Supporting Information

For

Expedient Drug Synthesis and Diversification *via ortho*-C–H Iodination Using Recyclable PdI_2 as the Precatalyst

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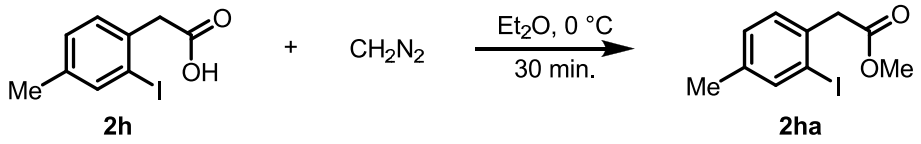
General Information:

Unless otherwise noted, all commercial materials were used as received from commercial resources without further purification. Anhydrous *N*,*N*-dimethylformamide (DMF) was obtained from Acros and used as received. ^{1}H and ^{13}C NMR spectra were recorded on Varian-Inova (400 MHz and 100 MHz, respectively) and Bruker-DRX (500 MHz and 125 MHz, respectively) instruments internally referenced to $SiMe_4$ signal or chloroform. ^{1}H and ^{13}C chemical shifts are referenced to tetramethylsilane at 0.0 ppm and residue CH_3COCH_3 at 205.0 or $CHCl_3$ at 77.0 ppm respectively unless otherwise noted. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance. High resolution mass spectra for new compounds were recorded at Mass Spectrometry Facilities, The Scripps Research Institute (TSRI).

General procedure of Pd-catalyzed iodination of phenylacetic acids 1a–1k, **1m**, **1o**, **1r–1s** and **1u–1v**.

In a 20 mL seal tube, phenylacetic acid (0.5 mmol, 1 equiv. for **1a–1k**, **1m**, **1o**, **1r–1s** and **1u–1v**), $Pd(OAc)_2$ (5 mol% for **1a** and **1c–1h**; 2 mol% for **1b**; 10 mol% for **1i–1k**, **1m**, **1o**, **1r–1s** and **1u**), $PhI(OAc)_2$ (0.75 equiv.), I_2 (0.75 equiv.) were dissolved in 3 mL anhydrous DMF under air. The tube was sealed with a Teflon lined cap, wrapped by aluminum foil to keep the system in the dark. The reaction mixture was then stirred at 60 °C (40 °C for **2v**) for 12 h. After cooled to room temperature, the mixture was concentrated under vacuum and the residue was either subjected to column chromatography using hexanes:ethyl acetate:acetic acid/2:1:0.05 to get the acids or converted to methyl esters as follows.

Conversion to esters:

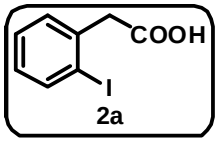


Excesses diazomethane[1] was added dropwise to the stirred crude coupling product in diethyl ether at 0 °C. After stirring for 30 minutes, the reaction mixture was warmed up to room temperature. The reaction was quenched with acetic acid and the excesses acetic acid was neutralized with aqueous sodium bicarbonate. The mixture was then extracted with diethyl ether (30 mL x 4), the combined organic layer was washed sequentially with 2*N* HCl (20 mL), water (20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4. After removing the solvent, the residue was subjected to column chromatography to get the methyl esters.

General procedure of Pd-catalyzed iodination of phenylacetic acids 1l, **1n, 1p-1q, 1t**

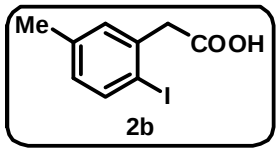
and 2a.

In a 20 mL seal tube, phenylacetic acid (0.5 mmol, 1 equiv.), $Pd(OAc)_2$ (5 mol% for **1l**, **1n** and **2a**; 15 mol% for **1p**–**1q** and **1t**), $PhI(OAc)_2$ (0.75 equiv.) and I_2 (0.75 equiv.) were dissolved in 3 mL anhydrous DMF under air. The tube was sealed with a Teflon lined cap, wrapped by aluminum foil to keep the system in the dark. The reaction mixture was then stirred at 60 °C for 12 h. After the reaction mixture cooled to room temperature, another batch of $PhI(OAc)_2$ (0.75 equiv.) and I_2 (0.75 equiv.) was added under atmospheric air. The tube was sealed with a cap, wrapped by aluminum foil to keep the system in the dark. And then the reaction mixture was stirred at 60 °C for another 12 hours. To the reaction mixture was added the third batch of $PhI(OAc)_2$ (0.5 equiv.) and I_2 (0.5 equiv.) under air after cooling to room temperature, and stirred for another 12 hours at 60 °C in the dark. After cooling to room temperature, the mixture was concentrated under vacuum and the residue was either subjected to column chromatography with hexanes:ethyl acetate:acetic acid (2:1:0.05)) as eluent, affording iodinated acids, or converted to the corresponding methyl esters using the method showed above.



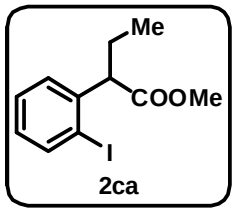
2a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.33–7.24 (m, 2H), 6.97 (t, *J* = 8.0 Hz, 1H), 3.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 139.5, 136.9, 130.7, 129.1, 128.4, 101.0, 46.0; HRMS (ESI–TOF) Calcd. for $C_8H_8IO_2$ $[M+H]^+$: 262.9564; found: 262.9561.



2b

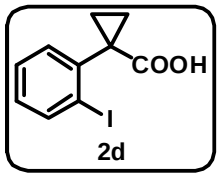
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 1H), 7.12 (s, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.81 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 139.2, 138.5, 136.6, 131.6, 130.2, 96.9, 45.8, 20.9; HRMS (ESI–TOF) Calcd. for $C_9H_{10}IO_2$ $[M+H]^+$: 276.9720; found: 276.9716.



2ca

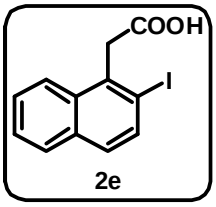
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.34–7.26 (m, 2H), 6.56–6.91 (m, 1H), 3.97 (t, *J* = 8.0 Hz, 1H), 2.10–1.99 (m,

1H), 1.83–1.73 (m, 1H), 0.93 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 142.0, 139.7, 128.8, 128.6, 127.8, 101.8 56.4, 52.0, 26.9, 12.0; HRMS (ESI–TOF) Calcd. for $C_{11}H_{14}IO_2$ $[M+H]^+$: 305.0033; found: 305.0018.



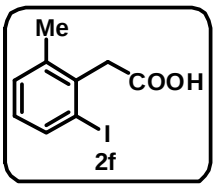
2d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 1H), 7.31–7.25 (m, 2H), 6.97 (t, J = 8.0 Hz, 1H), 1.86 (br, 2H), 1.27 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 141.6, 139.4, 131.9, 129.1, 128.0, 103.4, 33.5, 20.2; HRMS (ESI–TOF) Calcd. for $C_{10}H_{10}IO_2$ $[M+H]^+$: 288.9720; found: 288.9719.



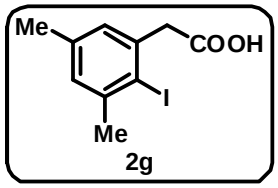
2e

^{1}H NMR (400 MHz, d_6-acetone) δ 8.11 (d, J = 8.0 Hz, 1H), 7.96–7.93 (m, 2H), 7.63–7.55 (m, 3H), 4.42 (s, 2H); ^{13}C NMR (100 MHz, d_6-acetone) δ 170.7, 136.1, 135.2, 133.5, 133.2, 129.4, 128.8, 127.4, 126.5, 124.9, 101.0, 43.2; HRMS (ESI–TOF) Calcd. for $C_{12}H_{10}IO_2$ $[M+H]^+$: 312.9720; found: 312.9705.



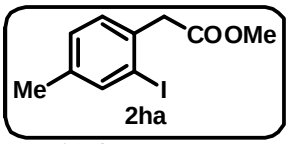
2f

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.88 (t, J = 8.0 Hz, 1H), 3.98 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 138.6, 137.5, 135.4, 130.4, 129.2, 102.8, 43.6, 21.5; HRMS (ESI–TOF) Calcd. for $C_9H_{10}IO_2$ $[M+H]^+$: 276.9720; found: 276.9712.



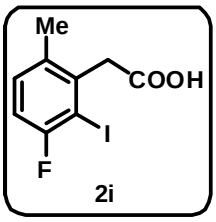
2g

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.92 (s, 1H), 3.88 (s, 2H), 2.45 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 142.4, 137.8, 137.4, 129.8, 128.9, 104.2, 47.1, 29.6, 20.6; HRMS (ESI–TOF) Calcd. for $C_{10}H_{12}IO_2$ $[M+H]^+$: 290.9877, found: 290.9872.



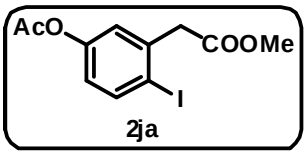
2ha

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.17-7.11 (m, 2H), 3.77 (s, 2H), 3.72 (s, 3H), 2.29(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 139.9, 138.9, 134.6, 130.2, 129.3, 100.8, 52.2, 45.6, 20.4; HRMS (ESI–TOF) Calcd. for $C_{10}H_{12}IO_2$ $[M]^+$: 290.9877; found: 290.9876.



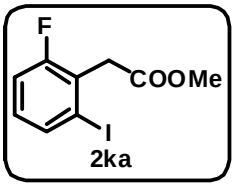
2i

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, J_1 = 8.0 Hz, J_2 = 6.0 Hz, 1H), 6.91 (t, J = 8.0 Hz, 1H), 4.02 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 160.2 (d, $J_{C–F}$ = 241.0 Hz), 137.2, 133.8 (d, J_{C-F} = 3.0 Hz), 131.1 (d, $J_{C–F}$ = 7.0 Hz), 114.2 (d, $J_{C–F}$ = 25.0 Hz), 90.3 (d, $J_{C–F}$ = 25.0 Hz); 43.2 (d, $J_{C–F}$ = 3.0 Hz); 20.7; HRMS (ESI-TOF) Calcd. for $C_9H_9FIO_2$ $[M+H]^+$: 294.9626; found: 294.9629.



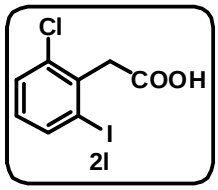
2ja

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 4.0 Hz, 1H), 6.78 (dd, J = 4.0 Hz, J = 8.0 Hz, 1H), 3.79 (s, 2H), 3.72 (s, 3H), 2.28(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 169.0, 150.9, 140.1, 139.0, 123.9, 122.4, 96.6, 52.3, 46.0, 21.1; HRMS (ESI–TOF) Calcd. for $C_{11}H_{12}IO_4$ $[M+H]^+$: 334.9775; found: 334.9775.



2ka

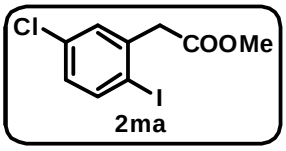
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 7.00–6.96 (m, 1H), 3.89 (d, J = 4.0 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 160.3 (d, $J_{C–F}$ = 250.0 Hz), 134.9 (d, $J_{C–F}$ = 4.0 Hz), 130.2 (d, $J_{C–F}$ = 9.0 Hz), 126.0 (d, $J_{C–F}$ = 18.0 Hz), 115.4 (d, $J_{C–F}$ = 23.0 Hz), 101.7 (d, $J_{C–F}$ = 2.0 Hz); 52.3, 39.1 (d, $J_{C–F}$ = 3.0 Hz); HRMS (ESI–TOF) Calcd. for $C_9H_9FIO_2$ $[M+H]^+$: 294.9626; found: 294.9614.



2l

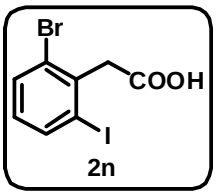
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 6.92 (t, J = 8.0 Hz, 1H), 4.16 (s, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 175.6, 138.1, 135.1, 134.6, 130.1, 129.7, 102.1, 44.4; HRMS (ESI–TOF) Calcd. for $C_8H_7ClIO_2$ $[M+H]^+$: 296.9174; found: 296.9175 Isotope $[(M+2)+H]^+$, $[M+H]^+$: $[(M+2)+H]^+$ = 3:1.



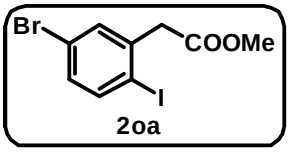
2ma

^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.0 Hz, 1H), 7.28 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 3.77 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 140.4, 139.4, 134.6, 130.6, 129.1, 98.0, 52.3, 45.8; HRMS (ESI–TOF) Calcd. for $C_9H_9ClIO_2$ $[M+H]^+$: 310.9330; found: 310.9328 Isotope $[(M+2)+H]^+$, $[M+H]^+$: $[(M+2)+H]^+$ = 3:1.



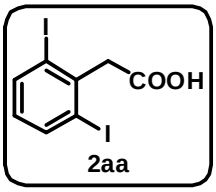
2n

^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 6.82 (t, J = 8.0 Hz, 1H), 4.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 138.9, 136.5, 133.1, 130.4, 124.7, 101.8, 47.2; HRMS (ESI–TOF) Calcd. for $C_8H_7BrIO_2$ $[M+H]^+$: 340.8669; found: 340.8673. Isotope $[(M+2)+H]^+$, $[M+H]^+$: $[(M+2)+H]^+$ = 1:1.



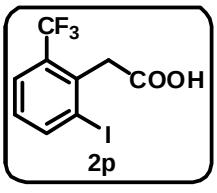
2oa

^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.11 (d, J = 8.0 Hz, 1H), 3.77 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 140.7, 139.7, 133.5, 132.0, 122.6, 98.9, 52.3, 45.7; HRMS (ESI–TOF) Calcd. for $C_9H_9BrIO_2$ $[M+H]^+$: 354.8825; found: 354.8815. Isotope $[(M+2)+H]^+$, $[M+H]^+$: $[(M+2)+H]^+$ = 1:1.



2aa

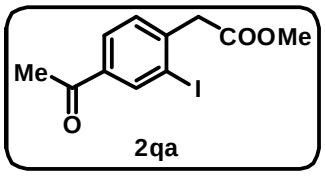
^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 2H), 6.61 (t, J = 8.0 Hz, 1H), 4.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 139.8, 139.2, 130.7, 100.3, 52.2; HRMS (ESI–TOF) Calcd. for $C_8H_7I_2O_2$ $[M+H]^+$: 388.8530; found: 388.8529.



2p

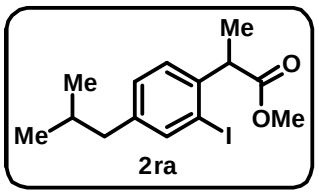
^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, 1H), 7.68 (d, J = 8.0 Hz,

1H), 7.10 (t, J = 8.0 Hz, 1H), 4.12 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 143.4, 135.1, 130.5 (q, $J_{C–F}$ = 30.0 Hz), 129.0, 126.2 (q, $J_{C–F}$ = 6.0 Hz), 123.4 (q, $J_{C–F}$ = 273.0 Hz), 105.1, 43.1; HRMS (ESI–TOF) Calcd. for $C_9H_7F_3IO_2$ $[M+H]^+$: 330.9437; found: 330.9434.



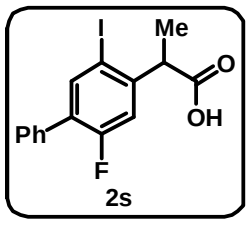
2qa

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 3.86 (s, 2H), 3.73 (s, 3H), 2.58(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 170.2, 142.7, 139.4, 137.4, 130.6, 128.2, 101.0, 52.3, 46.1, 26.6; HRMS (ESI–TOF) Calcd. for $C_{11}H_{12}IO_3$ $[M+H]^+$: 318.9826, found: 318.9824.



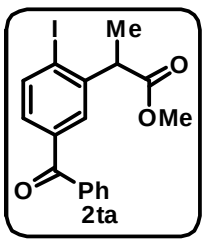
2ra

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 4.08 (q, J = 7.0 Hz, 1H), 3.68 (s, 3H), 2.42 (d, J = 7.5 Hz, 2H), 1.88–1.79 (m, 1H), 1.44 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 142.6, 140.7, 140.1, 129.6, 126.9, 100.7, 52.1, 49.1, 44.3, 30.0, 22.3, 18.3; HRMS (ESI–TOF) Calcd. for $C_{14}H_{20}IO_2$ $[M+H]^+$: 347.0503, found: 347.0502.



2s

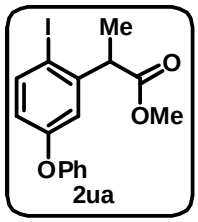
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 8.0 Hz, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 12.0 Hz, 1H), 4.17 (q, J = 8.0 Hz, 1H), 1.55 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 160.4 (d, $J_{C–F}$ = 249.0 Hz), 143.6 (d, $J_{C–F}$ = 9.0 Hz), 140.9 (d, $J_{C–F}$ = 5.0 Hz), 133.8, 130.2 (d, $J_{C–F}$ = 14.0 Hz),), 128.8 (d, $J_{C–F}$ = 3.0 Hz), 128.6, 128.2, 115.6 (d, $J_{C–F}$ = 24.0 Hz), 94.1 (d, $J_{C–F}$ = 3.0 Hz), 49.3, 18.0; HRMS (ESI–TOF) Calcd. for $C_{15}H_{13}FIO_2$ $[M+H]^+$: 370.9939; found: 370.9934.



