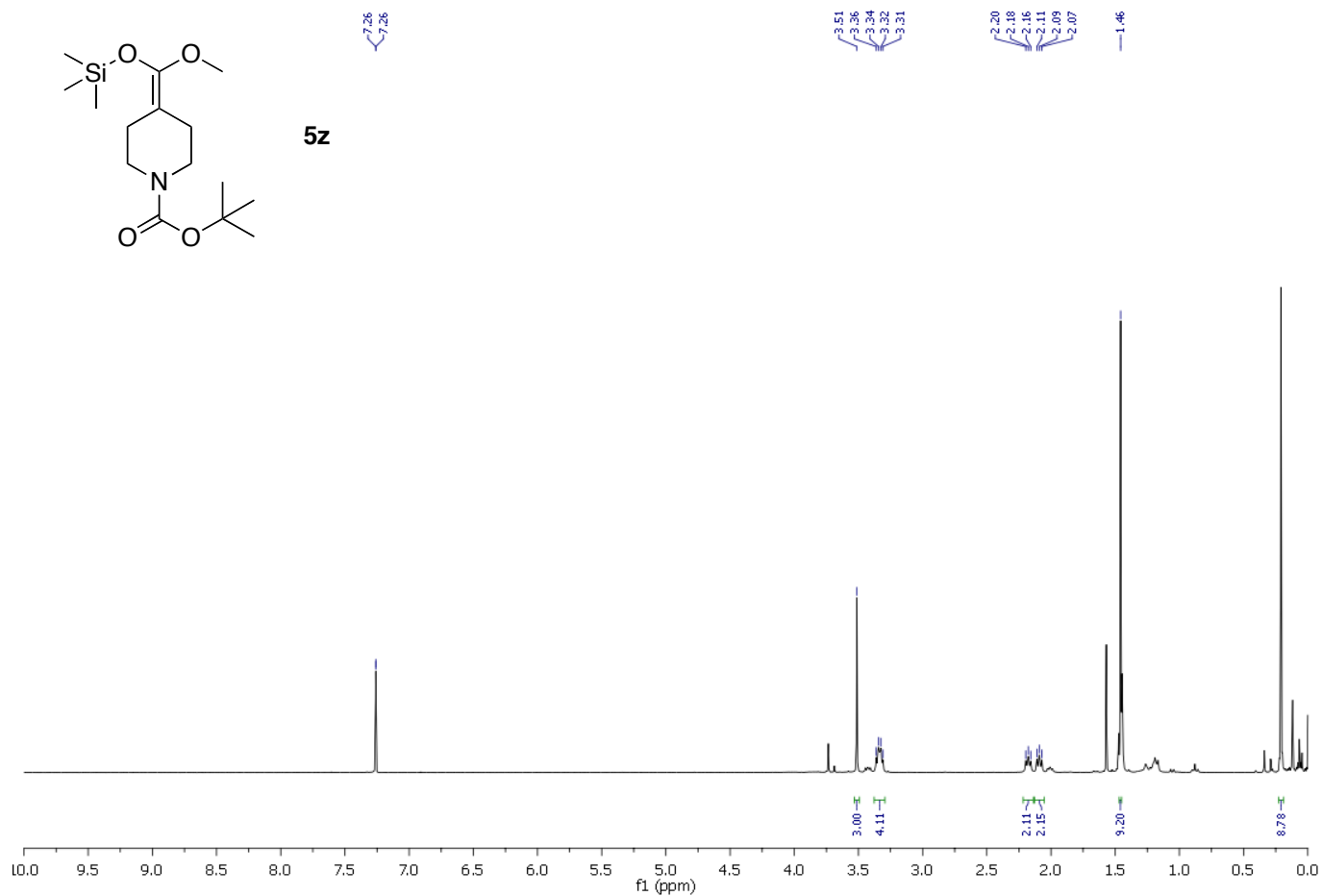


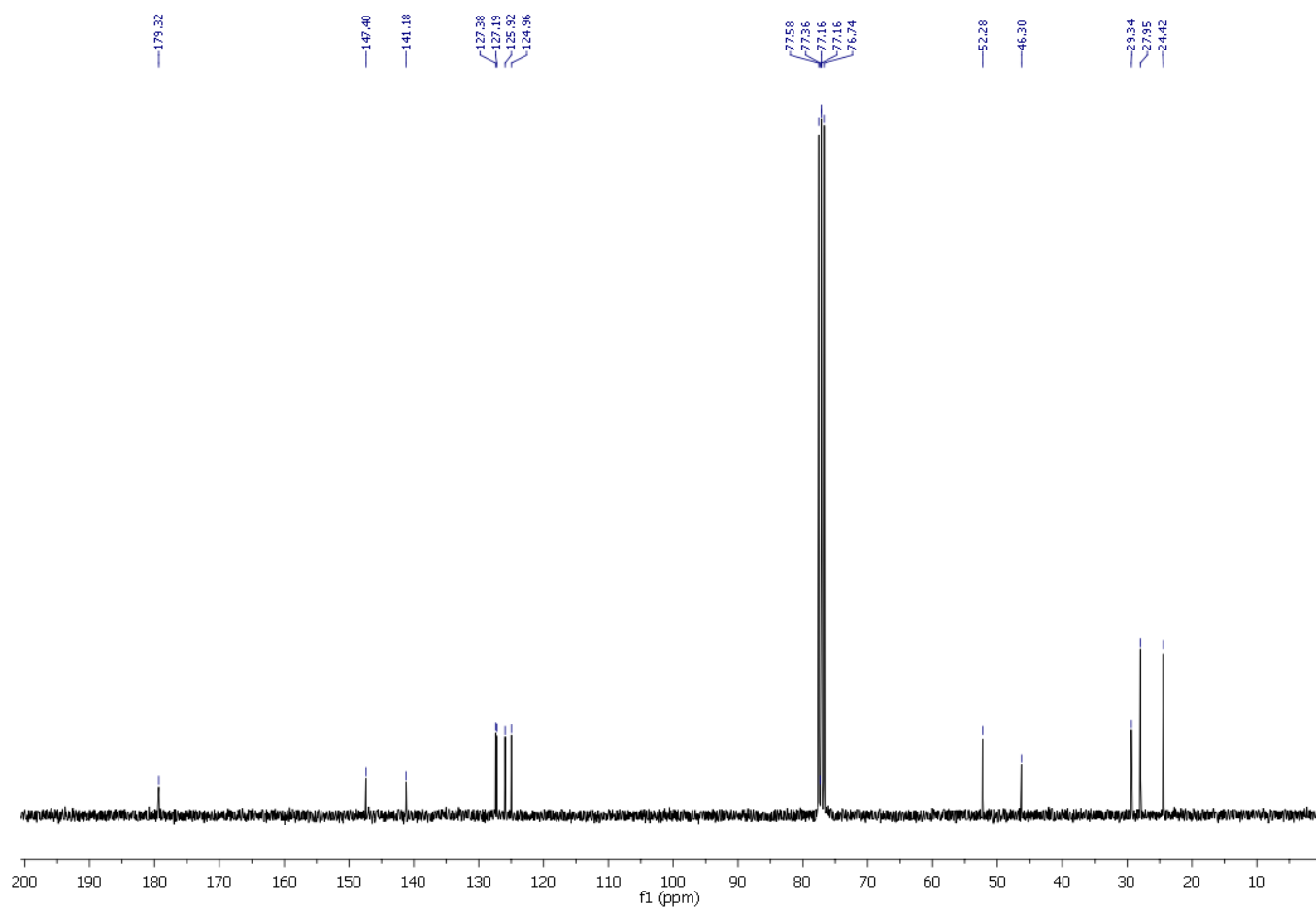
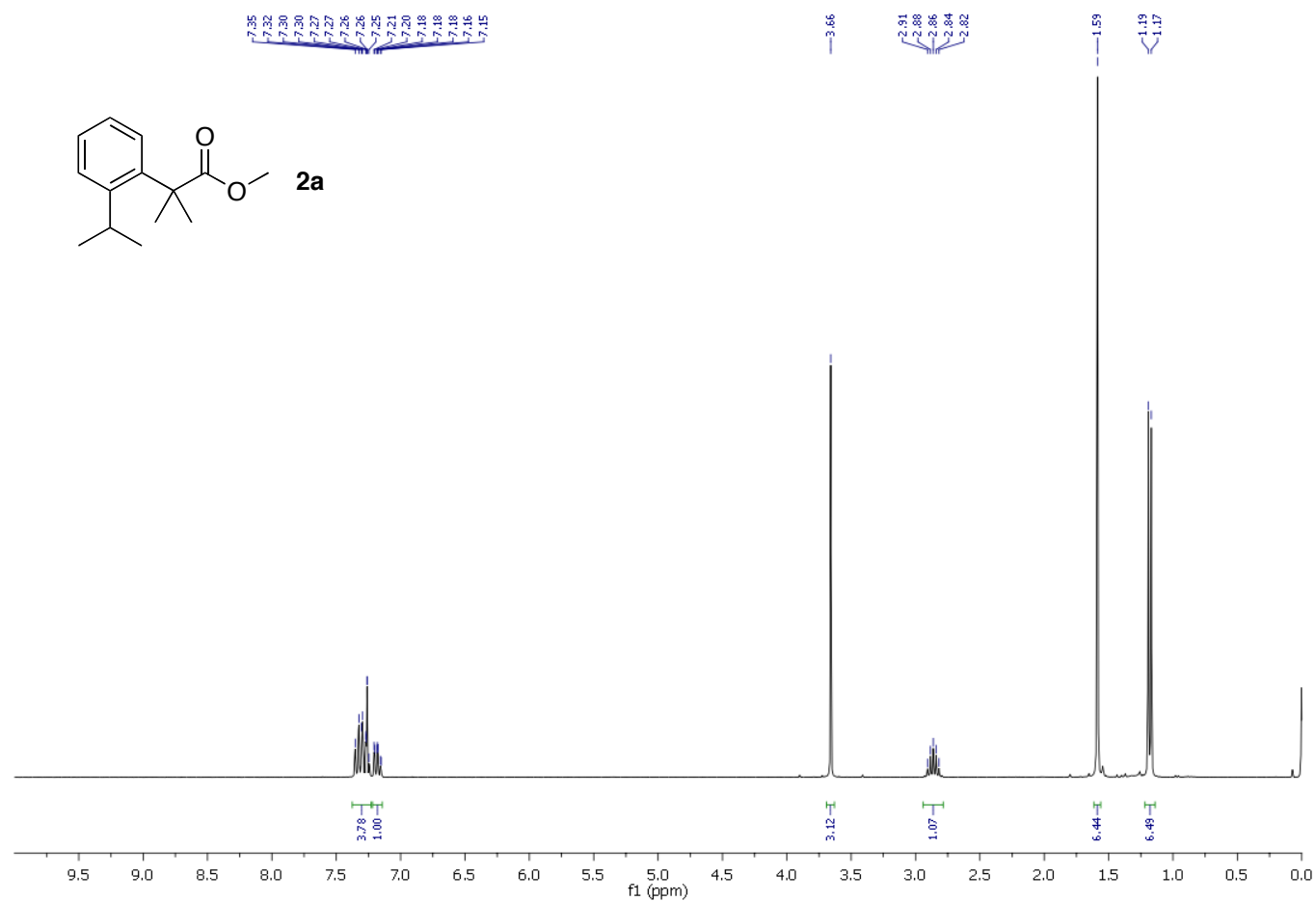
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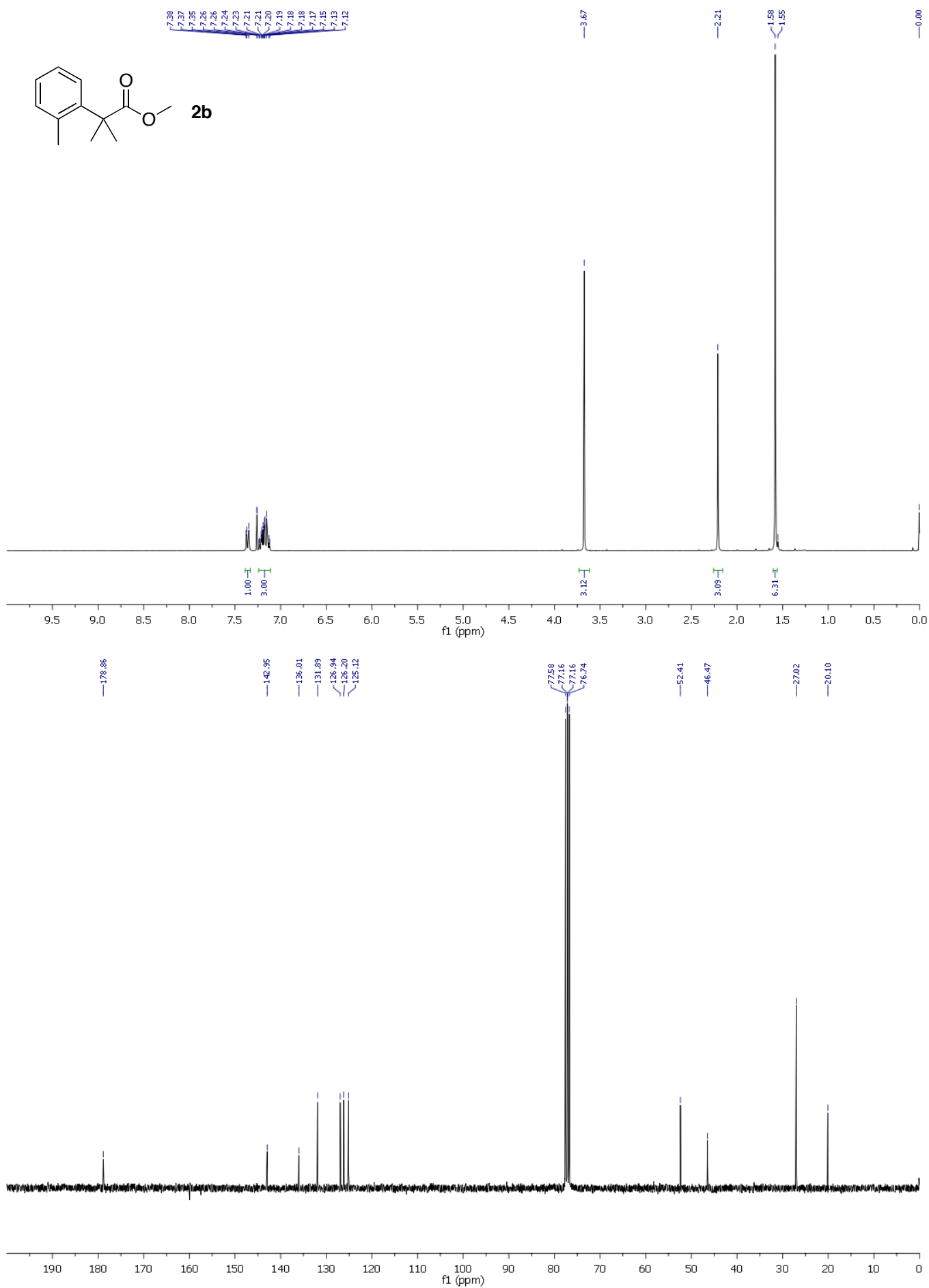


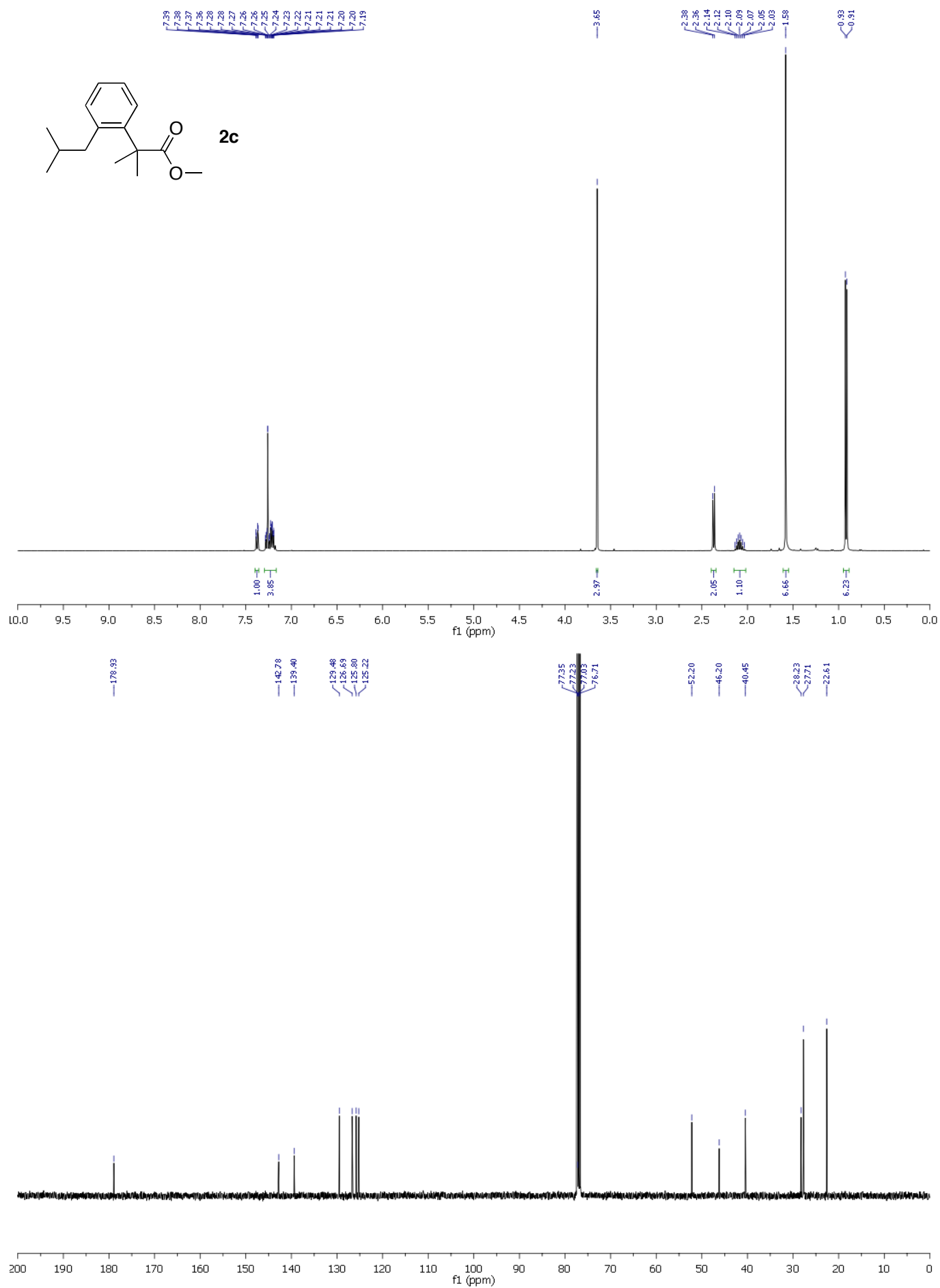


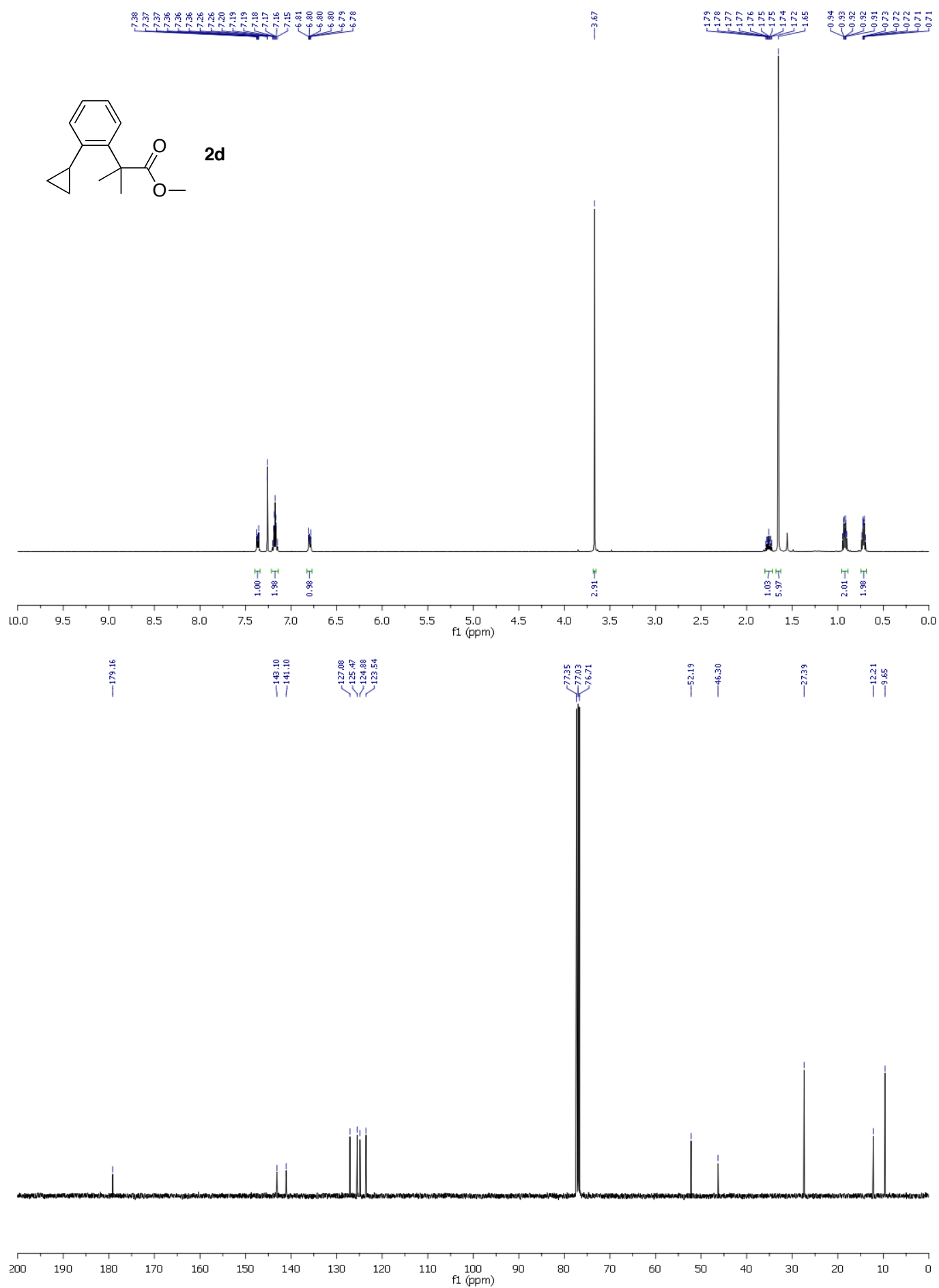
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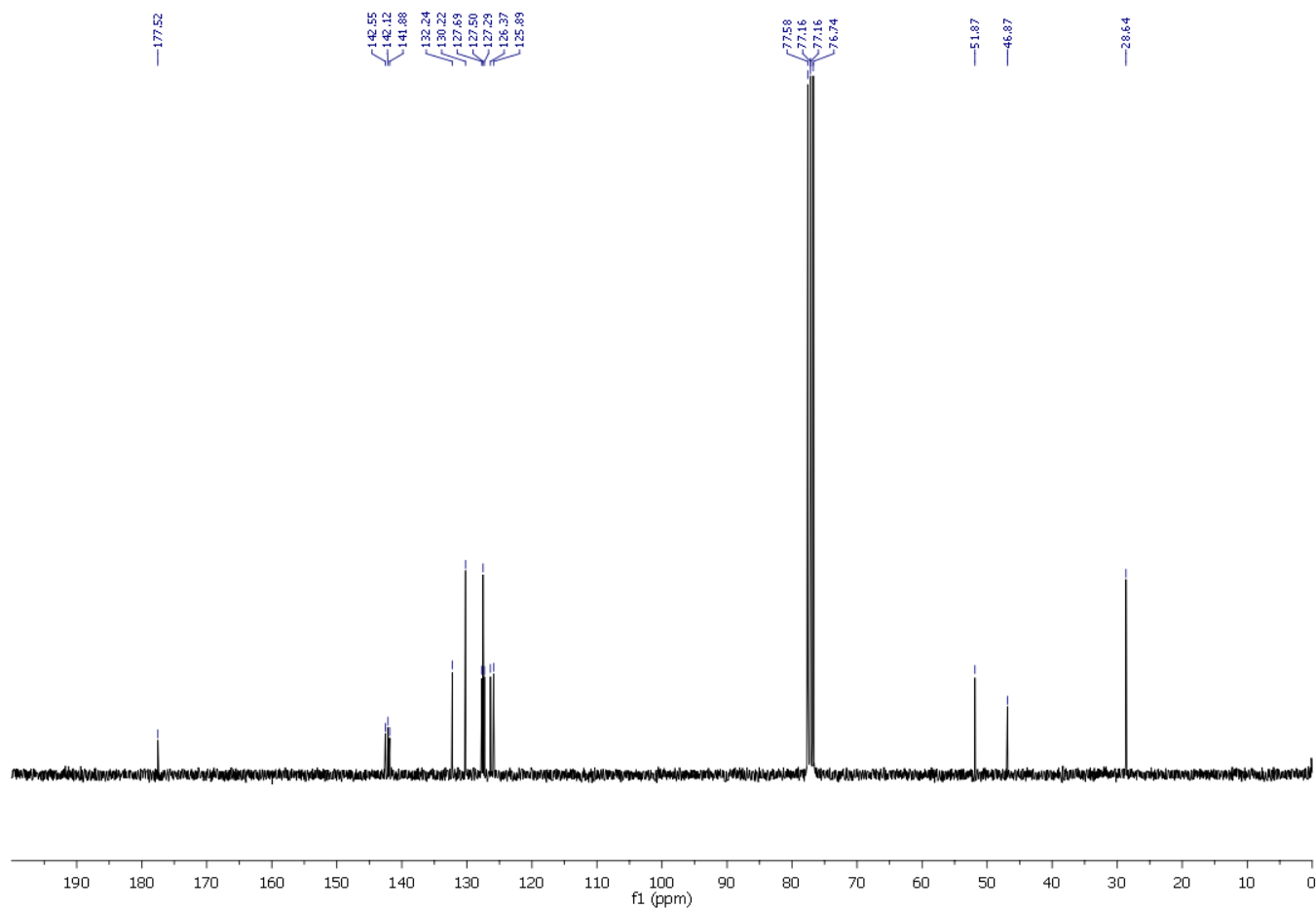
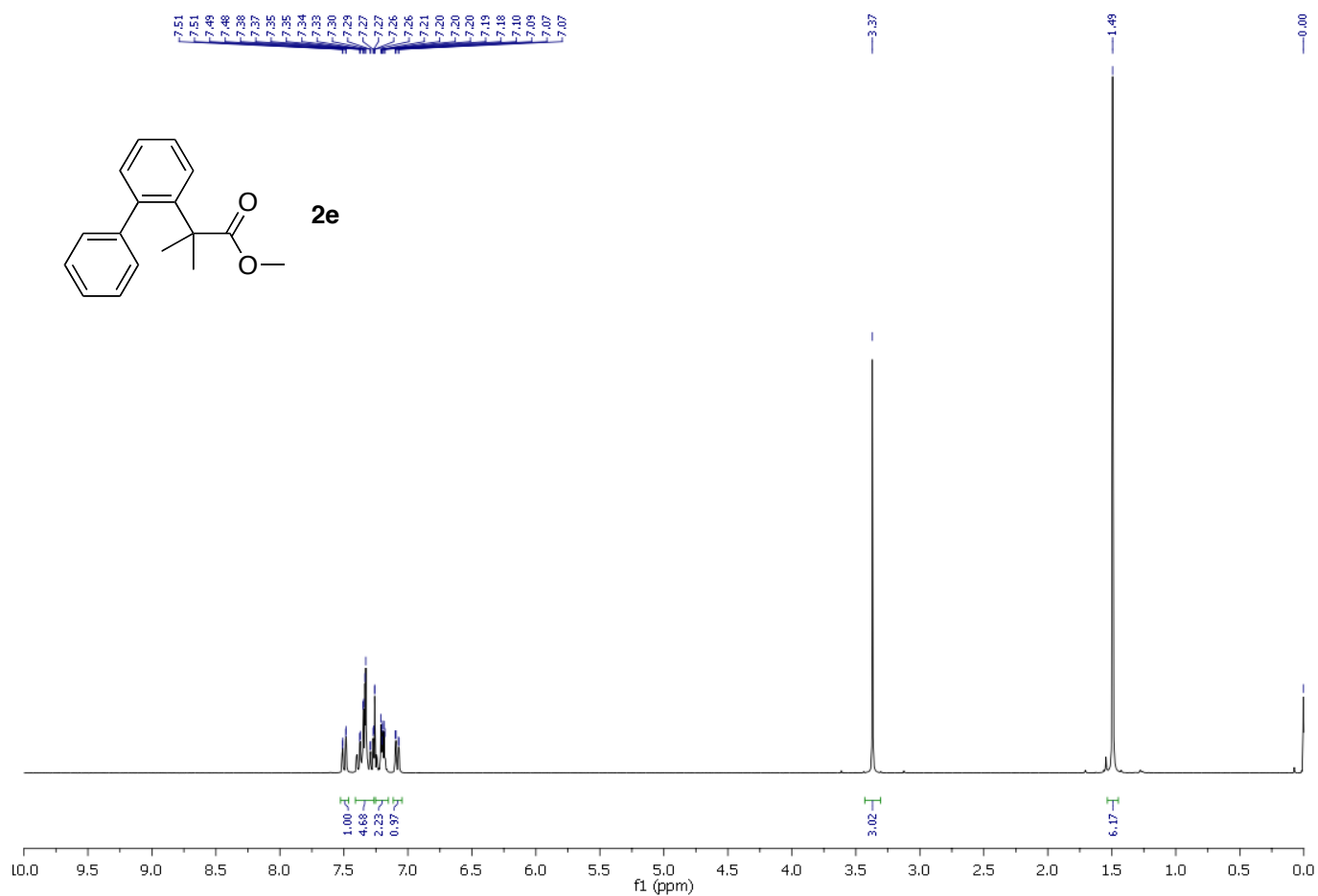