2ta

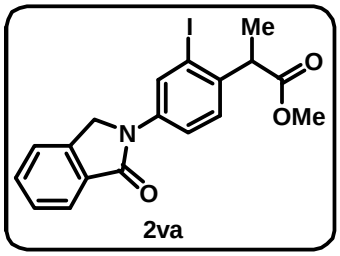
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.0 Hz, 1H), 7.77 (d, J =

8.0 Hz, 2H), 7.69 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 1H), 3.70 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 173.8, 143.9, 139.8, 137.9, 137.0, 132.8, 130.0, 129.8, 128.9, 128.4, 106.4, 52.3, 49.5, 18.1; HRMS (ESI–TOF) Calcd. for $C_{17}H_{16}IO_3$ $[M+H]^+$: 395.0139; found: 395.0137.



2ua

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.01–6.99 (m, 3H), 6.01 (d, *J* = 8.0 Hz, 1H), 4.07 (q, *J* = 8.0 Hz, 1H), 3.68 (s, 3H), 1.44 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 158.1, 156.4, 145.1, 140.4, 129.9, 123.8, 119.1, 119.0, 118.3, 92.4, 52.2, 49.5, 18.1; HRMS (ESI–TOF) Calcd. for $C_{16}H_{16}IO_3$ $[M]^+$: 383.0139; found: 383.0137.

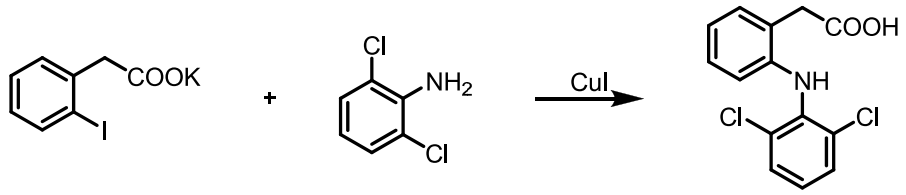


2va

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.94–7.90 (m, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.53–7.49 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 4.82 (s, 2H), 4.11 (q, *J* = 8.0 Hz, 1H), 3.67 (s, 3H), 1.48 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 167.4, 139.9, 139.4, 139.2, 132.7, 132.4, 129.7, 128.5, 127.5, 124.3, 122.7, 119.6, 100.9, 52.2, 50.5, 48.9, 18.3; HRMS (ESI–TOF) Calcd. for $C_{18}H_{17}INO_3$ $[M+H]^+$: 422.0248, found: 422.0235.

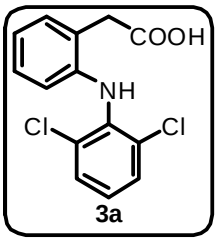
Synthetic applications:

Synthesis of diclofenac[2]



2ab **7** **3a**

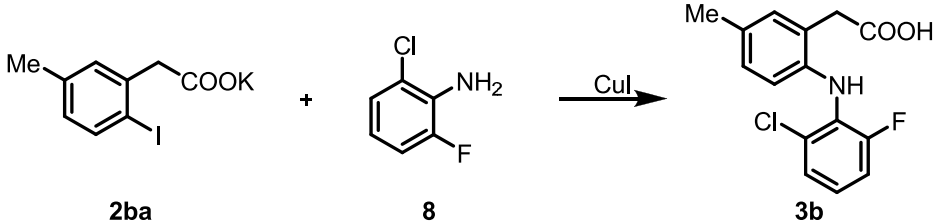
Potassium 2-iodophenylacetate **2ab** (150 mg, 0.50 mmol) was added to a mixture of 2,6-dichloroaniline **7** (322 mg, 2.0 mmol), anhydrous potassium carbonate (345 mg, 2.5 mmol), copper iodide (191mg, 1.0 mmol) and *N*-methylpyrrolidone (0.5 mL). The mixture was heated to 100 °C and stirred overnight. The mixture was then cooled to room temperature, ethyl acetate (20 mL), water (10 mL), concentrated hydrochloric acid (0.6 mL) as well as charcoal (2 g) and cellite (2 g) were added and stirring was continued for 1 h. The mixture was filtered to obtain two clear phases. The organic phase was separated, dried over Na_2SO_4, and concentrated. The residue was then purified by flash chromatography on silica with EtOAc–hexane as eluent to give the product **3a** (90 mg, 61%).



3a

^{1}H NMR (400 MHz, acetone-d_6) δ 7.47 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.21 (br, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 6.95 (t, J = 8.0 Hz, 1H), 6.48 (d, J = 8.0 Hz, 1H), 3.83 (s, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 173.2, 143.2, 138.1, 131.1, 129.7, 129.3, 127.9, 125.1, 124.9, 121.9, 117.7, 38.0; HRMS (ESI–TOF) Calcd. for $C_{14}H_{12}Cl_2NO_2$ $[M+H]^+$: 296.0240, found: 296.0240. Isotope $[(M+2)+H]^+$, $[(M+4)+H]^+$; $[M+H]^+$: $[(M+2)+H]^+$: $[(M+4)+H]^+$ = 9:6:1.

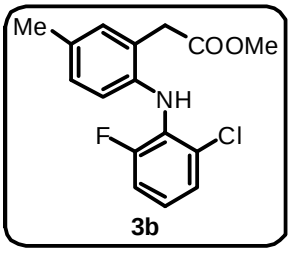
Synthesis of Lumiracoxib[2]



2ba **8** **3b**

Potassium 2-iodo-5-methylphenylacetate **2ba** (314 mg, 0.50 mmol) was added to a mixture of 2-chloro-6-fluoroaniline **8** (322 mg, 2.0 mmol), anhydrous potassium carbonate (345 mg, 2.5 mmol), copper iodide (191 mg, 1.0 mmol) and *N*-

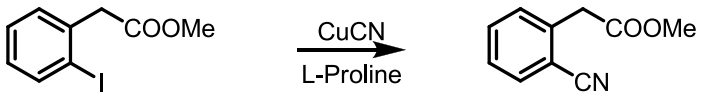
methylpyrrolidone (0.5 mL). The mixture was heated to 100 °C and stirred overnight. The mixture was then cooled to 30 °C, to which ethyl acetate (20 mL), water (10 mL), concentrated hydrochloric acid (0.6 mL) as well as charcoal (2g) and celite (2 g) were added and stirring was continued for 1 h. The mixture was filtered to obtain two clear phases. The organic phase was separated and dried over Na_2SO_4, concentrated, and the residue was purified by flash chromatography on silica with EtOAc–hexane as eluent to give the product **3b** (60 mg, 41%).



3b

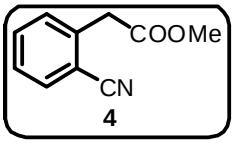
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (ddd, J = 8.0, 1.6, 1.6 Hz, 1H), 7.04–6.96 (m, 3H), 6.92 (ddd, J = 8.0, 8.0, 5.6 Hz, 1H), 6.76 (br, 1H), 6.65 (dd, J = 8.0, 3.2, 1H), 3.77 (s, 2H), 3.75 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 155.6 (d, $J_{C–F}$ = 247.5 Hz), 140.0, 131.8, 131.6, 129.8 (d, $J_{C–F}$ = 13.2 Hz), 128.7, 127.5 (d, $J_{C–F}$ = 3.4 Hz), 125.6 (d, $J_{C–F}$ = 2.3 Hz), 124.1, 122.3 (d, $J_{C–F}$ = 8.6 Hz), 118.3 (d, $J_{C–F}$ = 3.0 Hz), 115.1 (d, $J_{C–F}$ = 2.0 Hz), 52.6, 38.6, 20.8; HRMS (ESI-TOF) Calcd. for $C_{16}H_{16}ClFNO_2$ $[M+H]^+$: 308.0848, found: 308.0846, Isotope $[(M+2)+H]^+$, $[M+H]^+$: $[(M+2)+H]^+$ = 3:1.

Synthesis of methyl 2-(2-cyanophenyl)acetate[3]



2ac **4**

To a mixture of CuCN (179mg, 2 mmol), L-proline (115 mg, 1 mmol), and anhydrous DMF (3 mL) under argon, aryl iodide **2ac** (276 mg, 1 mmol) was added at room temperature. The mixture was stirred at 120 °C for 45 h. After the resulting suspension was cooled to room temperature., EtOAc (15 mL) was added, the mixture was then washed with H_2O (3 × 4 mL). The organic phase was dried over Na_2SO_4, concentrated, and the residue was purified by flash chromatography on silica with EtOAc–hexane as eluant to give the product **4** (149 mg, 85%).

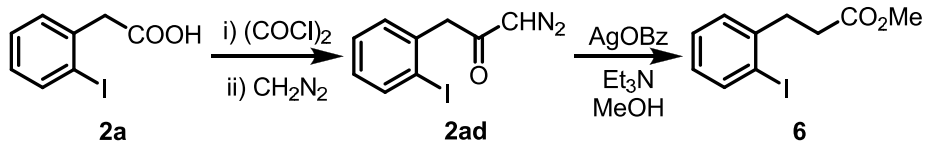


4

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.42–7.36 (m, 2H), 3.88 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 137.6, 132.8, 132.8, 130.6, 127.8,

117.5, 113.4, 52.3, 39.3; HRMS (ESI–TOF) Calcd. for $C_{10}H_8NO_2$ $[M+H]^+$: 162.0550, found: 162.0555.

Synthesis of methyl 3-(2-iodophenyl)propanoate[4]



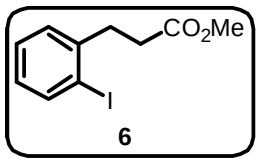
2a **2ad** **6**

To a solution of 2-iodophenylacetic acid **2a** (105 mg, 0.4 mmol) in dichloromethane (2 mL) at 0 °C, was added oxalyl chloride (175 μL, 2 mmol) followed by 2 drops of DMF. Vigorous bubbling ensued and the clear reaction mixture was stirred for 30 min. The reaction mixture was then concentrated *in vacuo*.

Diazomethane solution: To a 25 mL Erlenmeyer flask, KOH (40% aqueous solution, 745 μL) and diethyl ether (9 mL) was added. After cooled the Erlenmeyer flask to 0 °C with ice-water bath, nitrosomethyl urea (412 mg, 4 mmol) was added. After stirring for 20 min, the solution was cooled to –78 °C. The ether layer was carefully decanted into a clean Erlenmeyer and warmed up to 0 °C.

At this time, the crude acid chloride was added to the diazomethane as a solution in dichloromethane (5 mL). The reaction mixture was stirred for 2 h at 0 °C. The excess diazomethane was destroyed by addition of HOAc. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel with (EtOAc–hexane (1:4) as eluent to give diazoketone **2ad** (92 mg, 80%).

A solution of AgOBz (36 mg, 0.16 mmol) in 400 μL triethylamine was added drop-wise to a solution of diazoketone **2ad** (92 mg, 0.32 mmol) in 2 mL MeOH at room temperature. The resulting black solution was stirred for additional 30 min. The mixture was filtered through a pad of celite. the filtrate was concentrated *in vacuo*, the residue was purificated by flash chromatography on silica gel with EtOAc–hexane (1:4) as eluent to give iodoester **6** (84 mg, 72%).

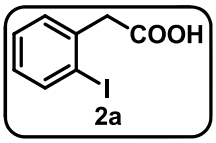


6

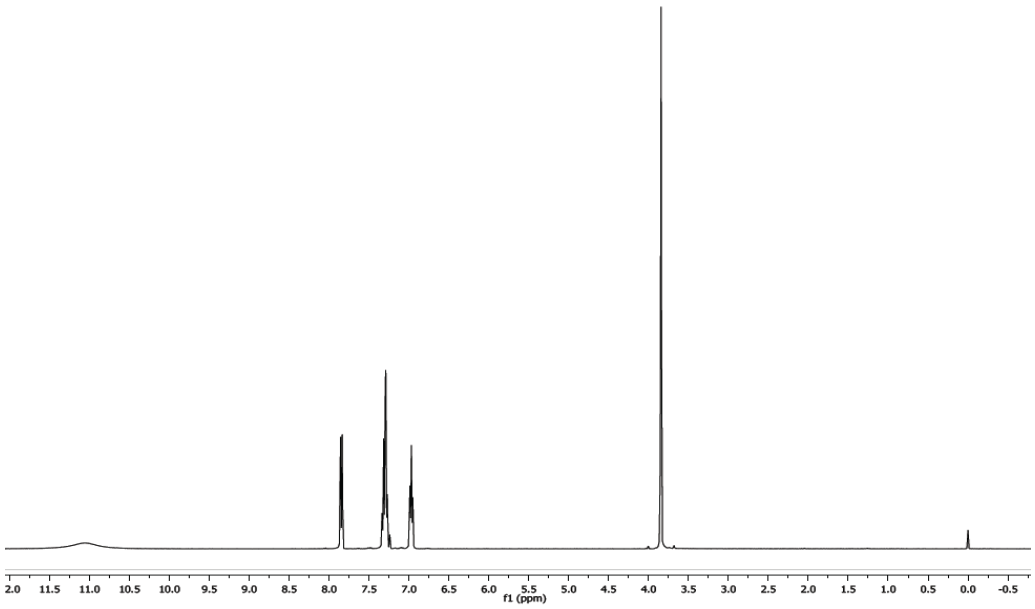
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 1H), 7.30-7.23 (m, 2H), 6.90 (t, J = 8.0 Hz, 1H), 3.69 (s, 3H), 3.05 (t, J = 8.0 Hz, 2H), 2.63 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 142.9, 139.6, 129.5, 128.5, 128.2, 100.2, 51.7, 35.9, 34; HRMS (ESI-TOF) Calcd. for $C_{10}H_{12}IO_2$ $[M+H]^+$: 290.9877, found: 290.9867.

References

1. (a) Arndt, F. *Organic Syntheses* **1943**, *Coll. Vol. 2*, 165. (b) Arndt, F. *Organic Syntheses* **1943**, *Coll. Vol. 2*, 461.
2. Moser, P.; Sallmann, A.; Wiesenbergt, I. *J. Med. Chem.* **1990**, *33,* 2358.
3. Wang, D.; Kuang, L.; Li, Z.; Ding, K. *Synlett* **2008**, 69.
4. Deville, J. P.; Behar, V. *Org. Lett.* **2002**, *4*, 1403.


COOH
I

2a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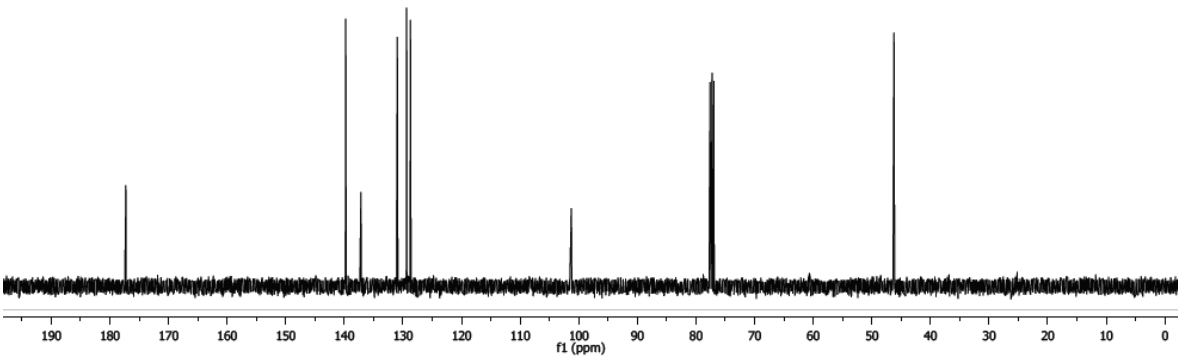
f1 (ppm)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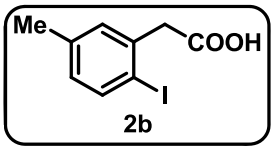
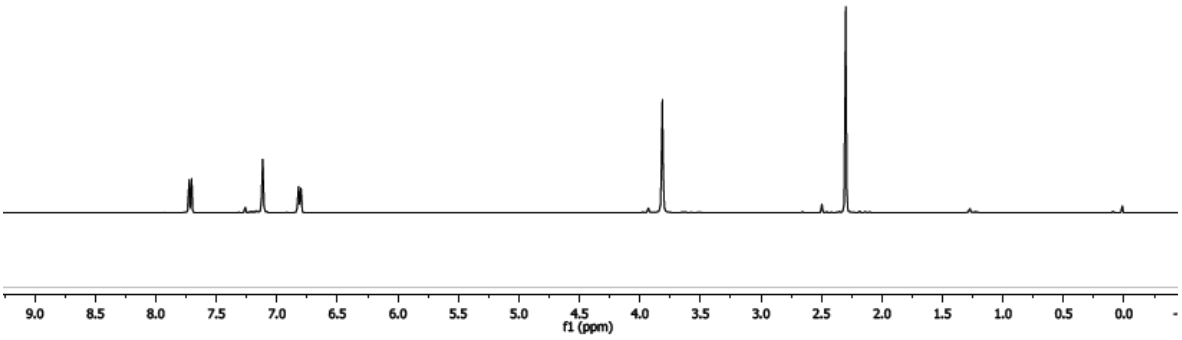
f1 (ppm)


Me
COOH
I

2b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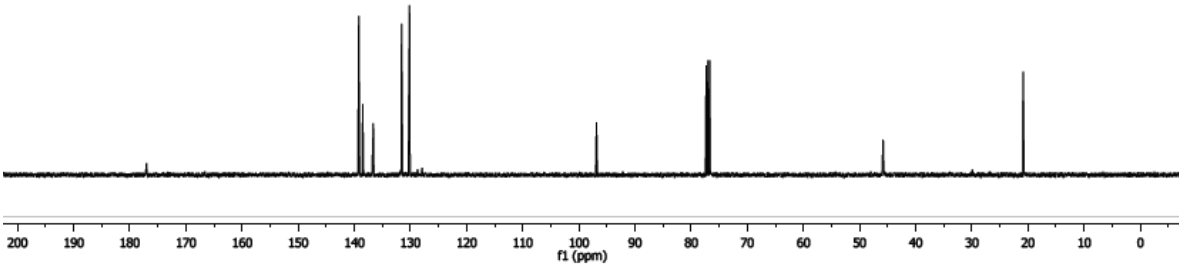
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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180
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100
90
80
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50
40
30
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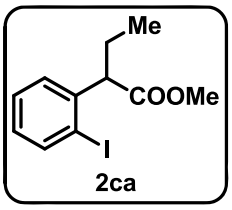
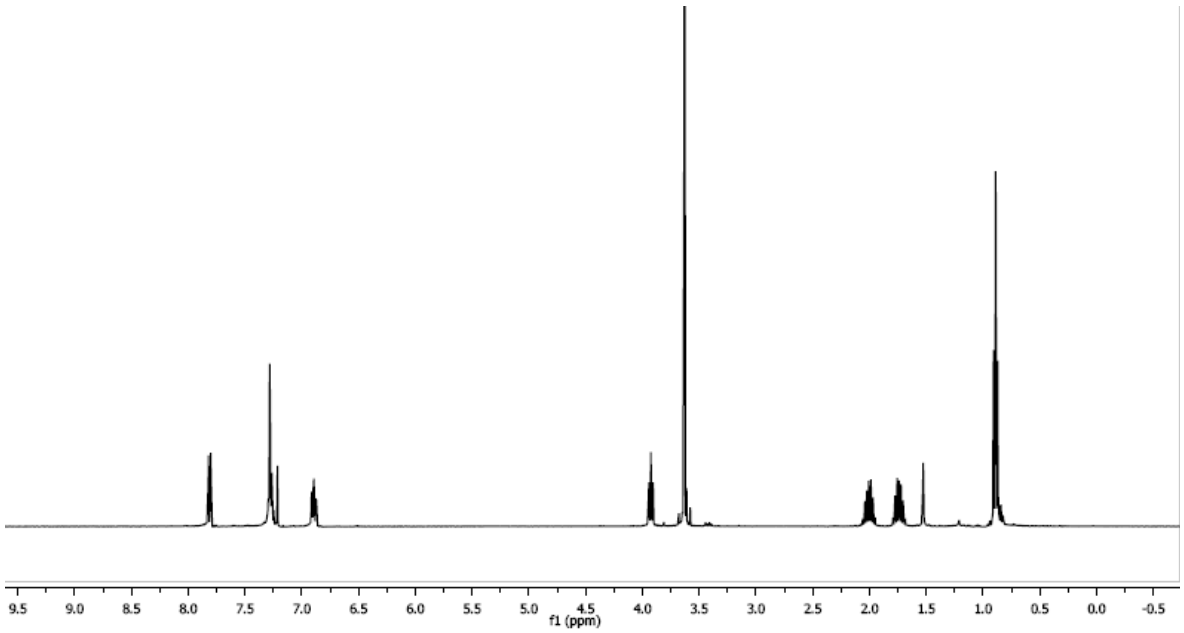
10
0
f1 (ppm)


Me
COOMe
I

2ca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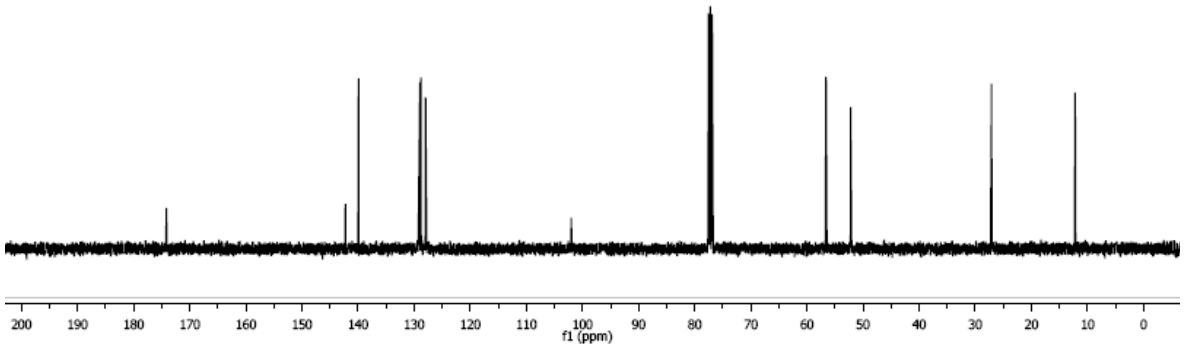
f1 (ppm)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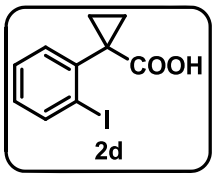
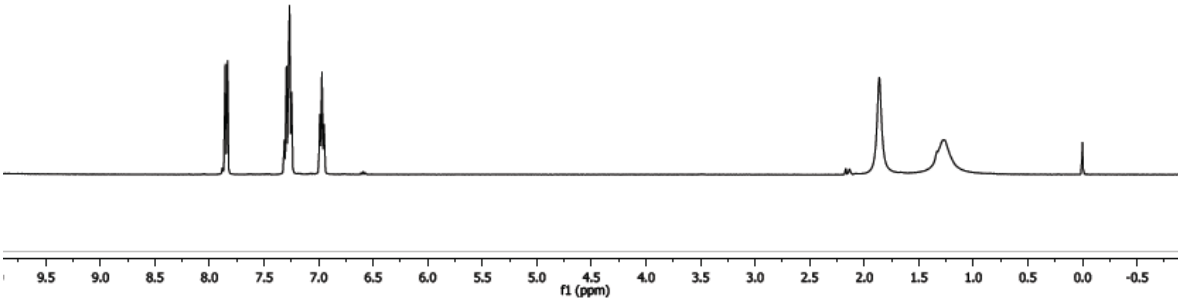
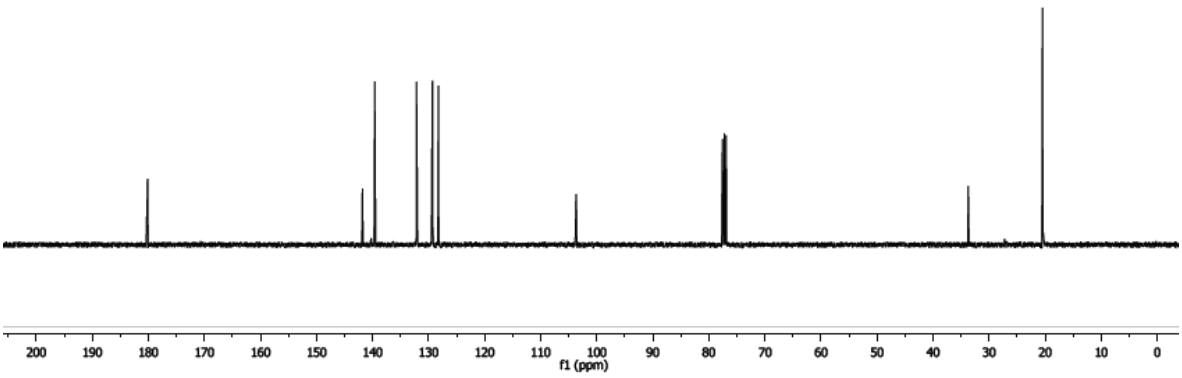

COOH
I

2d


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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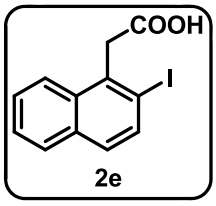
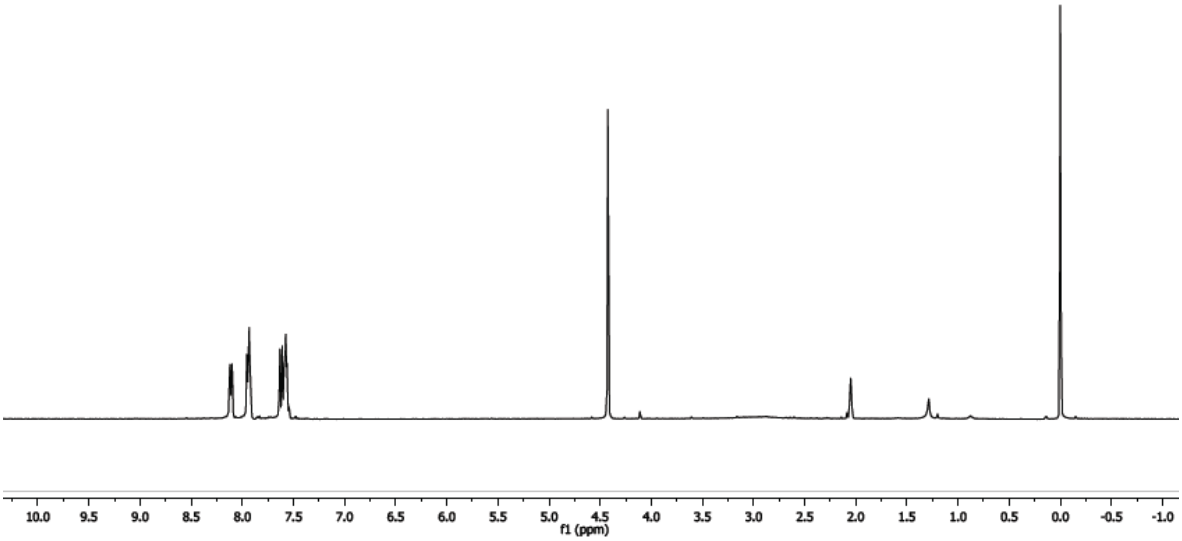
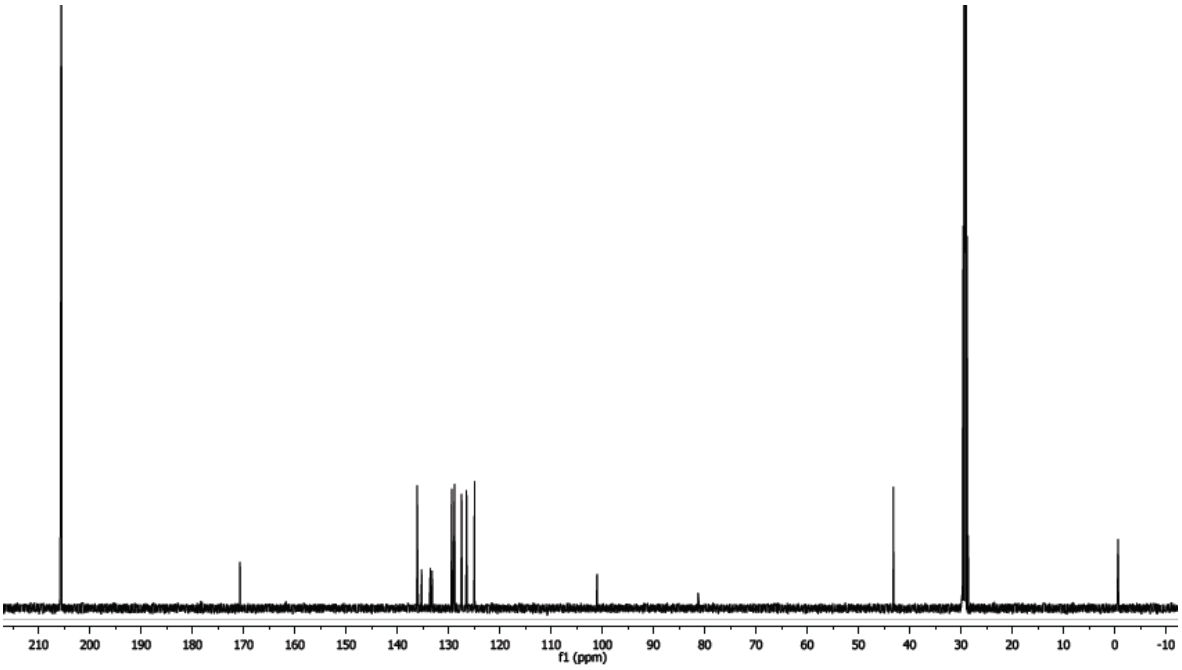
f1 (ppm)


COOH
I

2e


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 -1.0
f1 (ppm)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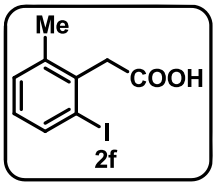
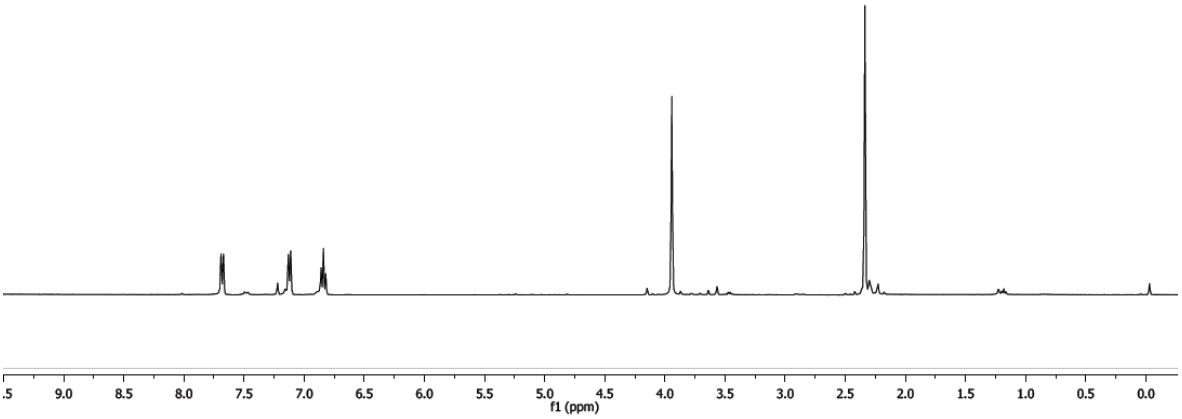
f1 (ppm)


Me
COOH
I

2f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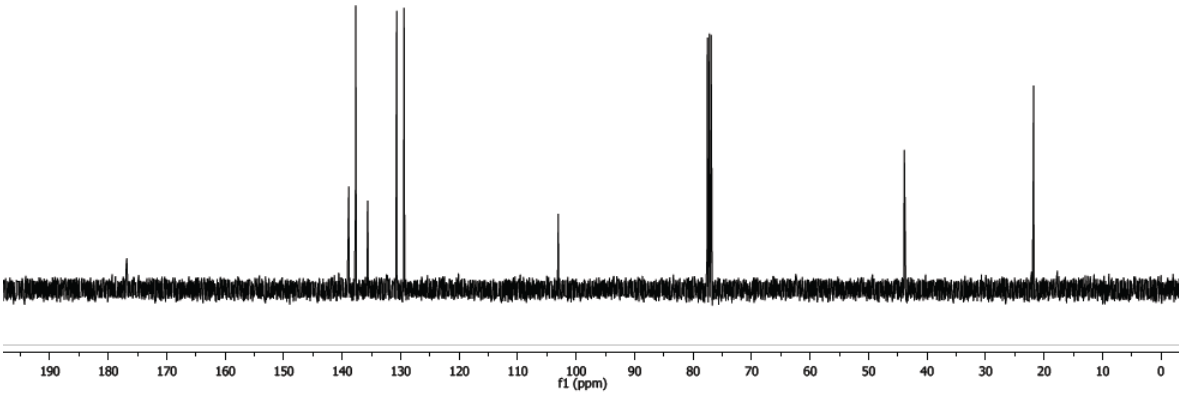
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190
180
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110
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90
80
70
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50
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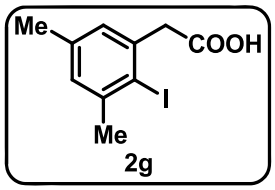
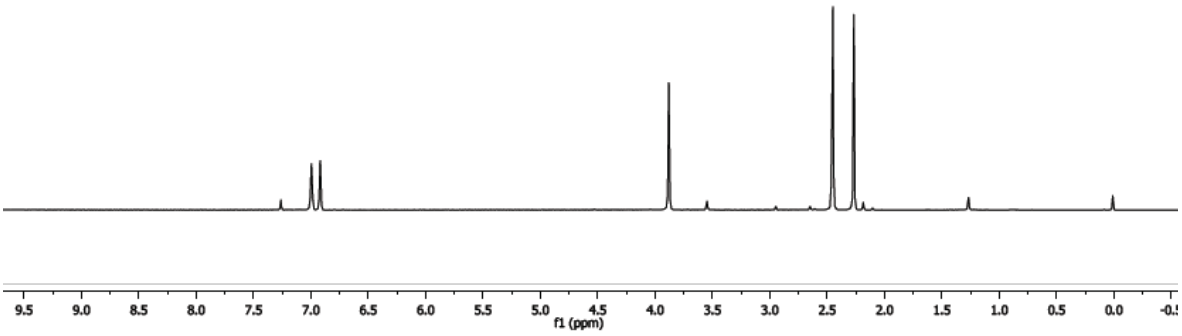
10
0
f1 (ppm)