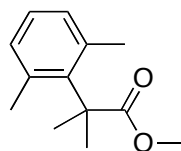












2g

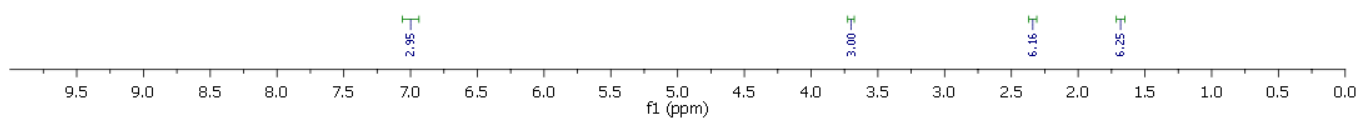
7.26
7.26
7.02
7.00
6.98
6.96

3.70

2.34

1.68

0.00



179.99

141.43

136.63

130.97

126.30

77.58

77.16

77.16

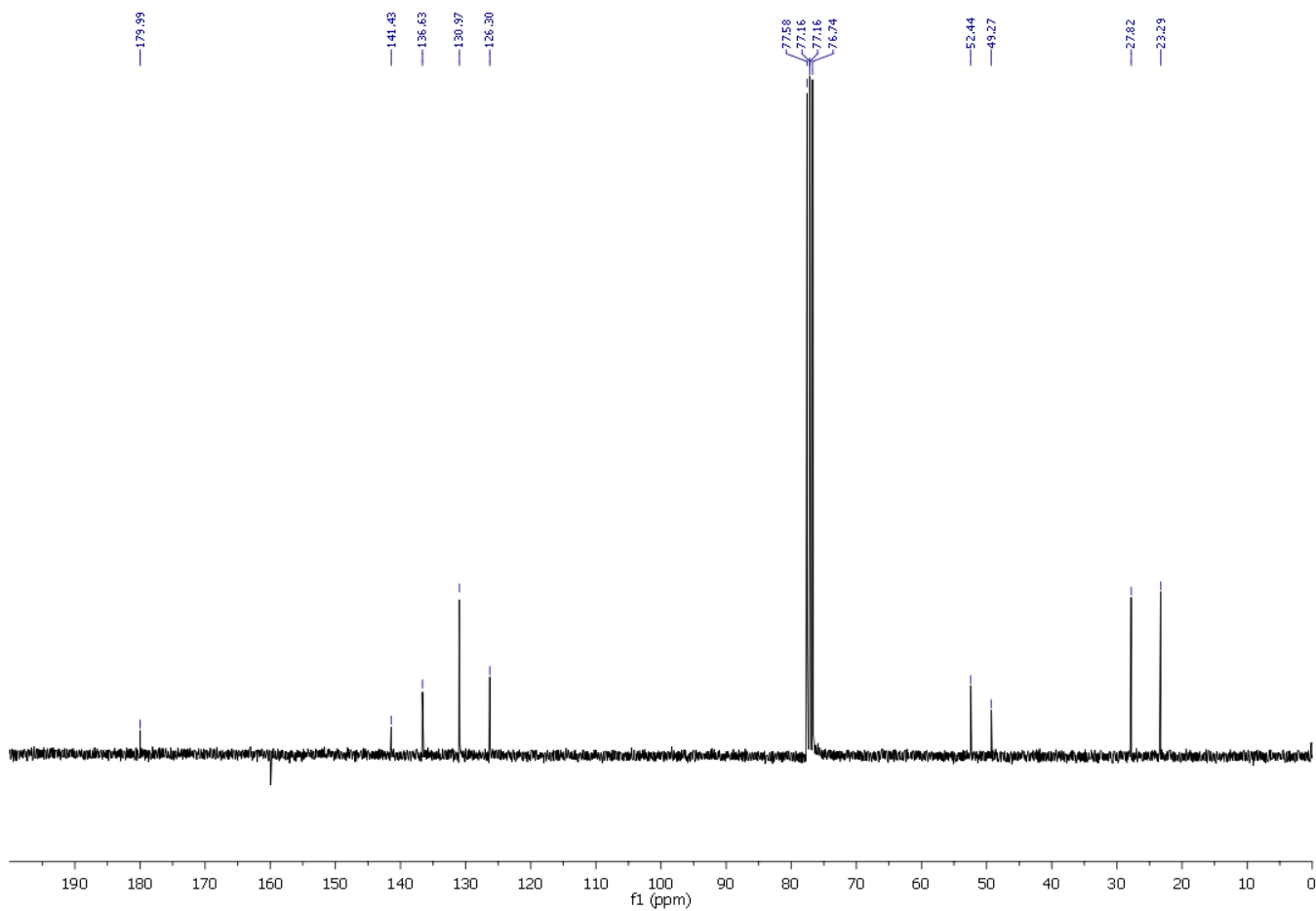
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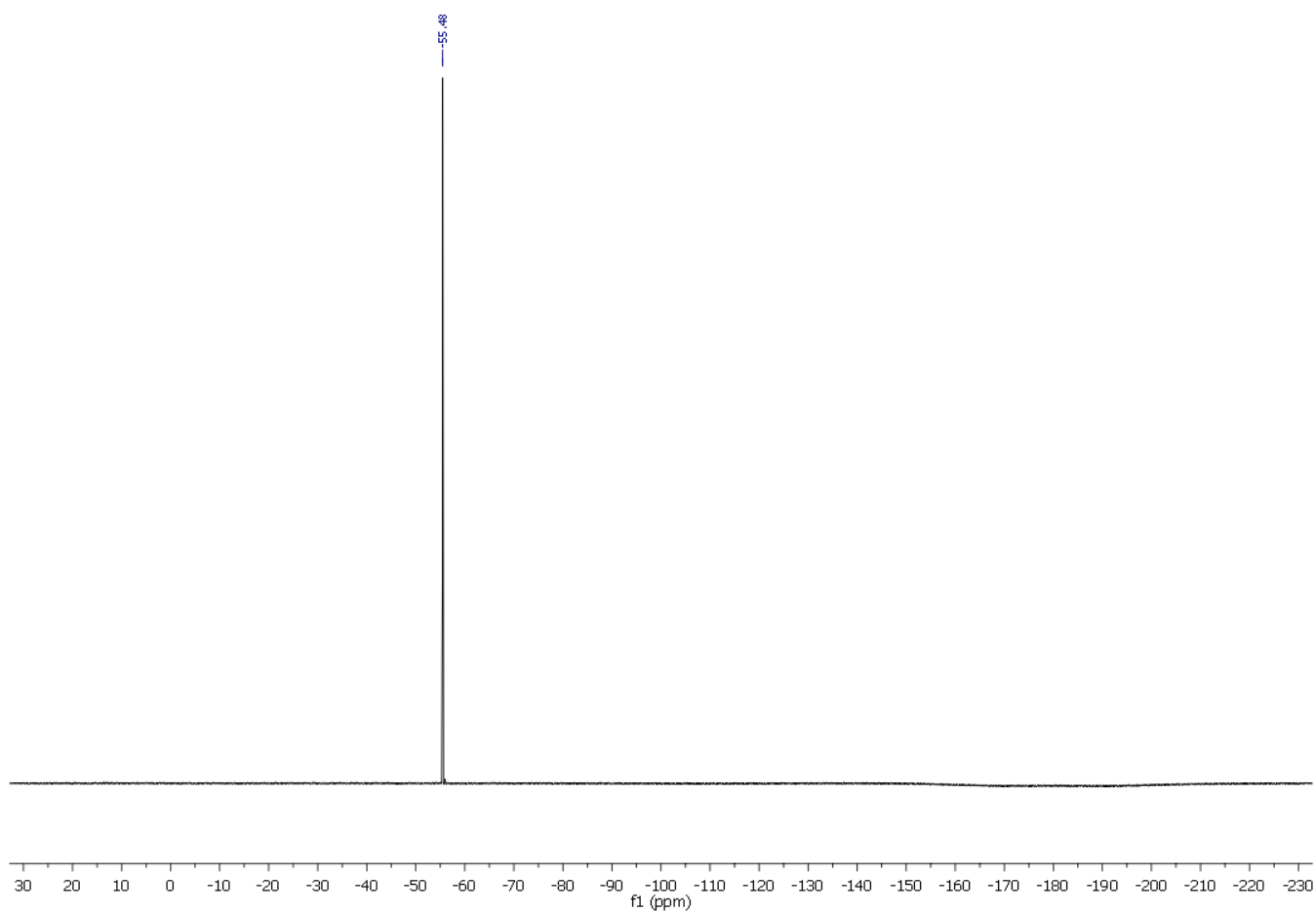
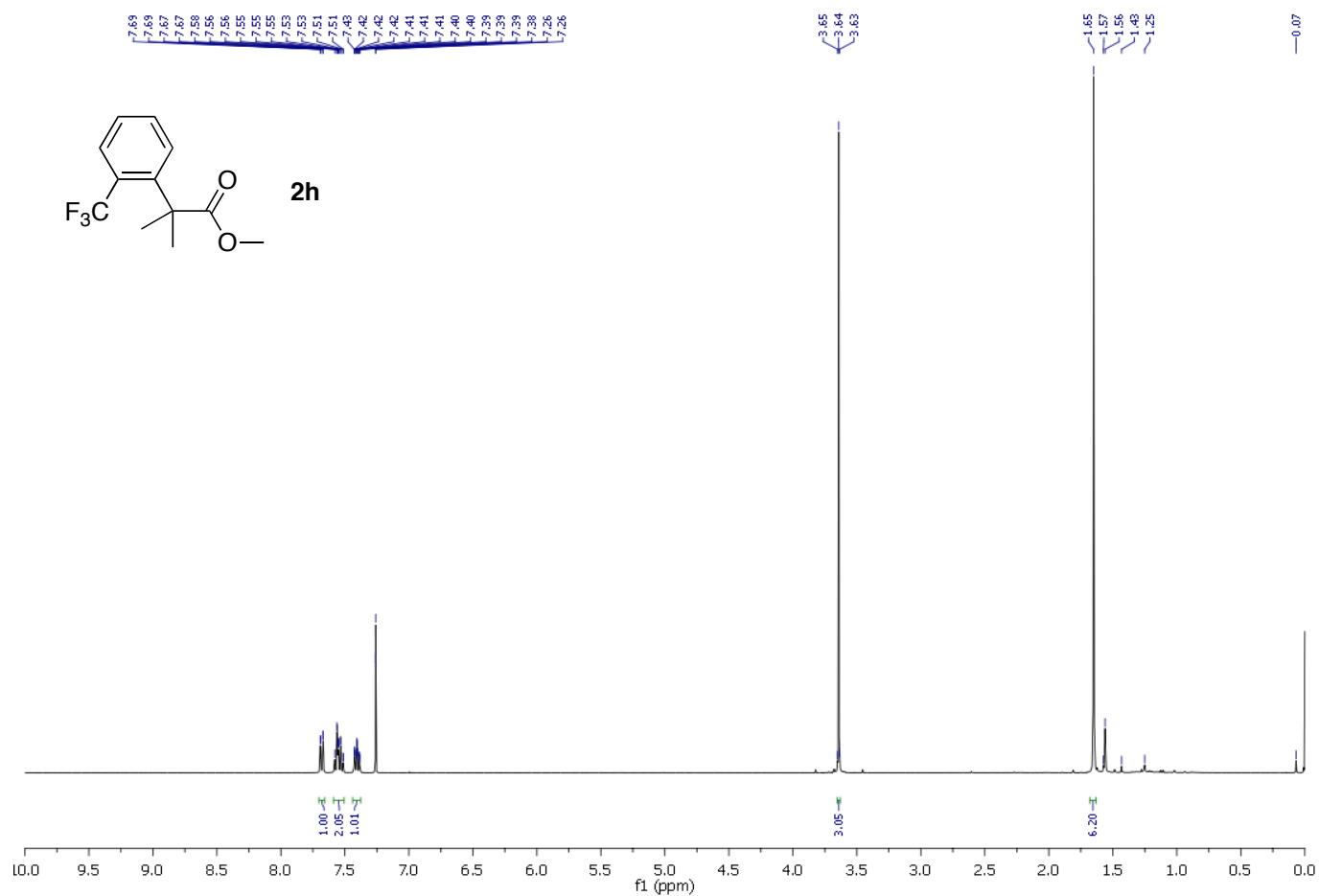
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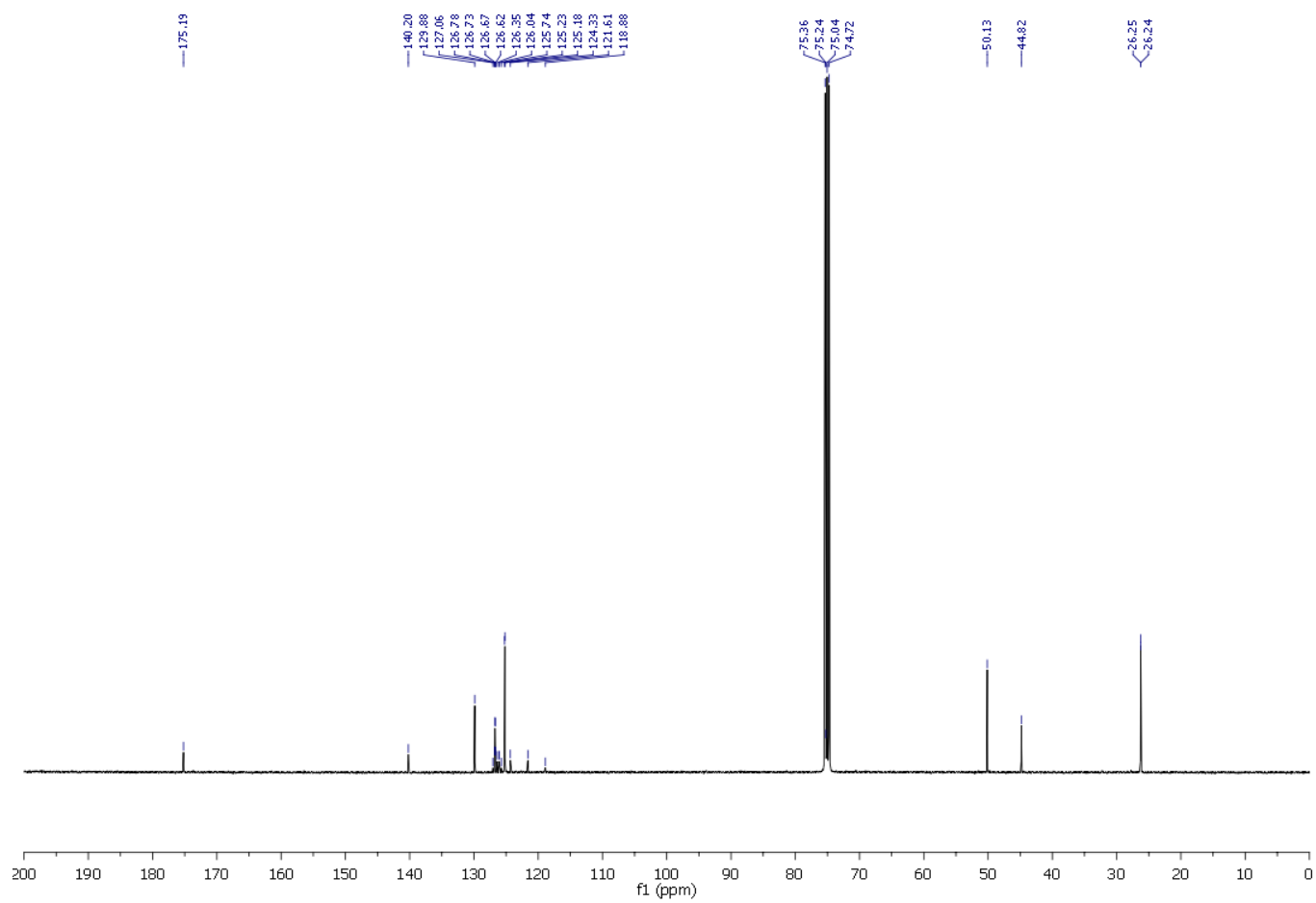
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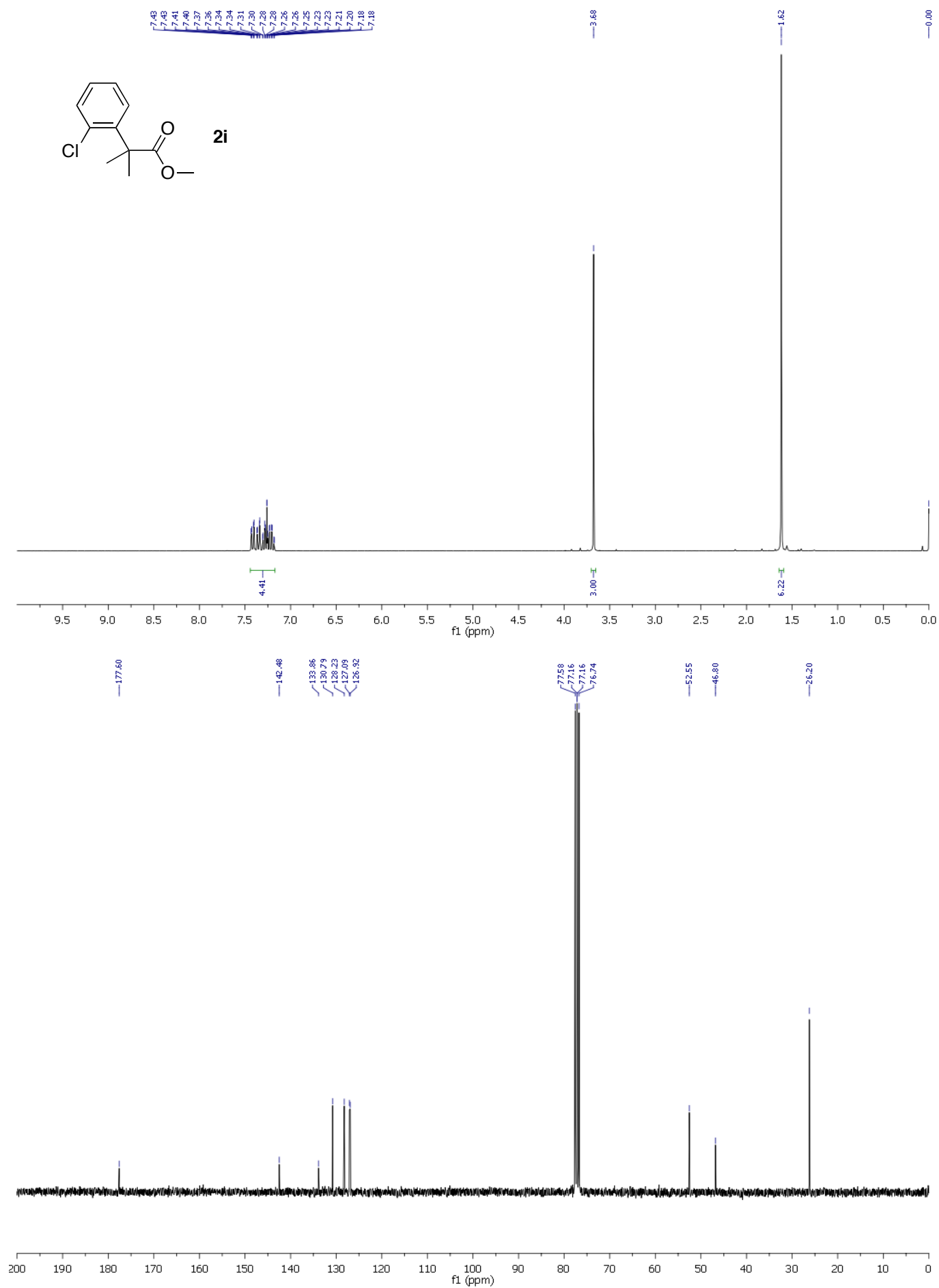
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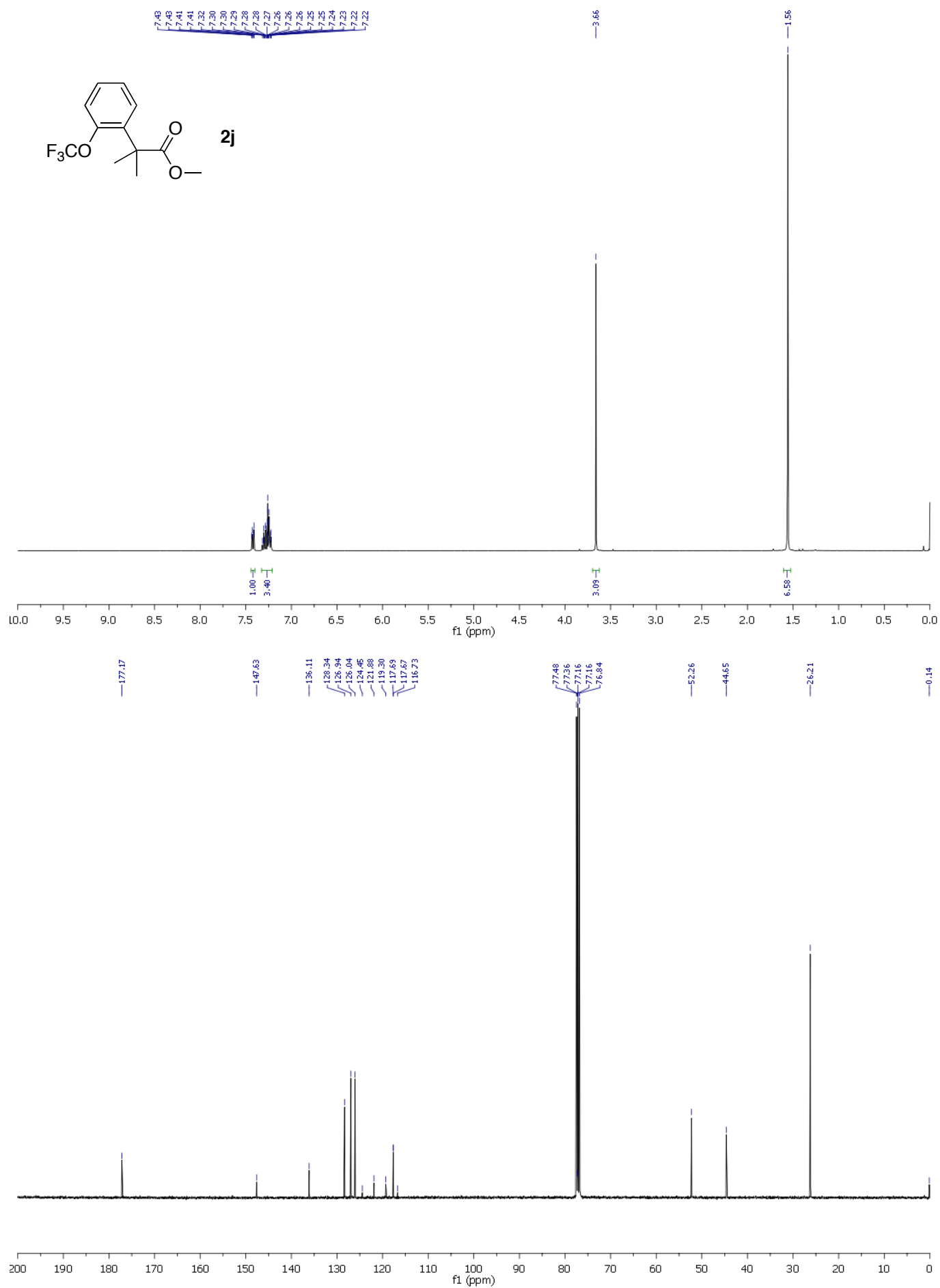
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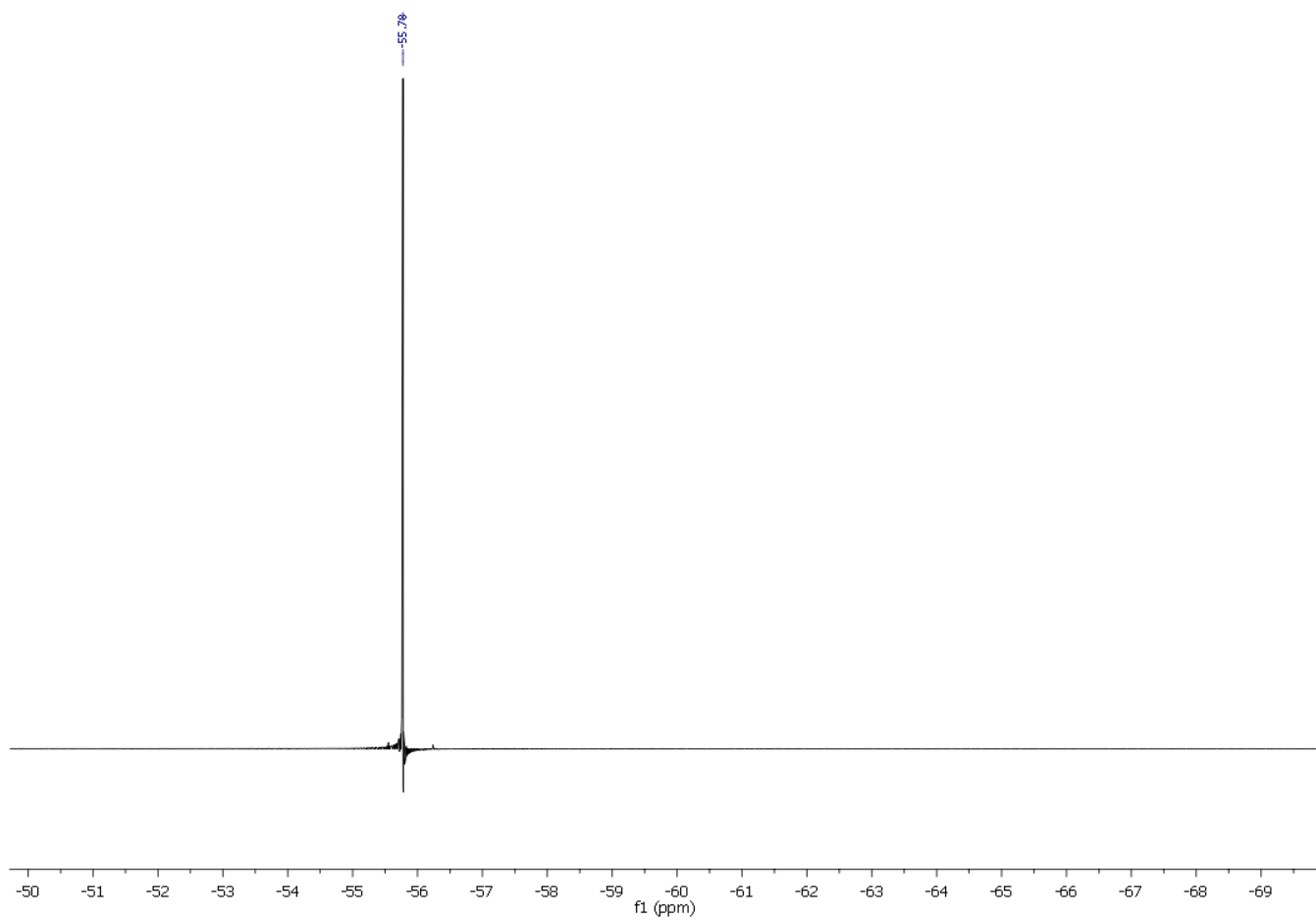


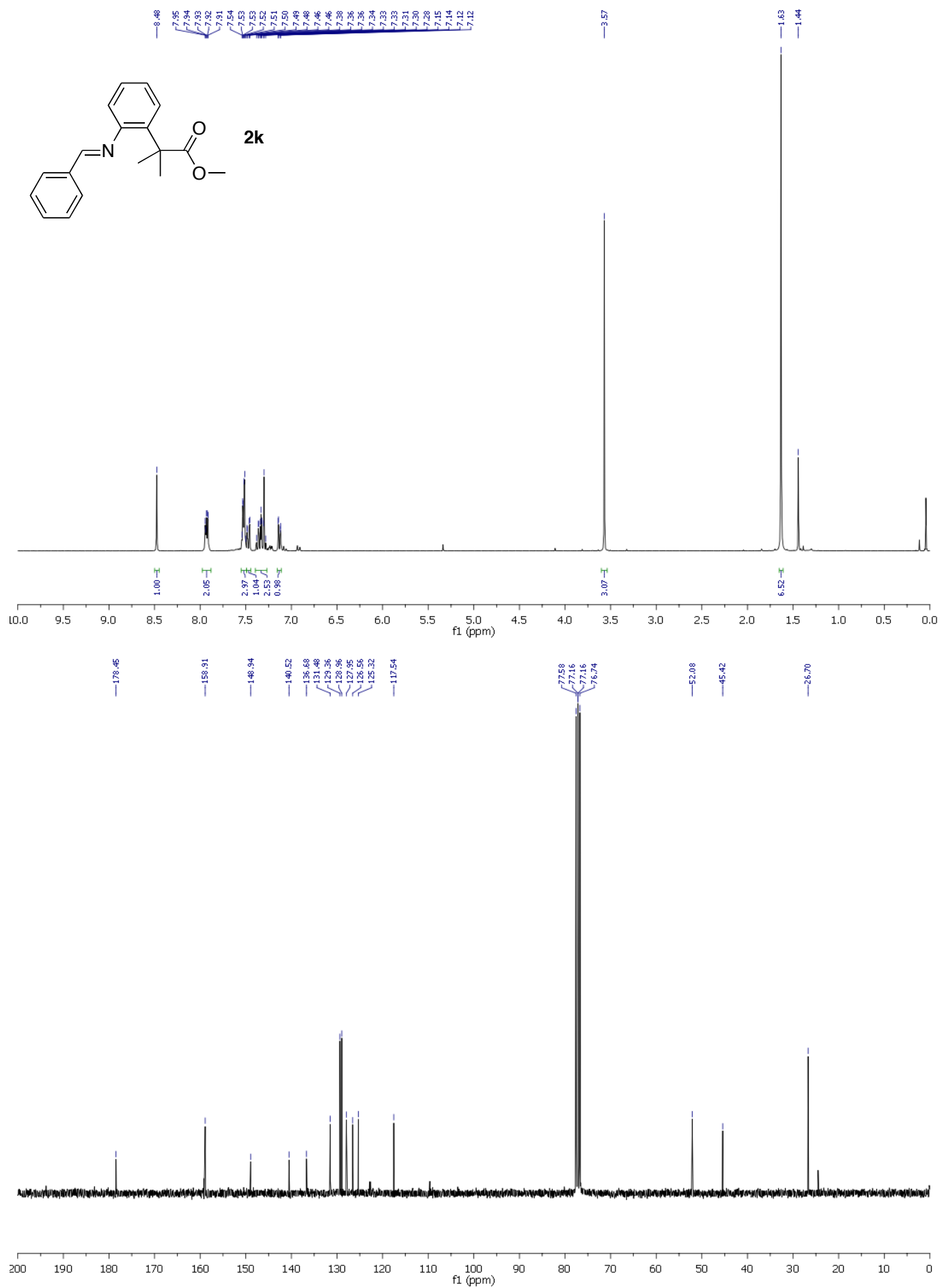


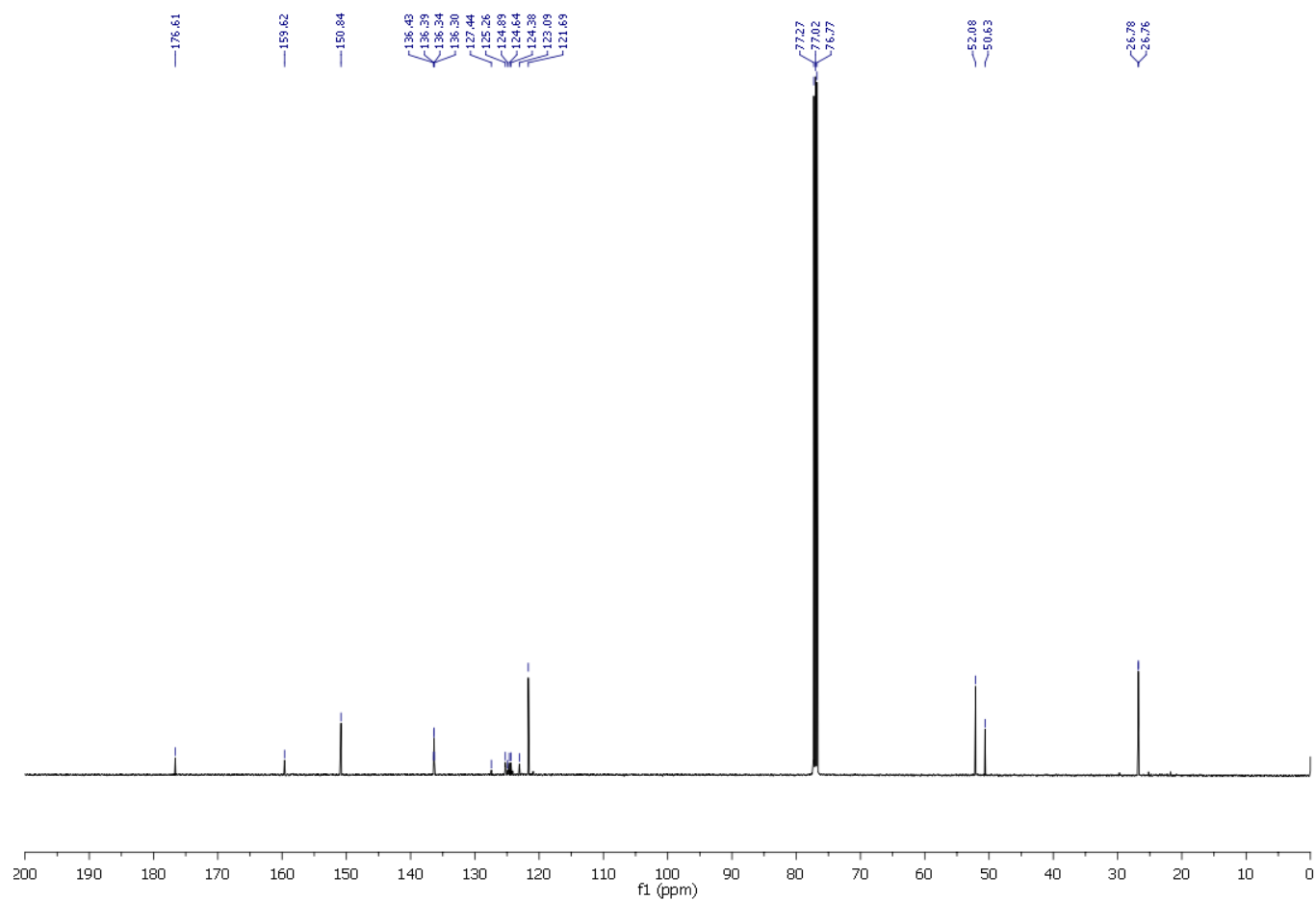
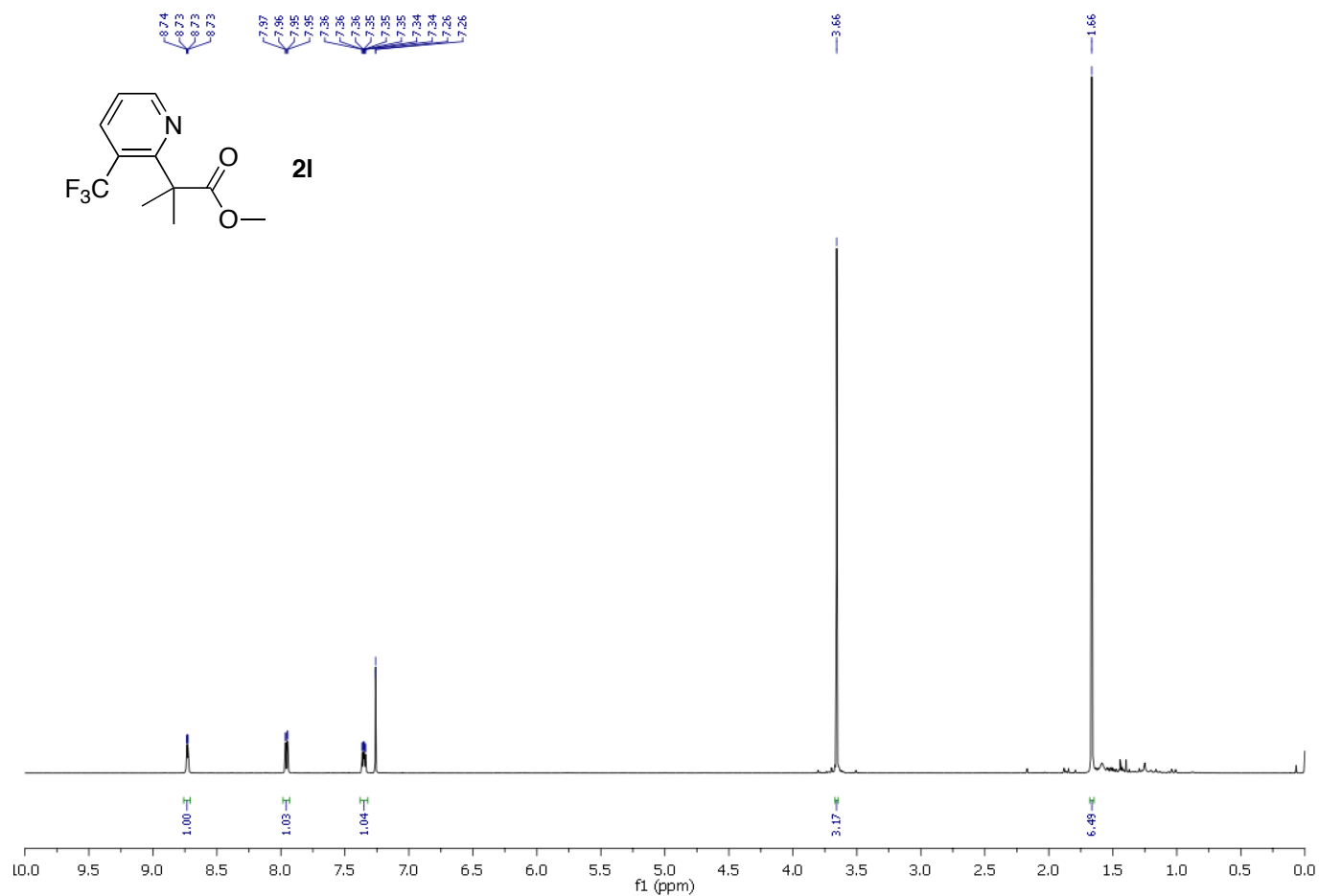