Me
COOH
I
Me

2g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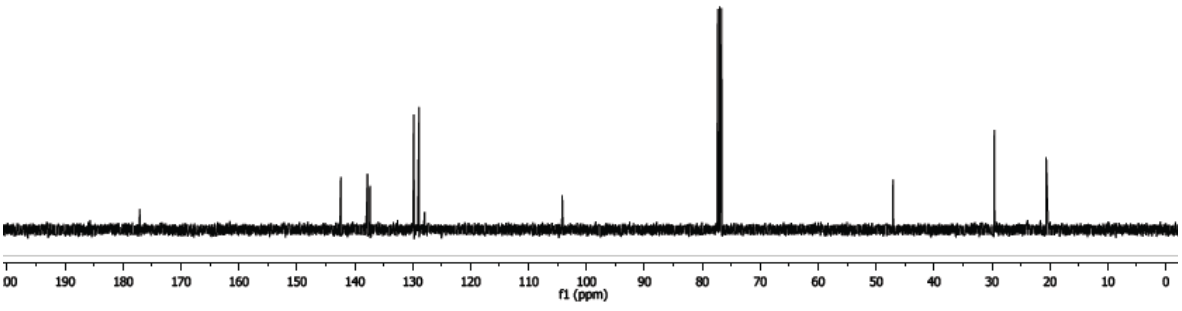
f1 (ppm)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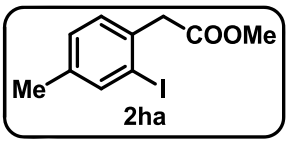
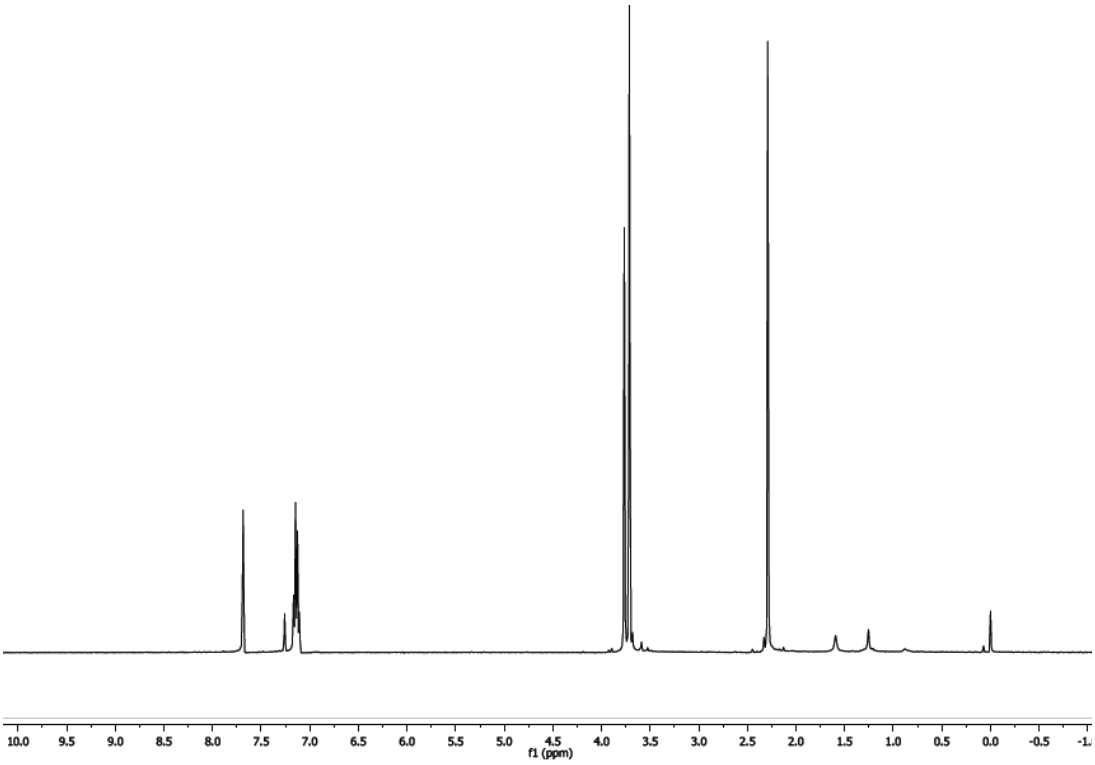
f1 (ppm)


COOMe
Me
I

2ha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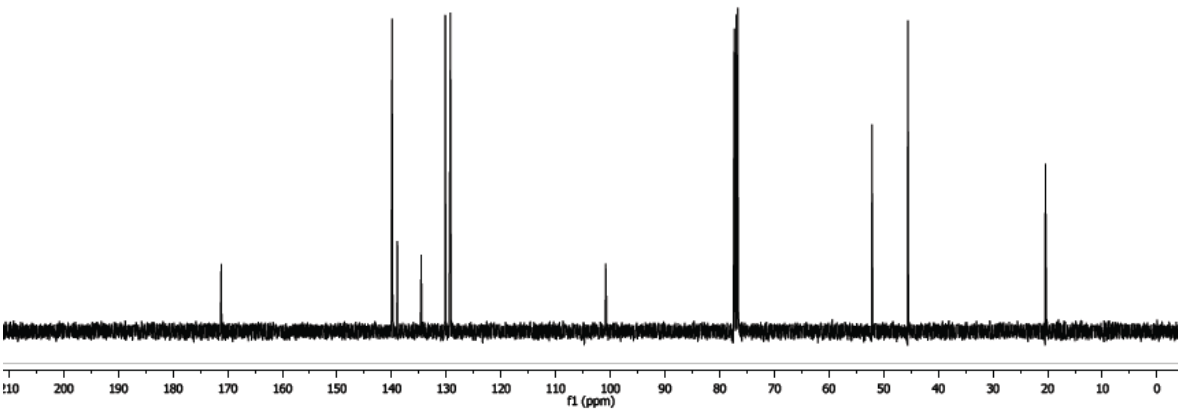
f1 (ppm)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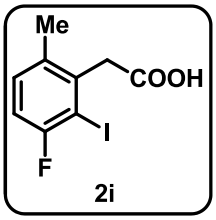
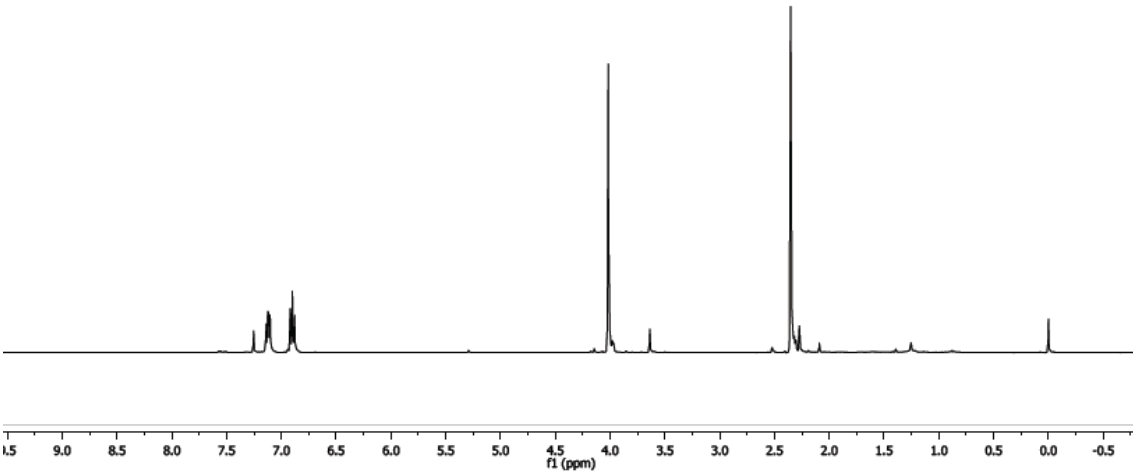
f1 (ppm)


Me
COOH
I
F

2i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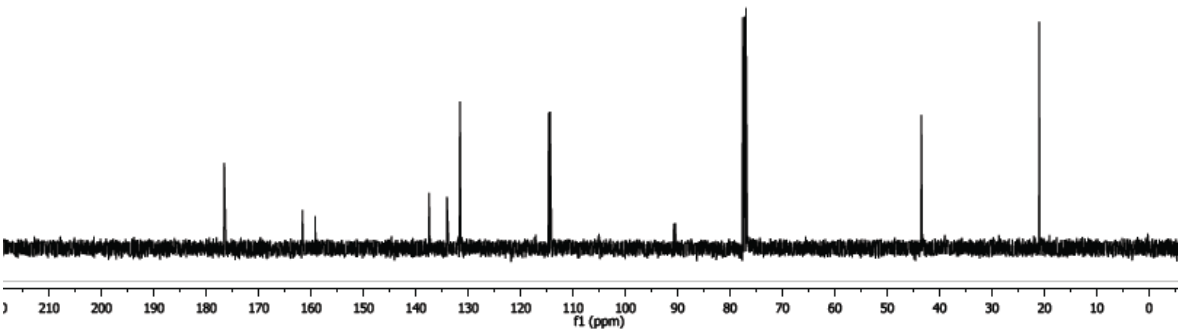
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


210
200
190
180
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90
80
70
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50
40
30
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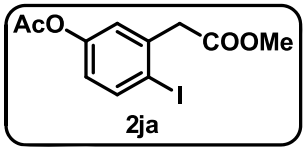
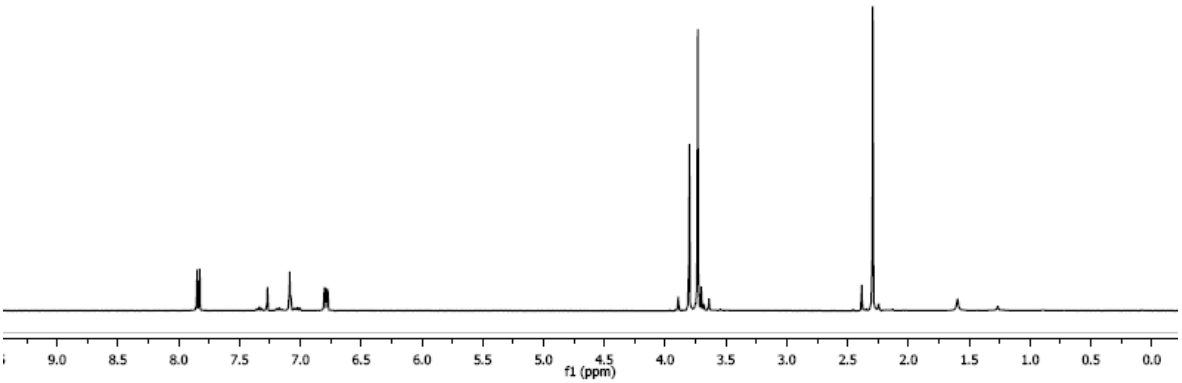
10
0
f1 (ppm)


AcO
COOMe
I

2ja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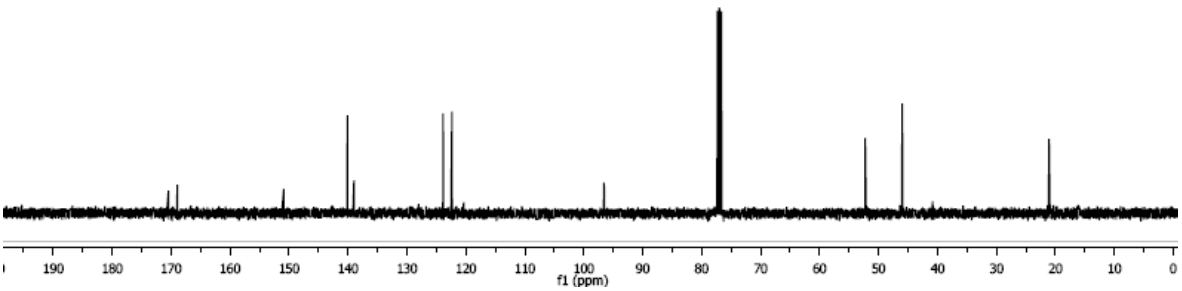
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190
180
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160
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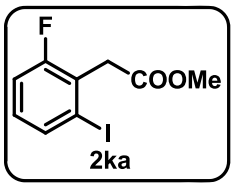
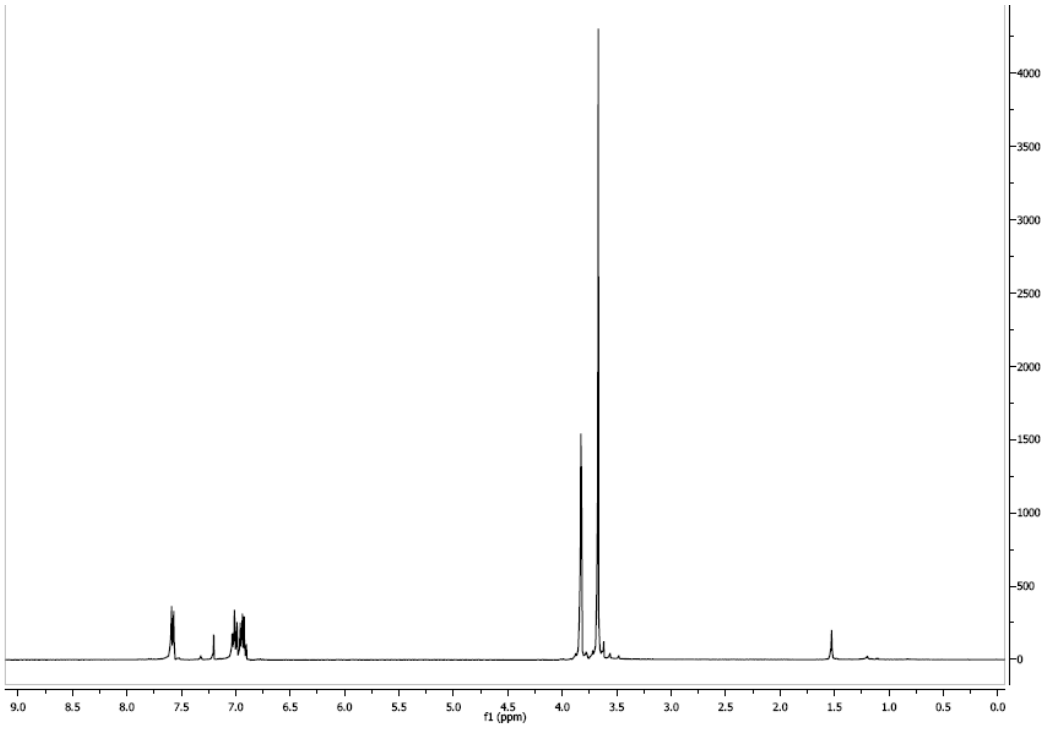
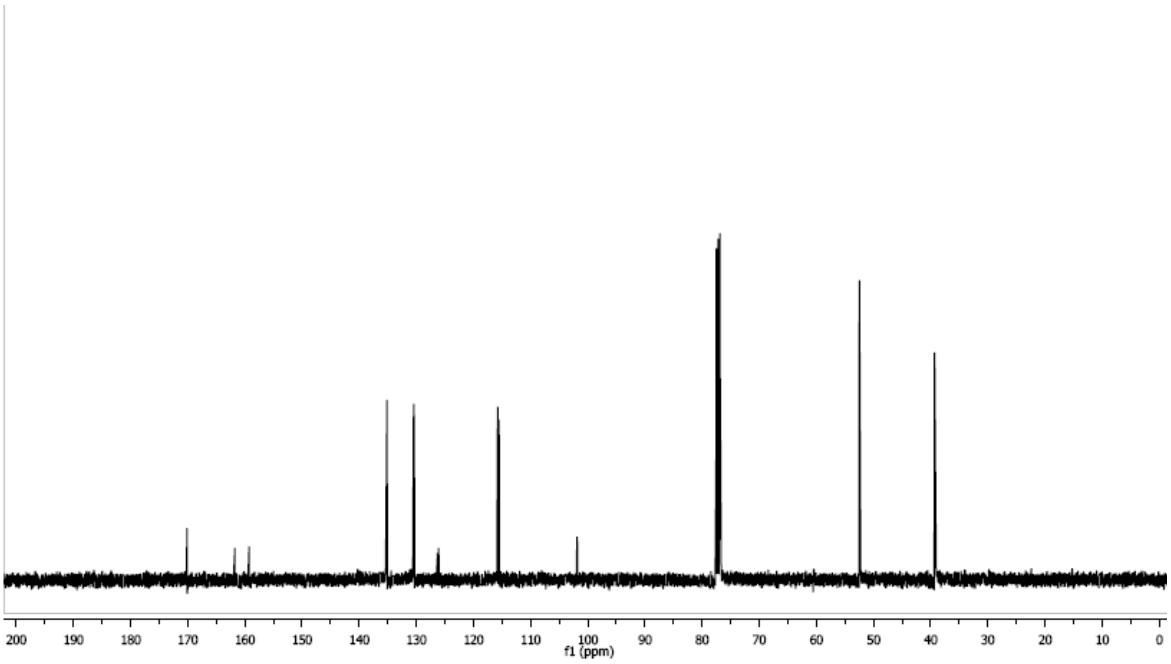
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