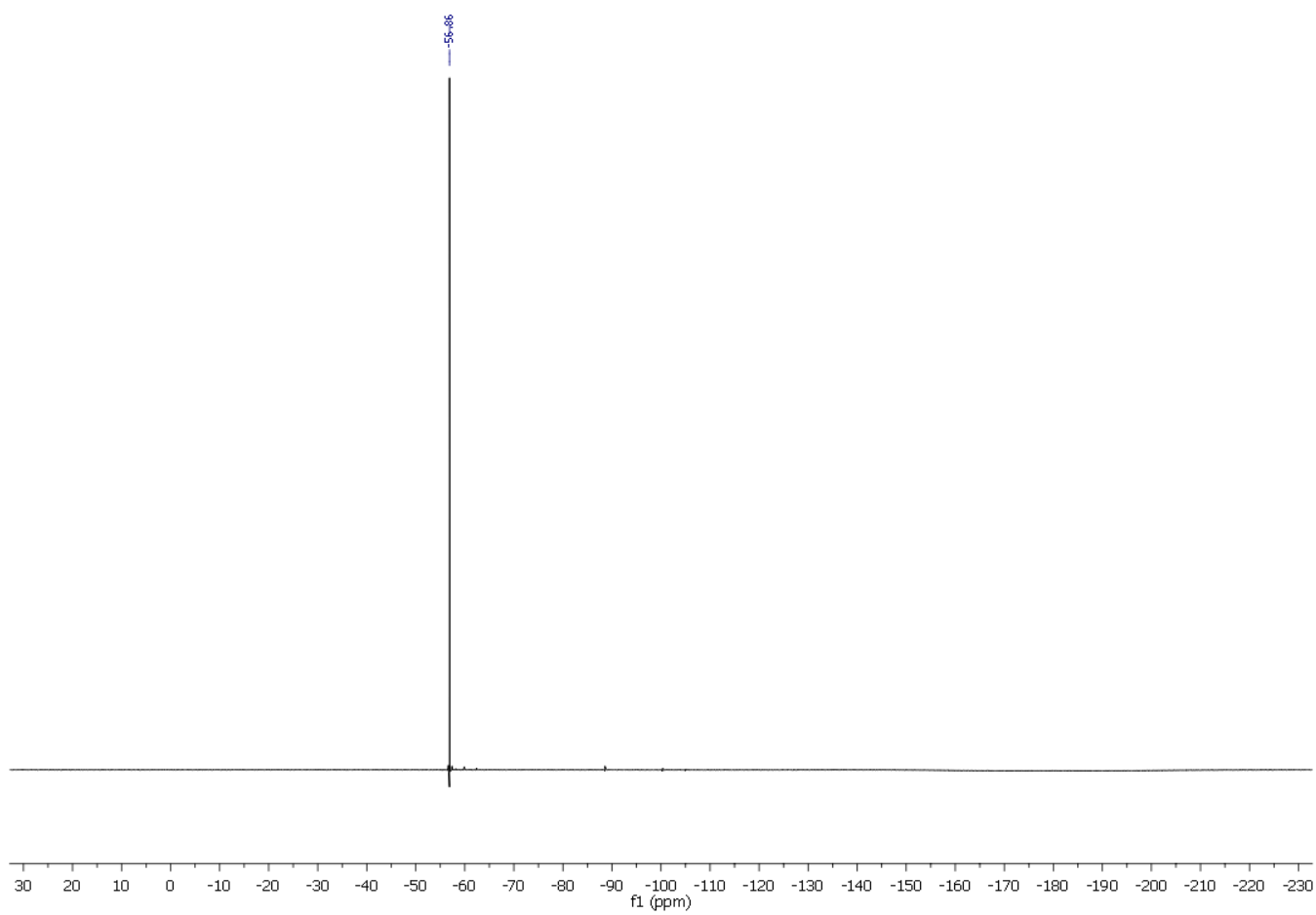


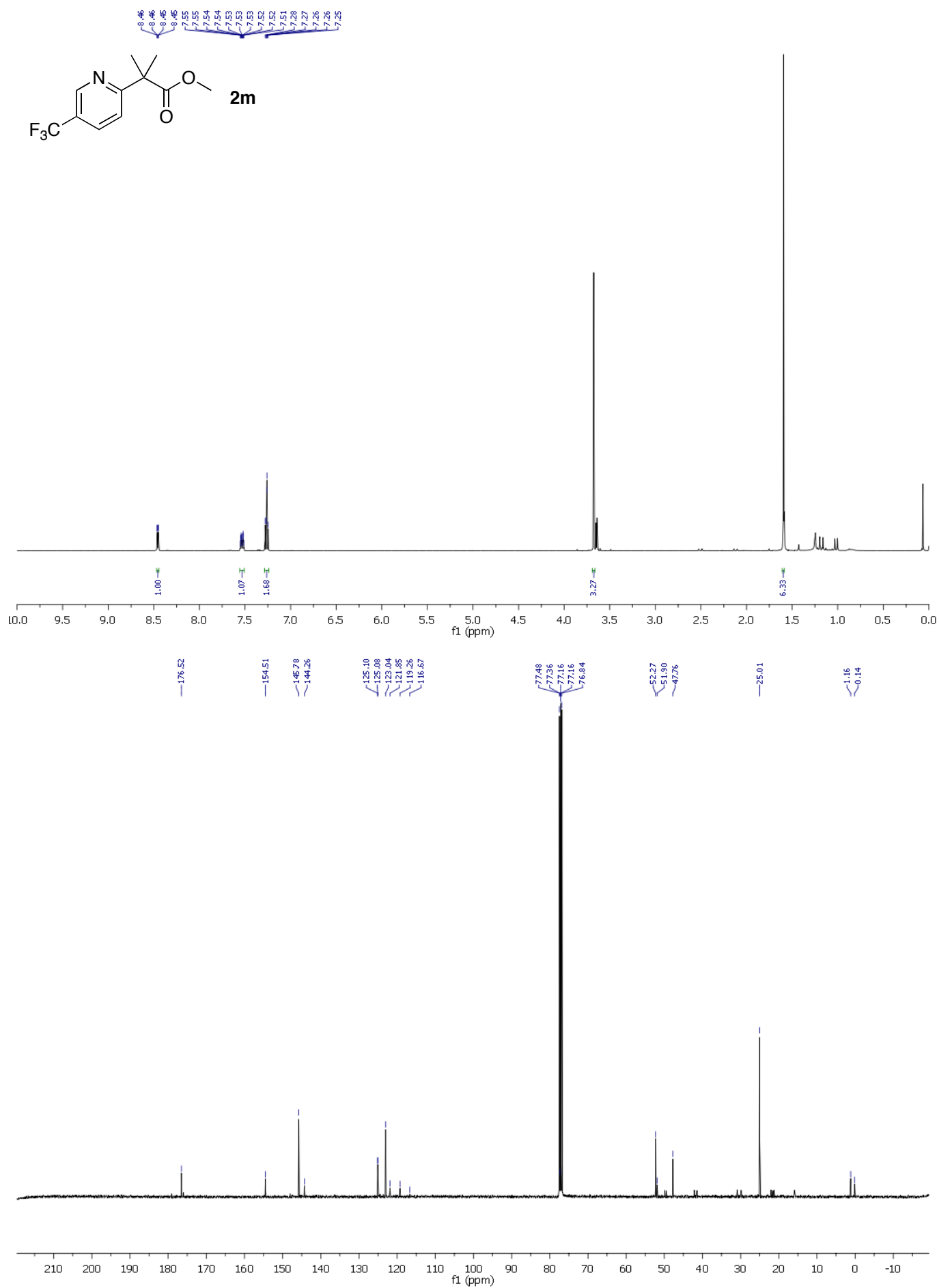


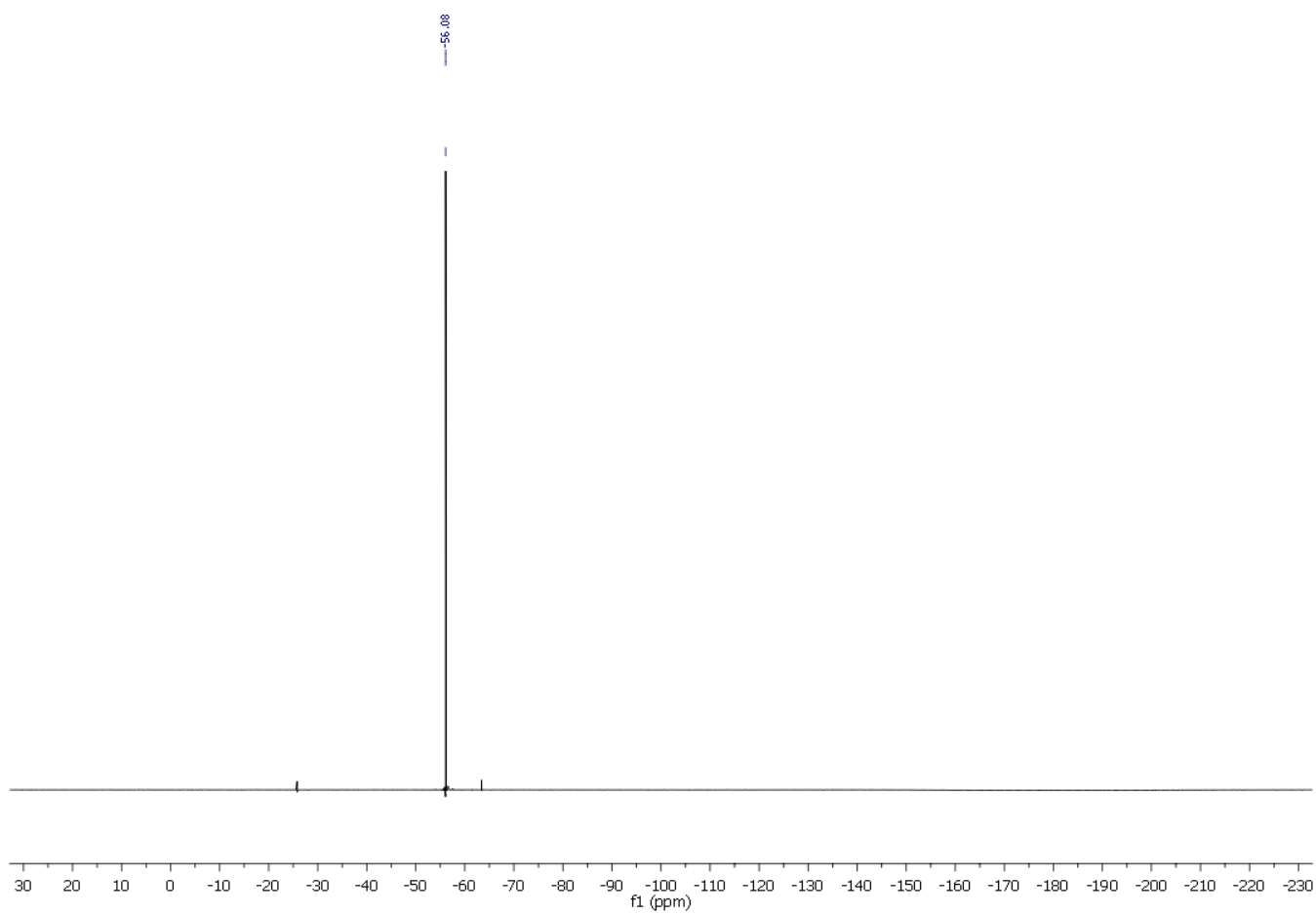


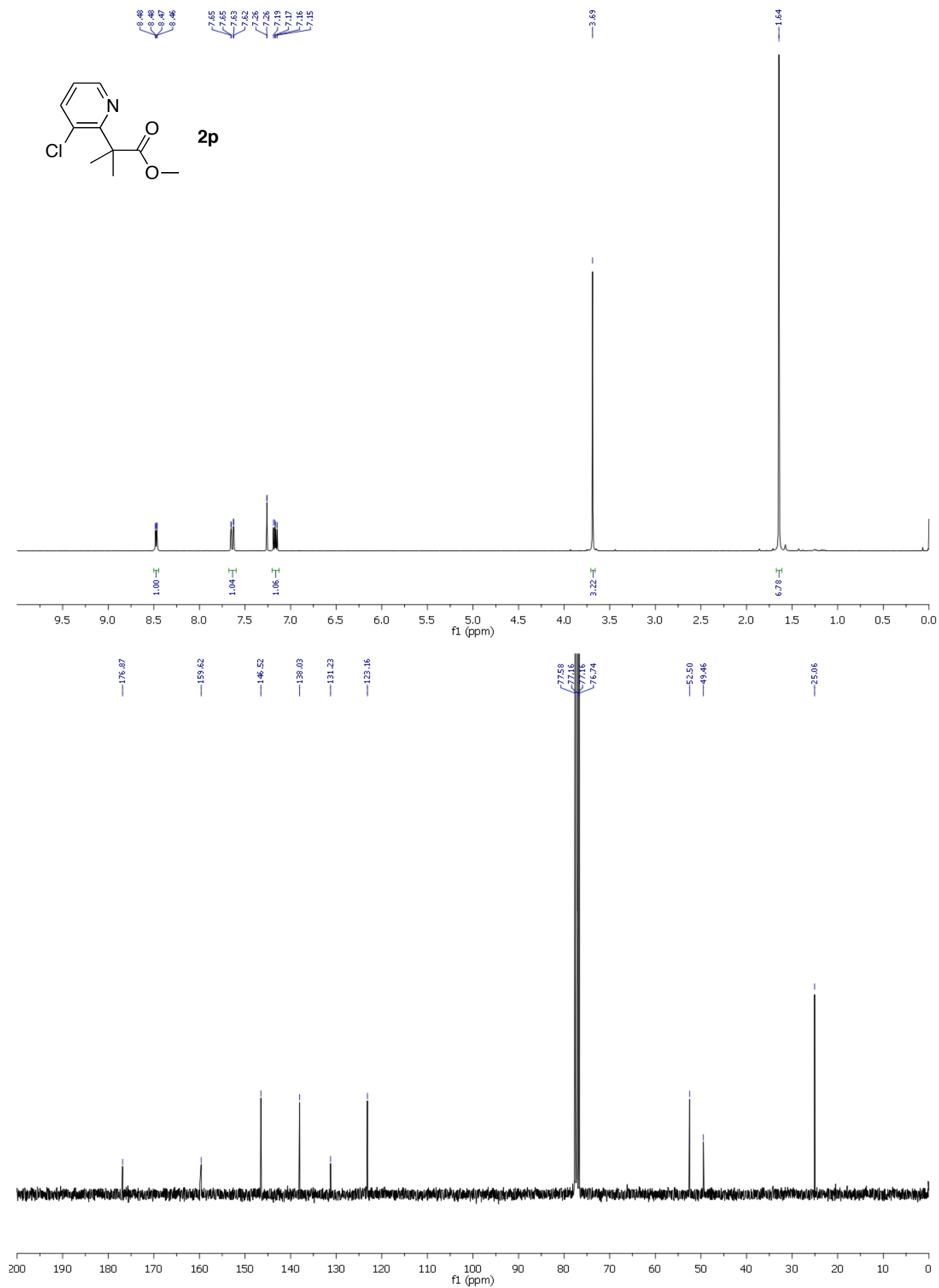


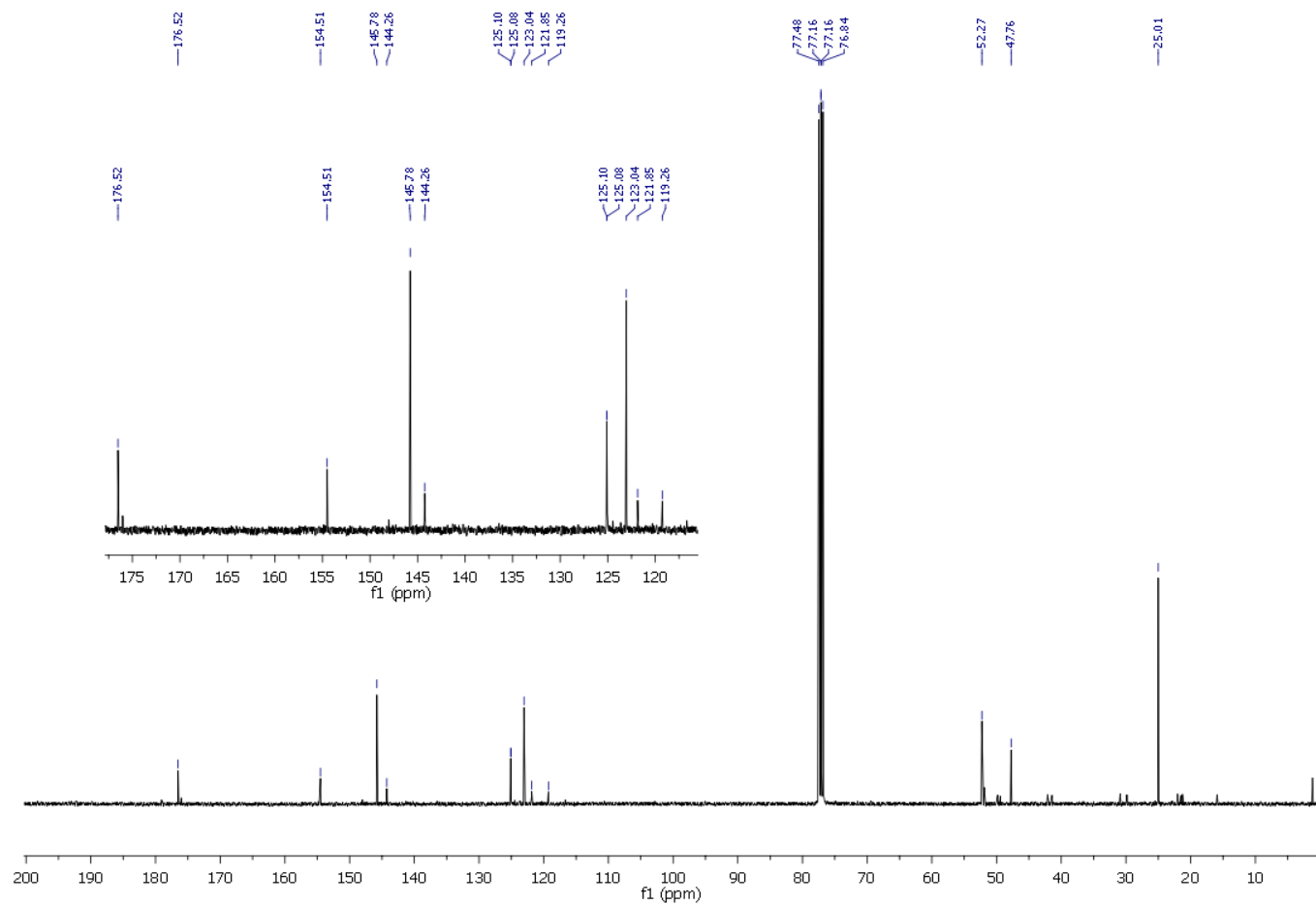
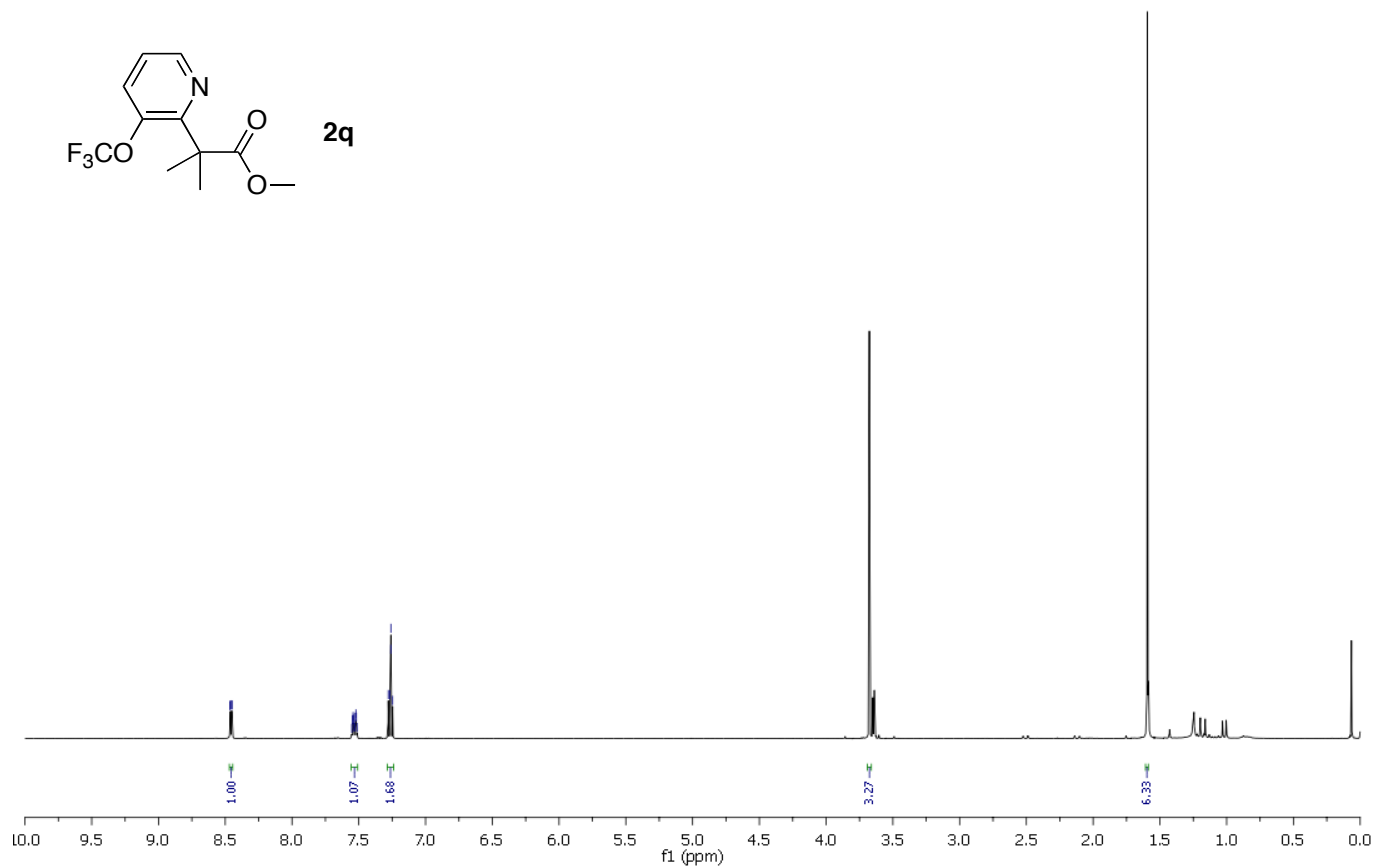
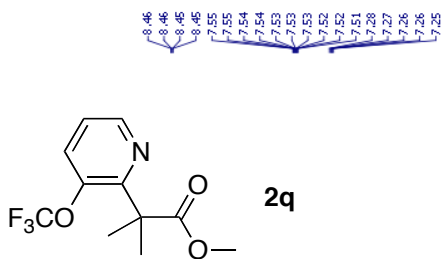


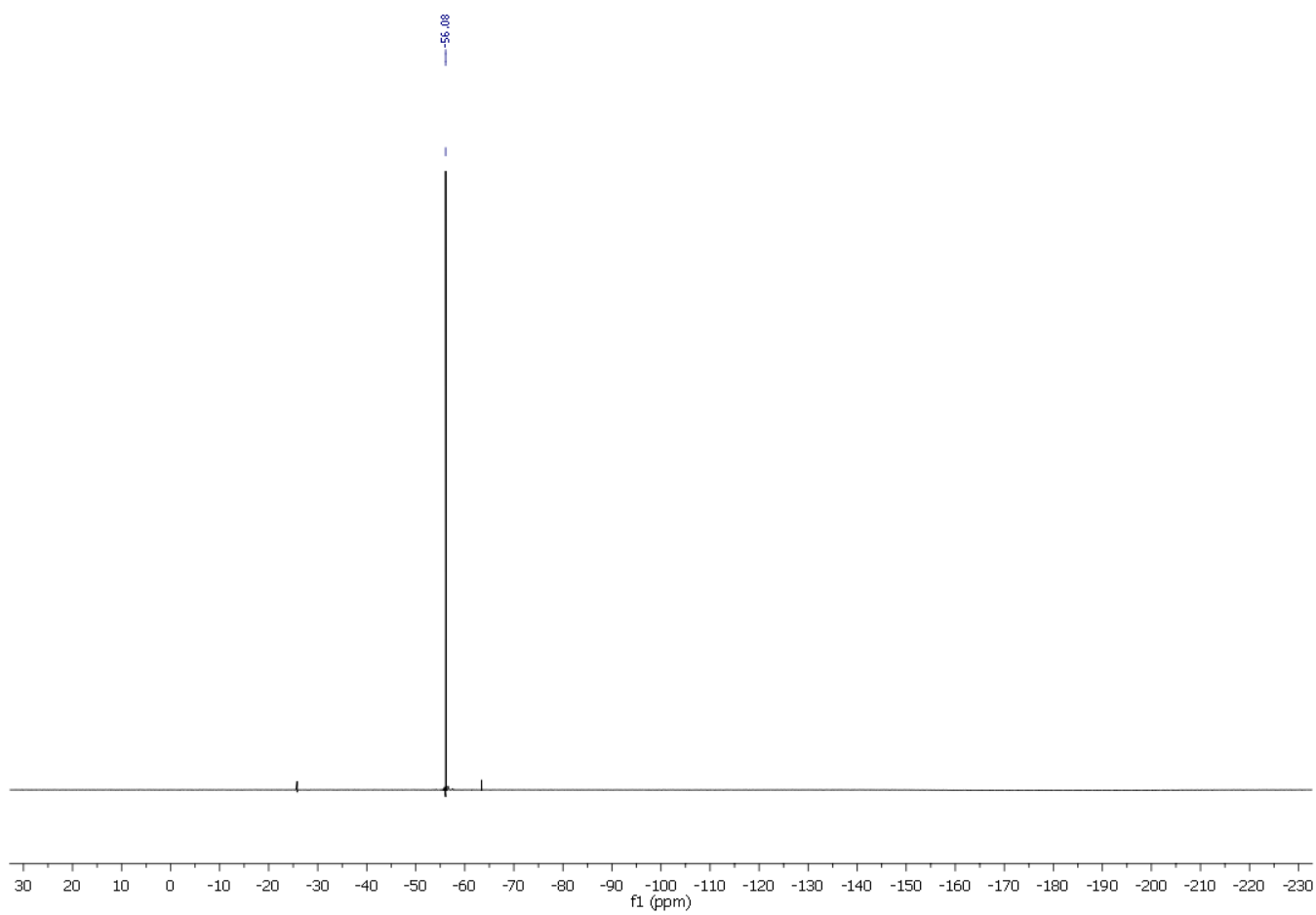


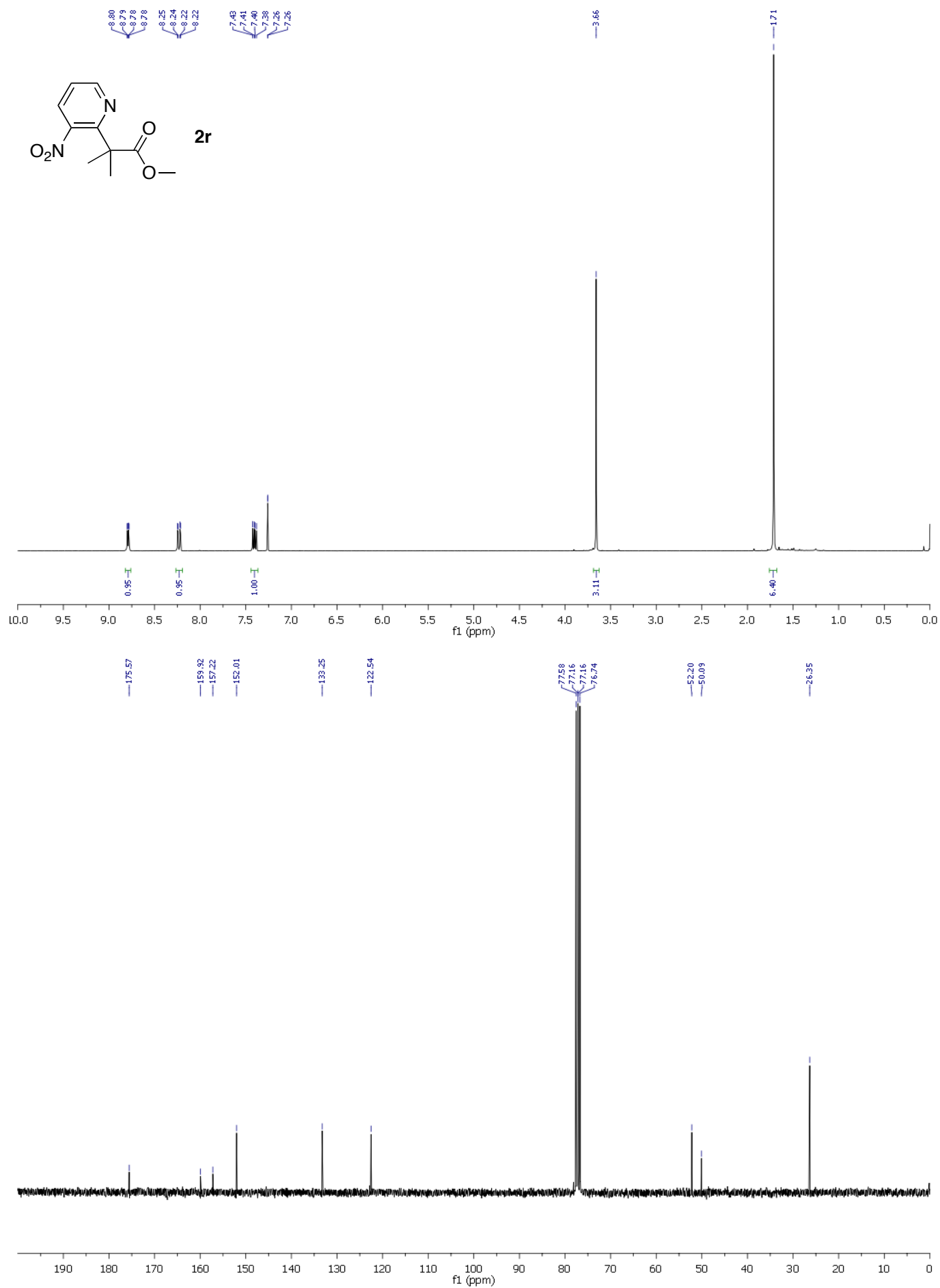


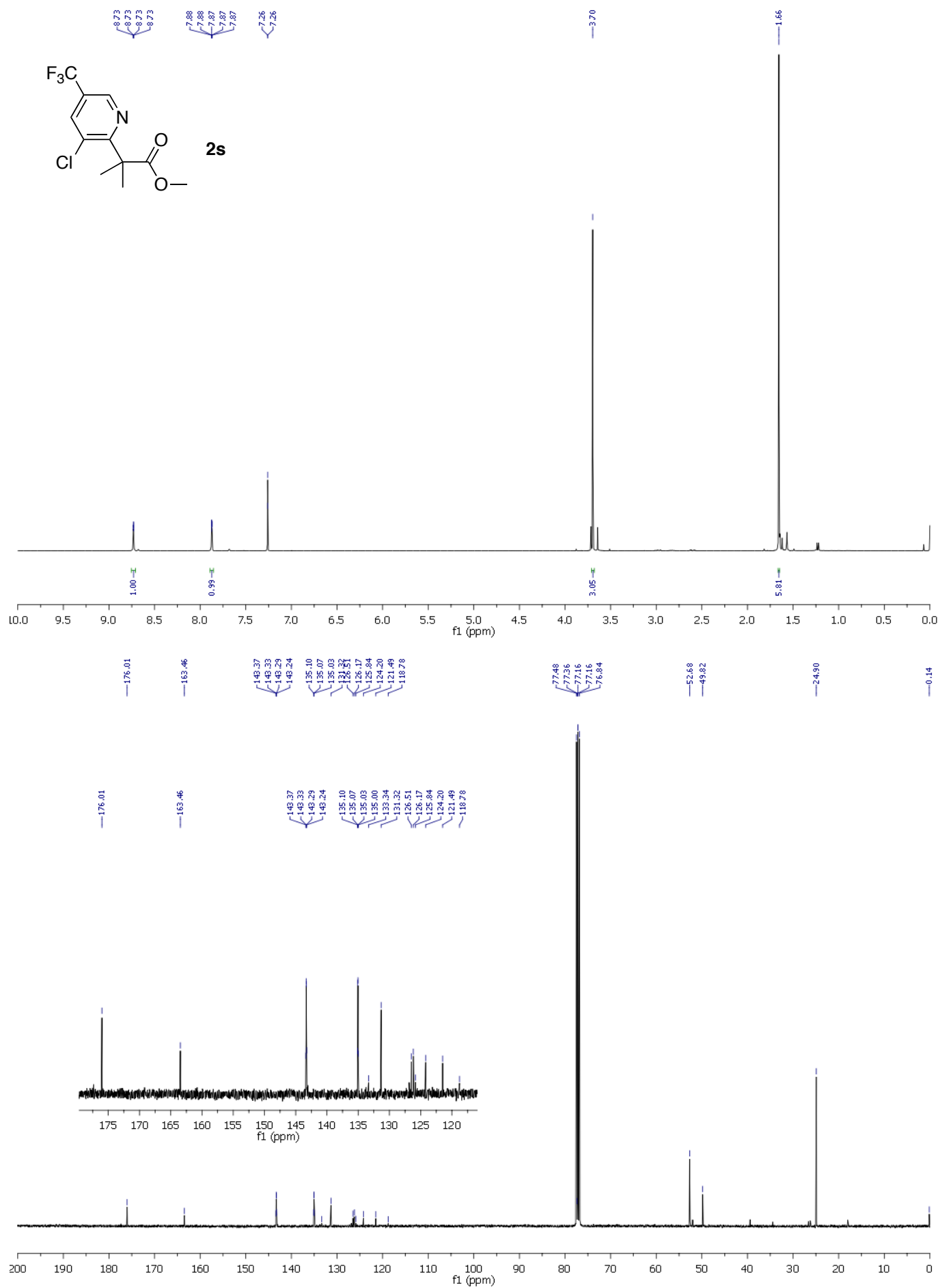


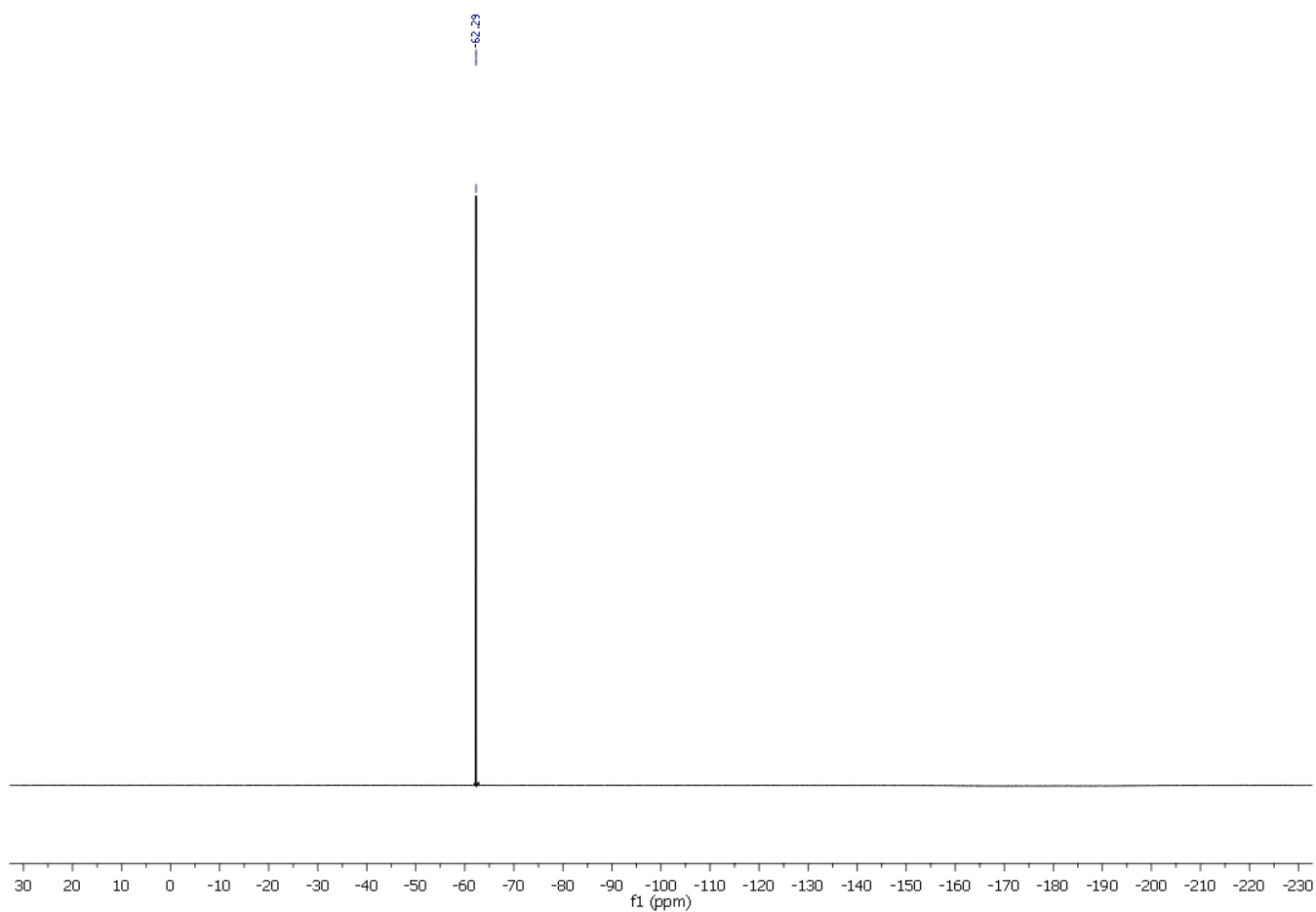


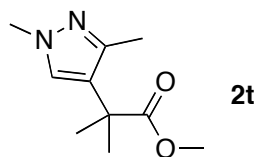










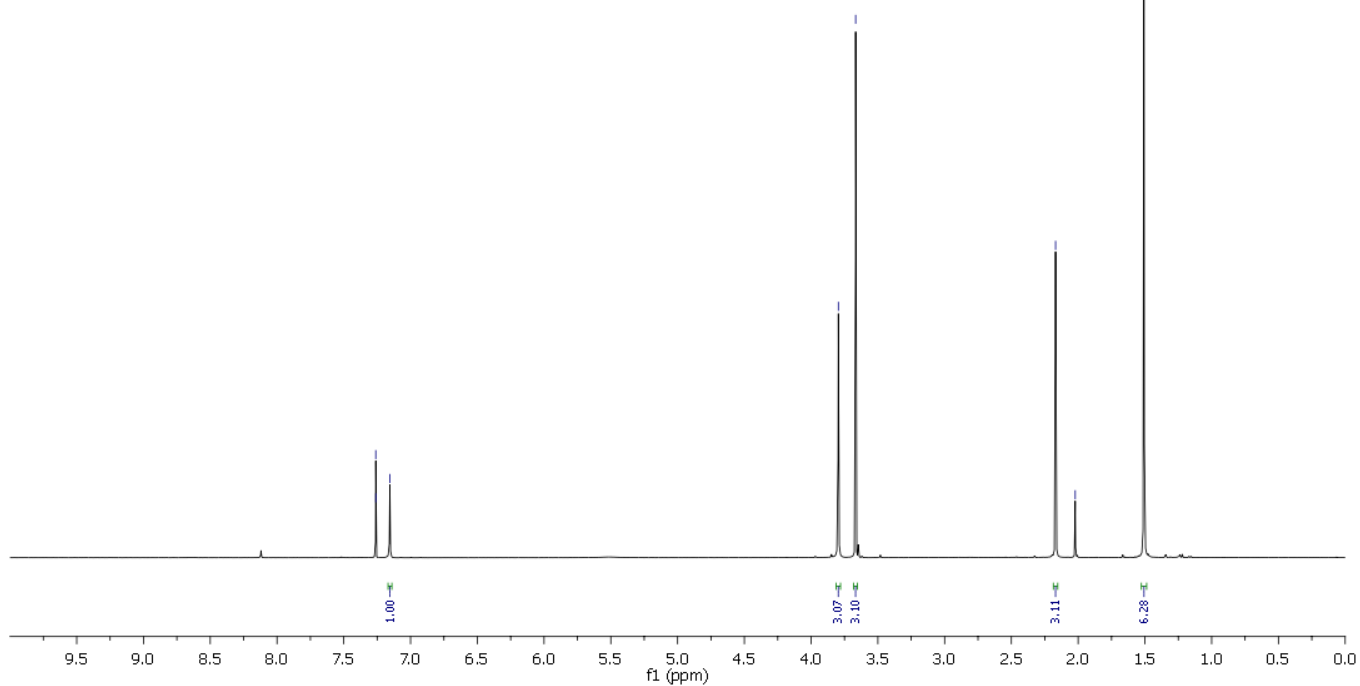


7.26
7.26
7.15

3.80
3.67

2.17
2.02

1.51



177.18

145.57

128.42

123.81

77.48
77.16
76.84

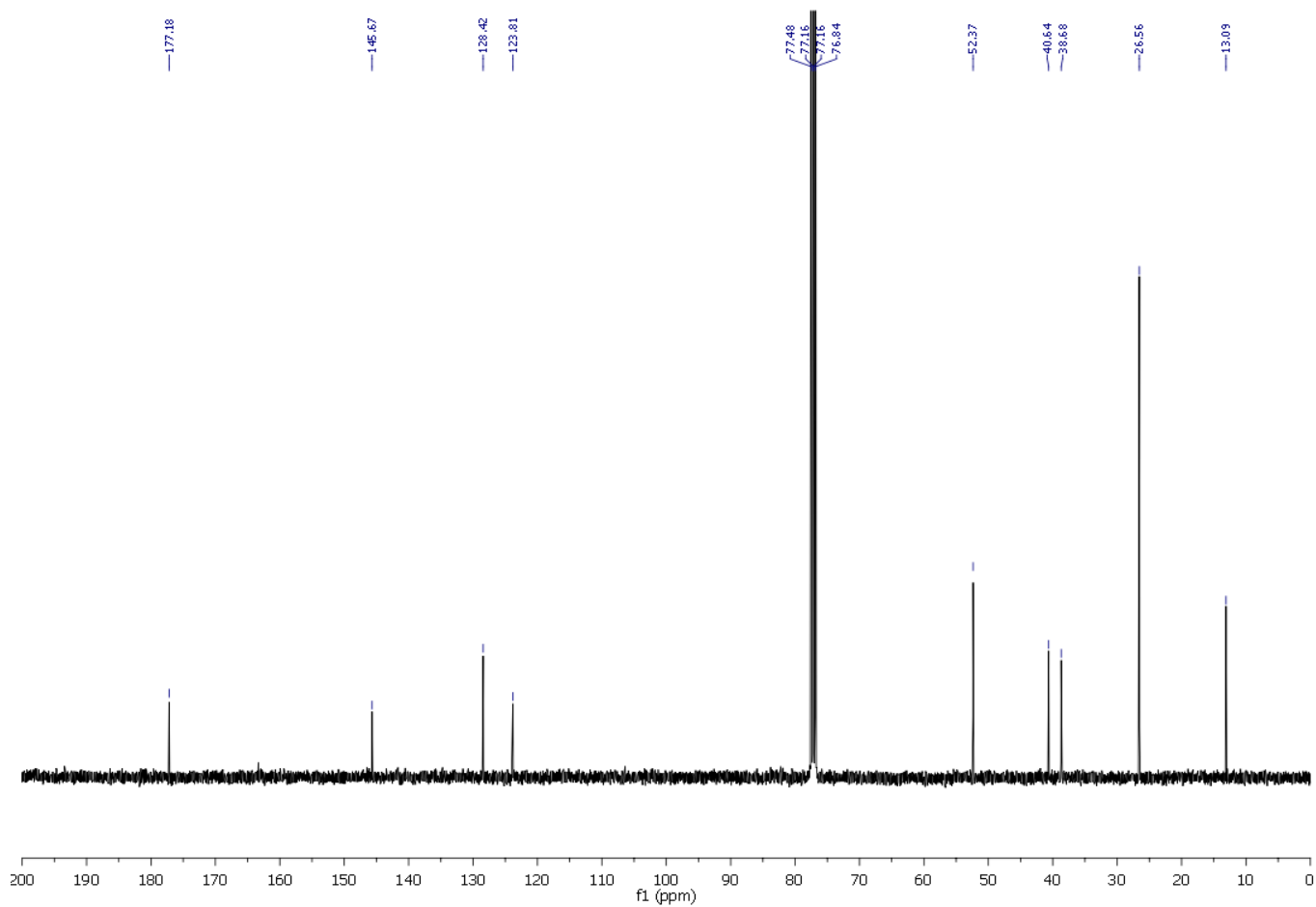
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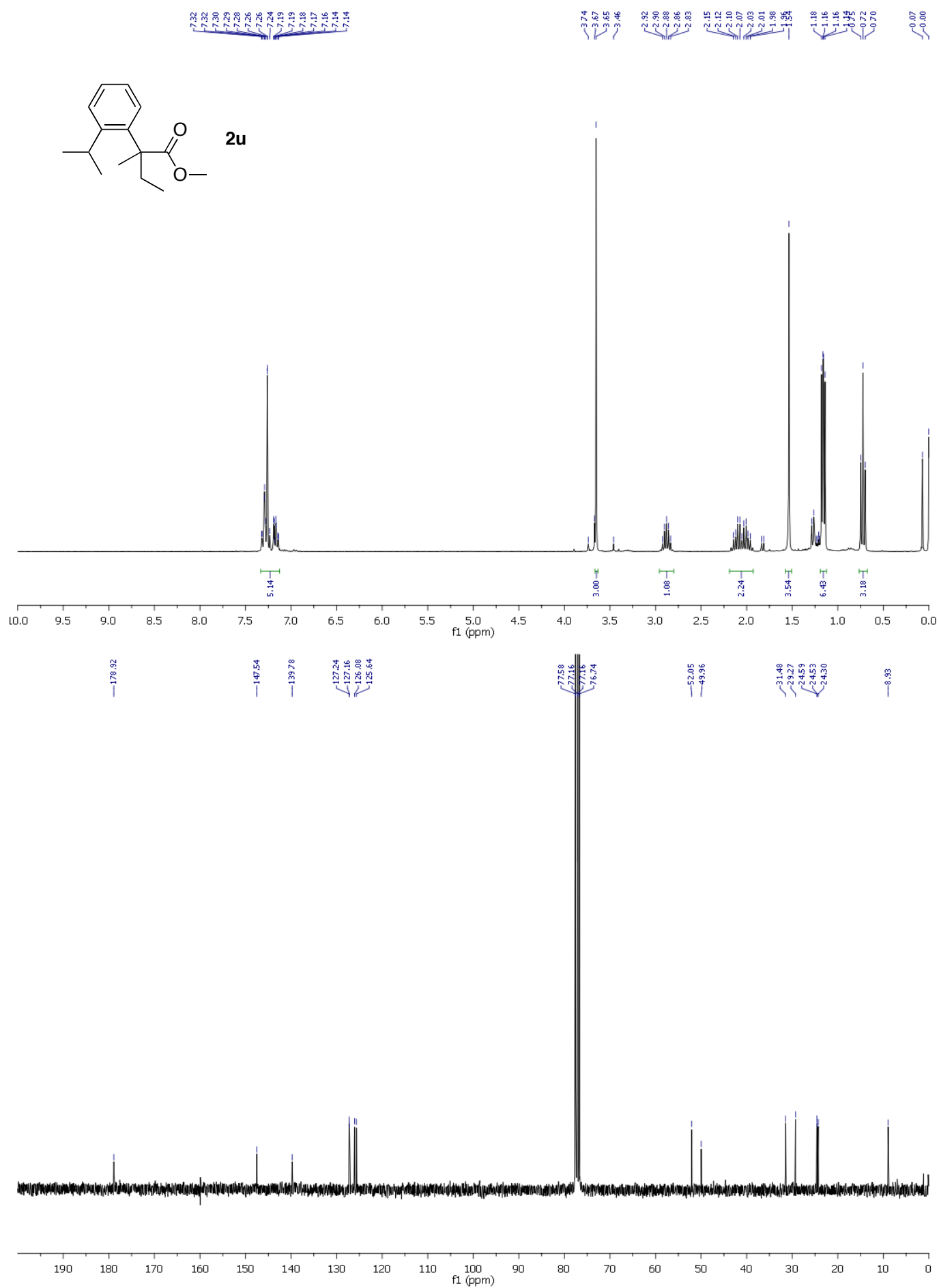
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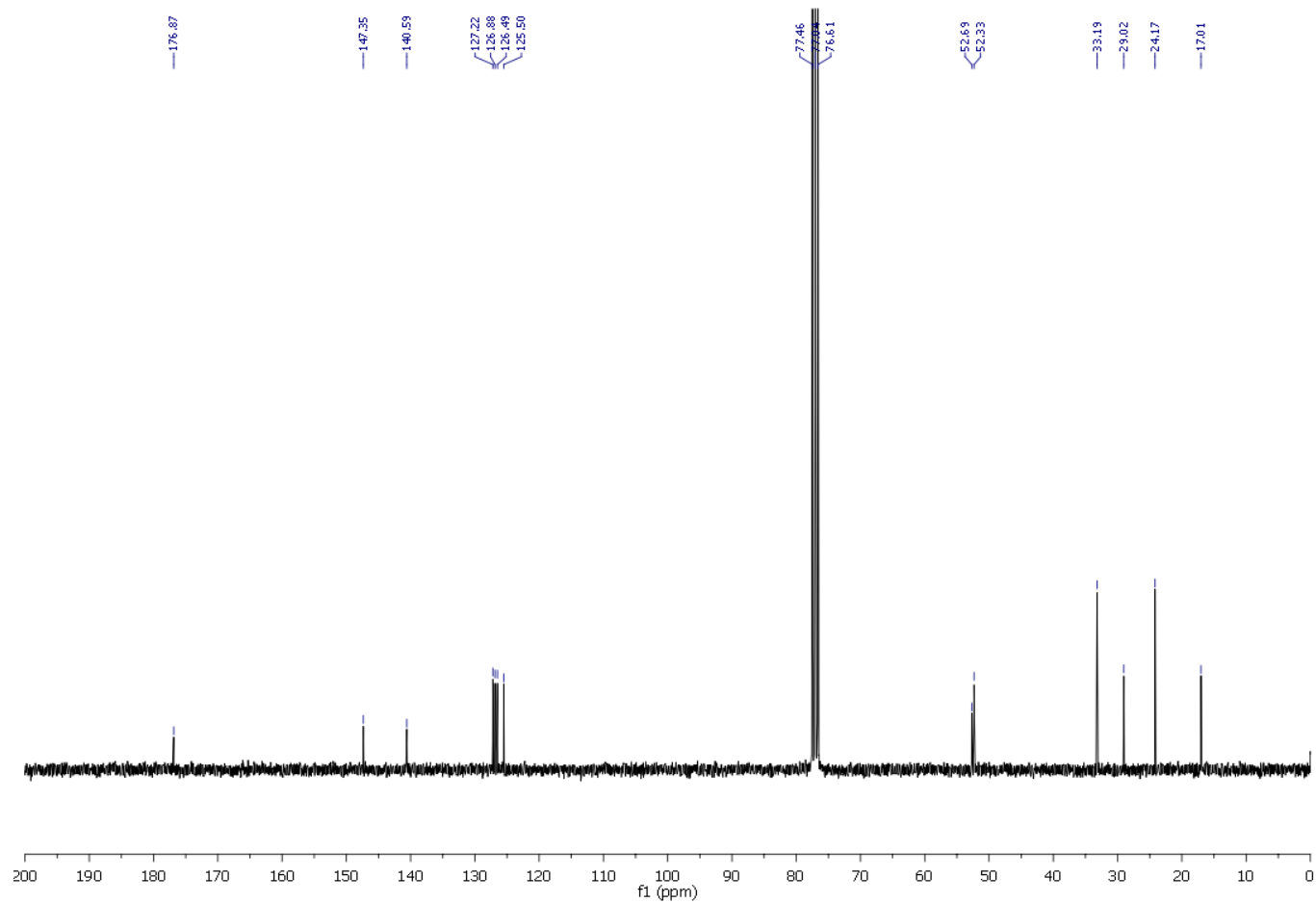
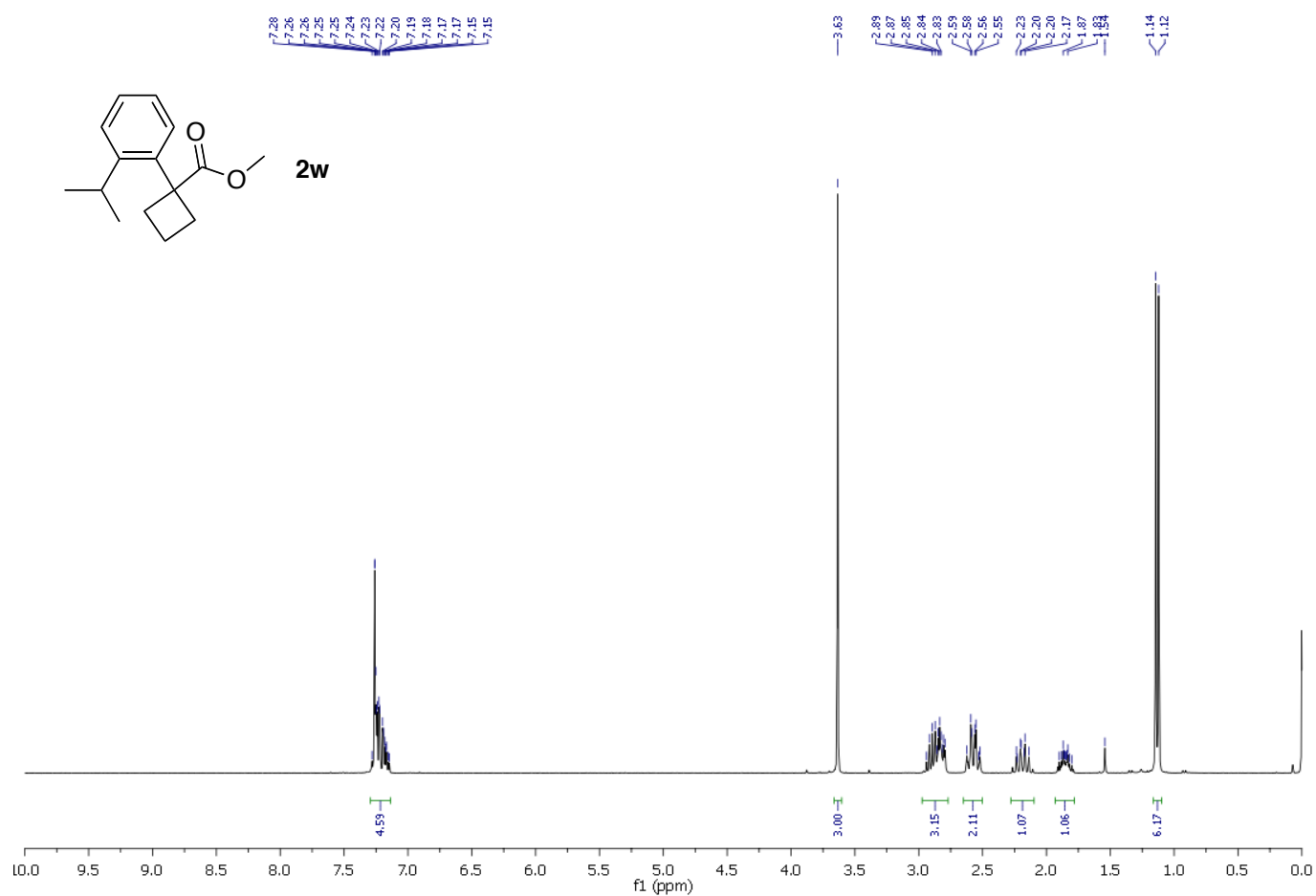
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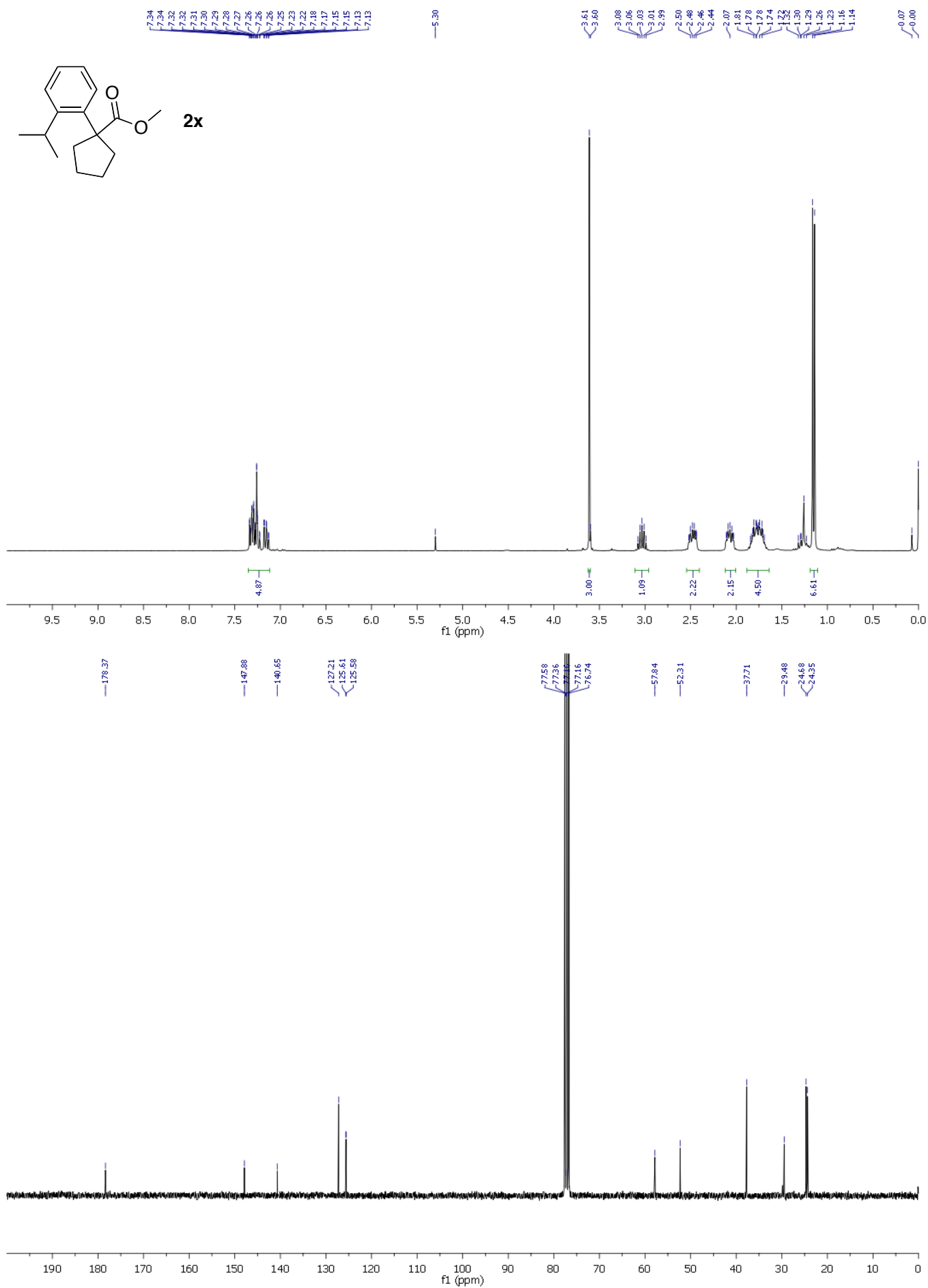
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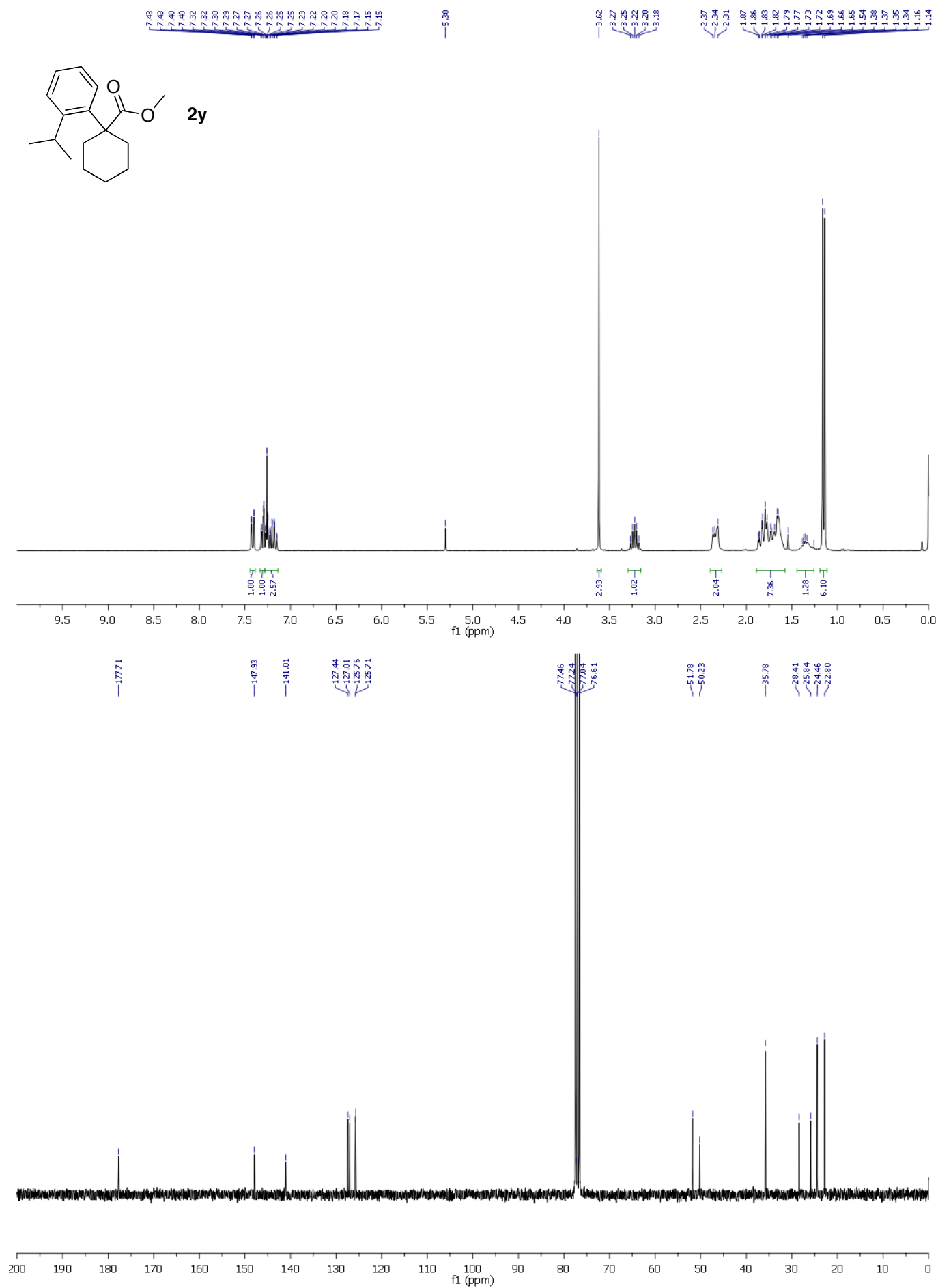
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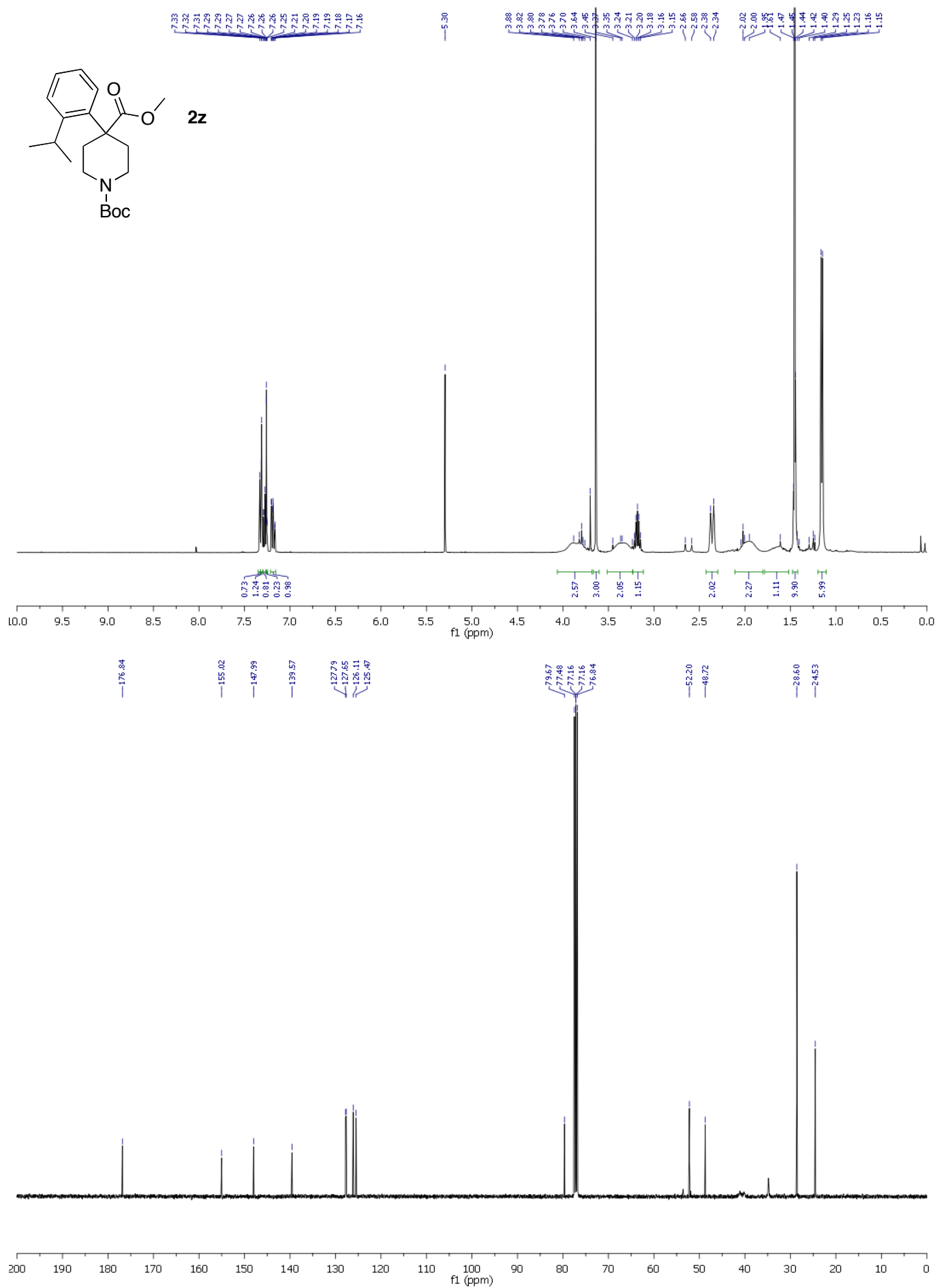