F
COOMe
I

2ka


4000
3500
3000
2500
2000
1500
1000
500
0
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
f1 (ppm)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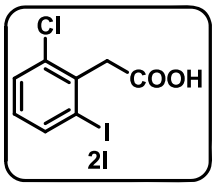
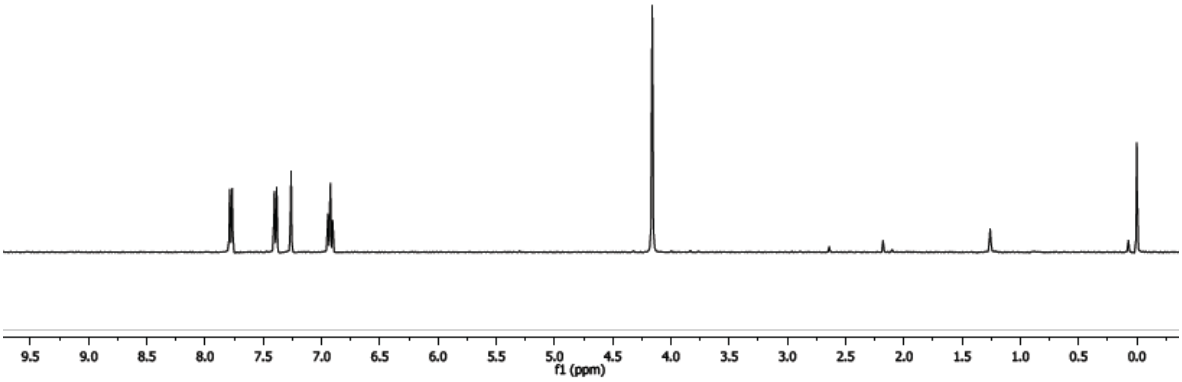
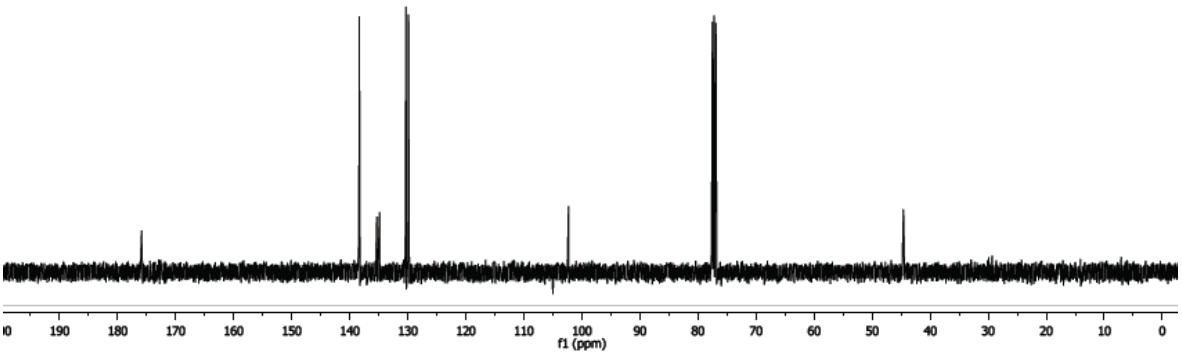
f1 (ppm)


Cl
COOH
I

2l


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
f1 (ppm)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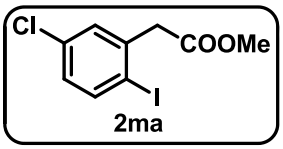
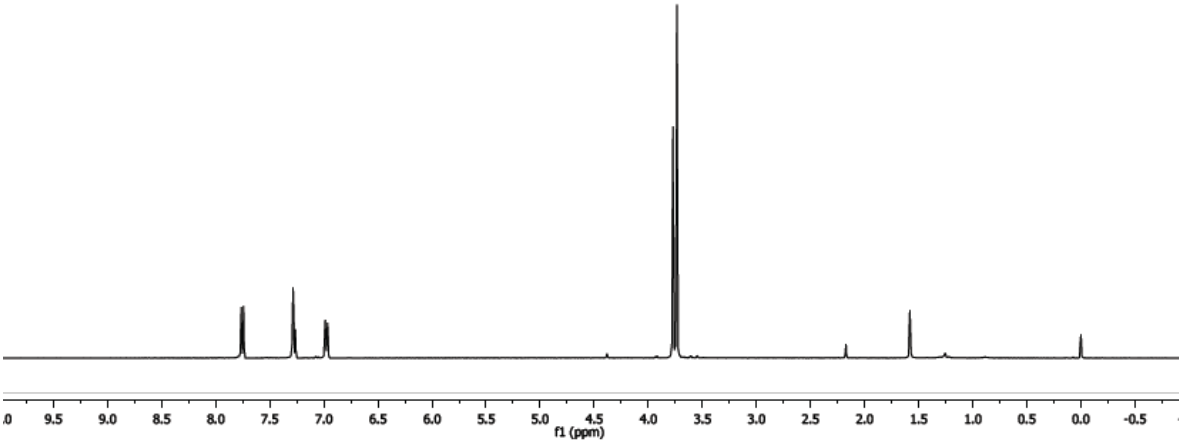
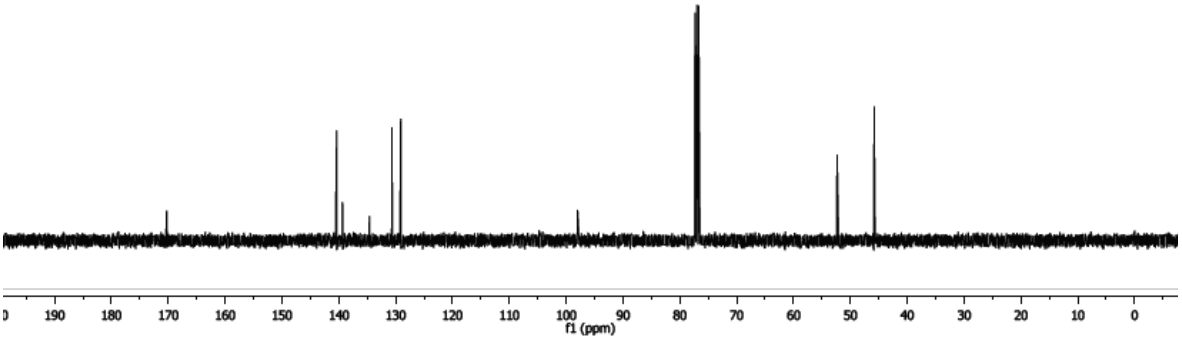
f1 (ppm)


Cl
COOMe
I

2ma


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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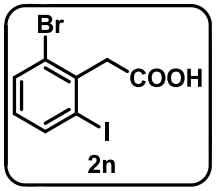
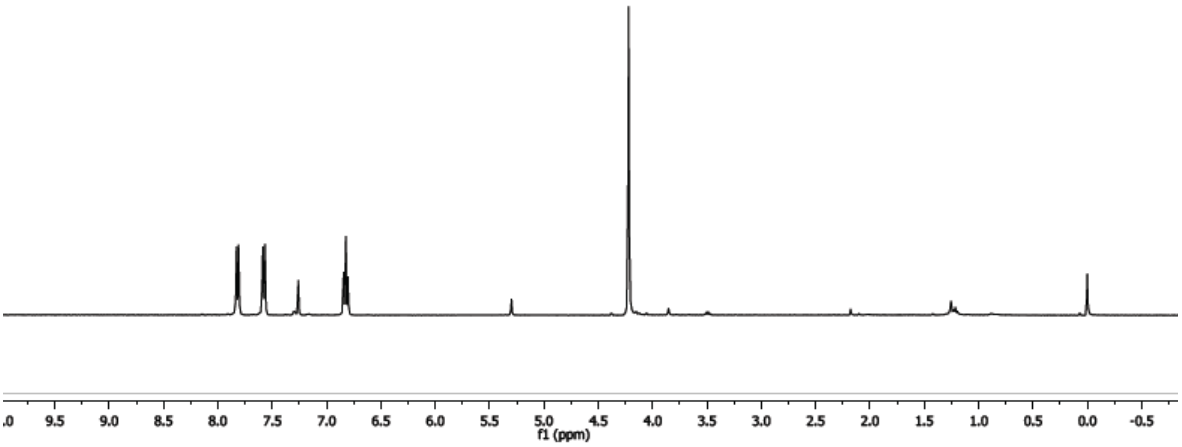
f1 (ppm)


Br
COOH
I

2n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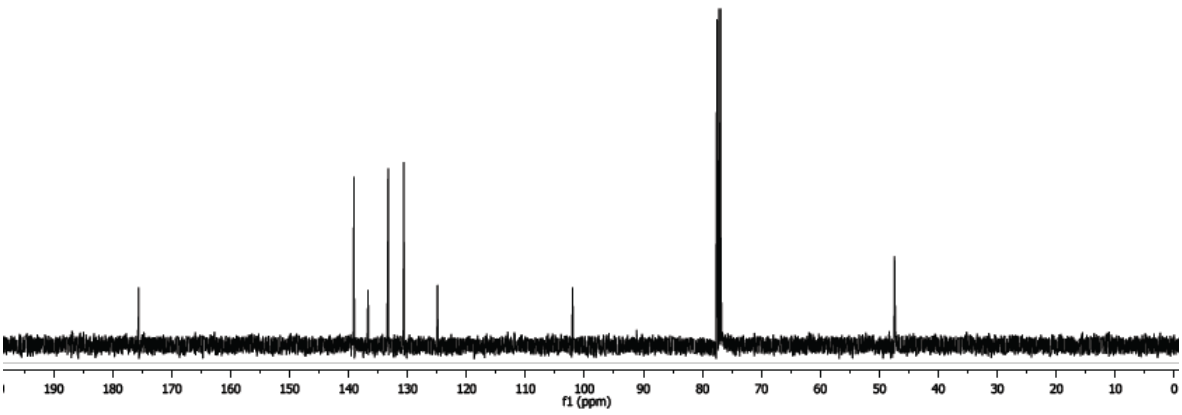
f1 (ppm)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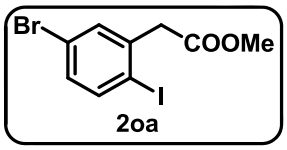
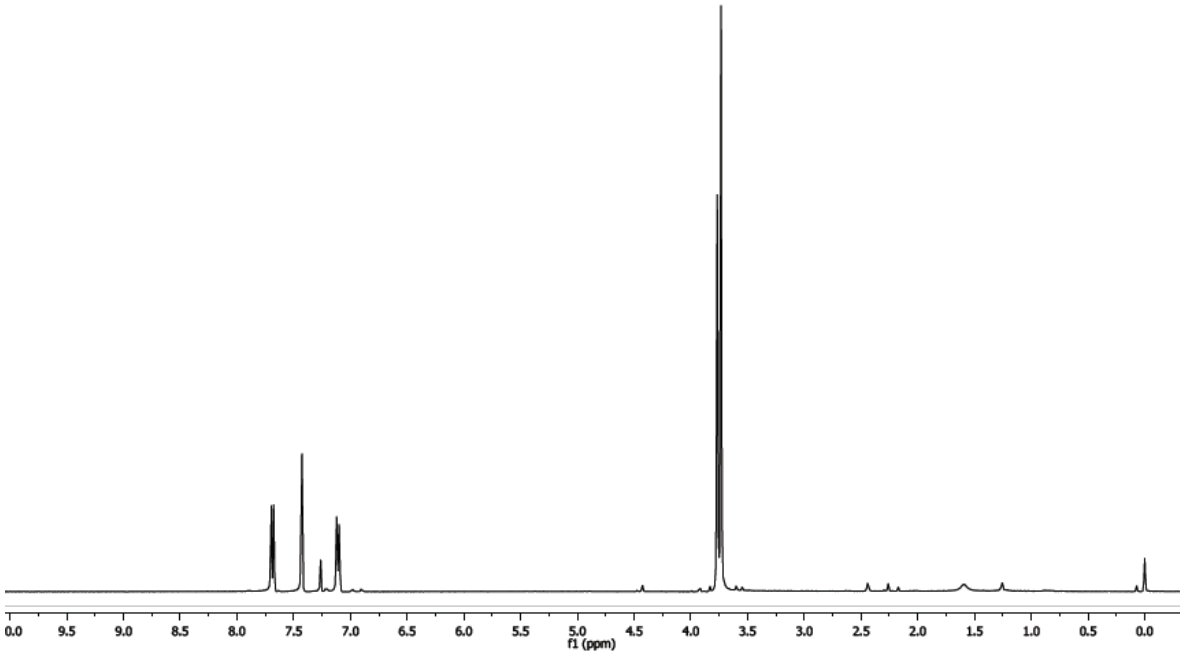
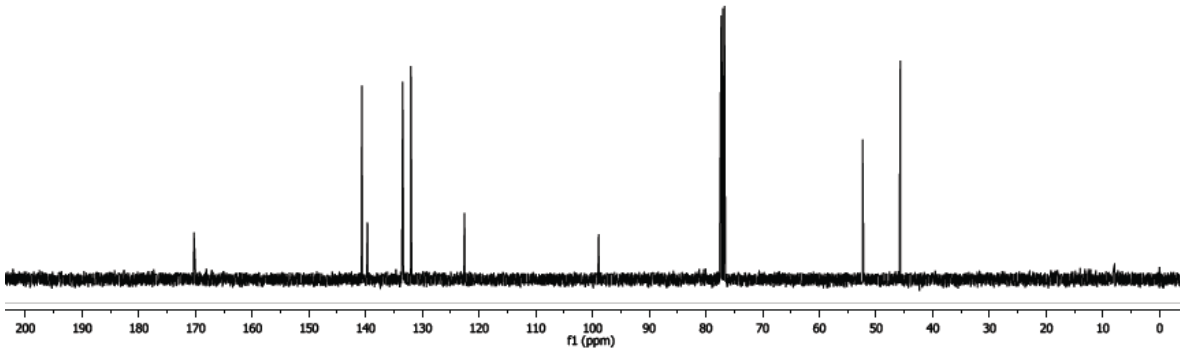
f1 (ppm)


Br
COOMe
I

2oa


0.0 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
f1 (ppm)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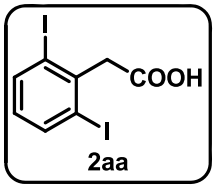
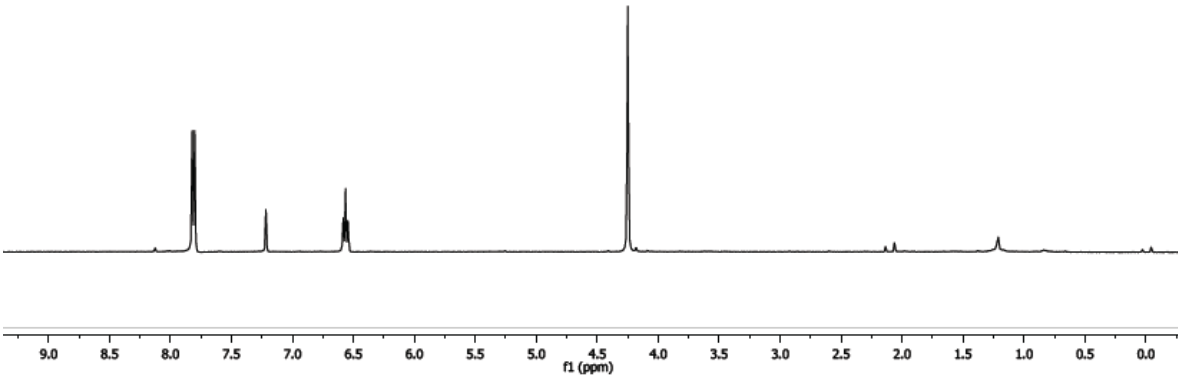
f1 (ppm)


I
COOH
I

2aa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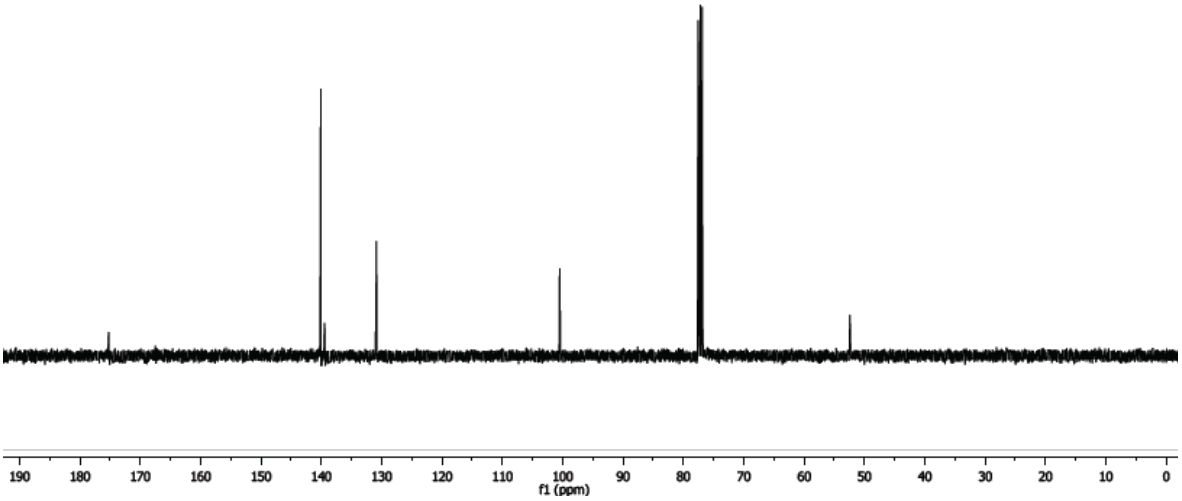
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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180
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110
100
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70
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50
40
30
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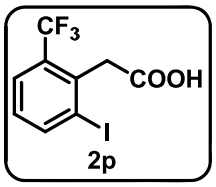
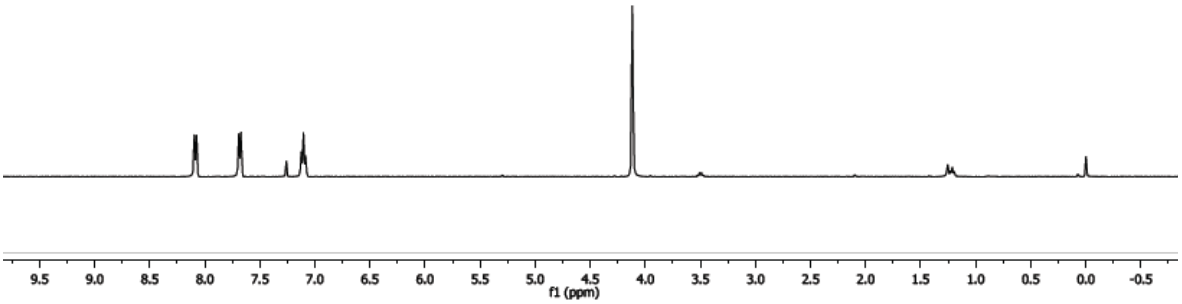
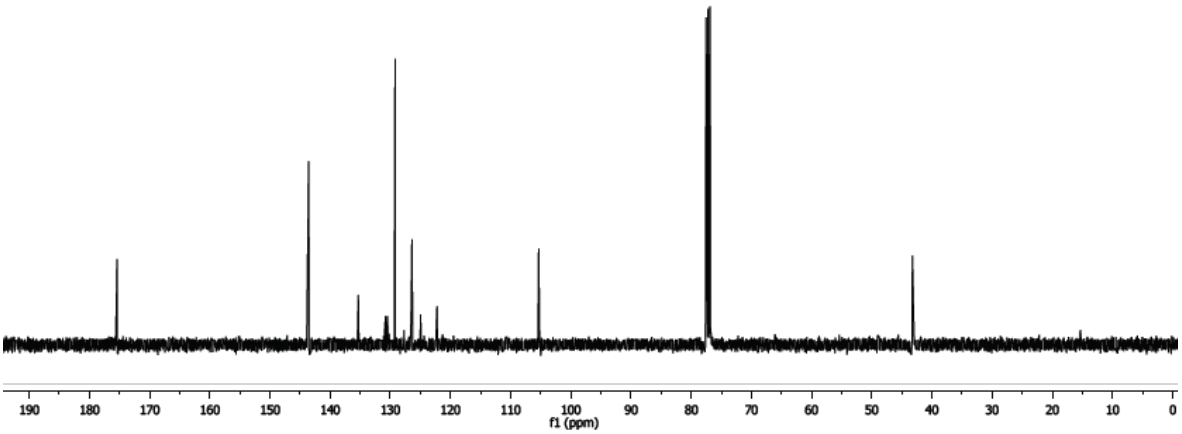
10
0
f1 (ppm)


CF3
COOH
I
2p


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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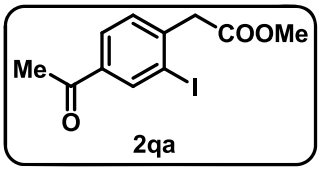
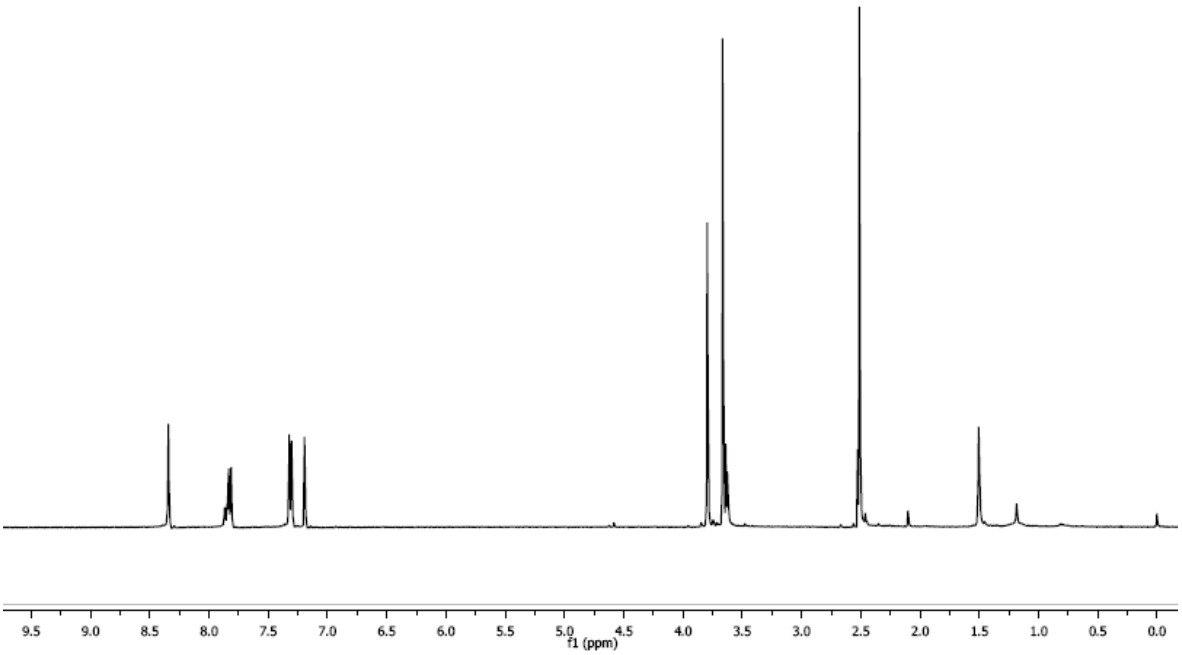
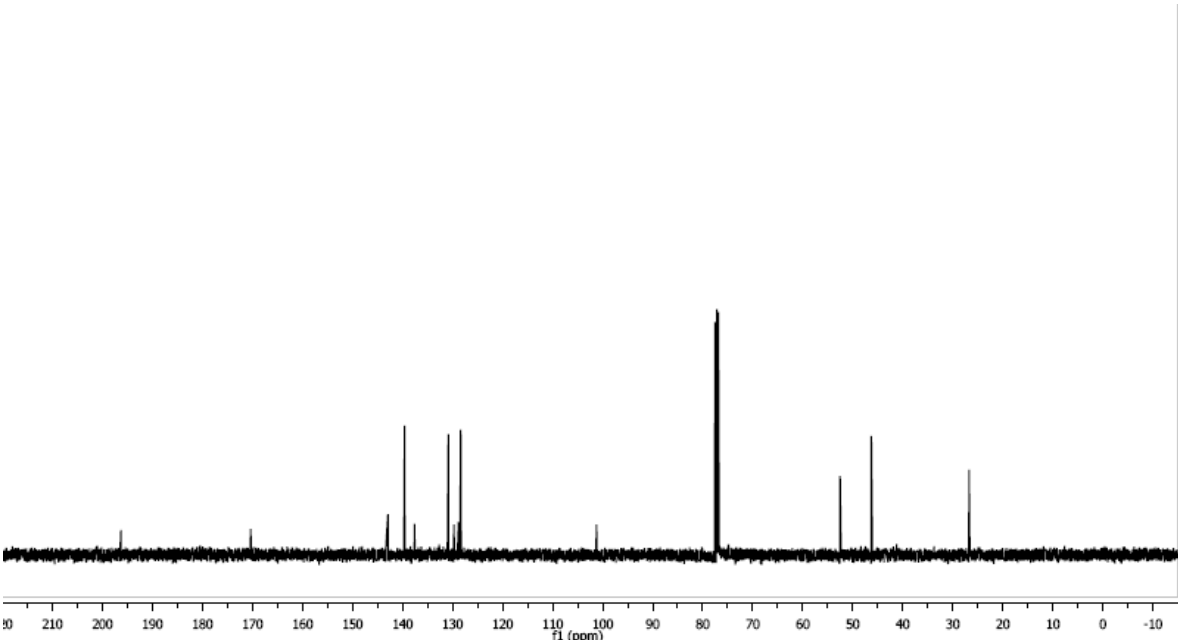
f1 (ppm)


COOMe
Me
O
I

2qa


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
f1 (ppm)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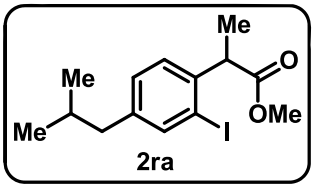
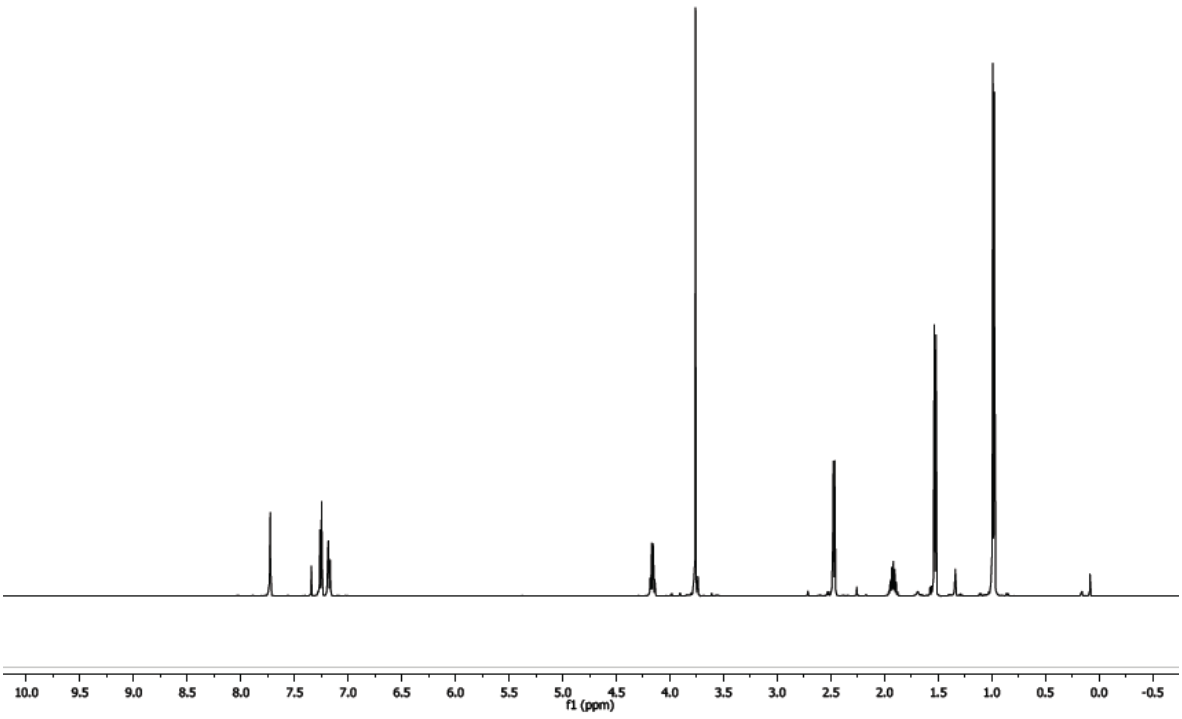
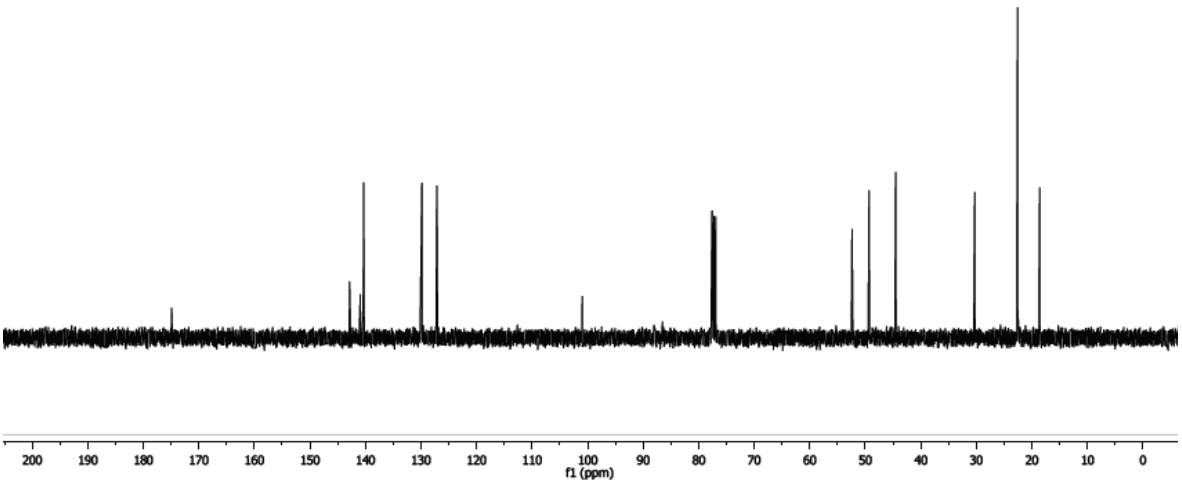
f1 (ppm)