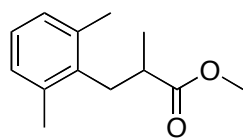




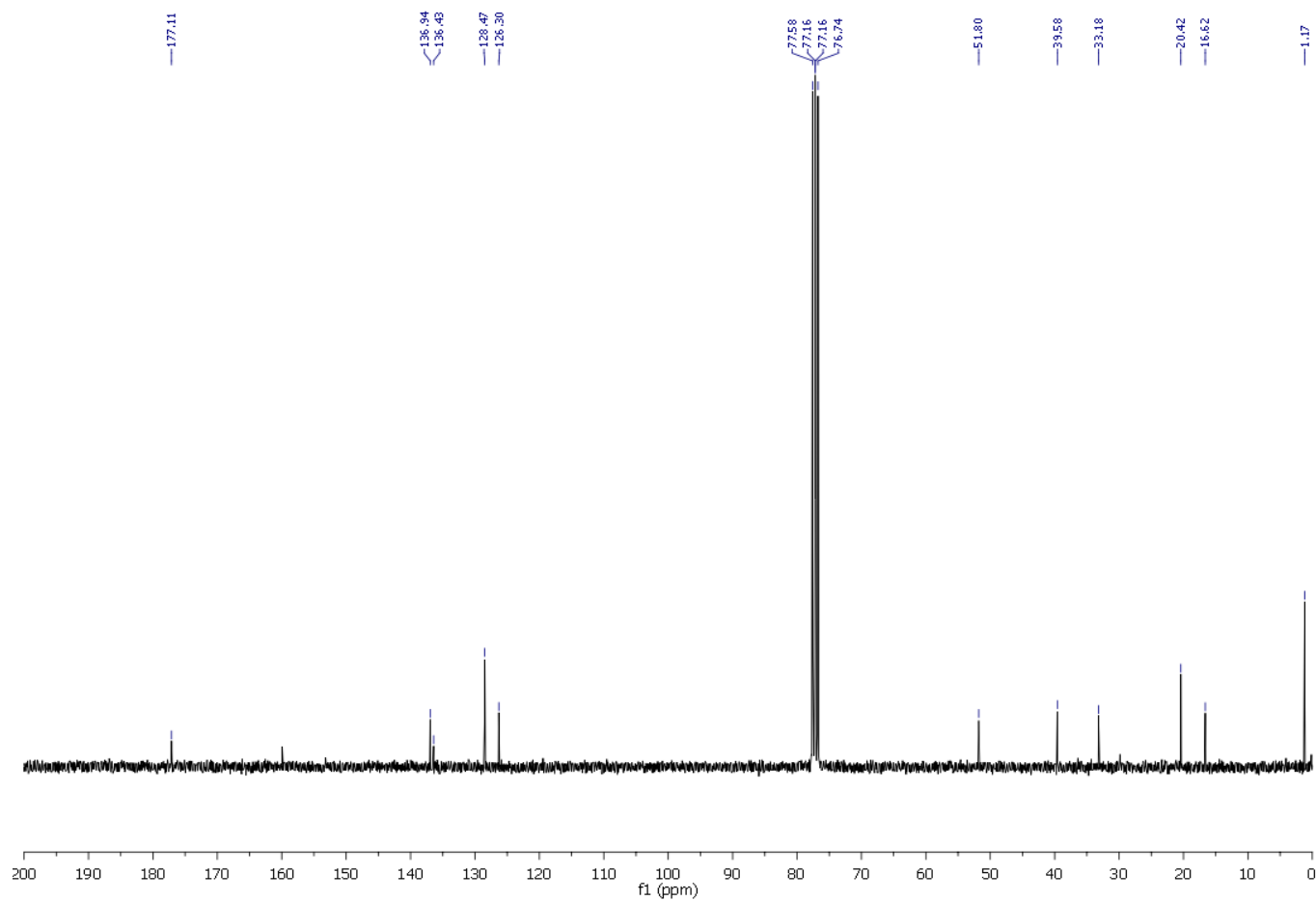
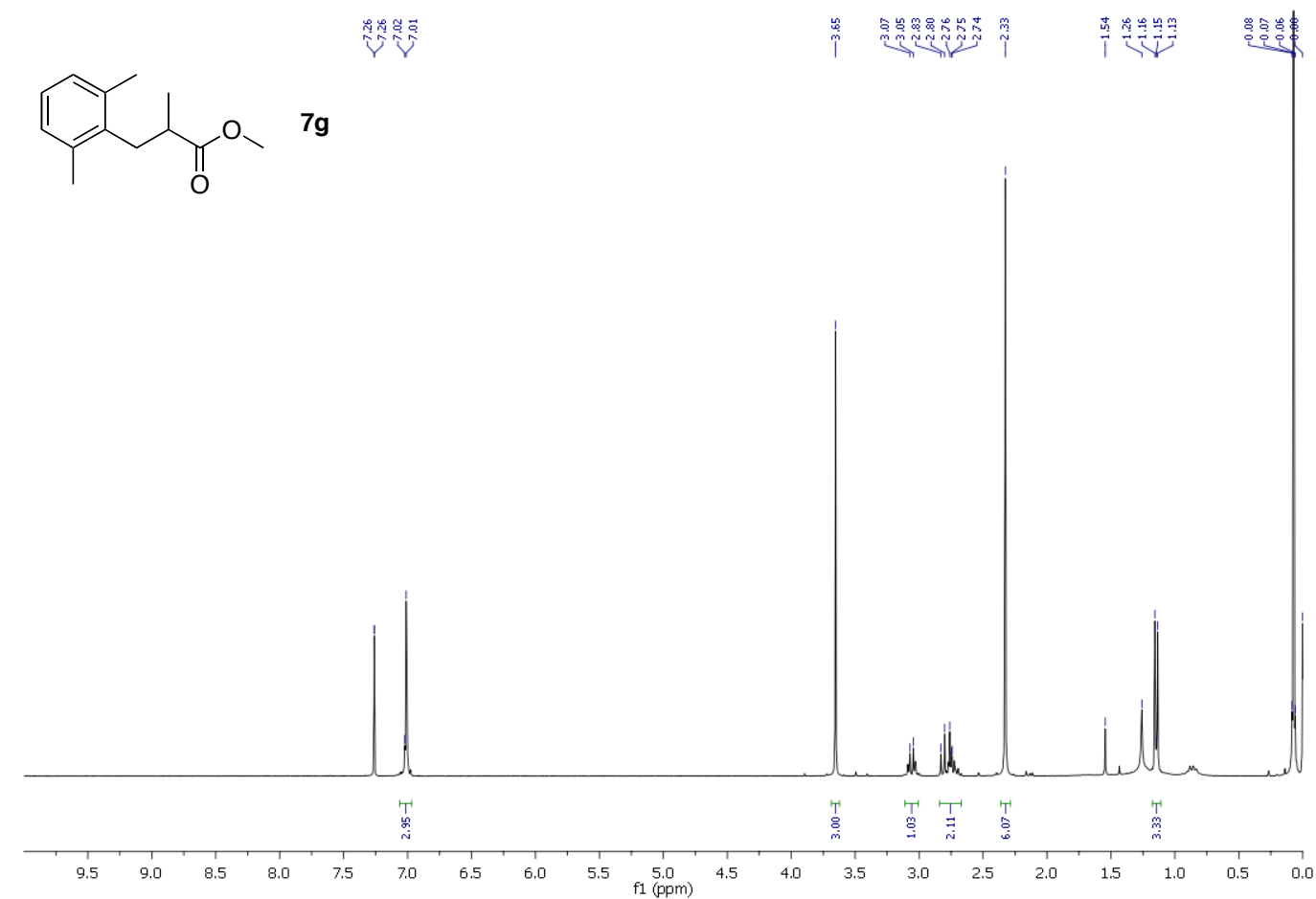