Me
O
Me
OMe
Me
I

2ra


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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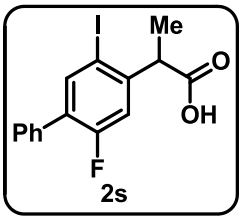
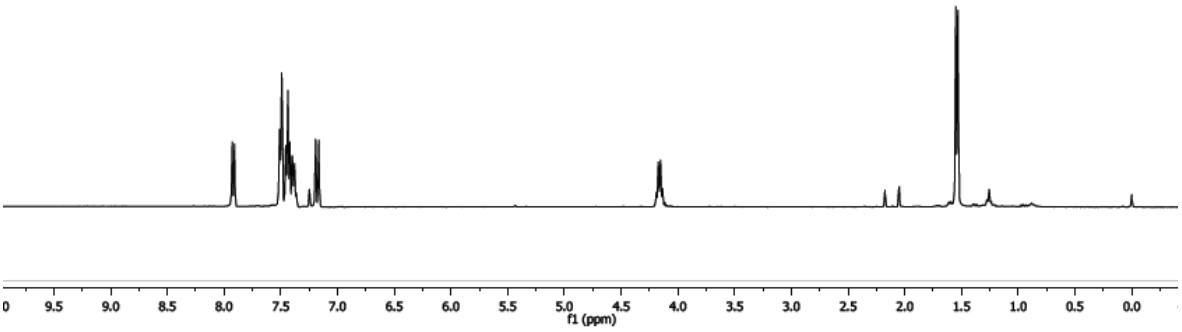
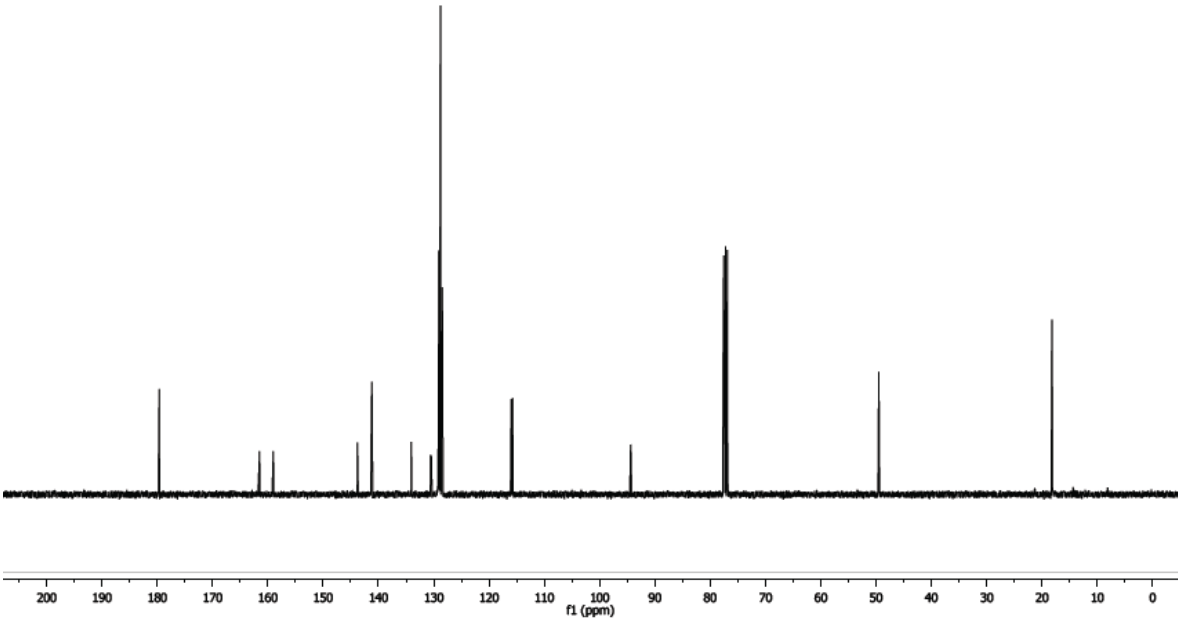
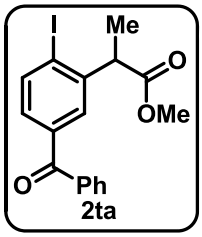
f1 (ppm)



2s






I
Me
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OMe
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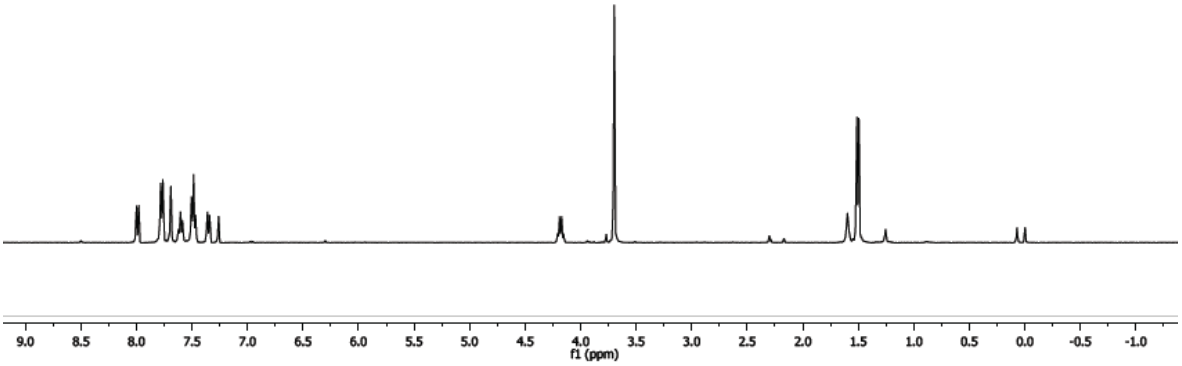
Ph
2ta


9.0
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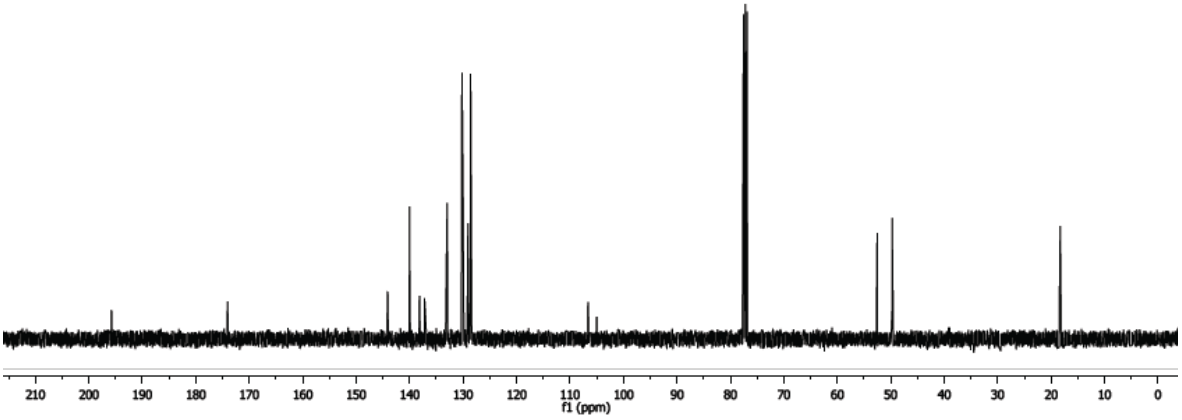
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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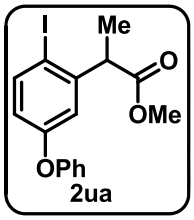
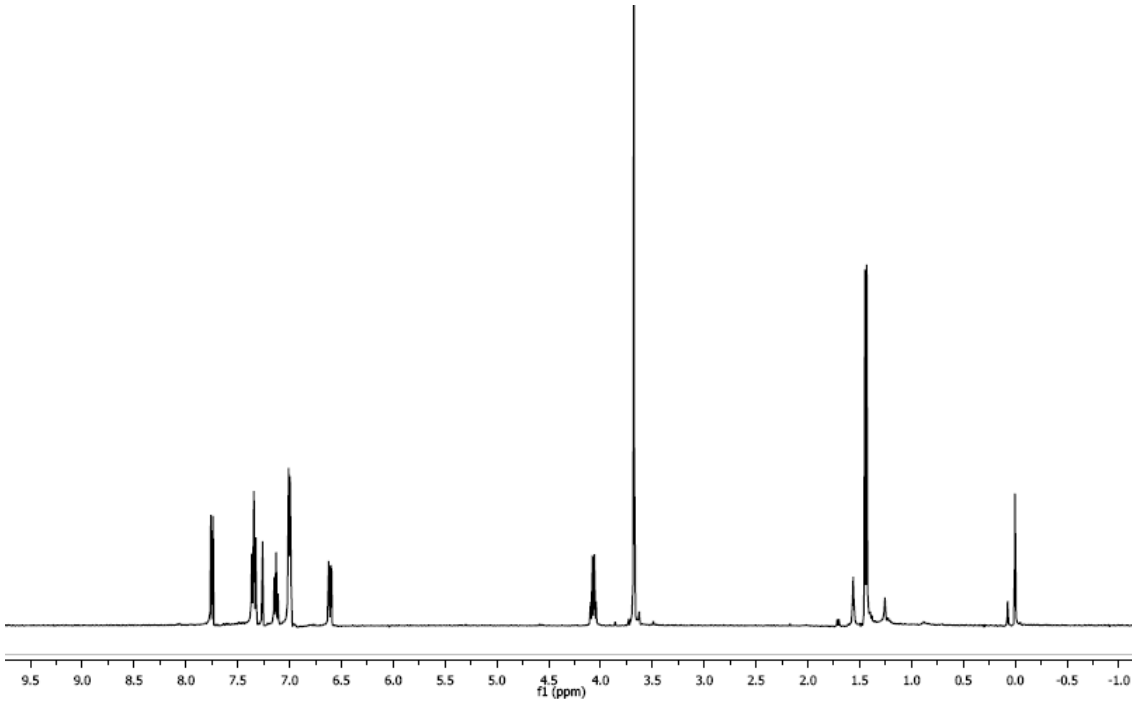
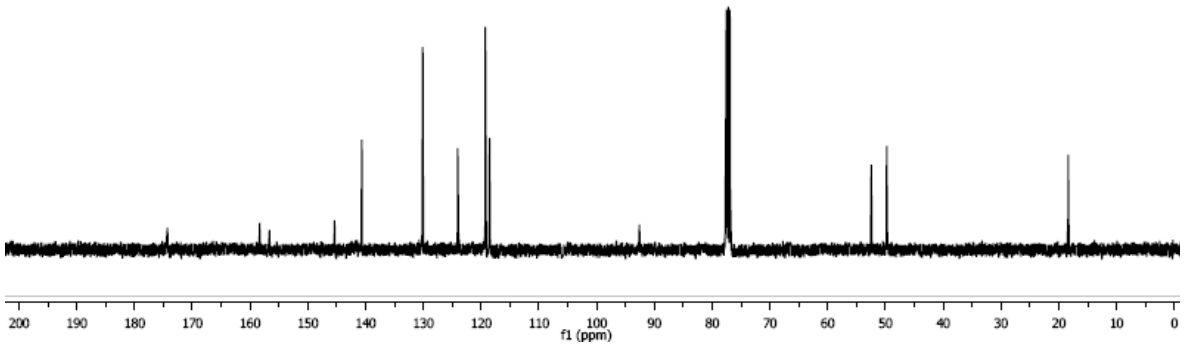
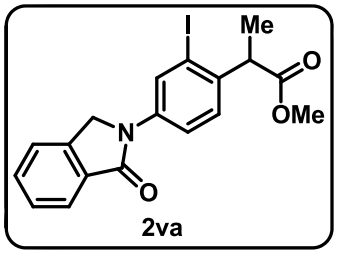
30
20
10
0
f1 (ppm)