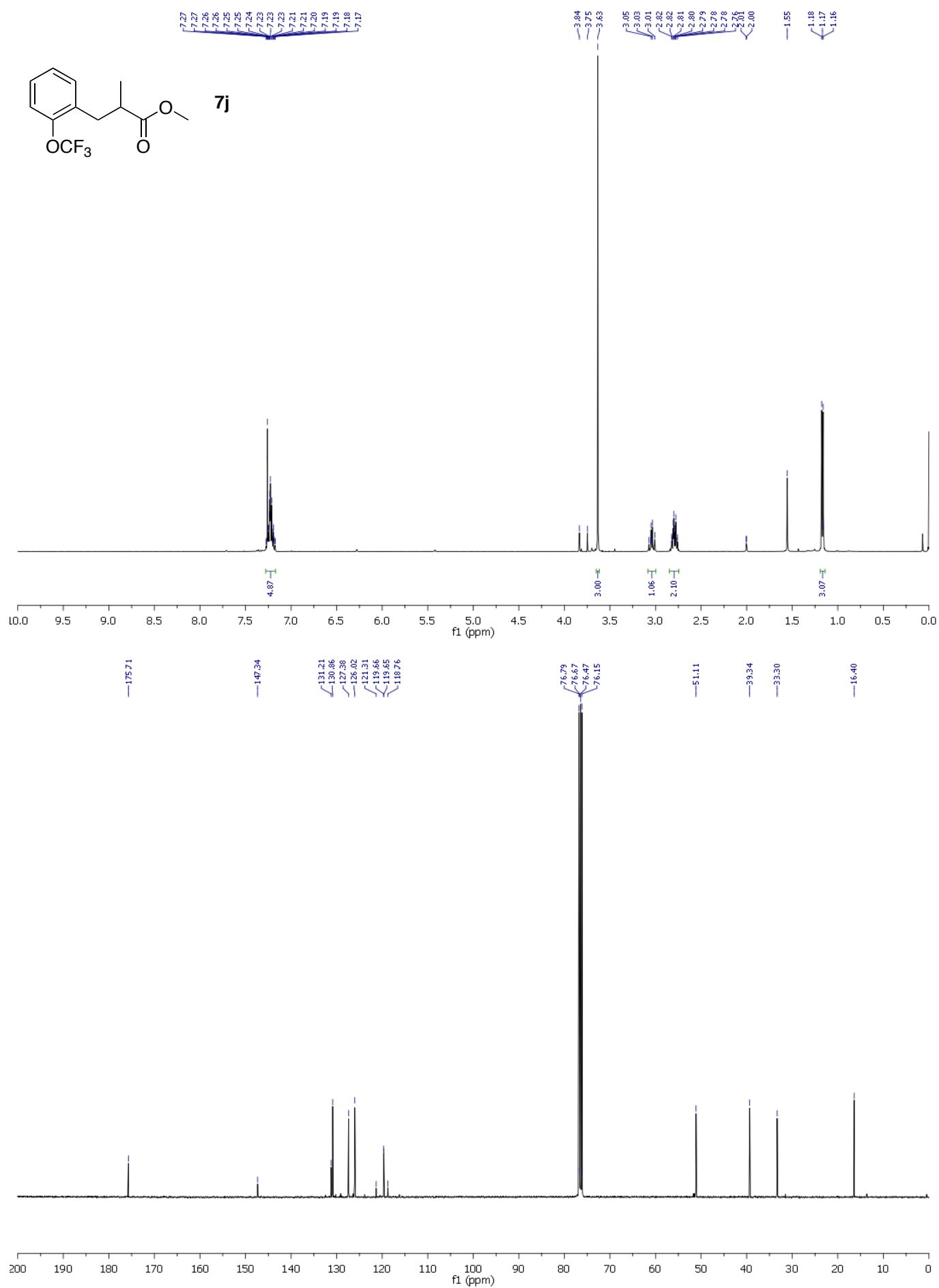


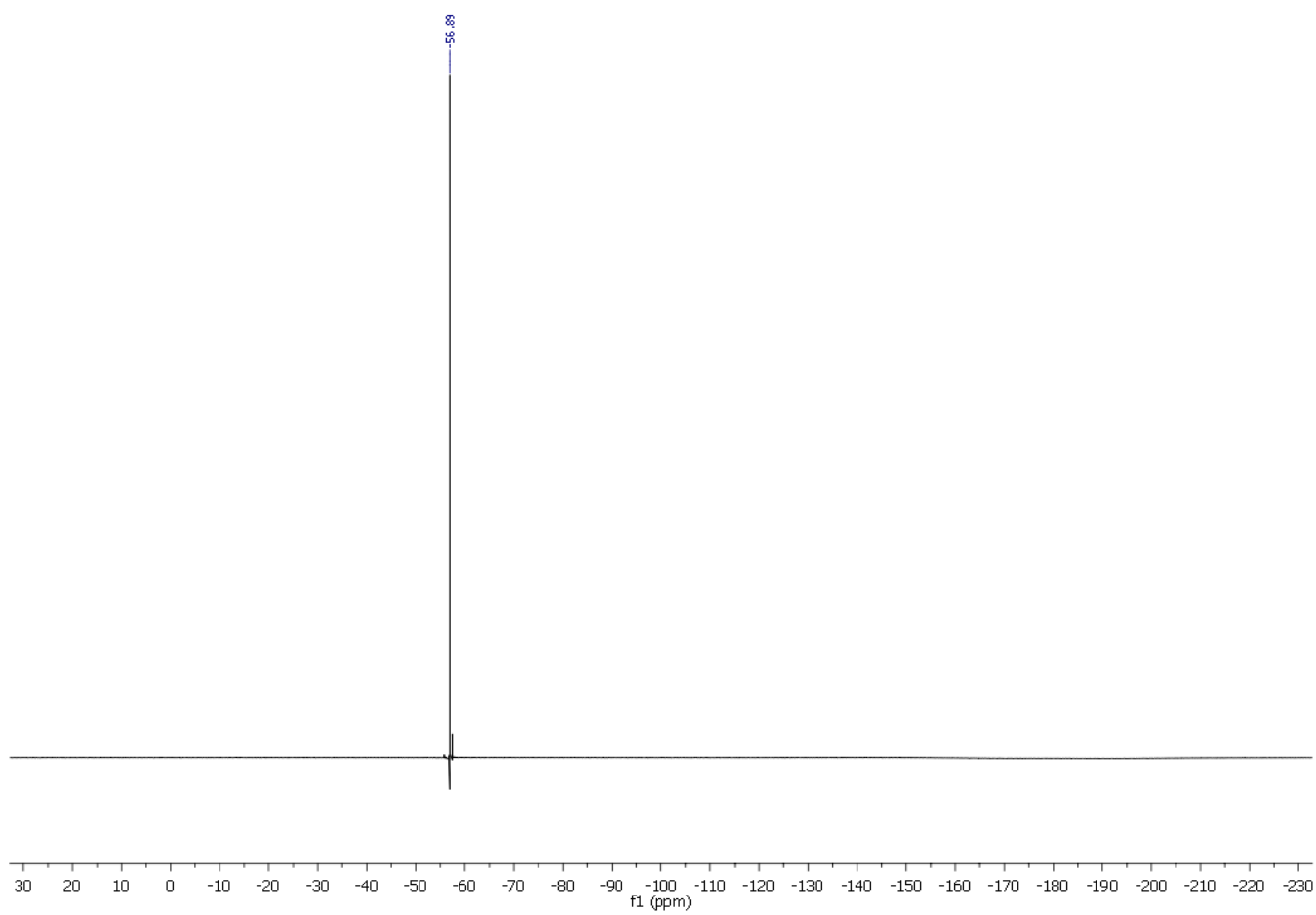


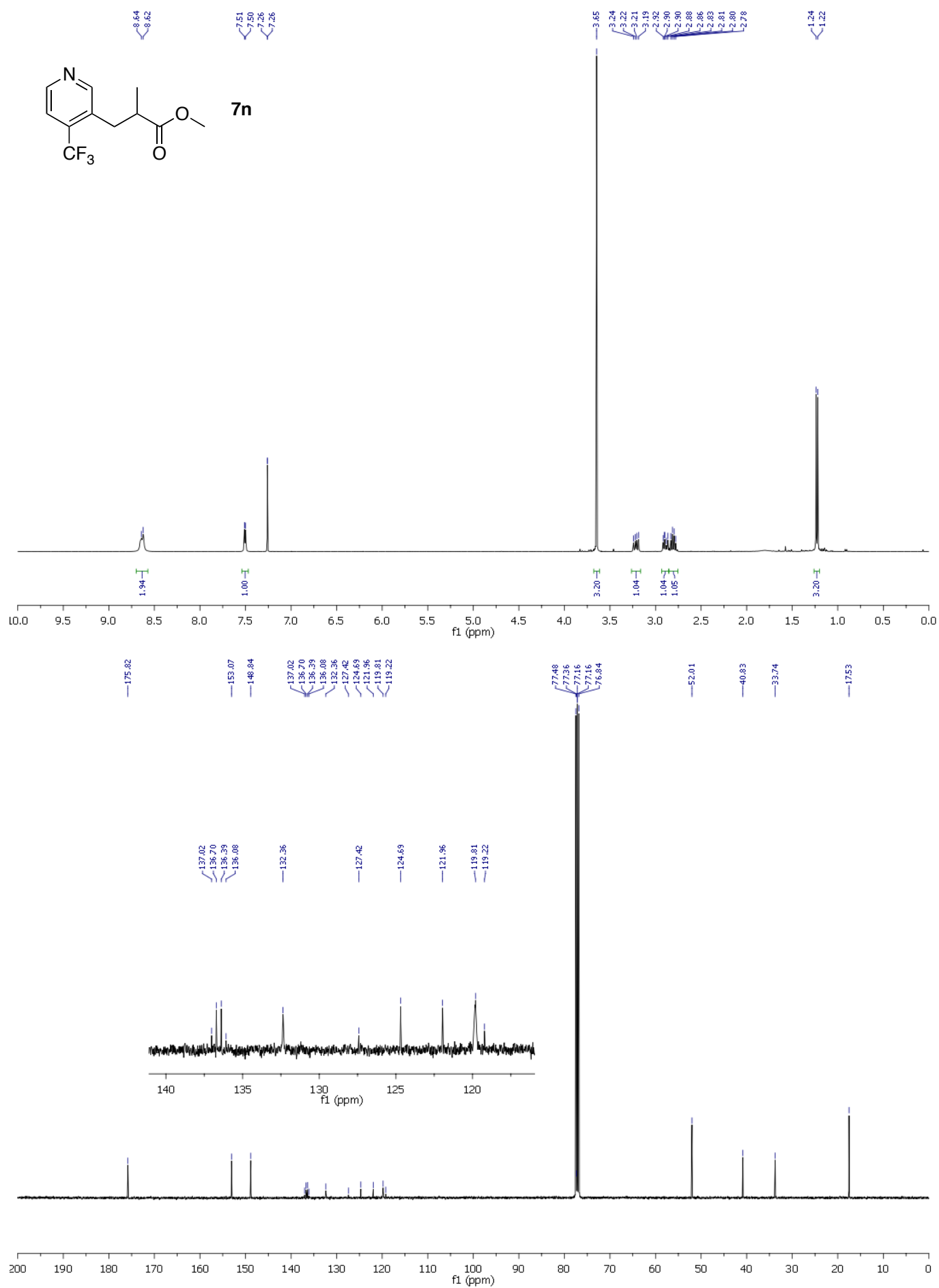


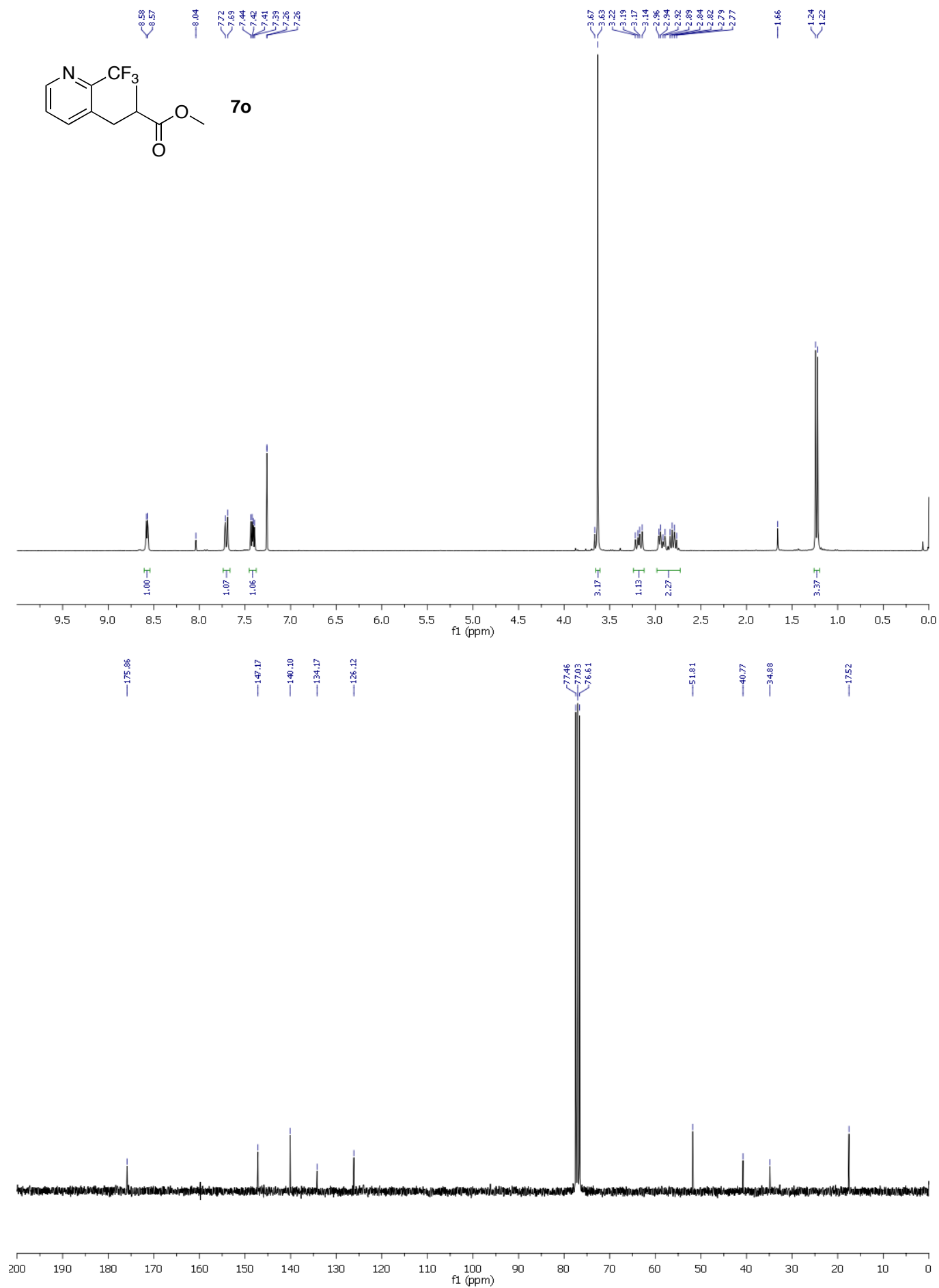
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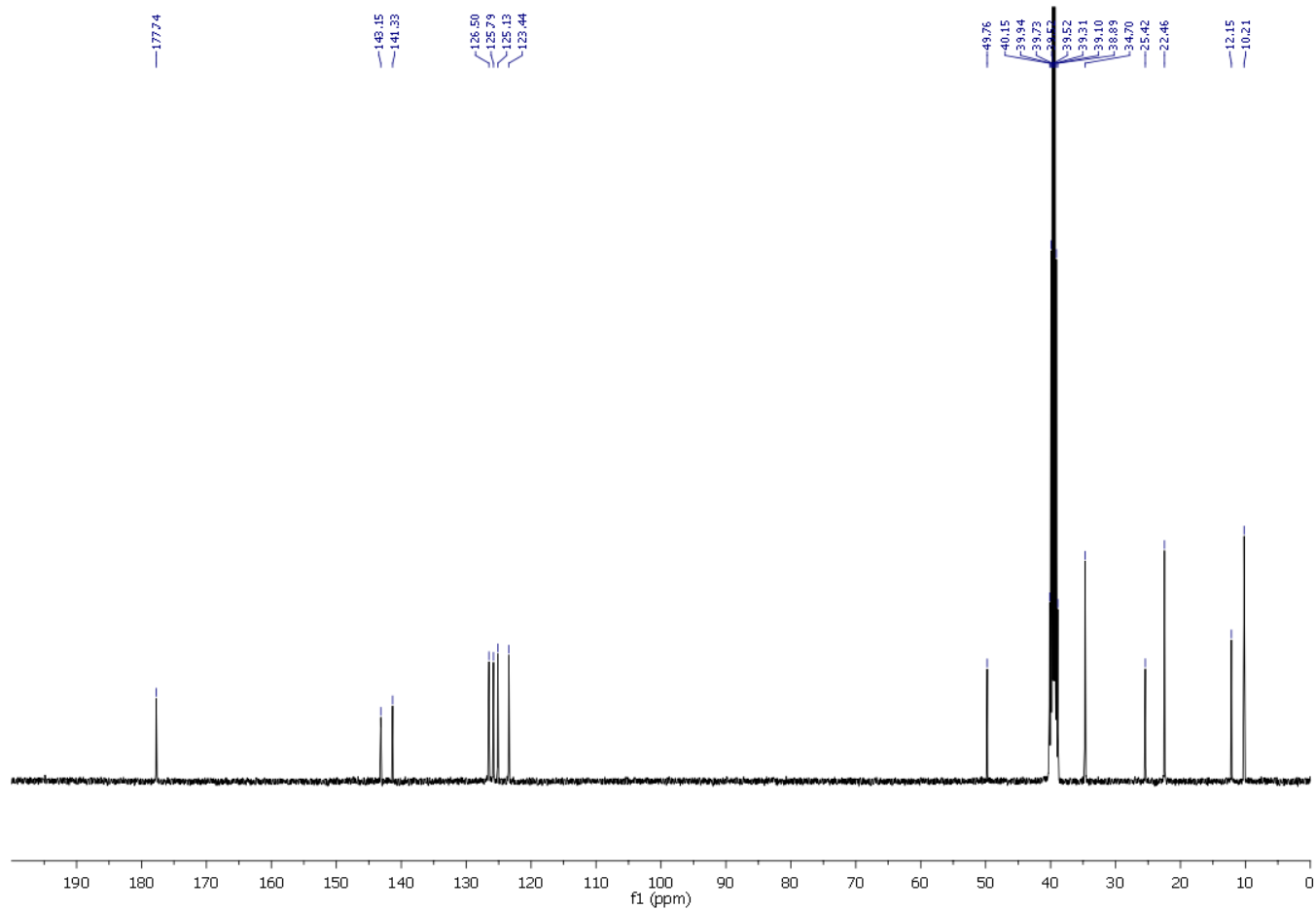
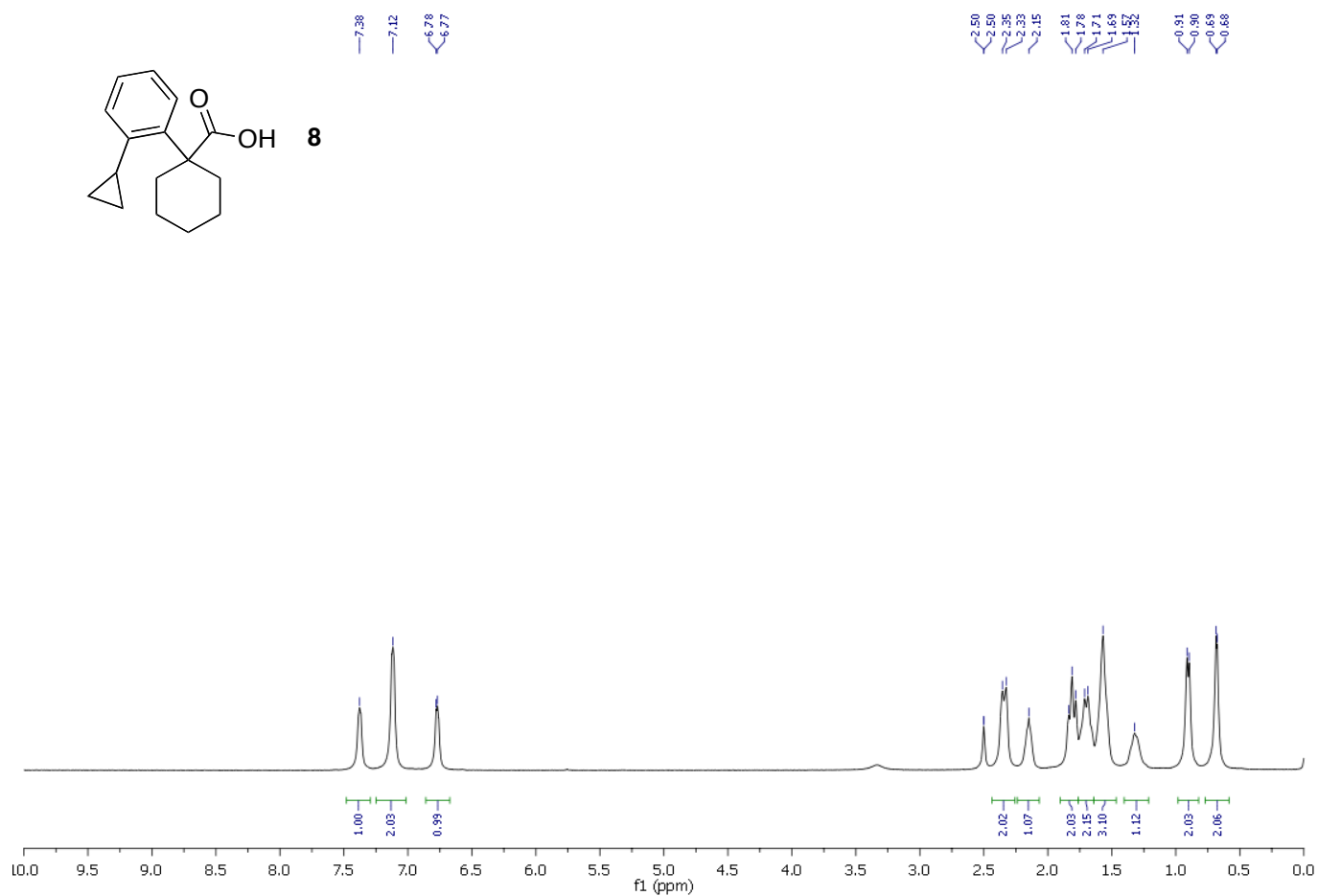
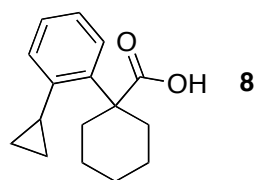


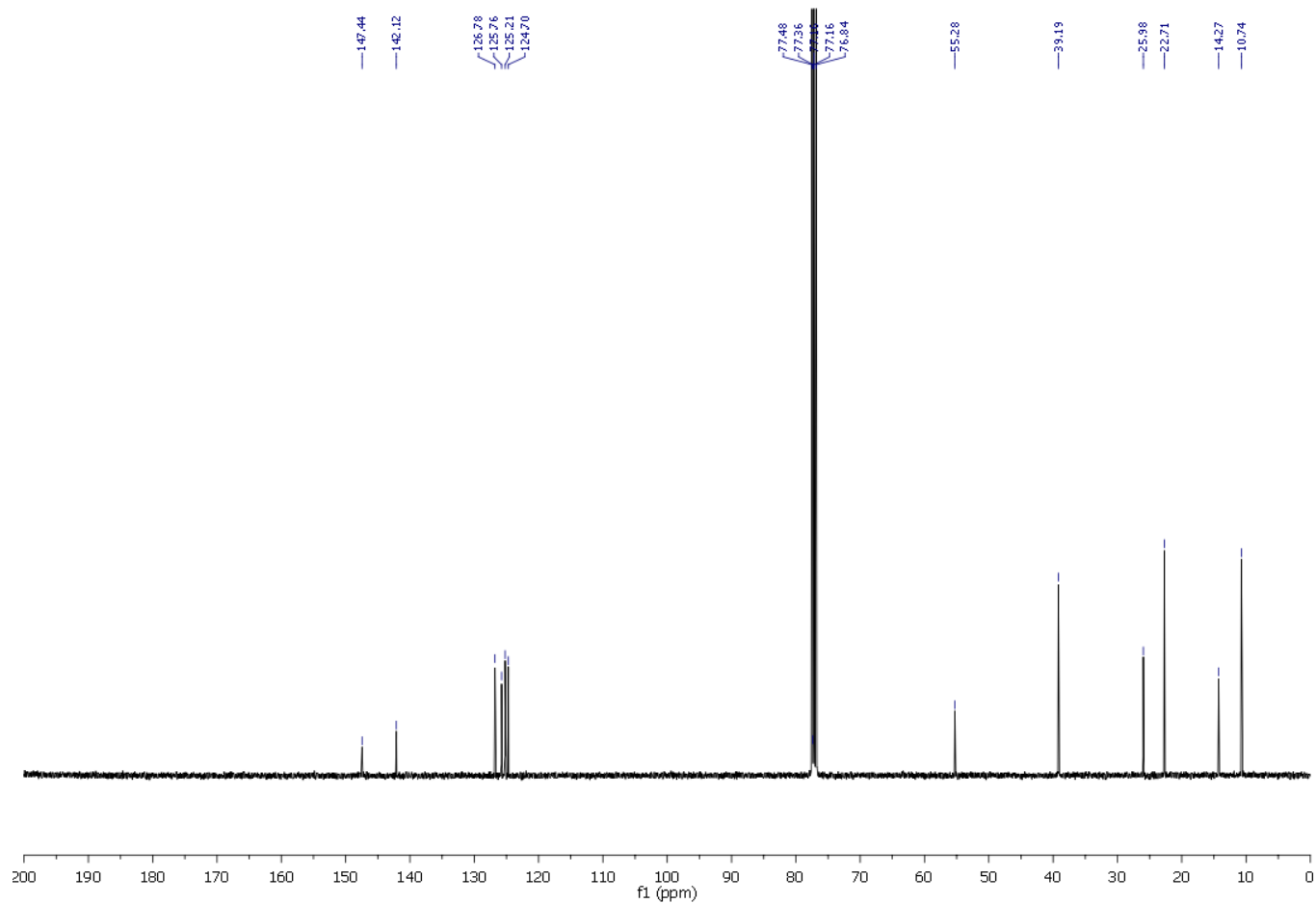
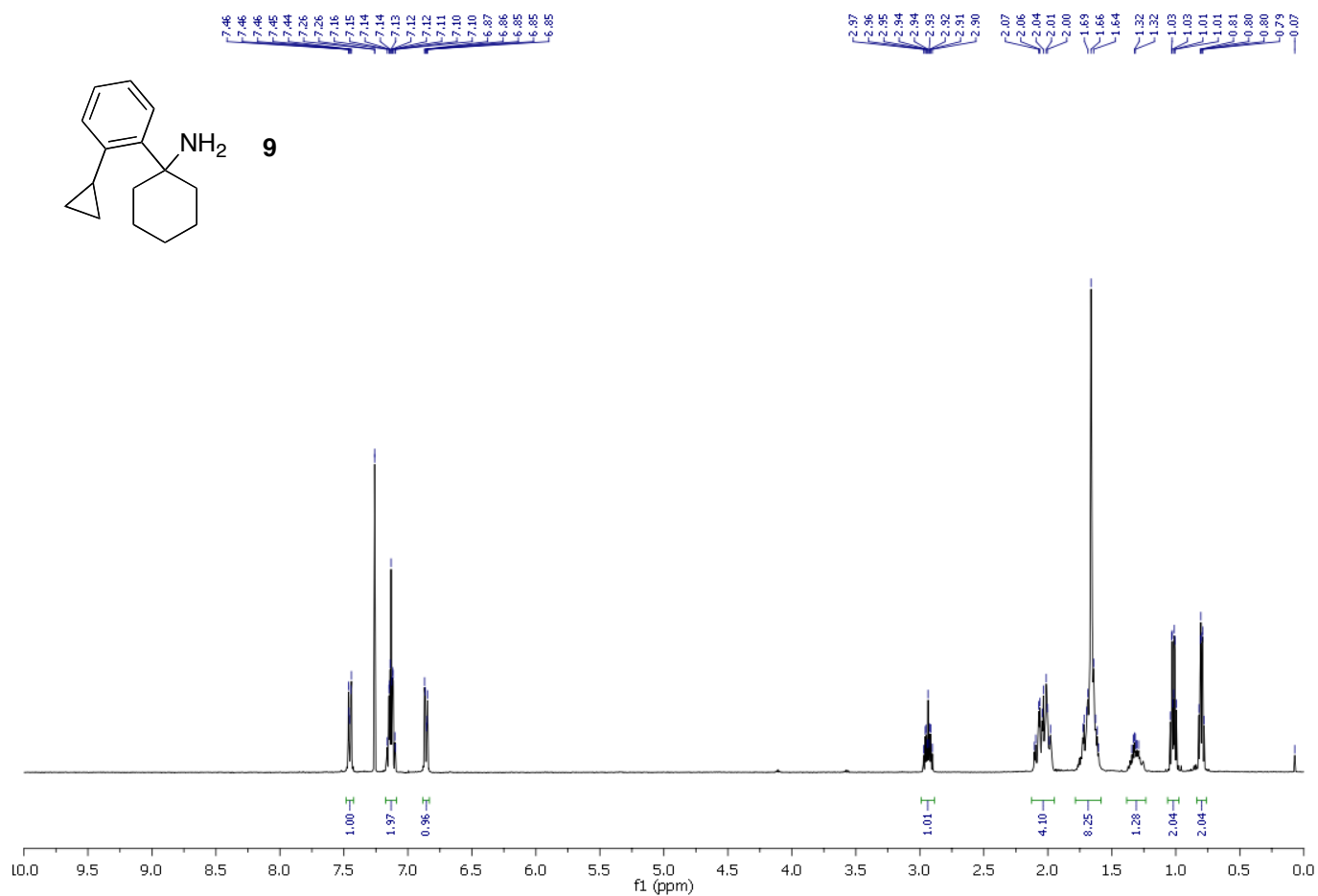
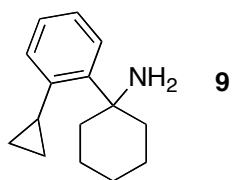


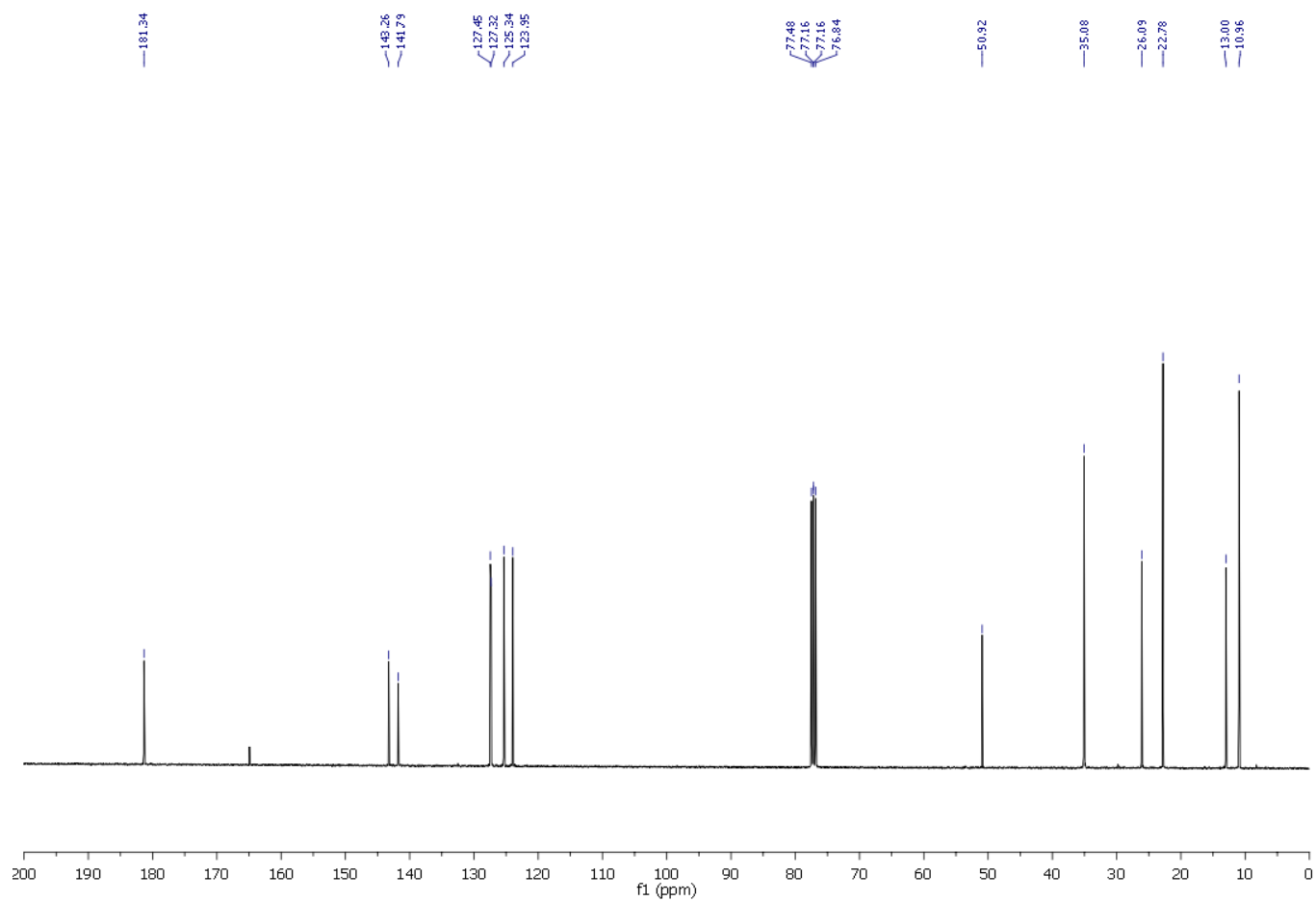
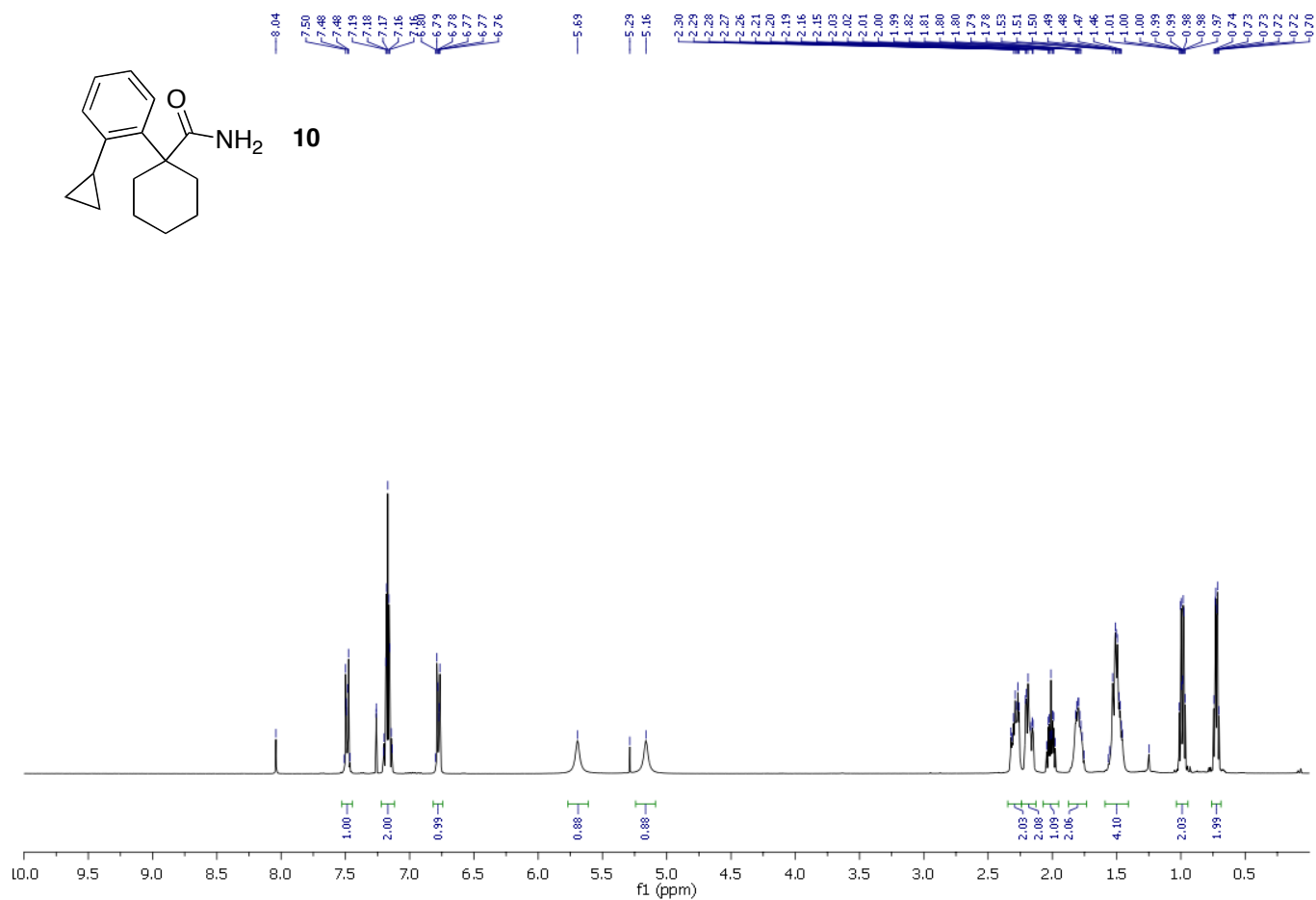
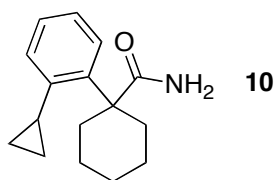


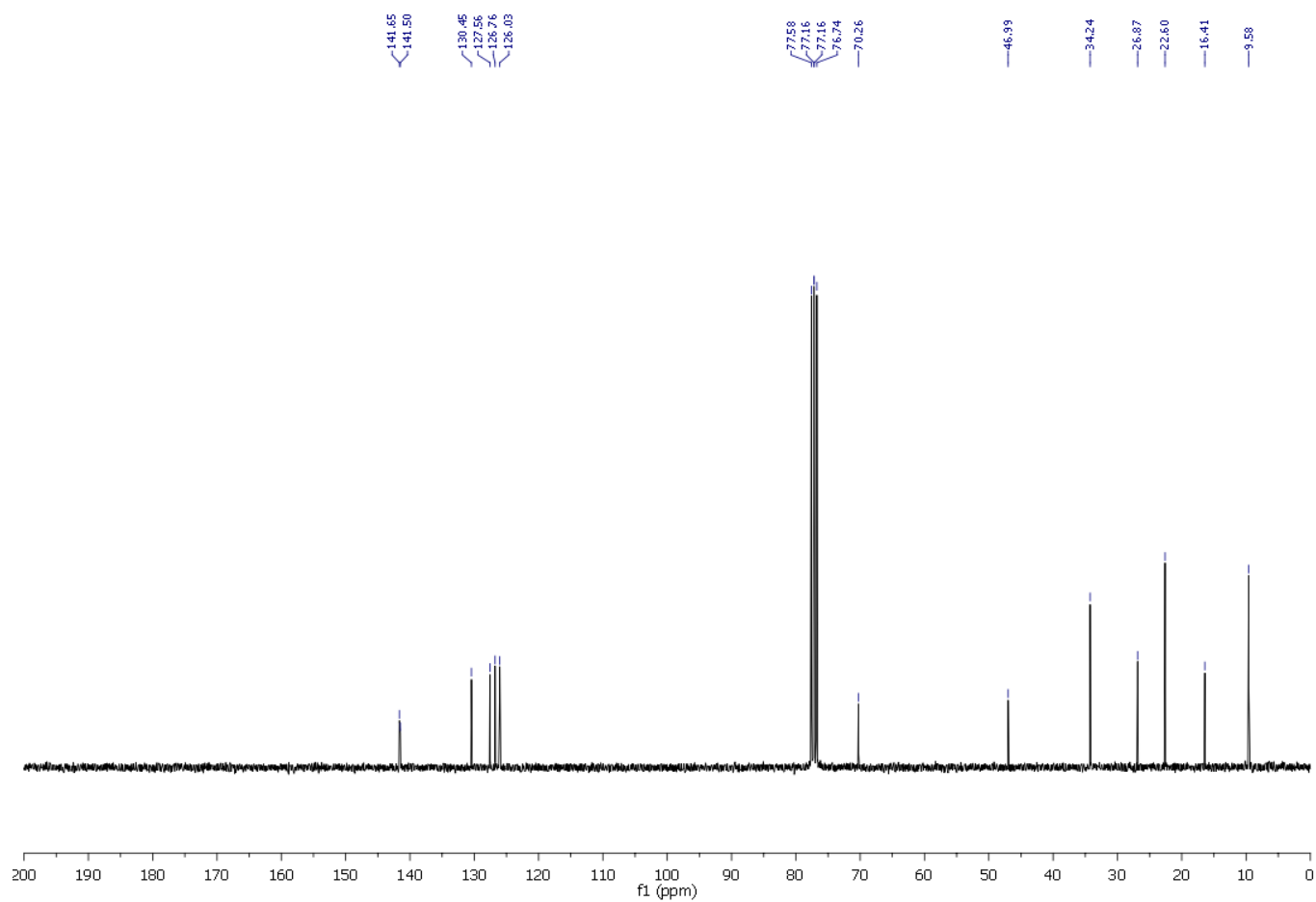
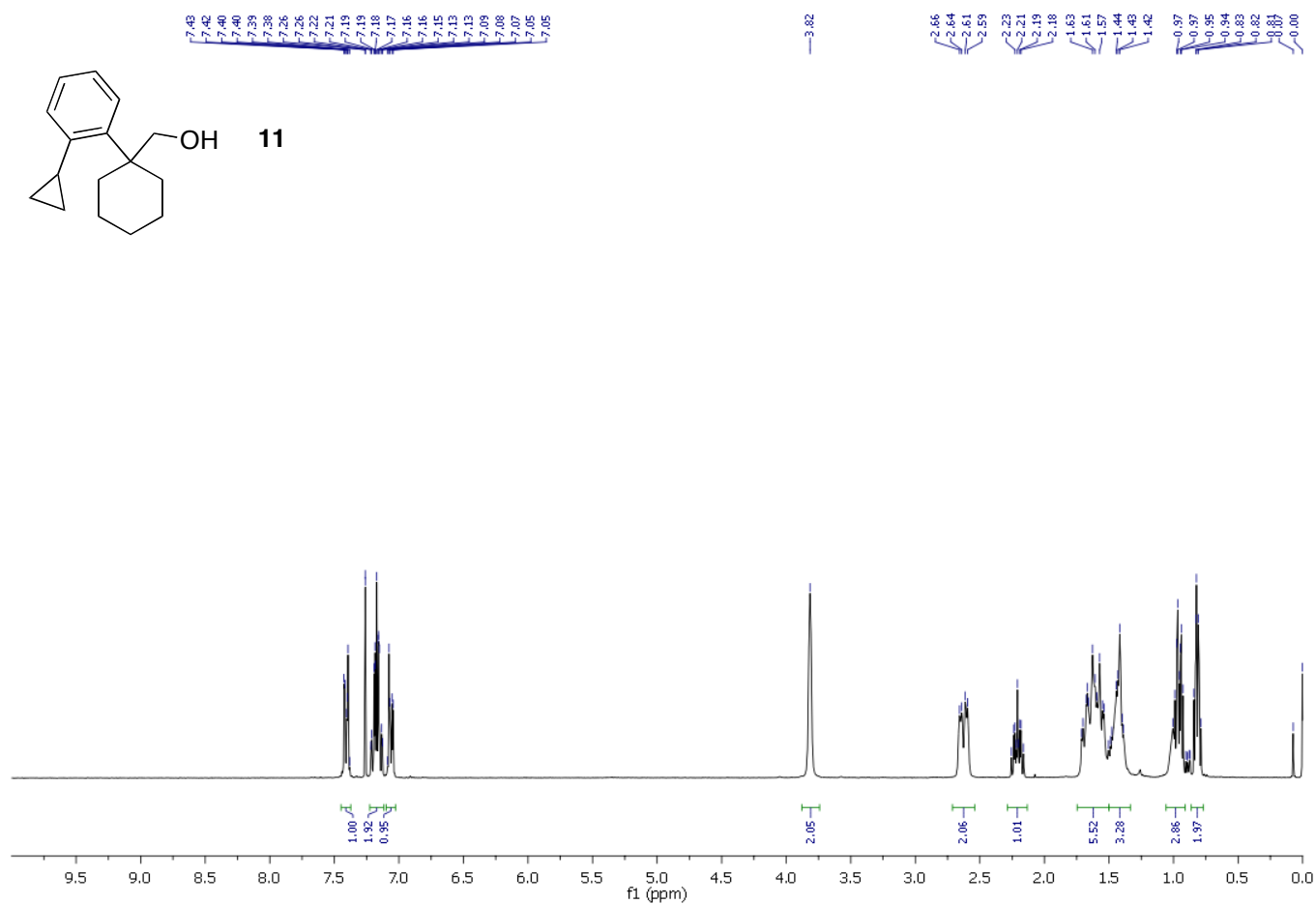
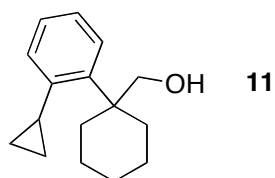


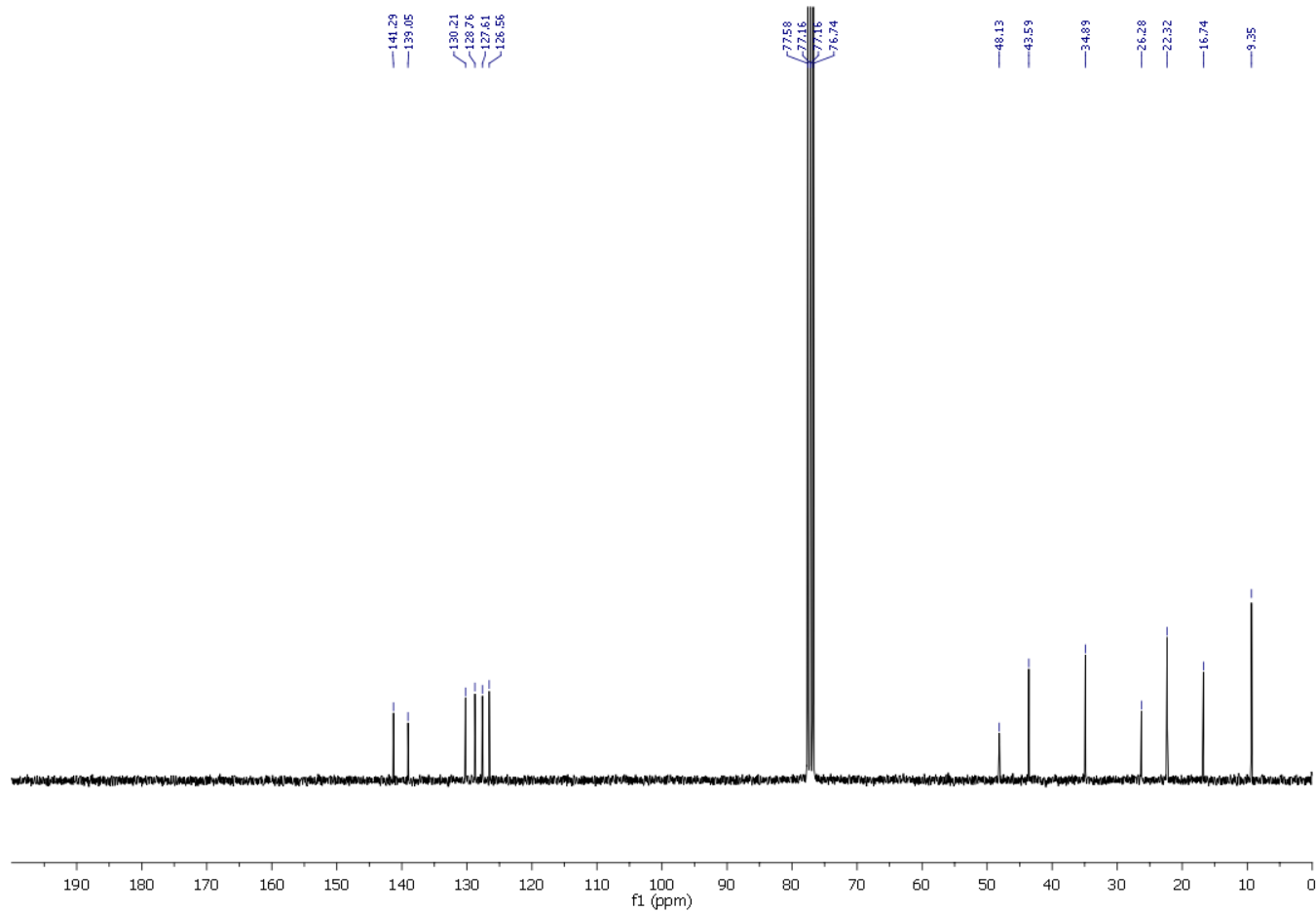
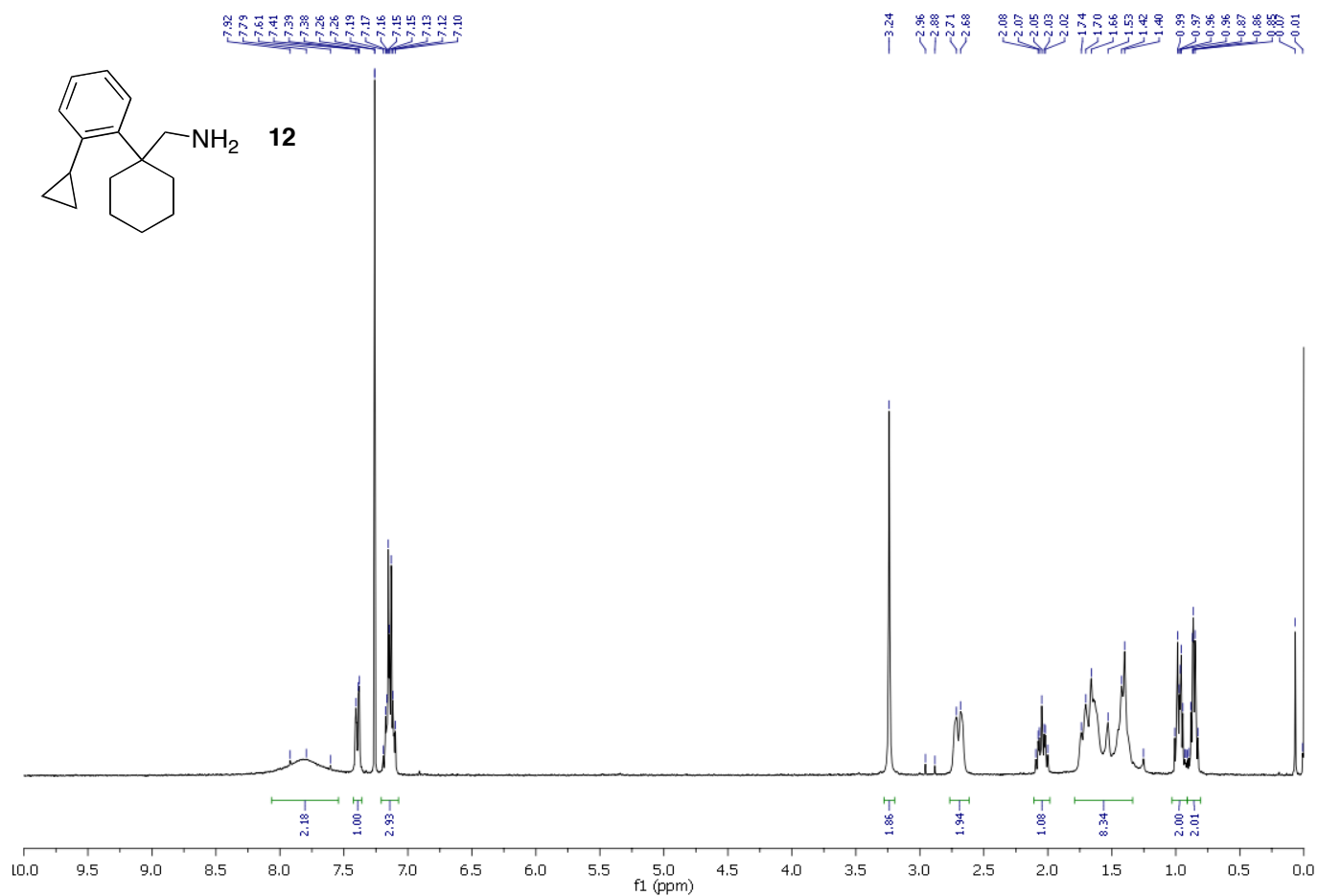








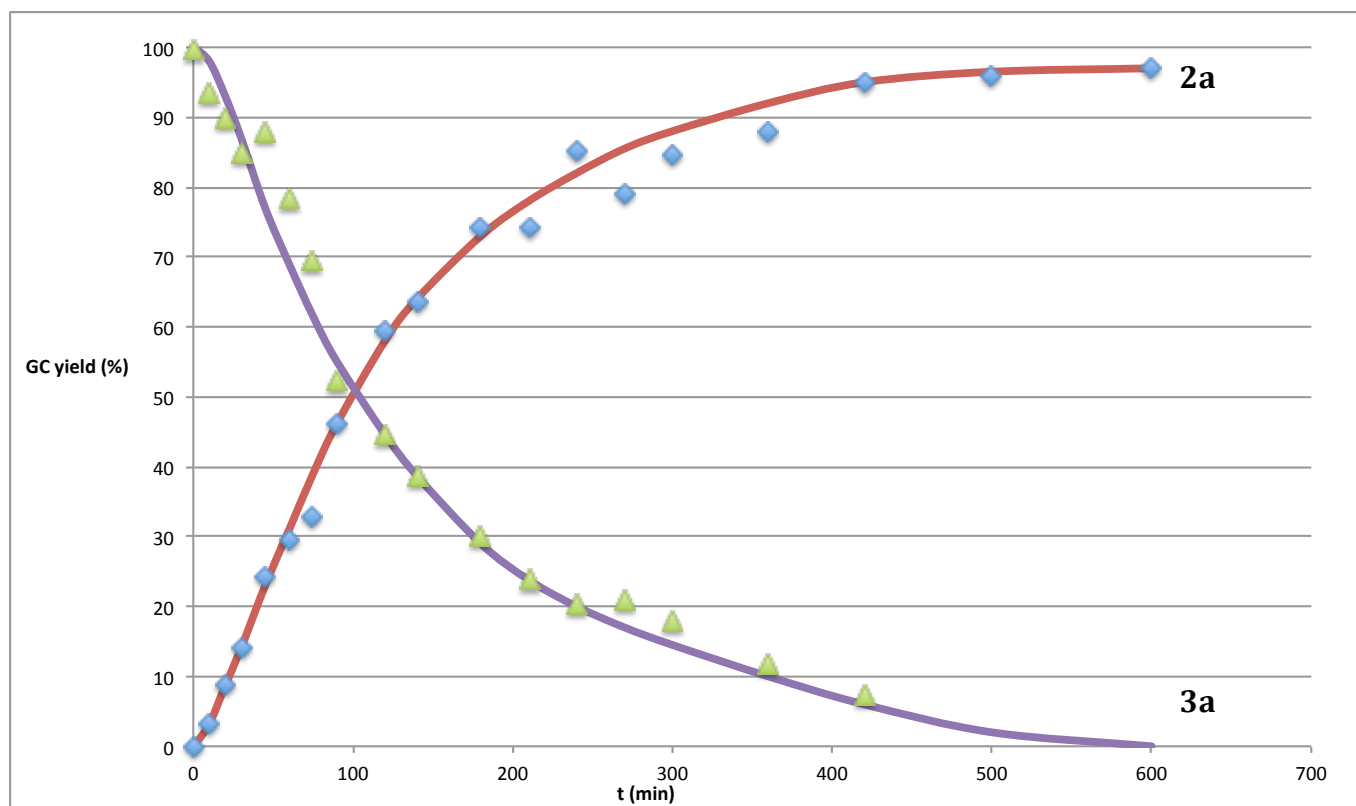




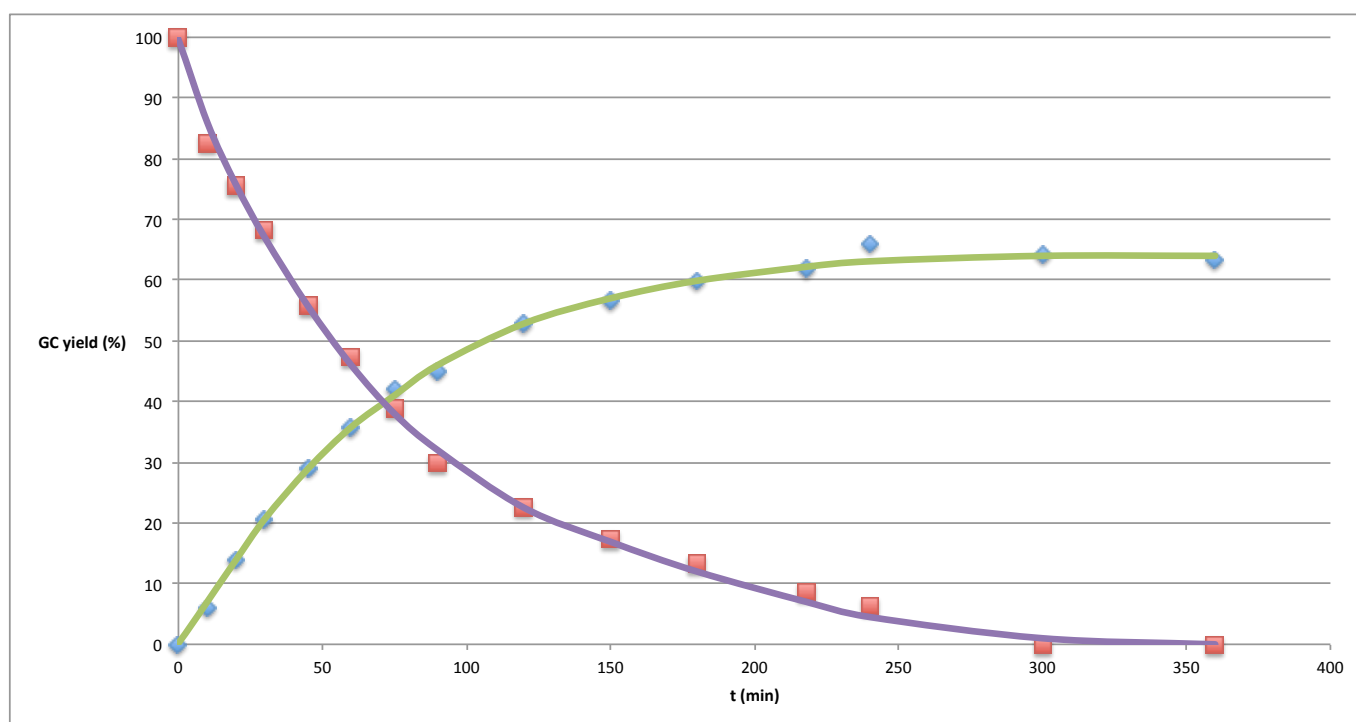
Kinetic profiles

Kinetic profiles for the formation of **2a** from **3a** and **5a** with various $P(t\text{-Bu})_3$ -based catalysts. All reactions were performed in DMF at 90 °C at the same reactant concentrations and at 2 mol% Pd. Determined by GCMS using tetradecane as the internal standard.

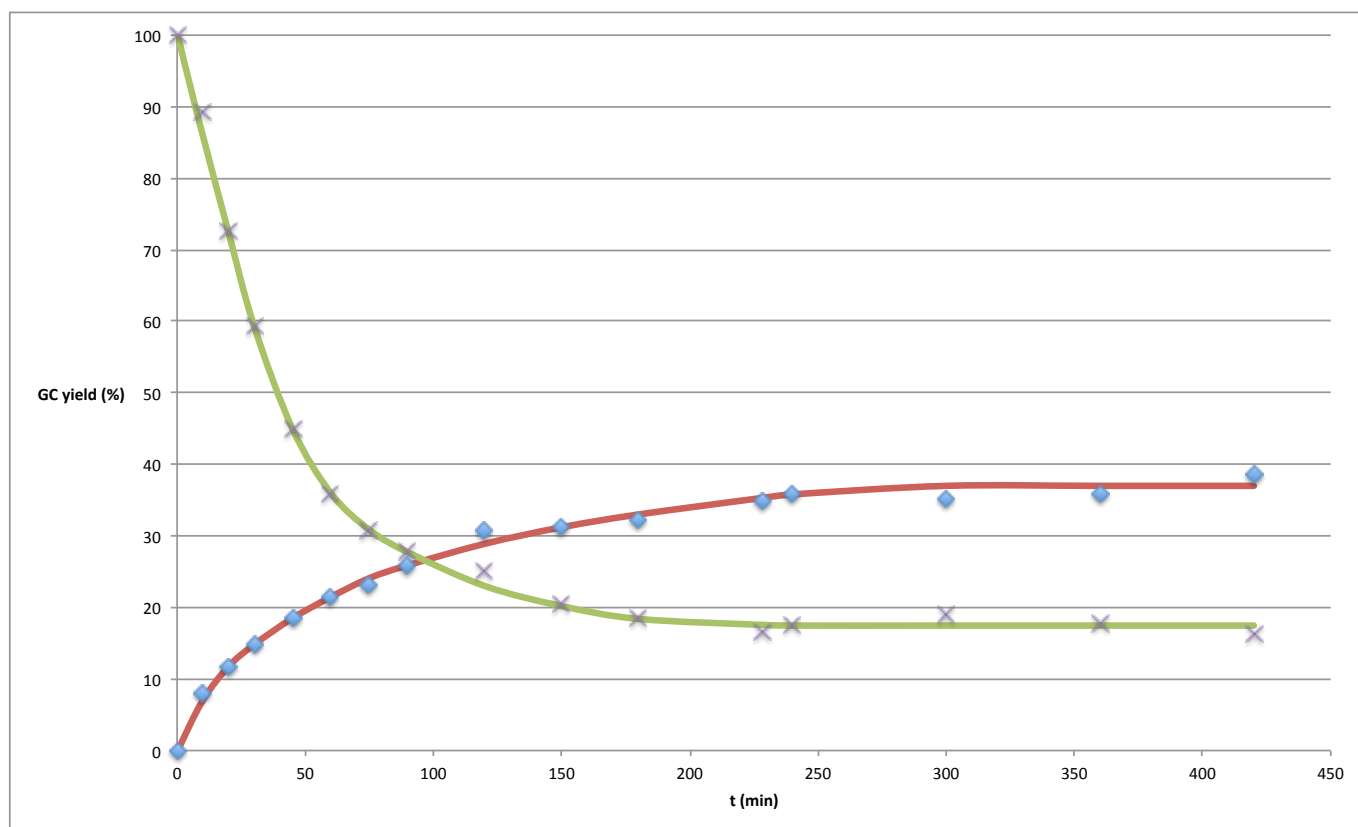
$Pd(PtBu_3)_2$



$Pd_2dba_3/2PtBu_3$



6/ NEt_3



References

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- ² Hatano, M.; Takagi, E.; Ishihara, K., *Org. Lett.* **2007**, *9*, 4527-4530.
- ³ Renaudat, A.; Jean-Gérard, L.; Jazzar, R.; Kefalidis, C. E.; Clot, E.; Baudoin, O., *Angew. Chem., Int. Ed.* **2010**, *49*, 7261-7265.