I
Me
O
OMe
OPh

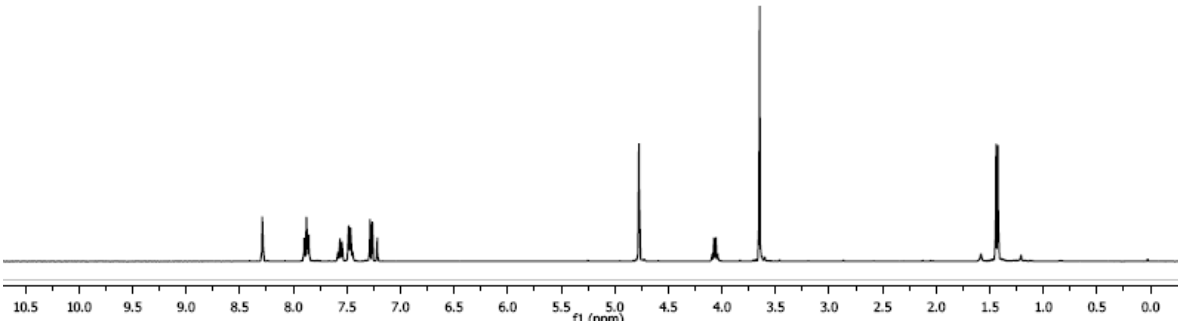
2ua

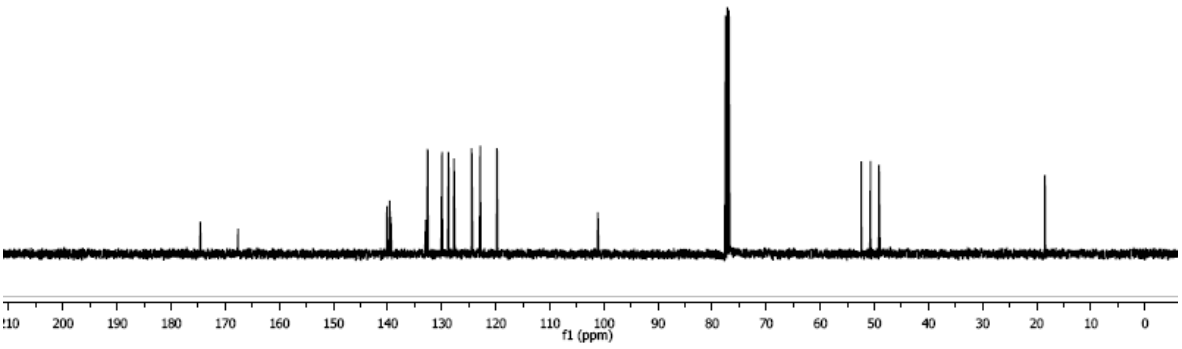

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

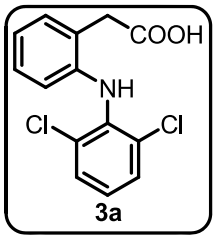

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


I
Me
O
OMe
N
O

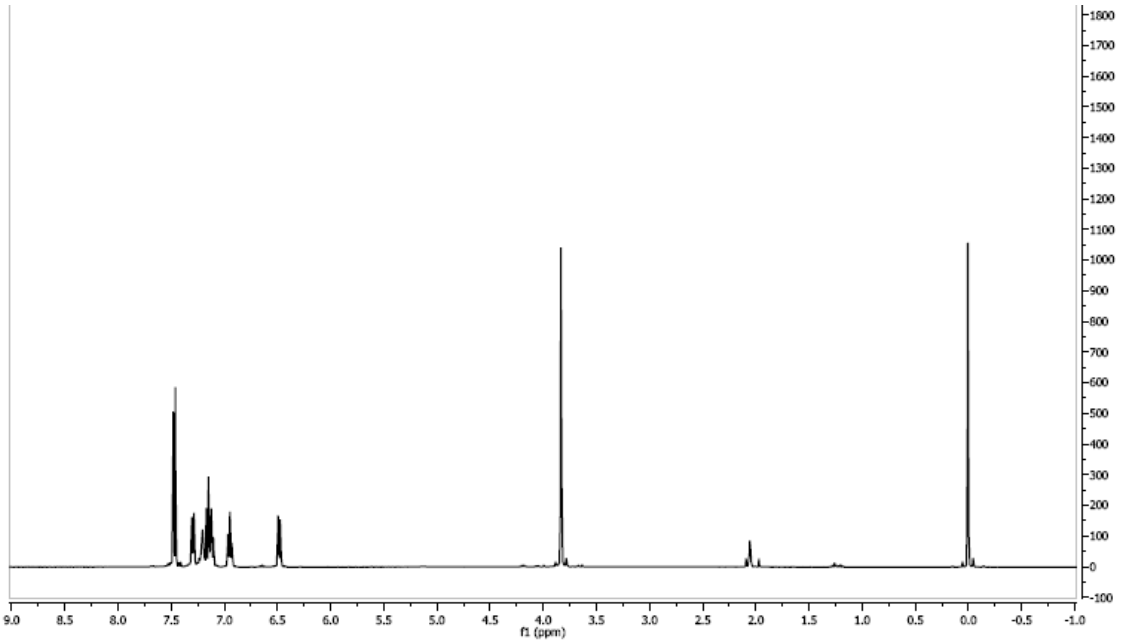
2va

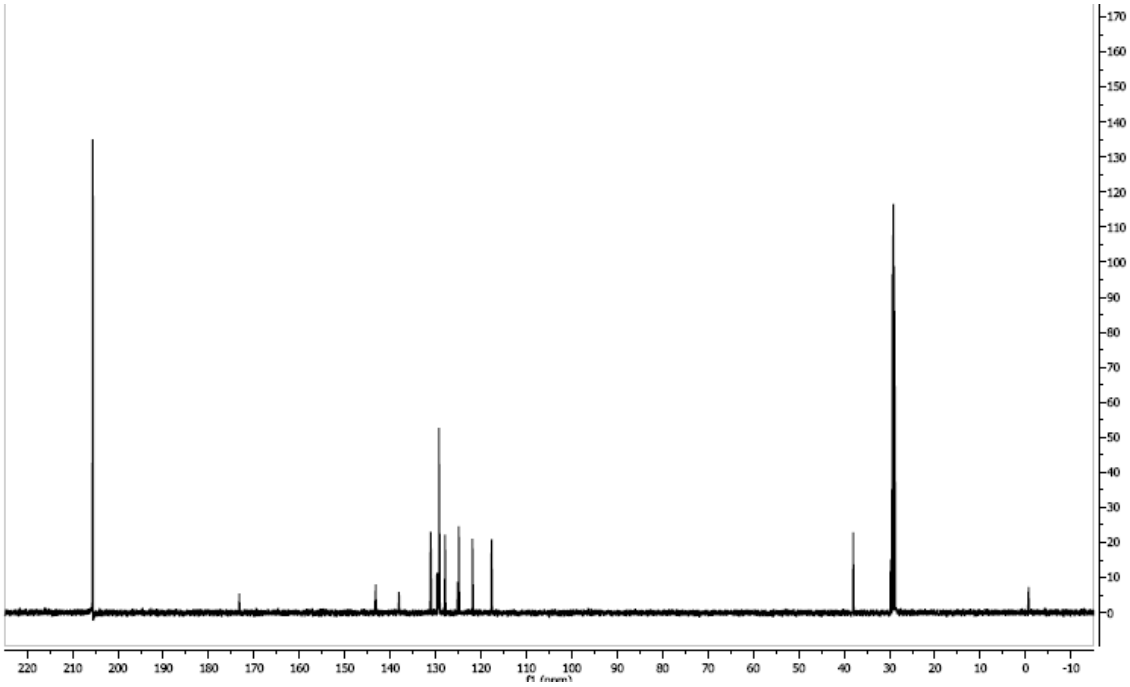

10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

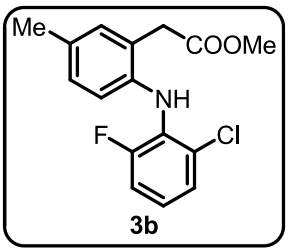

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



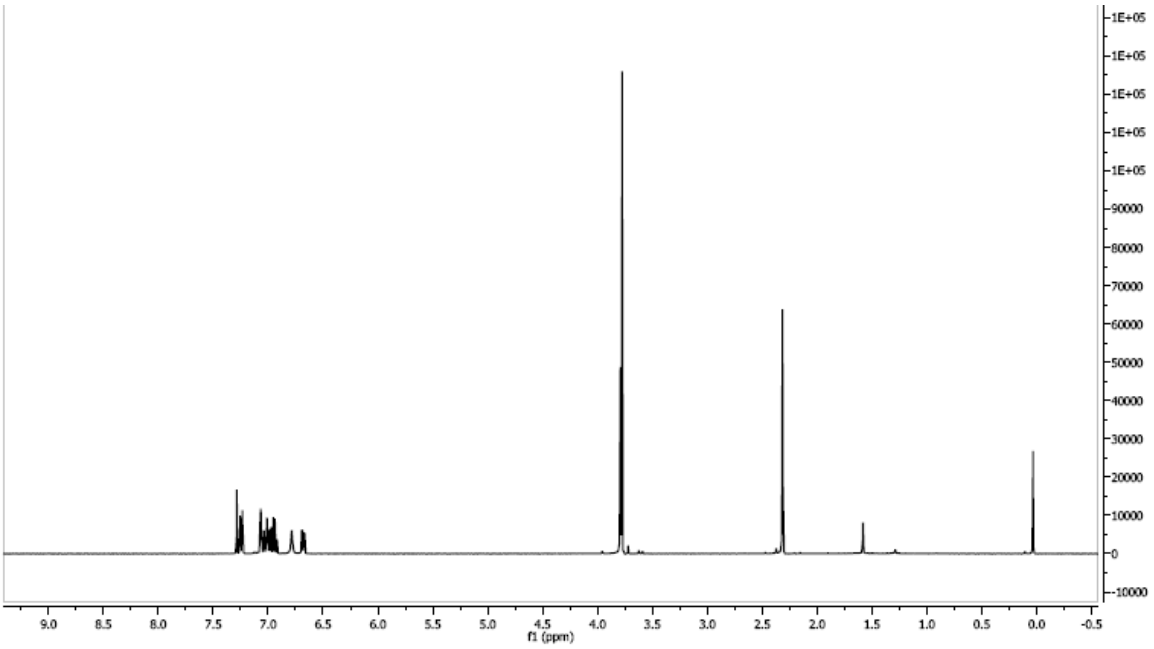
3a

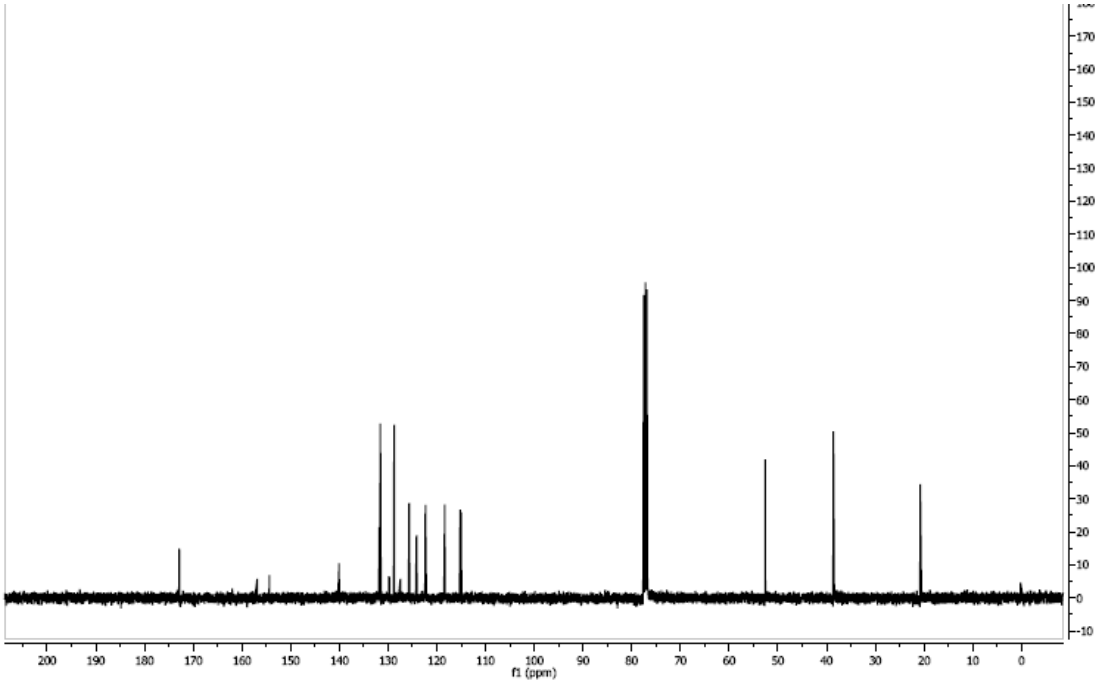


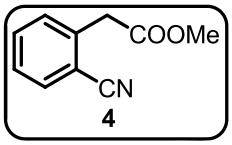




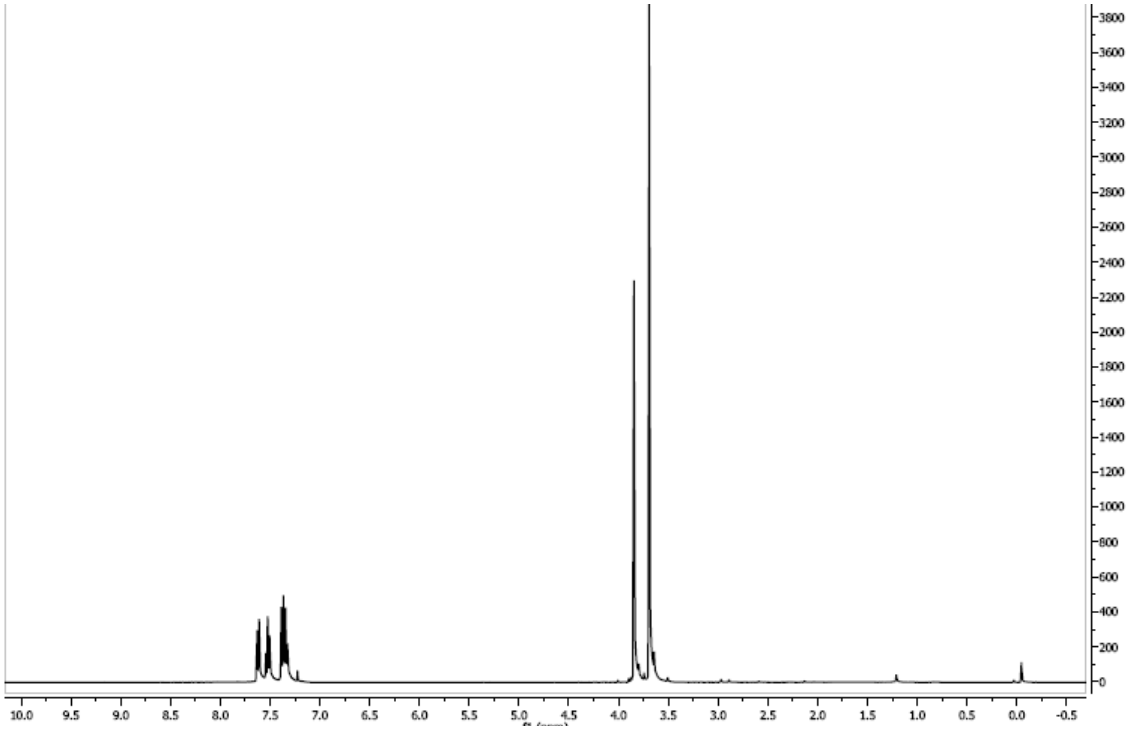
3b

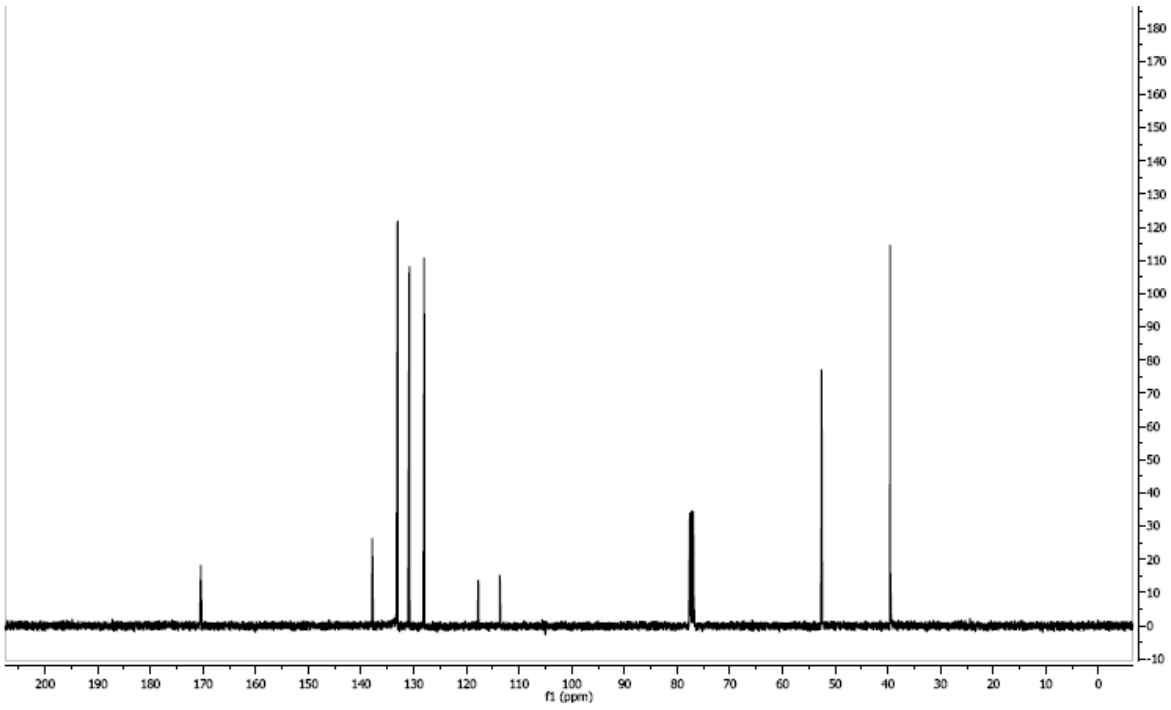


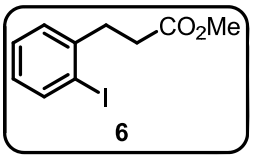




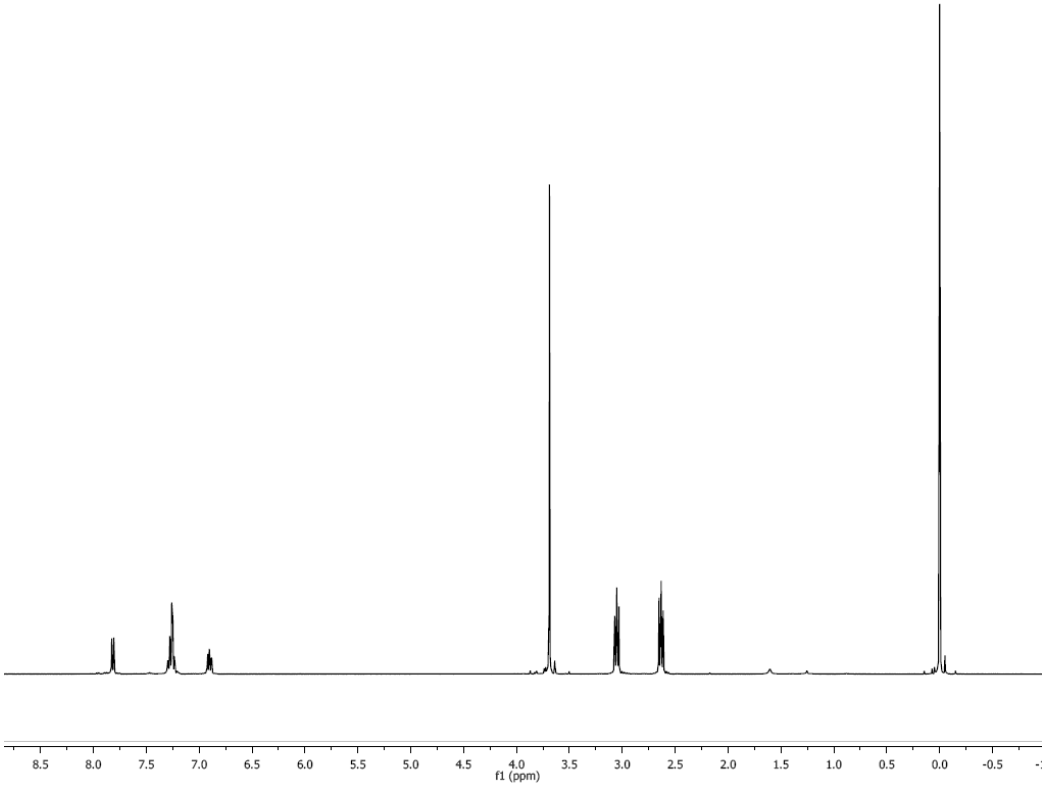
4

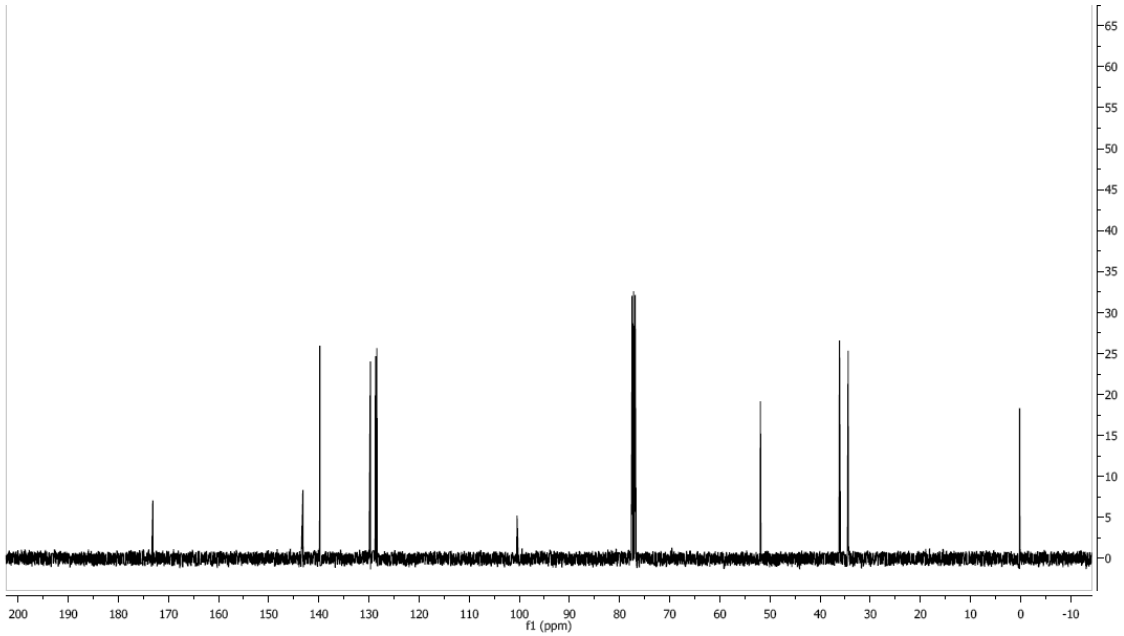





CO2Me
I

6


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)


65 60 55 50 45 40 35 30 25 20 15 10 5 0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)